Mass Spectrometry Reviews

WILEY

REVIEW ARTICLE OPEN ACCESS

Practical Applications of Secondary/Extractive Electrospray Ionization (SESI): A Versatile Tool for Real-Time Chemical Analysis

Xin Luo[1] | Huiling Wang[1] | Xiaolan Hu[1] | Sasho Gligorovski[2] | Xue Li[1] | Pablo Sinues[3,4]

[1]College of Environment and Climate, Institute of Mass Spectrometry and Atmospheric Environment, Guangdong Provincial Key Laboratory of Speed Capability Research, Jinan University, Guangzhou, China | [2]Department of Environmental Science and Engineering, Guangdong Technion – Israel Institute of Technology, Shantou, China | [3]University Children's Hospital Basel, Basel, Switzerland | [4]Department of Biomedical Engineering, University of Basel, Allschwil, Switzerland

Correspondence: Pablo Sinues (pablo.sinues@unibas.ch)

Received: 9 November 2024 | **Revised:** 22 March 2025 | **Accepted:** 28 April 2025

Funding: Financial support for this work was provided to PS by the Fondation Botnar (Switzerland) and the Swiss National Science Foundation (PCEGP3_181300). XL received funding from National Natural Science Foundation of China (No. 22122603), Guangdong Provincial International Science and Technology Cooperation Project (No. 2022A0505050044), Guangdong Major Project of Basic and Applied Basic Research (No. 2023B0303000013) and Research Fund Program of Guangdong Provincial Key Laboratory of Speed Capability Research (2023B1212010008).

Keywords: applications | electrospray extraction ionization | mass spectrometry | secondary electrospray ionization

ABSTRACT

In the 1980s, researchers discovered the remarkable ability of electrospray plumes to effectively ionize gas-phase molecules via secondary ionization. Around 20 years later—coinciding with the ambient mass spectrometry revolution—secondary electrospray ionization (SESI) and extractive electrospray ionization (EESI) coupled to mass spectrometry were revisited and further developed to analyze complex mixtures of gas and aerosol samples in real-time yet with high sensitivity. During the past two decades, these mass spectrometric techniques have been applied across a broad range of applications, such as the detection of illicit drugs, environmental aerosol analysis, and a series of metabolomic studies through the analysis of volatiles emitted from living organisms. This review offers a comprehensive overview of the progress of SESI and EESI applications since their emergence. Finally, we discuss the opportunities, challenges, along with future directions of SESI and EESI techniques.

1 | Introduction

In the early development of electrospray ionization (ESI), John B. Fenn and his co-workers noted the remarkable ability of electrospray plumes to effectively ionize gas-phase molecules at very low concentrations (Whitehouse et al. 1986; Fuerstenau 1994; Fuerstenau et al. 1999; Kiselev and Fenn 2001). In 1994, Hill's research group developed an electrospray-based

Abbreviations: AMS, aerosol mass spectrometer; AUC, area under the curve; CD, corona discharge; CF, cystic fibrosis; CFUs, colony-forming units; CHARON-PTR-MS, chemical analysis of aerosols online inlet coupled to a proton transfer reaction time-of-flight mass spectrometer; CIMS, chemical ionization mass spectrometer; COPD, chronic obstructive pulmonary disease; CWAs, chemical warfare agents; DBDI, dielectric barrier discharge ionization; DESI, desorption electrospray ionization; DMA, differential mobility analyzer; EBC, exhaled breath condensate; EBPs, exhaled breath particles; EDTA, ethylenediaminetetraacetic acid; EESI, extractive electrospray ionization; EI, electron ionization; ESI, electrospray ionization; FIGAERO-CIMS, filter inlet for gases and aerosols coupled to a chemical ionization mass spectrometer; GC-MS, gas chromatography–mass spectrometry; HOMs, highly oxygenated organic molecules; HPLC, high-performance liquid chromatography; ICP-MS, inductively coupled plasma mass spectrometry; IF, ion funnel; IMS, ion mobility spectrometry; LC-MS, liquid chromatography–mass spectrometry; LOD, li, limit of detection; ND, neutral desorption; OA, organic aerosol; OH, hydroxyl radicals; OSA, obstructive sleep apnea; PCA, principal component analysis; PCR, polymerase chain reaction; PK, pharmacokinetic; PLS-DA, partial least squares discriminant analysis; PMF, positive matrix factorization; ppq, parts per quadrillion; ppt, parts per trillion; PTR-MS, proton transfer reaction mass spectrometer; QqQ, triple quadrupole; Q-TOF, quadrupole time-of-flight; RSD, relative standard deviation; SECDI, secondary electrospray corona discharge ionization; SESI, secondary electrospray ionization; SESI-HRMS, secondary electrospray ionization-high resolution mass spectrometry; SESI-MS/MS, secondary electrospray ionization tandem mass spectrometry; SOA, secondary organic aerosol; SOP, standard operating procedure; SRM, selected reaction monitoring; TD, thermal desorption; TDM, therapeutic drug monitoring; VFAs, volatile fatty acids; VOCs, volatile organic compounds.

secondary ionization source, which successfully ionized the headspace vapor of diisobutylamine using charged microdroplets generated by electrospray (Chen et al. 1994). Building upon this foundational work, Hill and colleagues in 2000 employed this unique vapor ionization methodology for the detection of illicit drugs, marking the first formal introduction of the technique as secondary electrospray ionization (SESI) in the scientific literature (Wu et al. 2000). In this context, the term "secondary" refers to a secondary ionization mechanism, involving the introduction of electrospray to generate primary ions, which are then used to ionize neutral analytes in gas samples.

In 2004, Cooks' team developed a new ionization method using electrospray to ionize analytes present on surfaces, termed desorption electrospray ionization (DESI) (Takáts et al. 2004). In this study, they successfully detected the explosive RDX on insulating tanned leather surfaces and the chemical warfare agent dimethyl methylphosphonate (DMMP) on nitrile gloves. Furthermore, liquid samples such as urine and liquid-phase pharmaceuticals can also be analyzed by DESI through the examination of dried sample spots (Chen et al. 2005). However, this approach is unsuitable when real-time measurements are needed. In 2006, Chen et al. introduced extractive electrospray ionization (EESI) for the direct analysis of liquid-phase samples. They used two separate sprayers: one to nebulize the liquid sample into aerosol particles and another to introduce the electrospray (Chen et al. 2006). In the EESI process, analytes are extracted from the sample solution into the electrospray via liquid-liquid extraction between colliding microdroplets (Chen et al. 2006). This mechanism is the origin of the term "extractive" in the method's name. In subsequent applications, the way of sample introduction in EESI has been extended to directly introduce aerosol samples, serving as a supplement to nebulizing liquid samples (Chen and Zenobi 2007; Gu et al. 2012; Qin et al. 2023).

Both SESI and EESI share a similar ion source setup. As illustrated in Figure 1, this setup includes a sprayer for generating electrospray and an individual channel for introducing either gas-phase samples (in SESI) or aerosol-phase samples (in EESI). Analytes in the samples are ionized through interaction with charged droplets or charged ions, following the secondary ionization mechanism. However, despite many researchers proposing potential ionization processes based on experimental evidence (Law et al. 2010b; Meier et al. 2011; Martinez-Lozano Sinues et al. 2012; Rioseras et al. 2017), the ionization mechanisms of SESI and EESI remain not fully understood and lack a definitive explanation to date. This review primarily focuses on the applications of SESI and EESI, while a detailed discussion of ionization mechanisms is presented in a companion review titled "The Evolution of Secondary/Extractive Electrospray Ionization: From Ionization Mechanism to Instrumental Advances (Liao et al. 2025)," published in *Mass Spectrometry Reviews.*

The primary distinction between SESI and EESI lies in their original target sample types: SESI is designed for gaseous samples, while EESI is tailored for aerosol samples. However, in practical applications, gas-phase and aerosol-phase analytes often coexist in the samples of interest to researchers. Determining whether analytes originate from the gas or aerosol phase is not always the primary concern for researchers, leading to the frequent interchangeable use of 'SESI' and 'EESI' in publications. These factors have contributed to significant overlap in their application domains, including the analysis of human breath (Martínez-Lozano and de la Mora 2007; Chen et al. 2007a), environmental samples (Zeng et al. 2020a; Xu et al. 2022; Pospisilova et al. 2021), and food volatiles (Bean et al. 2015; Martínez-Lozano Sinues et al. 2012; Zhu et al. 2010a) and others. Over the past two decades, researchers have accumulated substantial application achievements in these fields.

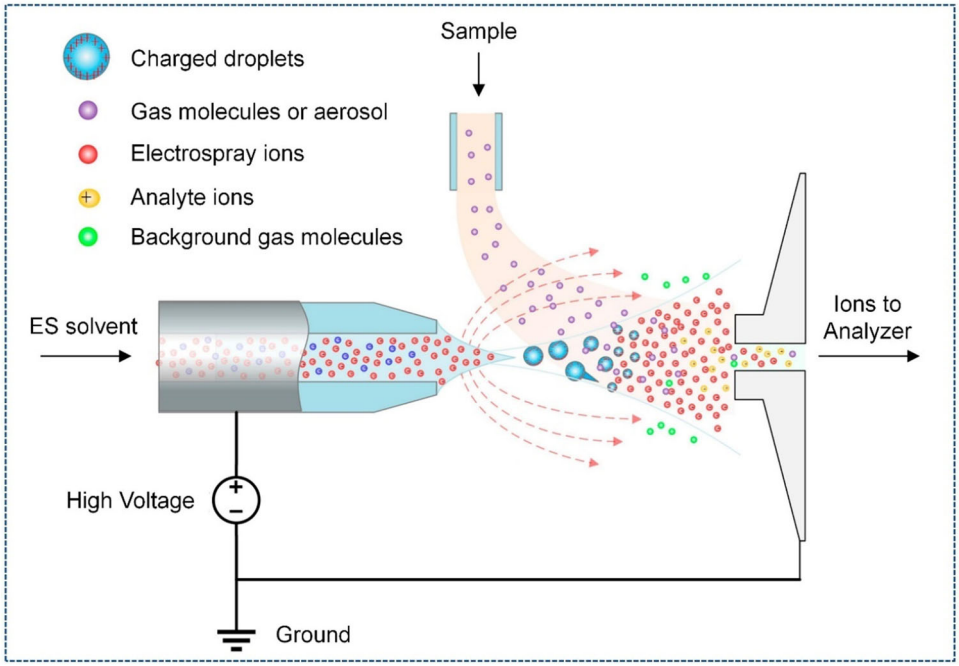

FIGURE 1 | The schematic diagram of secondary electrospray ionization (SESI)/extractive electrospray ionization (EESI) ion source. [Color figure can be viewed at wileyonlinelibrary.com]

Moreover, SESI and EESI have achieved significant progress in commercialization. Notable companies such as Fossiliontech (Spain) (Singh et al. 2018), A-HealthX (China) (Wang et al. 2024a), TOFWERK (Switzerland) (Lopez-Hilfiker et al. 2019) and SEADM (Spain) (Barrios-Collado et al. 2016a) have developed and brought to market commercial SESI and EESI sources. This marks a significant transition: SESI and EESI technologies are no longer limited to academic researchers who can modify their instrumentation but now offer accessible, ready-to-use solutions for a broader range of applications.

In recent years, several reviews focusing on specific applications of SESI and EESI in different fields have been published (Chen and Zenobi 2007; Gu et al. 2012; Qin et al. 2023; Singh et al. 2018; Streckenbach 2022; Li et al. 2018; Gaugg 2018; Zhang et al. 2013a; Blanco and Vidal-de-Miguel 2023; Wüthrich and Giannoukos 2024). This study represents the first review to simultaneously address both SESI and EESI, providing a comprehensive overview of their applications across various fields. The review aims to serve as a valuable resource for researchers to understand current research progress in SESI and EESI applications, while offering guidance for selecting appropriate analytical tools and identifying promising research directions.

A systematic literature search was conducted using the Web of Science database, using the detailed search criteria illustrated in Figure 2. Following manual screening, 237 articles were ultimately included in this review. It should be noted that the concept of "EESI" has spawned several variant techniques, such as internal-extractive electrospray ionization for direct analysis of biological samples (Wu et al. 2024a; Jianyong et al. 2017; Zhang et al. 2013b), and multiphase flow-extractive electrospray ionization (Sun et al. 2021; Wang et al. 2018; Sun et al. 2024) along with electrosonic spray ionization (Ge et al. 2023) for real-time chemical reaction monitoring. However, these techniques do not follow the common ion source setup of EESI, which includes a sprayer for generating electrospray and a separate aerosol sample inlet. As a result, articles related to these techniques were excluded from this review; however, they are worth exploring independently by readers interested in these variations.

Figure 3 displays the 10 most cited articles among the 237 publications in this review, providing a valuable starting point for readers to begin their exploration of SESI and EESI technologies. To organize this review, the included papers have been classified into seven themes based on application fields and analyte characteristics, as outlined in Figure 4. Notably, "Environmental Analysis and Chemical Reaction Monitoring," and "Human" represent the most extensively investigated application areas. It is also important to note that, given the similarities of SESI and EESI, and for the sake of simplicity, we will indistinguishably refer to SESI (except in Section 3.4.1).

2 | Analytical Approach and Strategies

2.1 | Detection Techniques

Mass spectrometry is the preferred detection technique for SESI applications. As an ambient ionization source, SESI can be coupled to various mass spectrometers, such as quadrupole time-of-flight (Q-TOF) (Chen et al. 2007b), triple quadrupole (QqQ) (Martínez-Lozano et al. 2009), ion trap (Berchtold et al. 2013), and Orbitrap (García-Gómez et al. 2015a), among others. When SESI is coupled with an Orbitrap mass spectrometer, researchers commonly refer to the integrated system as secondary electrospray ionization-high resolution mass spectrometry (SESI-HRMS) (García-Gómez et al. 2016a). The high mass resolution of SESI-HRMS (typically > 100,000)

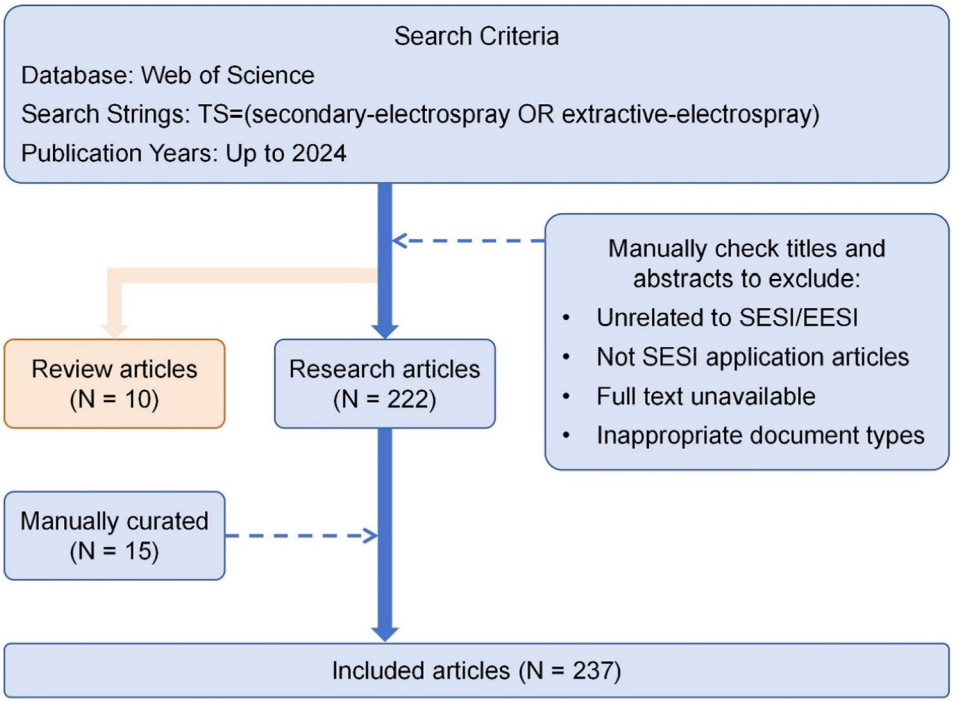

FIGURE 2 | The methodology for literature search and screening. [Color figure can be viewed at wileyonlinelibrary.com]

Ranking	Total Citations	Title	Authors	Publication Year
1	440	Extractive electrospray ionization for direct analysis of undiluted urine, milk and other complex mixtures without sample preparation	Chen et al.	2006
2	233	Secondary electrospray ionization ion mobility spectrometry/mass spectrometry of illicit drugs	Wu et al.	2000
3	213	Rapid detection of melamine in untreated milk and wheat gluten by ultrasound-assisted extractive electrospray ionization mass spectrometry (EESI-MS)	Zhu et al.	2009
4	203	Rapid in vivo fingerprinting of nonvolatile compounds in breath by extractive electrospray ionization quadrupole time-of-flight mass spectrometry	Chen et al.	2007
5	159	Secondary electrospray ionization-ion mobility spectrometry for explosive vapor detection	Tam et al.	2004
6	140	Fast Detection of Volatile Organic Compounds from Bacterial Cultures by Secondary Electrospray Ionization-Mass Spectrometry	Zhu et al.	2010
7	138	Neutral desorption sampling of living objects for rapid analysis by extractive electrospray ionization mass spectrometry	Chen et al.	2007
8	107	Secondary Electrospray Ionization (SESI) of Ambient Vapors for Explosive Detection at Concentrations Below Parts Per Trillion	Martinez-Lozano et al.	2009
9	105	Differentiation of maturity and quality of fruit using noninvasive extractive electrospray ionization quadrupole time-of-flight mass spectrometry	Chen et al.	2007
10	102	Neutral desorption sampling coupled to extractive electrospray ionization mass spectrometry for rapid differentiation of bilosamples by metabolomic fingerprinting	Chen et al.	2007

FIGURE 3 | The top 10 most cited articles among the 237 publications included in this review. [Color figure can be viewed at wileyonlinelibrary.com]

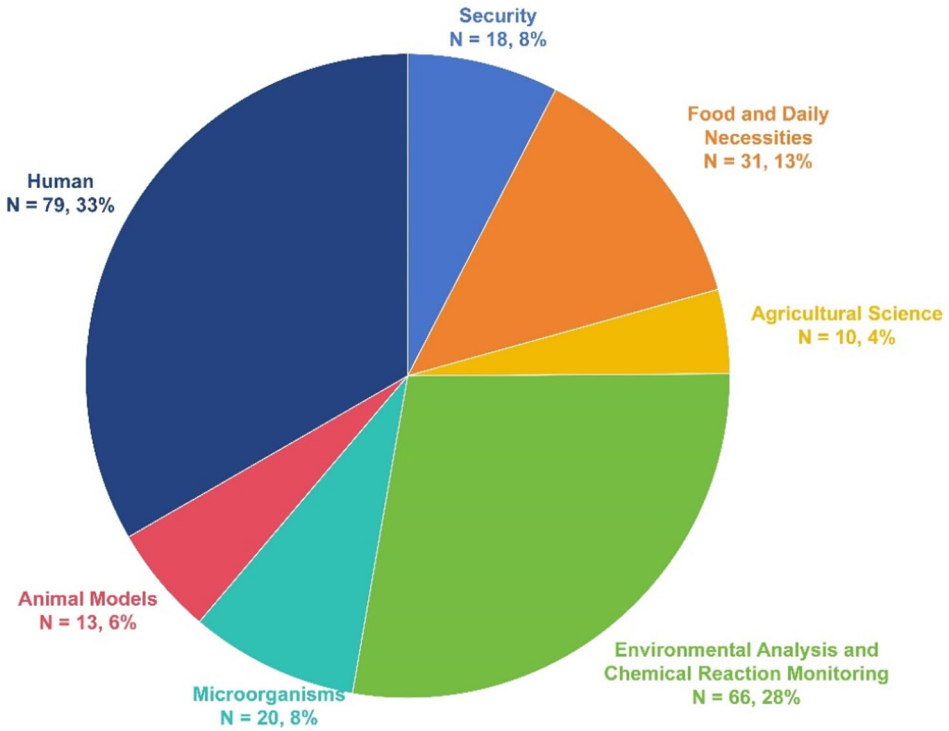

FIGURE 4 | Distribution of publications by theme. [Color figure can be viewed at wileyonlinelibrary.com]

provides enhanced compound identification capabilities. Additionally, when coupled with portable ion trap, this combination enables the development of on-site detection methods (Berchtold et al. 2013).

SESI can also be coupled with ion mobility spectrometry (IMS), including its variant the differential mobility analyzer (DMA) (Zamora et al. 2018). However, such applications remain limited in scope, primarily focusing on fields requiring on-site detection methods or portable devices, such as explosive detection (Tam and Hill 2004). Additionally, some studies have explored IMS as a complementary separation technique when integrated with MS, notably in hybrid configurations such as SESI-IMS-MS (Crawford and Hill 2013).

2.2 | Sampling Methods

Figure 5 presents the commonly used sampling methods in SESI. Since these methods are frequently mentioned in the application sections, this section will provide a summary of their application contexts sequentially to avoid redundant discussion.

1. Sample solution vaporized in the reaction region of IMS (Figure 5A) (Wu et al. 2000): This method was employed when SESI was coupled with IMS. The SESI source comprises a sprayer and an independent sample line. The sprayer is used for introducing the electrospray, while the sample line is designed to introduce the volatile

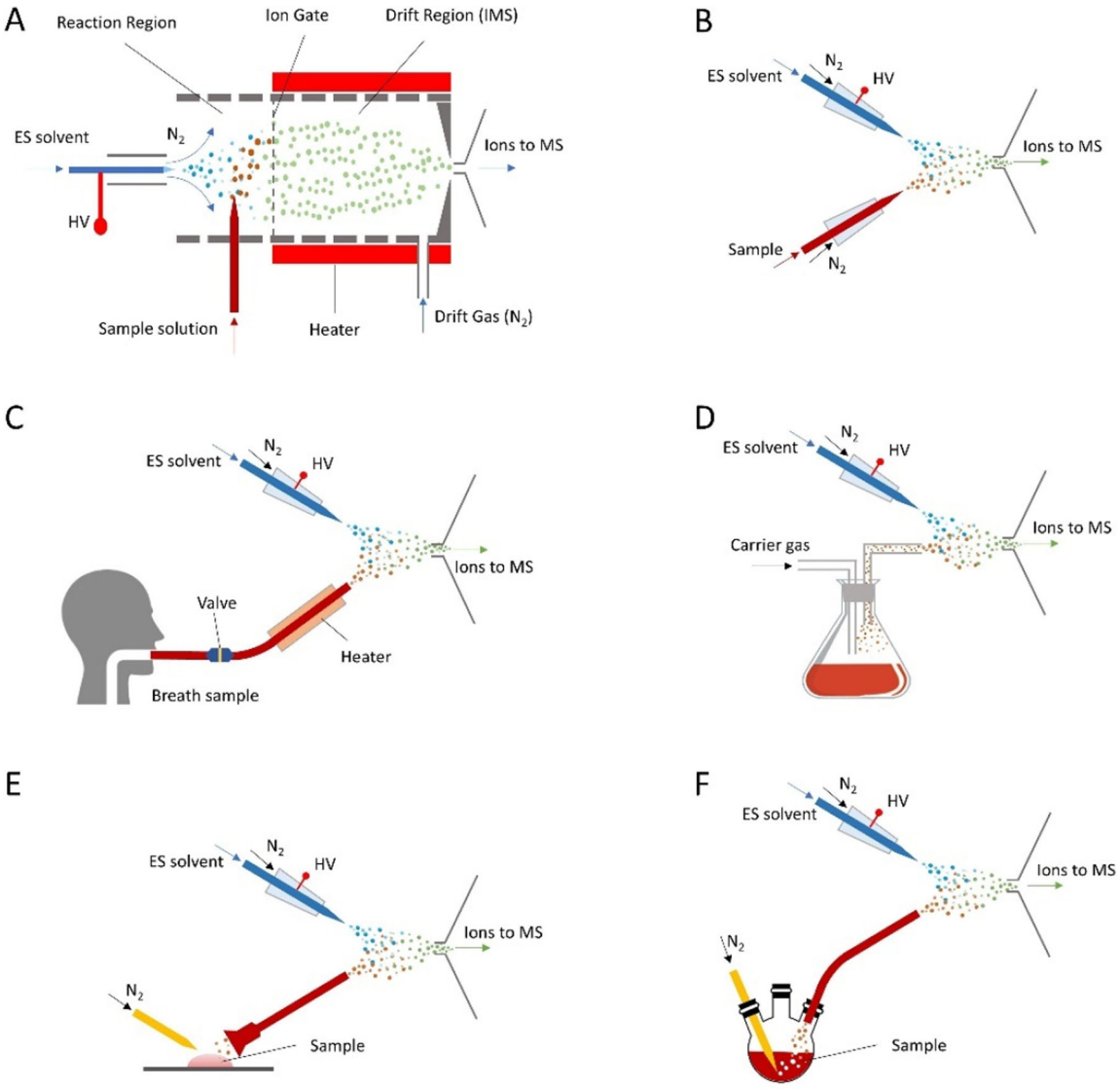

FIGURE 5 | Schematic diagram of commonly used sampling methods for secondary electrospray ionization mass spectrometry (SESI-MS): (A) sample solution vaporized in the reaction region of IMS (Wu et al. 2000), (B) sample solution nebulization (Chen et al. 2006), (C) human breath sampling (Martínez-Lozano and de la Mora 2007; Chen et al. 2007a), (D) headspace sampling (Zhu et al. 2010b), (E) neutral desorption (ND) sampling (Chen et al. 2007c; Chen and Zenobi 2008), (F) micro-jet ND sampling (Law et al. 2009; Li et al. 2011). [Color figure can be viewed at wileyonlinelibrary.com]

sample solution. In the reaction region, the sample solution evaporates into the gas phase under the influence of high-temperature counterflow nitrogen.

2. Sample solution nebulization (Figure 5B) (Chen et al. 2006): When SESI-MS is used for detecting liquid-phase samples, the liquid-phase sample is introduced into a capillary under positive pressure and nebulized into the particle-phase.
3. Human breath sampling (Figure 5C) (Martínez-Lozano and de la Mora 2007; Chen et al. 2007a): Subjects exhale into the sample tube, and their breath samples travel along the tube to the ionization region.
4. Headspace Sampling (Figure 5D) (Zhu et al. 2010b): This method is suitable for analyzing volatile compounds emitted from solid or liquid samples. The sample is typically placed in a sealed container equipped with gas inlet and outlet ports. By introducing a carrier gas (e.g., nitrogen or carbon dioxide) through the inlet, the gas in the container headspace is transported into the ionization region.
5. Neutral desorption (ND) sampling (Figure 5E) (Chen et al. 2007c; Chen and Zenobi 2008): This method employs a stream of nitrogen gas to impact and collect both the volatile and non-volatile analytes present on the sample surface, which are subsequently introduced into the ionization region.
6. Micro-jet ND sampling (Figure 5F) (Law et al. 2009; Li et al. 2011): The gas inlet tube is inserted into the liquid, and a gentle gas flow is introduced to generate aerosol droplets via bubble bursting. Using this method, both

volatile and surface-active species in the liquid-phase sample can be simultaneously collected into the aerosol droplets for SESI-MS analysis. In some literature, this method is also referred to as bubble-assisted sampling (Elpa and Urban 2024).

2.3 | Analytical Strategies

The analytical strategies of SESI-MS can be broadly divided into targeted and untargeted approaches. Targeted strategies are commonly used to develop detection methods for known analytes, optimize analytical protocols, or validate the reliability of potential biomarkers. On the other hand, quantification in SESI-MS relies on calibration curves for semi-quantitative analysis, and the use of reference standards to establish these calibration curves also falls under targeted methods.

In contrast to targeted methods, untargeted approaches do not involve predefined analytes. Untargeted SESI-MS measurements are also referred to in some literature as fingerprinting or profiling. This strategy is widely used in various metabolomic studies to identify discriminative features between experimental and control groups. Fields employing this approach include plant metabolomics, breath metabolomics, and others.

3 | Applications

3.1 | Security

Threat compounds, such as explosives, illicit drugs, and chemical warfare agents (CWAs), pose significant risks to humans and other organisms and can be used by criminals to disrupt societal activities. Sensitive and rapid detection of these substances is crucial for ensuring public security, with IMS and MS being commonly used for this purpose. When integrated with IMS and MS, SESI enables the direct analysis of threat compound vapors. Despite the current absence of commercial instruments, the feasibility of SESI for threat compound detection has been demonstrated by existing research, making it the oldest application area of SESI. This section will discuss the research progress in detecting explosives, illicit drugs, and CWAs using SESI and compare it with mainstream technologies. An overview of SESI's application in detecting threat compounds is provided in Table 1.

3.1.1 | Explosives

As early as before 2000, IMS had already been widely used for the on-site detection of trace levels of nitro-organic explosives, primarily utilizing a radioactive ^{63}Ni source for analyte ionization (Ewing 2001). In their influential 2001 review, Ewing et al. emphasized the significance of employing nonradioactive ion sources to improve the field deployability of IMS (Ewing 2001). Among the nonradioactive ion sources explored by researchers, ESI presents a viable option for the direct analysis of liquid-phase samples (Reid Asbury 2000). To extend ESI to the analysis of gas-phase samples, Hill and colleagues introduced SESI-IMS as a novel tool for the detection of explosive vapors in 2004 (Tam and Hill 2004). Notably, the explosive vapors mentioned in existing studies do not necessarily originate from the headspace gas of solid or liquid explosive samples. When analyzing explosive standard solutions or spiked sample solutions, researchers typically evaporate the solution into the gas phase, as this approach enables the quantification of explosives in the gas phase (Martínez-Lozano et al. 2009; Tam and Hill 2004; Vidal-de-Miguel et al. 2012). As a technique derived from ESI, SESI shares several advantages with ESI when coupled with IMS, including their nonradioactive nature and capability to ionize thermally unstable compounds (Aernecke et al. 2015; Jafari Horestani et al. 2018). In addition, both and non-volatile dopants can be utilized in SESI by adding into the electrospray, whereas conventional ^{63}Ni sources are restricted to the use of volatile dopants only. The expansion of dopant types can, in some cases, further enhance the detection sensitivity of SESI. In the research conducted by Hill et al. the SESI-IMS detection limit for RDX was 116 $\mu g\,L^{-1}$ when a traditional volatile chloride dopant was used, and 5.30 $\mu g\,L^{-1}$ when a non-volatile nitrate dopant was employed (Tam and Hill 2004).

In recent studies, researchers have made great efforts to enhance the sensitivity of SESI-IMS in explosive detection in various aspects. Horestani et al. employed a sample preparation method known as dispersive liquid-liquid microextraction, which enabled SESI-IMS to achieve a detection limit of 1 $\mu g\,L^{-1}$ for TNT in waste water samples, substantially outperforming traditional ^{63}Ni-IMS (Jafari Horestani et al. 2018). Amo-González et al. developed a detection system that integrates a thermal desorber, gas chromatography, and dual differential mobility analyzers, with SESI as the ionization source. By employing this system, they successfully detected vapors emitted from picogram quantities of Pentaerythritol tetranitrate (EGDN), Nitroglycerin (NG), Trinitrotoluene (TNT), and Pentaerythritol tetranitrate (PETN) concealed within cargo (Amo-González et al. 2019). Mullen et al. developed a secondary electrospray corona discharge ionization (SECDI) source that combines SESI with corona discharge (CD). Utilizing SECDI, the IMS signal enhancements for TNT and 2,6-DNT vapors at trace concentrations were increased by 2–26 times compared to those achieved using CD or SESI alone (Mullen and Giordano 2020). The aforementioned improvements have rendered SESI-IMS comparable to or even more sensitive than commercial IMS devices for explosive detection (Buryakov 2011). However, no instrument manufacturers have produced commercial SESI-IMS devices for explosive detection currently. The primary reason is that SESI requires more stringent power and gas supply, along with more challenging maintenance, compared to radioactive sources (Ewing 2001; Steiner et al. 2003). To date, IMS systems equipped with ^{63}Ni remain the most commonly used commercial explosive detection devices globally (To et al. 2020).

Compared to IMS, MS offers superior selectivity and can be utilized for both laboratory measurement and on-site operations (based on portable MS). Martínez-Lozano et al. first reported the sensitivity of SESI-MS to explosive vapors, achieving a lower detection limit of 0.4 parts per trillion (ppt) for TNT and 0.2 ppt for pentaerythritol tetranitrate (PETN), using a homemade SESI source coupled with a triple quadrupole MS (Martínez-Lozano

TABLE 1 | An overview of SESI applications for the detection of threat compounds.

Types	Instruments	Samples	Compounds (LODs)	References
Explosives	SESI-IMS	Vapor generated from standard solution	TNT (n.a.), RDX (5.30 $\mu g\,L^{-1}$ in solution), NG (n.a.), PETN (n.a.)	(Tam and Hill (2004))
	SESI-QqQ MS	Vapor generated from standard solution	PETN (0.2 ppt), TNT (0.4 ppt)	(Martínez-Lozano et al. (2009))
	SESI-QqQ MS	Vapor generated from standard solution	TNT (0.018 ppt), HMX (0.025 ppt), 2,4-DNT (0.023 ppt), RDX (0.005 ppt), PETN (0.006 ppt), NG (0.056 ppt)	(Mesonero et al. (2009))
	SESI-DMA-QqQ MS	Vapor generated from standard solution	TNT (20 fg)	(Vidal-de-Miguel et al. (2012))
	SESI-IMS-TOF MS	Vapor thermally desorbed from household products	TNT (n.a.), RDX (n.a.)	(Crawford and Hill (2013))
	SESI-QTOF MS	Vapor generated from solid explosive	HMTD (n.a.)	(Aernecke et al. (2015))
	SESI-QqQ MS	Vapor generated from solid explosive	2,4-DNT (0.4 ppt), 2,6-DNT (300 ppt), NG (20 ppt), TNT (1 ppb), TATP (10 ppb), HMTD (0.06 ppt), Cyclohexanone (3 ppm)	(Ong et al. (2017))
	SESI-DMA-QqQ MS	Ambient air	NG (n.a.), PETN (n.a.), RDX (0.01 ppq), TNT (0.01 ppq)	(Zamora et al. (2018))
	SESI-IMS	Vapor generated from water samples	TNT (3.0 $\mu g\,L^{-1}$ in waste water)	(Jafari Horestani et al. (2018))
	GC-SESI-DMA-DMA	Air samples collected from pallets with hidden explosives	TNT (ppq level), PETN (ppq level), NG (ppq level), EGDN (ppq level), RDX (ppq level)	(Amo-González et al. (2019))
	SECDI-IMS	Vapor generated from standard solution	TNT ($\leq$ 11.8 ppb), 2,6-DNT ($\leq$ 55.0 ppb)	(Mullen and Giordano (2020))
	SESI-Q MS	Vapor thermally desorbed from swab	HMTD (5 ng), PETN (2.5 ng), Tetryl (2.5 ng), TNT (2.5 ng), RDX (2.5 ng)	(Burns et al. (2022))
Drugs	SESI-IMS-Q MS	Vapor generated from standard solution	LSD (n.a.), THC (n.a.), Amphetamine (n.a.), Methamphetamine (n.a.), Cocaine (n.a.)	(Wu et al. (2000))
	SESI-IF-IT MS	Vapor generated from solid drug	Atenolol (13 fmol s^{-1}), Salbutamol (18 fmol s^{-1}), Cocaine (26 fmol s^{-1})	(Meier et al. (2012))
	(1) Rectilinear ion trap (2) 3D ion trap (3) QTOF.	Headspace gas from various beverages	GHB ($<$ 0.5 g L^{-1} in beverages), GBL ($<$ 0.5 g L^{-1} in beverages)	(Berchtold et al. (2013))
	SESI-IMS	Vapors emitted from solid NPPA or fentanyl	NPPA (detectable in the headspace of 5 mg NPPA or 5 mg fentanyl)	(Smith et al. (2022))

(Continues)

TABLE 1 | (Continued)

Types	Instruments	Samples	Compounds (LODs)	References
CWAs	SESI-IMS-TOF MS	Vapor generated from standard solution	DMMP (n.a.), PMP (n.a.), DEPA (n.a.), BAET (n.a.), CEES (n.a.)	(Steiner et al. (2003))
	SESI/DBDI-IT MS	Vapor generated from standard solution	DMMP (3.6 ppt), PMP (n.a.), DEEP (5.0 ppt), malathion (4.1 ppt), PHX (2.2 ppt), DCV (8.4 ppt), Scopolamine (n.a.), CEES (58.4 ppt), DEPA (1.4 ppt), MPA (n.a.), TDG (35.1 ppt), DIMP (11.1 ppt), Sarin (188 ppt)	(Wolf et al. (2015))

Abbreviations: **Instrument:** DBDI, dielectric barrier discharge ionization; IF, ion funnel; IT, ion trap; SECDI, secondary electrospray corona discharge ionization.
Explosives: TNT, trinitrotoluene; RDX, cyclo-1,3,5-trimethylene-2,4,6-trinitramine; NG, nitroglycerin; PETN, pentaerythritol tetranitrate; HMX, cyclotetramethylenetetranitramine; 2,4-DNT, 2,4-dinitrotoluene; HMTD, hexamethylene triperoxide diamine; 2,6-DNT, 2,6-dinitrotoluene; TATP, triacetone triperoxide; EGDN, ethylene glycol dinitrate.
Drugs: LSD, lysergic acid diethylamide; THC, tetrahydrocannabinol; GHB, γ-Hydroxybutyrate; GBL, γ-butyrolactone; NPPA, N-phenylpropanamide.
Chemical warfare agents (CWAs): BAET, 2-(butylamino)ethanethiol; DMMP, dimethyl methylphosphonate; PMP, pinacolyl methylphosphonate; DEEP, diethyl ethylphosphonate; PHX, phoxim; DCV, dichlorvos; CEES, 2-chloroethyl ethylsulfide; DEPA, diethyl phosphoramidate; MPA, methylphosphonic acid; TDG, thiodiglycol; DIMP, diisopropyl methylphosphonate; Sarin, isopropyl-methylphosphonofluoridate.

et al. 2009). Additionally, the detection probability of SESI-MS was estimated to be 10^{-8}, indicating that at least 10^{8} neutral sample molecules are required to produce a valid signal (Martínez-Lozano et al. 2009). The inefficiency primarily stems from three factors: 10% ion transmission and counting probability in the MS, 10^{-3} background noise interference, and 10^{-4} ionization probability from the SESI source. Among these, the MS-related inefficiency is relatively minor, suggesting that enhancing ionization efficiency and reducing background interference are key to improving SESI-MS detection performance (Martínez-Lozano et al. 2009). Subsequent research has made considerable efforts in these two aspects. For example, structural optimization of SESI sources has been implemented to achieve higher ionization efficiency (Vidal-de-Miguel et al. 2012; Mesonero et al. 2009). In terms of reducing background interference, efforts include utilizing IMS (Crawford and Hill 2013) or differential mobility analyzers (DMA) (Zamora et al. 2018) as real-time ion separation methods complemented to MS. As shown in Table 1, these efforts have brought the limits of detection (LOD) of SESI for some common organic explosives to the parts per quadrillion (ppq) or nanogram (ng) level. Traditional mass spectrometers are often characterized by their large size, which limits their field deployability. Burns et al. developed an explosive detection system based on a portable single quadrupole mass spectrometer, utilizing SESI as the ionization source and a swab desorber unit for sample introduction. When sampling with a glass fiber swab, the system successfully detects several ng of five common explosives: hexamethylene triperoxide diamine (HMTD), RDX, PETN, Tetryl, and TNT (Burns et al. 2022). This highlights the potential of SESI for on-site detection of explosives when coupled with a portable mass spectrometer.

Beyond on-site detection, the capability of SESI-MS to detect trace explosive vapors has been utilized in other applications. For instance, HMTD, due to its low volatility and thermal instability, poses challenges in determining its thermo-chemical parameters. Aernecke et al. developed a method using SESI-Q-TOF to measure vapor sublimated from solid HMTD standard in real time. This approach enabled the derivation of the HMTD vapor pressure curve over a temperature range of 28°C to 80°C, representing the first direct experimental measurement of its vapor pressure (Aernecke et al. 2015). This application highlights the high sensitivity of SESI-MS and its advantage of ionizing samples without requiring high temperatures. Subsequently, the method of detecting sublimation vapor by SESI-MS has been applied to enhance the training efficiency of sniffer dogs in three ways: (1) detecting and preventing cross-contamination of training materials; (2) determining the presence of explosive vapor instead of relying on the subjective judgment of trainers; and (3) identifying the headspace components of HMTD training aids (Ong et al. 2017). Given the ongoing demand for sniffer dogs (To et al. 2020), this method demonstrates that SESI-MS can provide indirect support in explosive detection.

3.1.2 | Illicit Drugs

The first reported application of SESI was the detection of illicit drugs by Hill and colleagues in 2000 (Wu et al. 2000). They developed an ESI/SESI-IMS-Quadrupole MS system capable of

operating in either ESI mode or SESI mode. Using this system, they detected a drug mixture containing amphetamine, methamphetamine, cocaine, lysergic acid diethylamide (LSD), and tetrahydrocannabinol (THC), demonstrating that SESI exhibited superior sensitivity compared to ESI (Wu et al. 2000). To enhance the sensitivity of SESI-MS, Meier et al. employed an ion funnel (IF) to improve ion transmission efficiency (Meier et al. 2012). They constructed a SESI-IF-Ion Trap MS system and successfully detected vapors of atenolol, salbutamol, and cocaine at the ppt level. Compared to the sensitivity obtained without the IF, the ppt range represents a two orders of magnitude improvement (Meier et al. 2012).

On-site detection of illicit drugs is an essential step in crime prevention, imposing high requirements on the sensitivity and selectivity of detection instruments. Berchtold et al. investigated the feasibility of detecting the party drugs γ-hydroxybutyrate (GHB) and γ-butyrolactone (GBL) using SESI-MS. When SESI was coupled to a 3D ion trap MS mounted on a cart for the analysis of headspace from various beverages (such as water, tea, wine, and others) spiked with GHB and GBL, the detection limits were consistently below 0.5 g L^{-1}. Furthermore, when using a fully portable rectilinear ion trap MS, the identification of 0.5 g L^{-1} GHB in water was achieved. Considering the typical dosage of 2 g L^{-1}, their findings suggest that, with a mobile MS instrument, SESI has the potential for on-site detection of illicit drugs (Berchtold et al. 2013). Furthermore, the noncontact nature of SESI detection reduces the health risks associated with direct sample contact compared to swab-based sampling methods. This approach demonstrates particular utility in monitoring potent drugs, with the opioid fentanyl serving as a representative example. To achieve noncontact detection of fentanyl, Smith et al. developed a method using SESI-IMS to detect N-phenylpropanamide (NPPA, a degradation product of fentanyl) vapor in the headspace of fentanyl. With this method, solid fentanyl samples weighing 5 mg or more can be indirectly identified (Smith et al. 2022).

3.1.3 | Chemical Warfare Agents

CWAs are a class of highly toxic compounds developed for use in warfare. CWAs are categorized into four types: choking agents, blister agents, blood agents, and nerve agents. Due to their extreme toxicity and stringent regulatory restrictions, most existing studies are conducted using CWA simulants, which exhibit lower toxicity but share similar chemical properties.

Currently, research on SESI for CWAs detection is limited and primarily focused on evaluating ion source performance. In 2003, Hill and colleagues reported that SESI exhibited a higher total product ion intensity than ^{63}Ni and CD when detecting a vapor-phase mixture of diethyl phosphoramidate (DEPA) and 2-(butylamino)ethanethiol (BAET) CWA simulants (Steiner et al. 2003). Wolf et al. compared the detection performance between dielectric barrier discharge ionization (DBDI) and SESI coupled with an ion trap MS. When detecting vapors of 13 CWA-related compounds, both ion sources demonstrated comparable LOD in the low ppt range, outperforming traditional liquid chromatography–mass spectrometry (LC-MS) and gas chromatography–mass spectrometry (GC-MS) (Wolf et al. 2015). For the majority of the compounds, both DBDI and SESI exhibited a linear dynamic range spanning three orders of magnitude, extending from the low ppt to the ppb range. However, SESI showed stronger in-source fragmentation during the detection of malathion and sarin (Wolf et al. 2015). The study by Wolf et al. demonstrated the feasibility of SESI and DBDI for on-site detection of CWAs and related compounds. Future research could consider developing detection methods based on portable MS and validating their effectiveness using ambient air sample.

3.2 | Food and Consumer Products

Food fraud typically encompasses several types, such as counterfeiting of origin, adulteration, illegal additives, and others. In this field, researchers have employed SESI-MS for targeted and untargeted analysis of various food fraud phenomena. They have developed rapid differentiation methods for food samples and rapid quantitative detection techniques for toxic substances. Furthermore, similar strategies have also been applied to the analysis of consumer products.

3.2.1 | Food Quality Control and Authentication

Various sampling methods can be employed depending on the texture of food samples. Current studies mainly utilize the following methods: (1) Headspace sampling to analyze volatile compounds emitted from fruits (Chen et al. 2007b), oils (Martínez-Lozano Sinues et al. 2012), and so on; (2) ND sampling to detect analytes on surfaces of cheese (Wu et al. 2010), meat (Chen et al. 2007d), and so on; (3) Micro-jet ND sampling for analyzing liquid food samples, including beer (Zhu et al. 2010a), and honey (Luo et al. 2017); (4) Sample Nebulization to detect dissolved substances in liquid foods, such as lead dissolved in beverages (Liu et al. 2012). To avoid redundancy, detailed discussions of sampling methods for specific food types will not be repeated in subsequent content.

In food analysis, SESI-MS research strategies include both targeted and nontargeted approaches. To better illustrate SESI-MS for nontargeted food analysis, we use the study by Bean et al. (2015) as an example. Their research aimed to distinguish Cheddar cheeses with different aging periods through SESI-MS headspace analysis and identify discriminative compounds. In their experiment, they prepared eight cheese samples divided into three groups aged for 1 to 3 years and conducted headspace analyses in both positive and negative ion modes six times per sample. As shown in Figure 6, all SESI-MS fingerprints within an aging category clustered together and were separable from other aged groups using the first three principal components ($p < 0.0001$). Additionally, applying the criterion of z-scores exceeding the 5% significance cutoff in Mann−Whitney U test, they identified 35 peaks with intensity increase or decrease during cheeses aging. These peaks were validated as contributors to cheese classification by aging period, as their VIP scores exceeded 0.8 in PLS-DA (Bean et al. 2015). Their research suggests that SESI-MS can be employed to differentiate cheeses with different aging periods and identify peaks correlated with aging.

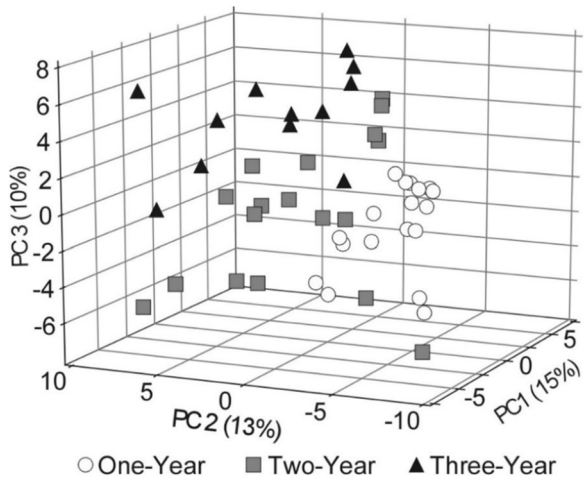

FIGURE 6 | Principal component analysis of the secondary electrospray ionization mass spectrometry (SESI-MS) measurement of 1-, 2-, and 3-year-aged Cheddar cheeses (Bean et al. 2015).

Similar strategies have also been employed in the following research, albeit with variations in sampling and data analysis methods: (1) Food flavor monitoring: including distinguishing the maturity stages of fruits (Chen et al. 2007b; Farrell et al. 2017); (2) Food authentication: including identifying food types (Zhu et al. 2010a; Wu et al. 2010), geographic origins (Martínez-Lozano Sinues et al. 2012), and detecting adulteration (Wang et al. 2021a; Law et al. 2010a; Gao et al. 2020); (3) Food safety detection: detecting food spoilage (Chen et al. 2007d; Dryahina et al. 2020) or bacterial contamination (Chen et al. 2007d). Notably, these studies have only demonstrated the capability of SESI-MS to discriminate food samples with distinct characteristics under laboratory conditions, but have not yet been translated into practical real-world applications. Furthermore, since the untargeted classification method does not rely on specific biomarkers (Ballin and Laursen 2019), future research should consider building a database using the SESI-MS fingerprints of authentic foods for standardized discriminant analysis, as exemplified by the work of Sinues et al. (2012).

When applying SESI-MS to targeted food analysis, the primary objective lies in establishing rapid quantitative detection methods for food safety-related substances. The research workflow can be summarized as follows: (1) Selection of target food samples and analytes: This step is guided by addressing food safety concerns. (2) Design of detection strategy: This step involves selecting appropriate sampling methods, establishing sample concentration ranges in compliance with regulatory standards, selecting dopants (if needed), and determining MS data acquisition parameters. (3) Preparation and analysis of spiked samples: Food samples spiked with gradient concentrations of analytes are prepared and analyzed via SESI-MS to establish calibration curves. (4) Evaluation of method performance: Key parameters, including LOD, linear range, linear correlation coefficient (R^2), recovery rate, relative standard deviation (RSD), and detection time, are systematically evaluated. These metrics are then compared with those of traditional methods to validate the approach's efficacy.

To better illustrate the workflow of SESI-MS in targeted food analysis, we use the study by Liu et al. (2012) as an example. Inspired by lead poisoning incidents, they aimed to develop a novel method for the fast and sensitive detection of lead in liquid samples. For the detection strategy, they utilized a sprayer to nebulize beverage samples and introduced ethylenediaminetetraacetic acid (EDTA) into the electrospray solvent due to its strong affinity for lead. During analysis, several beverage samples (e.g., beer, tea brew, cola, etc.) spiked with lead at concentrations ranging from 1 ppt to 1 ppb were measured using SESI-Ion Trap MS, with m/z 407 ($[EDTA + {}^{208}Pb\text{-}3H]^-$) as the characteristic fragment. The developed method exhibited the following performance parameters: a linear dynamic range generally exceeding two orders of magnitude, calibration curve R^2 values > 0.90, LOD as low as 3.0×10^{-13} g mL^{-1}, recovery rates (at 5.0×10^{-12} g/mL) between 91.5% and 129.0% depending on sample matrices, and RSD around 10%. These parameters demonstrated that the detection performance of the SESI-MS method was comparable to the traditional inductively coupled plasma mass spectrometry (ICP-MS) method. However, the SESI-MS analysis required only 2 min per sample, significantly more efficient than ICP-MS, which often involves hours of sample preparation (Liu et al. 2012).

The targeted analytical strategy described above has been applied to the development of rapid SESI-MS detection methods for the following hazardous substances: melamine in milk (Zhu et al. 2009), histamine (Cai et al. 2014) and phthalic acid esters (Sun et al. 2015) in alcoholic beverages, chloramphenicol (Huang et al. 2014) and pesticides (Luo et al. 2017; Deng et al. 2017) in honey. This strategy has also been extended to the detection of active ingredients or impurities in pharmaceuticals (Gu et al. 2010; Williams and Scrivens 2008; Devenport et al. 2013). Although the SESI-MS method has demonstrated practical analytical performance in these studies and can complete detection within a few minutes. However, unknown matrix compositions may introduce measurement bias. For example, Liu et al. pointed out that the presence of organic acids in the matrix with higher affinity for lead than EDTA could impair SESI-MS detection accuracy (Liu et al. 2012). Conventional approaches involving sample pretreatment and LC/GC separation demonstrate superior adaptability to complex sample matrices (González-Domínguez et al. 2014). In comparison, SESI-MS shows greater potential for high-throughput screening of hazardous compounds instead of precise quantification. Therefore, developing in situ detection methods based on portable MS or IMS for food production quality control in manufacturing environments represents a promising future direction (Zhu et al. 2009; Cai et al. 2014; Fang et al. 2023). Interestingly, in recent years, researchers have applied SESI-MS for targeted monitoring of changes in toxic substances during the decoction process of traditional Chinese medicine, hinting at an emerging research direction (Qiu et al. 2020, 2021).

3.2.2 | Consumer Products

The research strategies and objectives of SESI-MS in consumer products are similar to those in food analysis; therefore, they will not be redundantly discussed here. In nontargeted analysis, SESI-MS has been employed to authenticate genuine versus

counterfeit perfumes (Chingin et al. 2008). On the other hand, based on targeted analysis strategies, researchers have developed rapid SESI-MS detection methods for some harmful substances in consumer products, including diethyl phthalate in perfumes (Chingin et al. 2009), diethylene glycol in toothpaste (Ding et al. 2009), sunscreen agents (Zhang et al. 2011), hormones, and sulfonamides (Liu et al. 2011a) in cream cosmetic products, as well as nicotine and other harmful substances in e-cigarette liquids (García-Gómez et al. 2016). However, these products are all industrially formulated products, where their compositions depend on manufacturers' proprietary formulations and production processes. In practice, manufacturers and regulatory authorities may prioritize accurate quantitative methods over rapid screening approaches.

3.3 | Agricultural Science

Understanding plant and animal physiology is critical in agricultural science to enhance productivity, stress resilience, and health management. In this field, SESI-MS serves as a tool for metabolite detection. Specifically, in plant studies, researchers have employed SESI-MS to analyze liquid extracts and volatiles from plant organs, identifying metabolites associated with circadian rhythms and stress response processes. In studies involving dairy cows, SESI-MS has been applied to analyze metabolites in the exhaled breath of dairy cows, aiming in discover ruminal fermentation biomarkers. Although the functional roles of these specific metabolites require further validation, existing research demonstrates the potential of SESI-MS as a noninvasive method for monitoring physiological states in plants and animals.

3.3.1 | Plants

The existing research of SESI-MS for plant analysis follows a nontargeted metabolomics approach. The primary sampling methods include: (1) detection of volatile metabolites in live plants via headspace sampling (Barrios-Collado et al. 2016b); (2) ND sampling of analytes on the leaf surface (Wu et al. 2019a); and (3) nebulizing the liquid extracts of plant organ, such as seeds and leaves (Zhou et al. 2018; Liu et al. 2020).

A common research approach involves using SESI-MS to analyze liquid extracts of different plant organs for investigating plant metabolic responses to environmental stress. For instance, Liu et al. demonstrated that SESI-MS detected elevated signal intensities of epicatechin and caffeic acid in *Citrus limon* (*C. limon*) leaves under prolonged asian citrus psyllid infestation. These compounds were subsequently quantified and validated using high-performance liquid chromatography (HPLC), revealing a significant upward trend in their concentrations ($p < 0.05$) and suggesting their potential role as biomarkers of induced resistance in *C. limon* against asian citrus psyllid (Liu et al. 2020). In the study by Du et al. SESI-MS identified a significant increase in methyl jasmonate (MeJA) signal intensity in chilling-tolerant rice seedlings under cold stress, while polymerase chain reaction (PCR) analysis revealed marked upregulation of genes in the MeJA biosynthesis pathway. The PCR results elucidated the molecular mechanism underlying the MeJA level changes observed through EESI-MS (Du et al. 2020). In these studies, SESI-MS served as rapid screening tools for stress-induced metabolites, whereas conventional analytical techniques like HPLC and PCR remained essential for precise metabolite quantification and molecular biological validation.

On the other hand, sampling methods such as ND sampling and headspace sampling enable in situ detection of metabolites of live plants. The former targets metabolites present on the leaf surface (Wu et al. 2019a, 2024b), while the latter specifically captures VOCs emitted by plants (Barrios-Collado et al. 2016b). Barrios-Collado et al. investigated the metabolic response of Begonia semperflorens to light levels and mechanical damage through real-time headspace analysis by SESI-Orbitrap MS, with the experimental setup illustrated in Figure 7. During the light-induced metabolism experiment, they continuously monitored metabolite changes in the glass beaker over 3 days with a time resolution of 2 min. They discovered that around 400 species were correlated with light levels, a number far exceeding previous reports using PTR-MS, with some substances' variation patterns validated by existing GC-MS studies (e.g., β-caryophyllene). In the mechanical damage experiment, they mimicked an insect attack by piercing some upper leaves and observed a significant increase in over 1,000 damage-specific metabolites, with certain compounds sharply rising within 8 min after leaf injury. Finally, they proposed that SESI-Orbitrap is an attractive tool to complement GC-MS due to its ability to detect hundreds of VOCs covering the typical GC-MS range (i.e., 50−500 Da), yet with unparalleled time resolution and no sample preparation required (Barrios-Collado et al. 2016b).

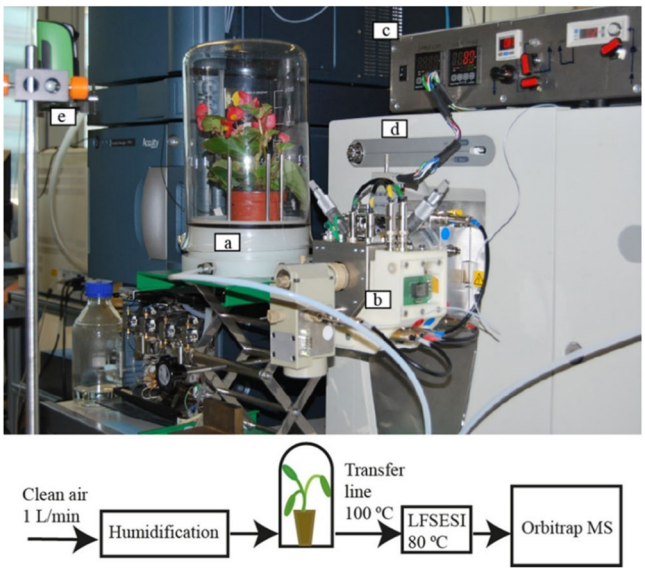

FIGURE 7 | Experimental setup used to analyze in vivo plant volatile emissions. Metabolites emitted by the plant were continuously dragged into the ion source and mass analyzed in real time: (A) glass beaker containing the plant; (B) secondary electrospray ionization (SESI) source; (C) SESI control module; (D) Orbitrap MS; (E) time-lapse camera (Barrios-Collado et al. 2016b). [Color figure can be viewed at wileyonlinelibrary.com]

3.3.2 | Dairy Cows

In dairy cow farming, rumen fermentation parameters are key indicators of nutrient digestion and utilization. Traditional methods for assessing rumen fermentation are invasive, such as obtaining representative rumen digesta samples through surgical fistulation (Larsen et al. 2020). Recently, researchers have explored the use of SESI-MS to analyze exhaled breath from dairy cows, aiming to identify biomarkers associated with rumen fermentation and ultimately develop noninvasive detection methods (Islam et al. 2023).

In a preliminary study conducted by Islam et al. three exhaled volatile fatty acids (VFAs)—acetate, propionate, and butyrate—were detected in cattle breath using SESI-MS (Islam et al. 2023), which were key indicators of rumen fermentation (Senshu et al. 1980). Further investigations revealed that exhaled VFAs and ruminal VFAs measured via invasive method exhibited similar variation patterns across different dietary conditions. These findings suggest that exhaled VFAs may serve as surrogate indicators for ruminal VFAs (Islam et al. 2024). Their research lays the groundwork for developing breath-based, noninvasive assessment tools to evaluate rumen fermentation in dairy cows, which could enhance both animal welfare and precision farming practices.

3.4 | Environmental Analysis and Chemical Reaction Monitoring

In the field of organic aerosol (OA) analysis, EESI-MS holds a prominent position. It offers multiple advantages, including real-time capability, soft ionization, and the elimination of sample pretreatment processes such as thermal desorption (TD). These strengths grant it irreplaceable advantages in this field. On the other hand, the application of SESI-HRMS in surface and indoor chemistry studies enables real-time, unambiguous detection and identification of gas-phase and particle-phase organic compounds, significantly enhancing air quality monitoring in both outdoor and indoor environments. Considering the naming conventions in the field of aerosol analysis, in the "organic aerosol" sections, we will use the name EESI, while in other sections, we will uniformly refer to it as SESI.

3.4.1 | Organic Aerosol

A comprehensive introduction to the existing mass spectrometry techniques used for OA analysis is provided in other reviews (Zhang et al. 2023a, 2023b; Johnston and Kerecman 2019). Among these techniques, EESI-MS is classified as an online method with the capability of determining the OA composition at the molecular level in real time (Zhang et al. 2023b; Gallimore and Kalberer 2013). Due to the lack of sample preparation and a softer ionization process, EESI-MS exhibits less fragmentation compared to those techniques with TD sampling and/or high ionization energy, such as the FIGAERO-CIMS (filter inlet for gases and aerosols coupled to a chemical ionization mass spectrometer), CHARON-PTR-MS (chemical analysis of aerosols online inlet coupled to a proton transfer reaction time-of-flight mass spectrometer), and the aerodyne aerosol mass spectrometer (AMS) (Zhang et al. 2023b; Surdu et al. 2021). Notably, AMS is a semi-online instrument that combines TD and electron ionization (EI). However, the simultaneous TD and EI processes in AMS make it challenging to distinguish individual molecules from the resulting mass spectra (Johnston and Kerecman 2019). Despite this limitation, AMS provides quantitative information about the elemental composition of OA, a capability not shared by EESI-MS (Tong et al. 2021). In addition, existing studies have demonstrated the following performance of EESI-MS: (1) Capable of detecting particles within a few seconds (Lopez-Hilfiker et al. 2019); (2) Capable of detecting ultrafine particles with diameters as small as 20 nm (Surdu et al. 2021); (3) The detection limit is down to tens of ng m^{-3}, depending on the species (Lopez-Hilfiker et al. 2019; Lee et al. 2020); (4) Semi-quantification of known compounds can be achieved through establishing calibration curves (Gallimore and Kalberer 2013).

Laboratory experiments is one of the common research types in aerosol analysis aimed at understanding the formation, chemical evolution, and aging mechanisms of OA (Pospisilova et al. 2021, 2020; Gallimore et al. 2017a). The experiments are conducted in specially designed reaction chamber (Gallimore et al. 2017a, 2017b) or aerosol flow tube (Gallimore et al. 2017c; Bell et al. 2023a; Luo et al. 2024; Kruse et al. 2024). The procedure of reaction chamber experiment is described below as an example. Depending on research objectives, appropriate precursor gases, including VOCs (e.g., α-pinene [Liu et al. 2019a], isoprene [Wu et al. 2021a]) and oxidants (e.g., ozone [Gallimore et al. 2017a], hydroxyl radicals [Kumar et al. 2023], or nitrate radicals [Wu et al. 2021a]), are introduced into the chamber to facilitate chemical reactions. The parameters of the reaction chamber, such as temperature, humidity, and light intensity, are controlled to promote either aerosol formation or degradation. During the reaction, EESI-MS (typically equipped with a denuder to remove gas-phase compounds) is employed to monitor the changes in the composition of the aerosol. Normally, the detected ions are assigned to $[M+H]^+$ (positive mode) or $[M-H]^-$ (negative mode) (Gallimore et al. 2017b), while sometimes metal salt can be added to the electrospray solvent to produce metal cationized species (Pospisilova et al. 2020; Surdu et al. 2024). Chemical composition and time series data obtained from EESI-MS measurements can be used to establish aerosol numerical models to gain insights into reaction mechanisms and kinetics (Gallimore et al. 2017a, 2017b, 2017c). This study methodology can also be applied to study the evolution of environmental pollutants in the atmosphere (Liu et al. 2019b; Xu et al. 2024).

In some studies, EESI-MS is combined with gas-phase detection techniques to determine the distribution of compounds between the gas phase and particle phase. Commonly used techniques include PTR-MS and nitrate CIMS (chemical ionization mass spectrometer coupled with a nitrate ion source, also refer to as NO_3-CIMS). Among these techniques, PTR-MS is typically used to monitor precursor gases, and nitrate CIMS is commonly used to detect highly oxygenated organic molecules (HOMs). In the study by Pospisilova et al. (2020), EESI-TOF, PTR-TOF-MS, and nitrate CIMS were used to monitor the dynamic variations of

HOMs generated from α-pinene ozonolysis in both gas and particle phases. Figure 8A,C shows the time series of $C_{20}H_{32}O_{10}$, $C_{17}H_{28}O_{9/10}$, and $C_{10}H_{16}O_8$ in the gas phase (measured by the nitrate CIMS, along with α-pinene from the PTR-TOF-MS), and in the particle phase (measured by the EESI-TOF). Figure 8B,D displays the time evolution of C_{16}-C_{20} dimers and C_6-C_{10} monomers in the particle phase, respectively, represented as the summed signal of all ions with the same carbon number (Pospisilova et al. 2020). This result demonstrates EESI-MS's ability to identify and track monomers and dimers in secondary organic aerosol (SOA) in real time, which is also highlighted in other studies (Garner et al. 2024). To enhance the comparability of gas-phase and particle-phase measurement, Lee et al. developed the dual-phase extractive electrospray ionization time-of-flight mass spectrometer, which enables automated and alternating measurements of the gas and particle phases (Lee et al. 2022). Moreover, some aerosol analysis techniques can also be used simultaneously to provide OA characteristics that cannot be obtained through EESI-MS measurements. For instance, FIGAERO-CIMS can provide the volatility information of OA (Wu et al. 2021a) and a quantitative overview of OA can be obtained by analyzing the elemental ratios observed by the AMS (Kumar et al. 2023).

Field measurement is another key research method in aerosol analysis, capturing their behavior in real-world environments. EESI-TOF-MS can be deployed at ground-based observation sites or aboard research aircraft (Lopez-Hilfiker et al. 2019; Pagonis et al. 2021), and it is currently used for aerosol field measurements in multiple locations worldwide, including cities like Zurich (Switzerland) (Stefenelli et al. 2019; Qi et al. 2019), Beijing (China) (Tong et al. 2021), Delhi (India) (Kumar et al. 2022), and others. The field measurement data obtained by EESI-TOF-MS are often used as input for positive matrix factorization (PMF), a type of source apportionment model (Hopke 2016), which helps identify and quantify the contribution of different factors to OA composition. Compared to another commonly used field measurement technique, AMS, the reduced fragmentation in EESI-TOF-MS facilitates SOA source identification by PMF (Stefenelli et al. 2019; Qi et al. 2019; Ge et al. 2024). For example, in the study carried by Qi et al, the source apportionment of EESI-TOF-MS identifies organic-nitrogen-containing factors as a primary-dominated nitrogen factor or an organonitrate-containing secondary factor, which are not possible for AMS PMF analyses (Qi et al. 2019). On the other hand, EESI exhibits lower sensitivity toward compounds with low polarity, which prevents it from capturing information about hydrocarbon-like organic aerosols associated with vehicle exhaust, while AMS can identify them (Ge et al. 2024). This phenomenon of species-dependent sensitivity in EESI-TOF-MS introduces uncertainties in the apportionment of factor contributions during PMF analysis (Tong et al. 2022).

Although AMS provides limited chemical resolution, its robust quantification capabilities are highly complementary to EESI-TOF-MS (Tong et al. 2021). Therefore, existing research often combines AMS and EESI-TOF-MS to achieve better source separation and enhance interpretability (Tong et al. 2021; Kumar et al. 2022; Ge et al. 2024; Casotto et al. 2022; Siemens et al. 2023; Cui et al. 2024). This combination is capable of performing on-line field measurements (Tong et al. 2021;

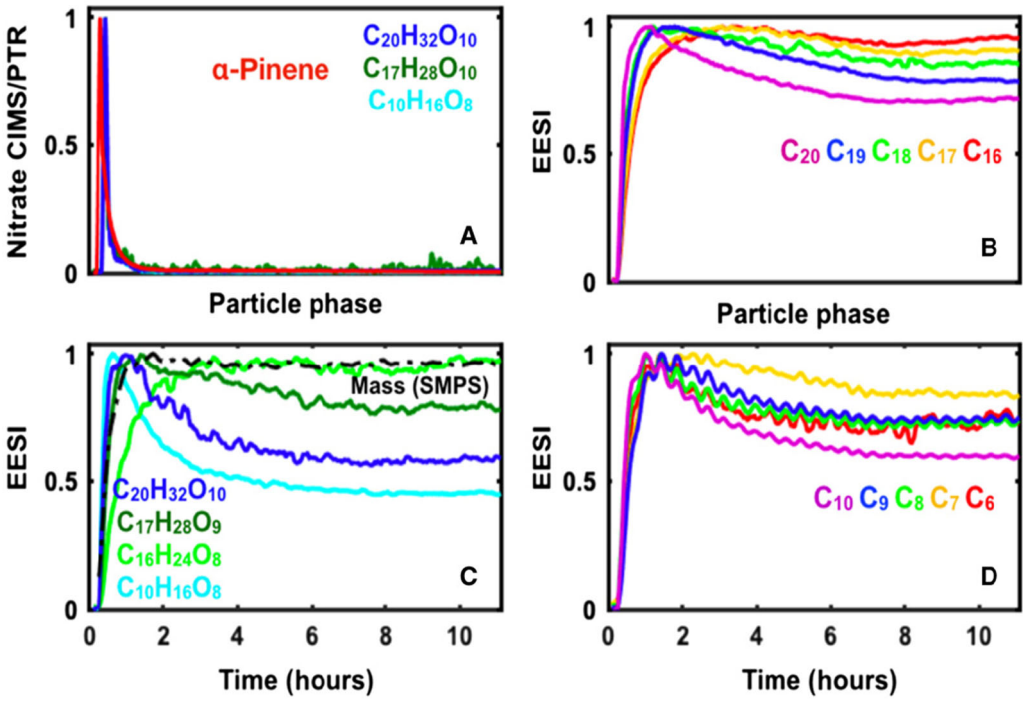

FIGURE 8 | Time evolution of particle and gas-phase composition for α-pinene ozonolysis. (A) α-Pinene injection into the chamber measured by the PTR-TOF-MS and gas-phase evolution of its oxidation products measured by the nitrate CIMS. The measured highly oxygenated molecules show fast production and immediate depletion from the gas phase due to their low volatility. (B) Time evolution of particle phase dimers, grouped by their carbon number. (C) Time evolution of three dimers and one monomer measured in the particle phase. (D) Time evolution of particle phase monomers, grouped by their carbon number (Pospisilova et al. 2020). [Color figure can be viewed at wileyonlinelibrary.com]

Kumar et al. 2022) and also performs off-line analysis of re-nebulized water extracts from ambient filter samples (Cui et al. 2024; Qi et al. 2020). To better link quantitative information with chemical identification, Tong et al. present a method for PMF analysis on a single data set combining data from AMS and EESI-TOF-MS, termed combined PMF (Tong et al. 2022). Their test results demonstrated that the application of cPMF could correct factor contribution biases caused by factor-dependent sensitivities when conducting EESI-TOF-MS PMF alone (Tong et al. 2022). In contrast to the aforementioned combination, Wang et al. attempted to couple EESI-TOF-MS with PTR-TOF-MS, aiming to provide new insights into atmospheric processes through comparative analysis of molecular-level secondary components between gas and particle phases (Wang et al. 2024b).

In recent years, researchers have made efforts to improve the performance of EESI-MS in OA analysis in the following aspects: (1) Efforts to enhance OA identification capability include the adoption of Orbitrap MS for higher mass resolution (Lee et al. 2020; Xu et al. 2021), the integration of DMA as a separation technique (Skyttä et al. 2022), and the addition of NaI to improve sensitivity for carboxylic acids (Surdu et al. 2024). (2) Advancements in quantification accuracy involve developing response factors for diverse chemical species (Wang et al. 2021b) and compounds with different volatilities (Bell et al. 2023b). (3) To enhance source apportionment interpretability, experiments have been conducted to identify markers for distinguishing similar emission sources (e.g., wood, straw, and plastic burning), with experimental data leveraged to support source apportionment (Zhang et al. 2023c). These studies also represent promising directions for future research.

3.4.2 | Surface and Indoor Chemistry

The application of SESI-HRMS in surface chemistry mainly focuses on the real-time detection of secondary organic compounds generated from heterogeneous or gas-phase reactions occurring on various environmental surfaces under laboratory simulation conditions. In this field, SESI is primarily coupled to ultrahigh-resolution mass spectrometry, thereby possessing capabilities of high temporal and mass resolution. Researchers can clearly distinguish reaction products based on the time profile of the ions and unambiguously assign chemical formulas to the product ions, which can then be used to deduce chemical pathways. This strategy has currently been employed to conduct the following research: (1) the photochemical transformation processes occurring in the sea surface microlayer, where fluorene and dimethyl sulfoxide (DMSO) are activated by sunlight in the presence of halide ions, and the organic sulfur compounds generated in these processes (Mekic et al. 2020); (2) heterogeneous chemical reactions on urban building surfaces, particularly the compounds released from the reaction between sulfur dioxide (SO_2) and urban grime under near-ultraviolet light irradiation (Deng et al. 2022); (3) the nitrogen (N)-containing organic compounds formed during the interfacial ozone oxidation of river surface microlayer (Wang et al. 2022), and (4) formation of N-containing gas phase products from the heterogeneous (photo)reaction of gaseous NO_2 with humic like substances in liquid water of aerosols (Li et al. 2023).

Human presence can affect indoor air quality because of secondary organic compounds formed upon reactions between gas-phase oxidants, for example, O_3, hydroxyl radicals, and chemical compounds from skin, exhaled breath, and from daily activities like cooking emissions. The application of SESI in indoor chemistry is very similar to surface chemistry in terms of instruments and research strategies, providing insights into the formation and transformation of secondary organic compounds. Zeng et al. utilizing SESI-HRMS detected 526 new product ions generated during the cooking process (Zeng et al. 2020b). Based on the accurate mass and isotopic pattern, linoleic acid, oleic acid, and their intermediate and final products have been distinctly identified. The temporal evolution profiles of certain compounds are depicted in the Figure 9, including oleic acid (OA, $C_{18}H_{34}O_2$), linoleic acid (LA, $C_{18}H_{32}O_2$), 9-oxononanoic acid (9-ON, $C_9H_{16}O_3$), azelaic acid (AA, $C_9H_{16}O_4$), and other unidentified compounds. 9-ON and AA, two well-known SOA materials were identified as secondary products of oleic acid due to OH reaction, indicating the occurrence of OH radical reactions in indoor chemistry. Recently, secondary organic compounds formed from the reaction of human skin lipids (Zeng et al. 2020a) and exhaled VOCs (Xu et al. 2022) with ozone have also been characterized using the same method.

3.4.3 | Pollutants

The application of SESI in pollutant detection primarily focuses on establishing quantitative detection methods for target pollutants in environmental samples. In this field, the research strategies are quite similar to the establishment of methods for detecting toxic substances in food samples (see Section 3.2.1), with the main difference being the replacement of food samples with environmental samples.

Existing studies are primarily conducted on water samples, including industrial waste water, lake water, sea water, and more. One of the target analytes is radioactive inorganic species (Luo et al. 2010; Liu et al. 2011b; Wu et al. 2013). Luo et al. nebulized water sample spiked with uranyl acetate for SESI-ion

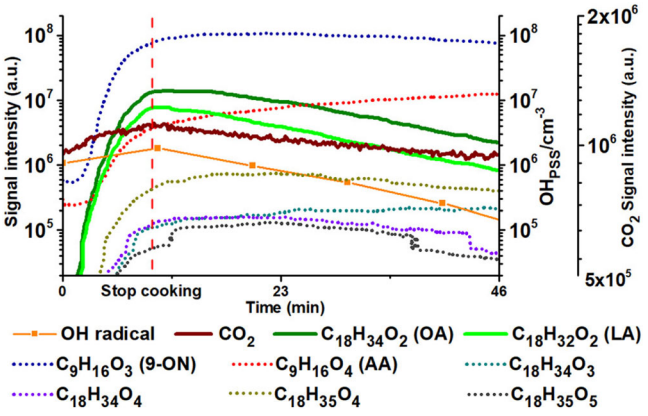

FIGURE 9 | Time–intensity profiles of primarily emitted oleic acid (OA), linoleic acid (LA), and products of OA or LA by OH oxidation, signal intensities of CO_2, and estimated OH radical concentrations. Reprinted with permission from (Zeng et al. 2020b). Copyright 2020 American Chemical Society. [Color figure can be viewed at wileyonlinelibrary.com]

trap analysis, using the *m/z* 346 signal observed in the MS^3 spectrum as characteristic fragment, corresponding to $(UO_2(Ac)_2)Ac^-$ losing $CH3COO^\bullet$ and CH_2CO. The developed method achieved a LOD of 2.33×10^{-3} ng L^{-1}, which is much lower than the levels of uranium typically found in natural water (Luo et al. 2010). Additionally, the two isotopes of uranium (^{234}U and ^{235}U, abundance < 1%) were detectable in uranyl acetate at a concentration of 1×10^3 ng L^{-1} (Luo et al. 2010). The detection performance of this method is comparable to ICP-MS, requiring a shorter measurement time (5 min) (Liu et al. 2011b). In addition to radioactive species, detection methods for the following pollutants in water samples have been established: 1-hydroxypyrene (Li et al. 2012a), tetrabromobisphenol A (Tian et al. 2014), malachite green (Fang et al. 2016), and dimethyl sulfide (Jiang et al. 2017). These methods are developed based on benchtop mass spectrometry. To fully leverage the rapid detection capability of SESI-MS, future research could consider evaluating its performance on portable mass spectrometry and conducting field application demonstrations.

Metal emissions are also a key focus for researchers due to their highly toxic impacts on human health and ecosystems. Giannoukos et al. developed an online method for the detection of 27 different metals in aerosol particles using EESI-TOF-MS. This method uses a disodium EDTA dihydrate as a metal chelation agent, achieving good linearity (R^2 up to 0.999), 1 Hz time resolution, and LODs down to several ng/m^3 (Giannoukos et al. 2020). Compared to traditional methods like LC-MS, GC-MS, and AMS, this method eliminates the need for sample collection while providing high coverage of metal species (Giannoukos et al. 2020). The detection performance of this method was further validated by field measurements of biogas, successfully detecting a range of trace metals (e.g., Fe, Cu, Zn, Cd, Pb, etc.) with detection limits below 3 ng/m^3.

3.4.4 | Chemical Reaction Monitoring

SESI-MS can be used as a tool for real-time monitoring the dynamic changes of reactants, products, and intermediates in the chemical reaction process, which helps identify key parameters to improve reaction efficiency. There is already a review article published in *Mass Spectrometry Reviews* that has summarized the application of ambient mass spectrometry techniques in chemical reaction monitoring, including SESI/EESI-MS (Sun et al. 2022). Therefore, we primarily focus on the methodological aspects of existing studies.

In most studies, chemical reactions are typically conducted in the liquid phase of the reactor. In this case, sampling methods such as headspace sampling (Zhu et al. 2008) and micro-jet ND sampling (Wu et al. 2019b) can be employed to continuously generate samples for SESI-MS, addressing different analytes. In data analysis, researchers identify key intermediates and products in the spectrum and combine their time series to infer chemical reaction progress and mechanisms. Interestingly, Marquez et al. proposed a novel method for studying bimolecular reactions, wherein precursor solutions are separately sprayed and electrosprayed, and the reaction is activated through a liquid–liquid extraction process between microdroplets. This method is suitable for studying short-lived transients of reactions in condensed phase, for example, the electron-transfer-catalyzed dimerization of trans-anethole (Marquez et al. 2008).

3.5 | Microorganisms

Microorganisms produce different combinations and quantities of VOCs during metabolic processes. Analyzing volatile metabolites using SESI-MS offers a method with high temporal resolution for understanding microbial metabolism without the need for sample preparation. This method has demonstrated its unique application value in the analysis of different microorganisms, such as diagnosing bacterial infections in vitro, monitoring yeast fermentation processes, and discovering cancer biomarkers.

3.5.1 | Bacteria

The SESI-MS fingerprint of bacterial VOCs demonstrates high specificity, and its discrimination ability has been extensively characterized using different bacterial strains. An overview of in vitro studies on bacterial VOCs is provided in Table 2. Jiangjiang Zhu is recognized as a pioneer in the applications of SESI-MS for the analysis of bacterial VOCs. In 2010, Zhu and co-workers first reported a study characterizing bacterial volatiles using SESI-MS (Zhu et al. 2010b). By combining SESI-MS fingerprinting with PCA, the study successfully distinguished between five bacterial groups at the species or serovar level. It further identified individual species or serovars within mixed cultures, elucidating the proportion of each bacterium present. Subsequently, they proposed a protocol for analyzing bacterial volatiles using SESI-MS (Bean et al. 2011). Using a similar approach, Gómez-Mejia et al. demonstrated that such discrimination ability can extend even to the strain level (Gómez-Mejia et al. 2022).

The analytical method is also effective in differentiating bacterial groups in simulated real-world media. For instance, using SESI-MS VOC profiling, a group of eleven *Escherichia coli* (*E. coli*) strains can be differentiated from *Staphylococcus aureus* (*S. aureus*) and *Salmonella Typhimurium* (*S. Typhimurium*) in three food modeling media (Zhu and Hill 2013). A similar result was obtained in the analysis of VOCs emitted from clinical blood simulated culture (Ballabio et al. 2014).

The high sensitivity of SESI-MS and the fact that it requires no sample preparation play important roles in monitoring bacterial metabolic perturbations. Zhu et al. monitored the headspace VOC profile changes of *S. aureus* strains and gut microbiota under ampicillin treatment (Li and Zhu 2018). Consequently, both *methicillin-susceptible Staphylococcus aureus* (MSSA) and *methicillin- resistant Staphylococcus aureus* (MRSA) showed a clear separation between the baseline (without any antibiotic treatment) and the ampicillin treatment group, as determined by partial least-squares discriminant analysis (PLS-DA). Another study found that the levels of C4 and C7 Volatile Fatty Acids (VFAs) in the headspace of gut microbial cultures were significantly elevated 6 h after ampicillin treatment

TABLE 2 | An overview of in vitro studies on bacterial volatile organic compounds using SESI-MS.

Bacterial strain	Medium or sample matrix	Aims	Results	References
P. aeruginosa (PA14), *S.* Typhimurium (ST5383), *S.* Pullorum (SA1685), *E. coli* (ATCC 25922) and *S. aureus* (ATCC 25923).	1. Monocultures of all strains were cultured in TSB. 2. PA14 was cultured in three additional media: LB-Lennox, synthetic cystic fibrosis medium, and MOPS.	Assess the feasibility of the SESI-MS profiling method for bacterial identification.	1. The combination of 13 VOCs creates a unique pattern for each genus. 2. PCA can clearly separate the VOC profiles of the five bacterial groups.	(Zhu et al. (2010b))
E. coli (K12), *P. aeruginosa* (PAO1)	LB-Lennox	Demonstrate the steps for obtaining bacterial volatile fingerprints using SESI-MS.	1. The spectrum of *E. coli*. is dominated by *m/z* 118. 2. The spectrum of *P. aeruginosa* contains a larger variety of protonatable peaks.	(Bean et al. (2011))
E. coli of 11 different serotypes (including EC O157:H7), *S. aureus* (ATCC 25923), *S.* Typhimurium (ST5383)	Three food modeling media: meat extract medium, vegetable extract medium, and apple extract medium.	Differentiate EC O157:H7 and non-O157 *E. coli* from *S. aureus* and *S.* Typhimurium.	Six common VOCs among all the *E. coli* strains.	(Zhu and Hill (2013))
S. aureus (ATCC 29213), *E. coli* (ATCC 25922), *S. pneumoniae* (ATCC 49619).	Modeling media for clinical blood culture.	Identify the three types of bacteria in blood cultures.	PCA can clearly separate the VOC profiles of the three bacterial groups.	(Ballabio et al. (2014))
A. actinomycetemcomitans, *P. gingivalis*, *T. denticola*, *T. forsythia*	1. *A. actinomycetemcomitans* and *P. gingivalis*: BHI 2. *T. denticola*: OMIZ-W68 3. *T. forsythia*: Modified OMIZ-W68 4. Human saliva samples (from a periodontitis patient and two healthy individuals)	1. Differentiate the four types of oral pathogens based on VOC profiles. 2. Test whether the discriminative VOCs identified in the in vitro study can also be found in the saliva samples of periodontitis patients.	1. 13 VOCs specific to *A. actinomycetemcomitans*. 2. 70 VOCs specific to *P. gingivalis*. 3. 7 VOCs specific to *T. denticola*. 4. 30 VOCs specific to *T. forsythia*. 5. 18 out of the 120 bacterial-specific compounds were enhanced in the saliva of the patient.	(Bregy et al. (2015))
S. aureus (MSSA and MRSA)	LB broth	1. Distinguish MSSA and MRSA strain based on the targeted SESI-MS/MS method. 2. Explore the metabolic changes of MSSA and MRSA in response to antibiotic perturbation.	1. MSSA and MRSA can be clearly differentiated before and after antibiotic treatment via PLS-DA based on their targeted VOC profiles. 2. The baseline and treatment groups for both MSSA and MRSA can also be differentiated using PLS-DA.	(Li and Zhu (2018))

(Continues)

TABLE 2 | (Continued)

Bacterial strain	Medium or sample matrix	Aims	Results	References
Human gut microbes	Bacterial culture samples were collected from the HCM before, during, and after the GTE treatment period.	1. Establish the targeted SESI-MS/MS method and the GOT-SESI-MS/MS method. 2. Compare the analytical performance of the two SESI-MS/MS methods by analyzing the headspace of HCM	1. 77 compounds were selected as targeted compounds in the targeted SESI-MS/MS method, while 75 features were included in the SESI-GOT-MS/MS selected reaction monitoring method. 2. PLS-DA indicates that both methods can clearly differentiate the stages of GTE treatment.	(Li et al. (2019))
Human gut microbes from fecal samples	GAM broth	Evaluate the impact of ampicillin treatment on the VFAs of the gut microbial cultures.	C4 and C7 VFAs were significantly elevated in the headspace of gut microbial cultures 6 h after ampicillin treatment.	(Lee and Zhu (2020))
E. coli (ATCC 25922), *H. influenzae* (ATCC 9006), *P. aeruginosa* (ATCC 27853), *S. aureus* (ATCC 29213), *S. maltophilia* (ATCC 13636) *and S. pneumoniae* (ATCC 49619)	BHI	Differentiate the six cystic fibrosis-related pathogens based on VOC profiles.	1. PCA can clearly separate the VOC profiles of the six pathogens. 2. The predictive analysis with a SVM using LOOCV exhibited 100% accuracy for sample discrimination. 3. 94 discriminative features yield 33 putatively identified biomarkers.	(Kaeslin et al. (2021))
S. aureus (JE2), *S. aureus* (Cowan I), *S. pneumoniae* (D39), *S. pneumoniae* (TIGR4)	1. Blood agar plates 2. 17 clinical samples from patients (lung tissue, blood, nasal aspirate, cardiac device or heart valve)	1. Assess whether the sensitivity of SESI-HRMS is sufficient to detect the early stages growth of bacteria and enable species differentiation. 2. Assess the feasibility of using SESI-HRMS for diagnosing bacterial infections in clinical samples.	1. *S. aureus* and *S. pneumoniae* with bacterial load as low as 10^3 CFUs are enough to be detected within 1 h by SESI-HRMS. 2. PCA can clearly separate the VOC profiles of the four strain groups after 12 h of growth. 3. 5 out of 7 clinical samples with an ongoing *S. aureus* growth cluster together in the t-SNE space.	(Gómez-Mejia et al. (2022))
Bacteroides thetaiotaomicron (ATCC 29148), *E. coli* (ATCC 25922), *Lactobacillus acidophilus* (ATCC 4356), Fecal bacteria isolates	Modified GAM	1. Develop the dGOT-SESI-HRMS method combined with the spectral stitching technique to improve	1. The dGOT method detected 88 bacterial-specific features, while GOT and DDA detected 48 and 4, respectively.	(Choueiry et al. (2023a))

(Continues)

TABLE 2 | (Continued)

Bacterial strain	Medium or sample matrix	Aims	Results	References
		analyte identification and coverage. 2. Compare the performance of the dGOT, GOT, and DDA methods in analyzing bacterial volatiles.	2. The dGOT method annotated 25 compounds, while GOT and DDA annotated 15 and 1, respectively. 3. The PCA results show that the dGOT method can distinguish substrate-level differences, while the other two methods cannot.	

Abbreviations: *A. actinomycetemcomitans*, Aggregatibacter actinomycetemcomitans; BHI, brain heart infusion; dGOT-SESI-HRMS, database-assisted globally optimized targeted-secondary electrospray ionization-high resolution mass spectrometry; *E. coli*, *Escherichia coli*; GAM, Gifu anaerobic medium; GOT-SESI-MS/MS, globally optimized targeted-secondary electrospray ionization-tandem mass spectrometry; GTE, green tea extract; *H. influenzae*, *Haemophilus influenzae*; HCM, human colonic model; LOOCV, leave-one-out cross-validation; MOPS, morpholinepropanesulfonic acid; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *P. gingivalis*, *Porphyromonas gingivalis*; *S. aureus*, *Staphylococcus aureus*; *S. maltophilia*, *Stenotrophomonas maltophilia*; *S. pneumoniae*, *Streptococcus pneumoniae*; *S. Pullorum*, *Salmonella enterica* serovar Pullorum; *S. Typhimurium*, *Salmonella enterica* serovar Typhimurium; SVM, support vector machine; *T. denticola*, *Treponema denticola*; *T. forsythia*, *Tannerella forsythia*; TSB, tryptic soy broth; VFAs, volatile fatty acids.

(Lee and Zhu 2020). Moreover, Gómez-Mejia et al. monitored the kinetic profiles of hundreds of metabolic species emitted by *S. aureus* and *S. pneumoniae*, and the results showed that bacterial loads in the order of 10^3 CFUs are enough to be detected within 1 h by SESI-HRMS (Gómez-Mejia et al. 2022).

Most bacterial studies utilize SESI-MS in untargeted approach to obtain richer metabolic information. This approach, however, brings great difficulty to compound identification. In contrast, the aforementioned study of *S. aureus* strains applies a targeted approach using secondary electrospray ionization tandem mass spectrometry (SESI-MS/MS) (Li and Zhu 2018), as shown in Figure 10a. The study specifically targeted twenty compounds based on their reported relationships with important metabolic pathways, and established the selected reaction monitoring (SRM) scan parameters by analyzing the standards of the targeted metabolites. Based on this targeted method, the headspace metabolic profiles of *S. aureus* culture were further examined.

Although the targeted SESI-MS/MS approach provides confident identification of the compounds of interests, the number of the targeted compounds are often limited by the availability of authentic standards. To achieve broader compound coverage, Zhu and co-workers integrated the globally optimized targeted-MS (GOT-MS) methodology into SESI, thereby developing the SESI-GOT-MS/MS approach (Figure 10b) (Gu et al. 2015). The main difference between the conventional targeted SESI-MS/MS method and the SESI-GOT-MS/MS lies in the source of targeted compounds for SRM. The latter retrieves potential precursors and their fragmentation information directly from a given biological matrix, rather than analyzing standards. The study demonstrated that both the GOT and targeted SESI-MS/MS methods possess comparable performance for monitoring the gut microbial volatile metabolome. Importantly, out of the 75 metabolic features detected by SESI-GOT-MS/MS, 71 are potentially new metabolites present in the headspace of gut microbial cultures. This suggests that SESI-GOT-MS/MS could serve as a complementary method to targeted SESI-MS/MS. However, most of the metabolic features need to be further identified and verified (Li et al. 2019). In recent years, the emergence of microbial-VOC (mVOC) databases has increased the number of available targeted compounds. When combined with the spectral stitching strategy, the sensitivity of detecting targeted VOCs can be further enhanced (Choueiry et al. 2023a). Overall, the application of targeted methods in the study of bacterial volatiles has enhanced detection sensitivity and identification reliability, and has the potential to be extended to other SESI-MS-based metabolomics studies.

Using SESI-MS to detect bacterial-related VOCs holds promise as a rapid tool for predicting infection occurrence, and several proof-of-principle studies have been conducted using different clinical samples. One common analytical strategy is to identify discriminative features in the headspace of pathogen culture and use these features for targeted analysis of clinical samples. Using this strategy, Bregy et al. discovered that 18 periodontal pathogen markers were significantly increased in the headspace of saliva from a periodontitis patient (Bregy et al. 2015). Furthermore, Mejia et al. showed that the majority of SESI-HRMS measurements of clinical samples with ongoing *S. aureus*

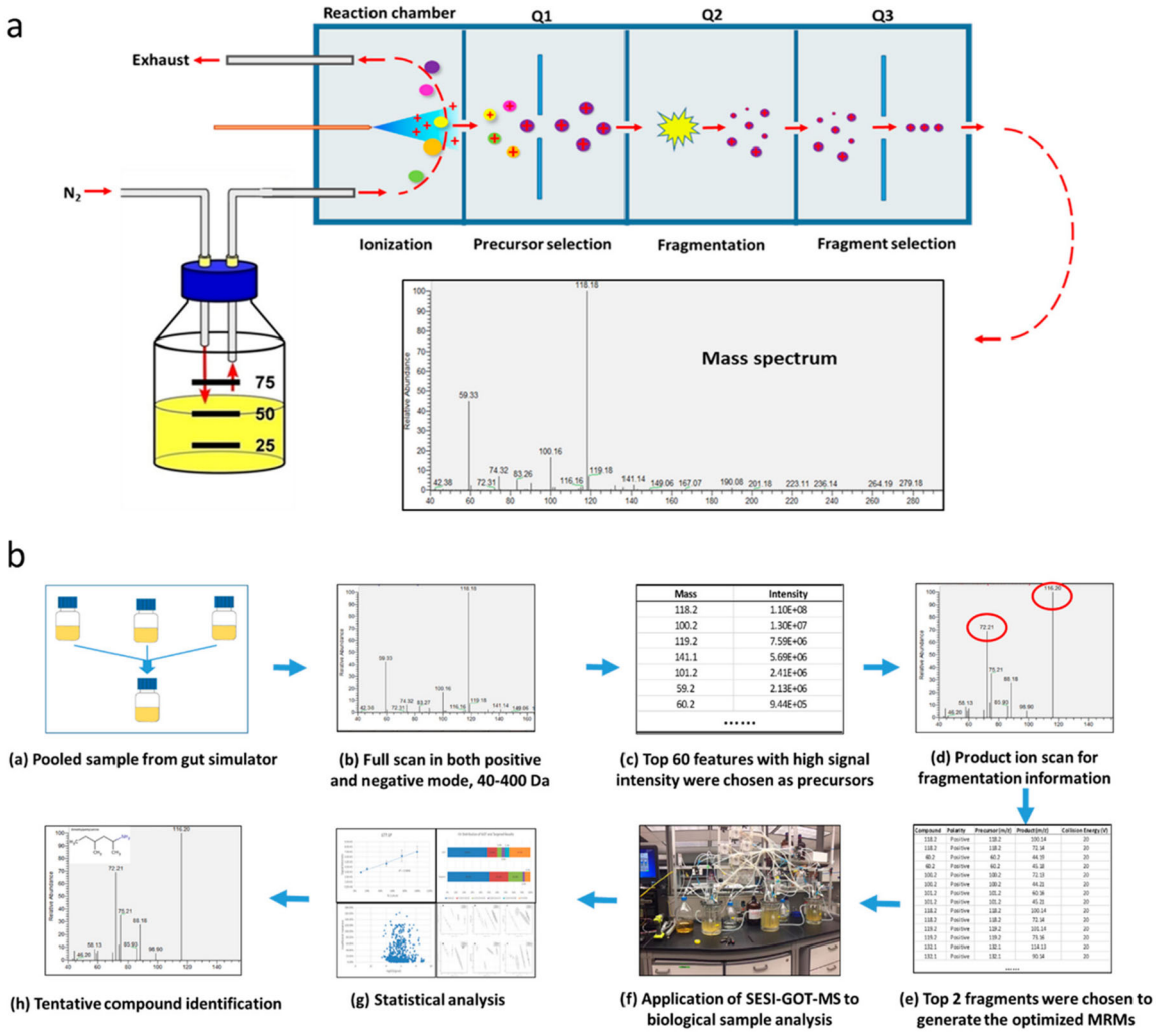

FIGURE 10 | (A) The key components of SESI-MS/MS can be summarized as follows: (i) The nitrogen stream carries the analytes from the headspace of the biological sample to the SESI reaction chamber; (ii) The analytes come into contact with the electrospray and are subsequently ionized; (iii) The analyte ions then enter the triple quadrupole MS, undergoing precursor selection, fragmentation, and fragment selection processes. (B) The workflow of SESI-GOT-MS/MS method. Reprinted with permission from (Li et al. 2019). Copyright 2019 American Chemical Society. [Color figure can be viewed at wileyonlinelibrary.com]

growth separated from those with negative bacterial growth in t-SNE (t-distributed Stochastic Neighbor Embedding) analysis (Gómez-Mejia et al. 2022). Interestingly, in an untargeted study, Weber et al. found that diethanolamine was significantly increased in the exhaled breath of cystic fibrosis patients (Weber et al. 2022). This compound had been tentatively identified as a bacterial metabolite uniquely emitted by *S. aureus* in a previous study (Kaeslin et al. 2021). The present studies have demonstrated the feasibility of SESI-MS fingerprinting of clinical samples. However, to meet the goals for clinical use, the confident identification and quantitative analysis of potential pathogen markers remain issues that need to be addressed.

3.5.2 | Yeast

The study of real-time analysis of the yeast volatilome using SESI-HRMS was first conducted by Rioseras and co-workers in 2017 (Tejero Rioseras et al. 2017). They benchmarked the technique by analyzing volatiles emitted by *Saccharomyces cerevisiae* during growth in ^{13}C-labeled glucose in real time. The results showed that the dynamics of nearly 300 metabolites can be tracked with a time resolution of less than 1 min. These metabolites included key markers related to yeast metabolic processes and industrial parameters, as well as a significant number of non-reported analytes. Mengers et al. further explored the feasibility of controlling fermentation reactions through on-line monitoring of baker's yeast volatilome (Mengers et al. 2022). The study primarily tracked ethanol and acetaldehyde online, with HPLC and GC measurements as a comparison. They found that while HPLC and SESI-Orbitrap MS measurements showed a high agreement for ethanol, SESI-Orbitrap MS demonstrated remarkable sensitivity for acetaldehyde, as it detected acetaldehyde 380 min earlier than GC. The example of acetaldehyde suggested that SESI-MS offers new possibilities for tracking in real-time low-abundance, high-volatility metabolic intermediates. The potential of SESI-Orbitrap MS in research on yeast physiology and food quality is gradually being revealed. Future studies could consider

exploring the following two aspects: (1) identifying the unreported compounds detected via SESI-Orbitrap MS to fully map the metabolism of yeast; (2) demonstrating practical applications of SESI-Orbitrap MS headspace analysis for modulating yeast fermentation processes.

3.5.3 | Cells

Similar to the aim of bacterial research, the analysis of volatile metabolites emitted from cells holds promise for the development of clinical diagnostic methods or may provide new insights into cell physiology studies. Volatile metabolite profiles from cancer cells are a key research target. He et al. found that the SESI-HRMS VOC profiles of normal mammary cells and breast cancer cells could be distinguished using PCA (He et al. 2014). Choueiry et al. demonstrated that therapeutic effects on cellular volatile organic compounds (VOCs) could also be captured by SESI-HRMS (Choueiry and Zhu 2022). In their study, they treated a pulmonary cancer cell line with cisplatin, a commonly used chemotherapy agent, and compared VOC profiles of baseline and cisplatin treatment. As shown in Figure 11A, the PLS-DA model revealed a clear distinction between VOC profiles of baseline and cisplatin treatment. Figures 11B,C showed that the abundance of the 14 features with the highest VIP values exhibited significant differences between baseline and cisplatin treatment. The random forest model constructed using the 14 discriminative features achieved an AUC of 1, as shown in Figure 11D. These data confirm that SESI-HRMS VOC profiles reflect changes in volatile features induced by cancer cell treatment (Choueiry and Zhu 2022). These findings support the use of SESI-MS for cancer diagnosis and provide potential biomarkers for the development of future breath diagnostic tools.

Additionally, headspace analysis by SESI-HRMS allows the monitoring of metabolic trajectories emitted by cells without the artificial interference introduced by sample preparation. Arnold et al. combined SESI-Orbitrap MS measurement with the ^{13}C-isotope labeling method, achieving real-time tracing of metabolic pathways in dendritic cells (Arnold et al. 2023). Based on this approach, they further discovered metabolic pathway

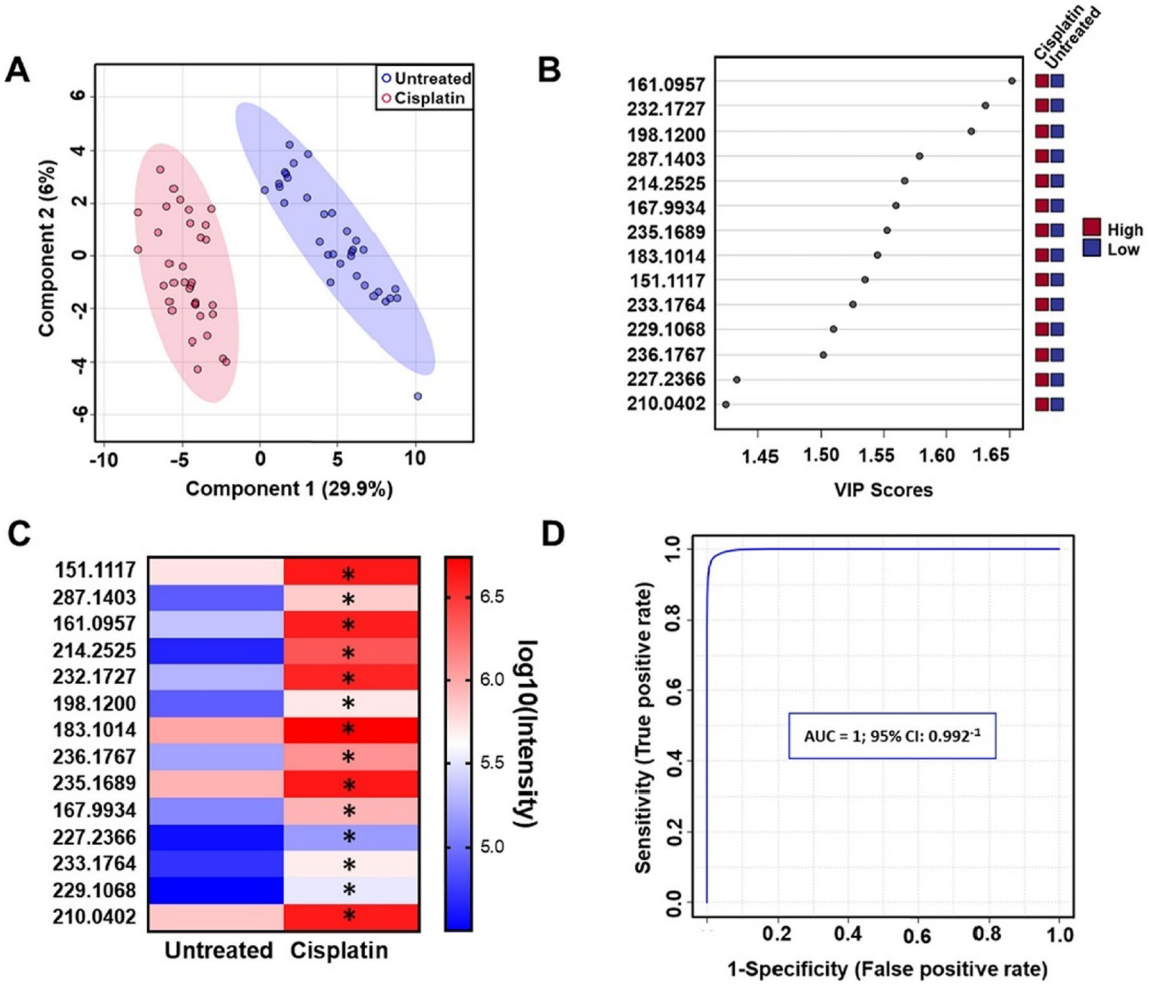

FIGURE 11 | Monitoring drug treatment to lung cancer cells using SESI-HRMS VOC profiles. (A) PLS-DA plot depicting the differences in VOC profiles of baseline and cisplatin treatment. (B) VIP plot showing the top features in VOC profiles driving the separation of baseline and treated cells. (VIP > 1.4). (C) Heatmap highlighting the relative abundance of the top VIP features in each treatment group, * indicates significant difference between group (p-value < 0.05). (D) ROC based on random forest algorithm to classify cancer treatment using the 14 discriminative features (Choueiry and Zhu 2022). [Color figure can be viewed at wileyonlinelibrary.com]

changes caused by the immune response of dendritic cells to lipopolysaccharide, highlighting the potential of SESI-HRMS in providing new insights into cell metabolism.

3.6 | Animal Models

Conducting preclinical research using animal models serves as a crucial link between basic research and clinical application. The analysis of exhaled breath or systemic emissions from animal models using SESI-MS offers a noninvasive and rapid approach for obtaining metabolic information. Currently, this method has been employed for the following biomedical research: (1) diagnosing pathogen infections in mice; (2) determining pharmacokinetics (PK) profiles; (3) characterizing the impact of the gut microbiota on host metabolism.

3.6.1 | Infection

An overview of pathogen infection studies in animal models is given in Table 3. Since 2013, Zhu and colleagues have published a series of studies assessing the ability of SESI-MS to diagnose pathogen infections by analyzing exhaled breath from mice, with lung pathogens as examples (Bean et al. 2014a). Their research demonstrated the high specificity of the SESI-MS breathprint of infected mice at different levels. It not only distinguished between infected and uninfected mice but also differentiated infections caused by one of seven lung pathogens, and even distinguished between *P. aeruginosa* strains PAO1 and FRD1 (Zhu et al. 2013a, 2013b). The diagnostic capability of SESI-MS breathprint analysis appears to be independent of time, as it can robustly distinguish acute *P. aeruginosa* and *S. aureus* lung infections at all time points from 6 to 120 h (Zhu et al. 2013c). Pathogens with different clinical phenotypes, such as MRSA and MSSA, can also be identified 24 h after bacterial inoculation (Bean et al. 2014b). Notably, the in vitro and in vivo SESI-MS fingerprints from the same strains may only contain 25-34% of shared peaks, indicating that discovering volatiles produced by the host in response to pathogens is very important (Zhu et al. 2013a). In addition, multiple peaks from the SESI-MS breathprints are required for discriminating the bacterial infections, supporting the use of biomarker panels to enhance the sensitivity and specificity of breath-based diagnostics (Zhu et al. 2013c; Bean et al. 2014b).

In the aforementioned study, the mouse breath was collected off-line. The mouse was first anesthetized, and then the breath coming out of the ventilator was collected using an air bag. However, in recent years, researchers prefer placing the mouse in a sealed chamber or falcon tube to measure metabolites from unrestrained mice in real-time (Arnold et al. 2024). Using this method, Yin et al. revealed the significantly altered metabolic pathways in mice infected with influenza A virus, avoiding the interference caused by anesthesia (Yin et al. 2021).

3.6.2 | Pharmacokinetics

The analysis of mouse breath by SESI-HRMS provides a noninvasive and real-time method to determine the pharmacokinetic (PK) profile. In contrast to conventional studies that require many animals to be killed even for low-resolution PK curves, this novel approach yields real-time PK curves with a high time resolution of 10 Hz, and none of the animals has to be killed. In the first proof-of-principle study, Li et al. performed breath PK analysis for three drugs: ketamine, propofol, and valproic acid (Li et al. 2015). Taking ketamine as an example, a significant correlation was observed between breath and plasma levels for ketamine ($r^2 = 0.9498$, p-value = 0.0254) and its main metabolite norketamine ($r^2 = 0.9739$, p-value = 0.0131). The PK curves for the other two drugs were also consistent with reported values. Sinues et al. further demonstrated the ability of SESI-HRMS PK analysis to assess the impact of dosing time on drug metabolism (Martinez-Lozano sinues et al. 2017). They found that evening administration of ketamine results in higher levels of hydroxynorketamine and norketamine in the breath of wild-type (WT) mice compared to morning administration. In contrast, mice with a liver-specific deletion of the core clock gene *Bmal1* (referred to as knock-out, KO) did not exhibit time-dependent differences in metabolite levels (Figure 12), indicating that the liver clock is necessary for creating the time-of-day effect. In conclusion, SESI-HRMS has potential not only to assess pharmacokinetic profiles by analysis of exhaled breath in mice, but also to further investigate the impact of time-of-day on drug behavior.

Although the potential of SESI-MS for monitoring the pharmacokinetics of nonvolatile drugs was validated by the analysis of ketamine, it remains unclear whether nonvolatile drugs exist in the mouse breath as gas molecules or as particles. This issue was clarified by Chen and co-workers by revealing the unnoticed transport of nonvolatile drugs from blood to breath (Chen et al. 2021). They used venlafaxine as a model nonvolatile drug and determined the PK profiles in the breath and blood of mice. Combining with the detection of exhaled breath particles using LC-MS and the results from the linear free-energy relationship analysis, it was indicated that venlafaxine was released into the exhaled breath as part of exhaled breath particles formed from lung lining fluid, rather than through a direct partitioning process from blood to gas. They noted that the exhaled concentration of non-volatile drugs was impacted by factors such as blood drug concentration, biological membrane permeability, and tissue binding/retention. This finding provided theoretical guidance for the applications of breath analysis in therapeutic drug monitoring (TDM).

3.6.3 | Gut Microbiome

SESI-HRMS provides a rapid and noninvasive method to understand the impact of the gut microbiome on the volatilome of mice. Lan et al. utilized SESI-HRMS to acquire the volatilome of mice with three distinct gut microbiota compositions—germ-free, colonized with three bacterial strains, and specific-pathogen-free (Lan et al. 2023). They observed a clear discrimination among the volatilome of these mice, with the volatilome of three bacterial strains-colonized mice exhibiting several shared peaks detected in the headspace of the individual bacterial strain cultures. Additionally, by detecting heavy-isotope-labeled metabolites after the administration of ^{13}C-labeled D-arabinose, they were able to track the metabolic processes of the gut microbiota and observe cross-feeding

TABLE 3 | An overview of studies on volatiles from animal models infected with pathogens.

Pathogens	Mice	Aims	Results	References
P. aeruginosa (PAO1-UW), *P. aeruginosa* (FRD1), *S. aureus* (RN450)	6-to 8-week-old male C57BL/6J mice	1. Identify lung infections caused by three strains through SESI-MS breathprints. 2. Compare the in vivo and in vitro SESI-MS fingerprints from the same strain.	1. The PCA showed that the three bacteria-infected mice groups and the uninfected group can all be separated. 2. Only 25–34% of the total peaks was shared between the in vitro and in vivo conditions.	(Zhu et al. (2013b))
H. influenzae (ATCC 51907), *P. aeruginosa* (PAO1-UW), *S. aureus* (RN450), *L. pneumophila* (ATCC 33152), *S. pneumoniae* (ATCC 6301), *M. catarrhalis* (ATCC 43628), *K. pneumoniae* (ATCC 13883)	6-to 8-week-old male C57BL/6J mice	Identify lung infections caused by one of seven lung pathogens through SESI-MS breathprints.	The PCA showed that the seven infected mice groups were separable using the first three principal components ($p < 0.0001$).	(Zhu et al. (2013a))
P. aeruginosa (PAO1-UW), *S. aureus* (RN450)	6-to 8-week-old male C57BL/6J mice	1. Develop a model for acute lung infections caused by *P. aeruginosa* and *S. aureus* in mice. 2. Determine whether the SESI-MS breathprints of infected mice are distinguishable, independent of the duration of infection.	The PLS-DA showed that the groups infected with *P. aeruginosa* and *S. aureus*, as well as the uninfected groups, were clearly separated at six time points over a 120-h period.	(Zhu et al. (2013c))
S. aureus RN450 (MSSA), *S. aureus* 450 M (MRSA)	6-to 8-week-old male C57BL/6J mice	Identify lung infections caused by MSSA and MSRA through SESI-MS breathprints.	The PCA showed that the MSSA and MRSA infected groups were separable using the first principal component ($p < 0.001$).	(Bean et al. (2014b))
IAV	6-to 8-week-old female BALB/C mice	Assess the feasibility of using SESI-HRMS for diagnosing IAV infections in mice.	The receiver operating characteristic area under the curve (AUC) for the diagnostic model was above 0.95 in every day's measurement after infection (except on the third day).	(Yin et al. (2021))

Abbreviation: *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*; *H. influenza*, *Haemophilus influenza*; *L. pneumophila*, *Legionella pneumophila*; *M. catarrhalis*, *Moraxella catarrhalis*; *K. pneumonia*, *Klebsiella pneumonia*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin- resistant *Staphylococcus aureus*; IAV, influenza A (H1N1) virus.

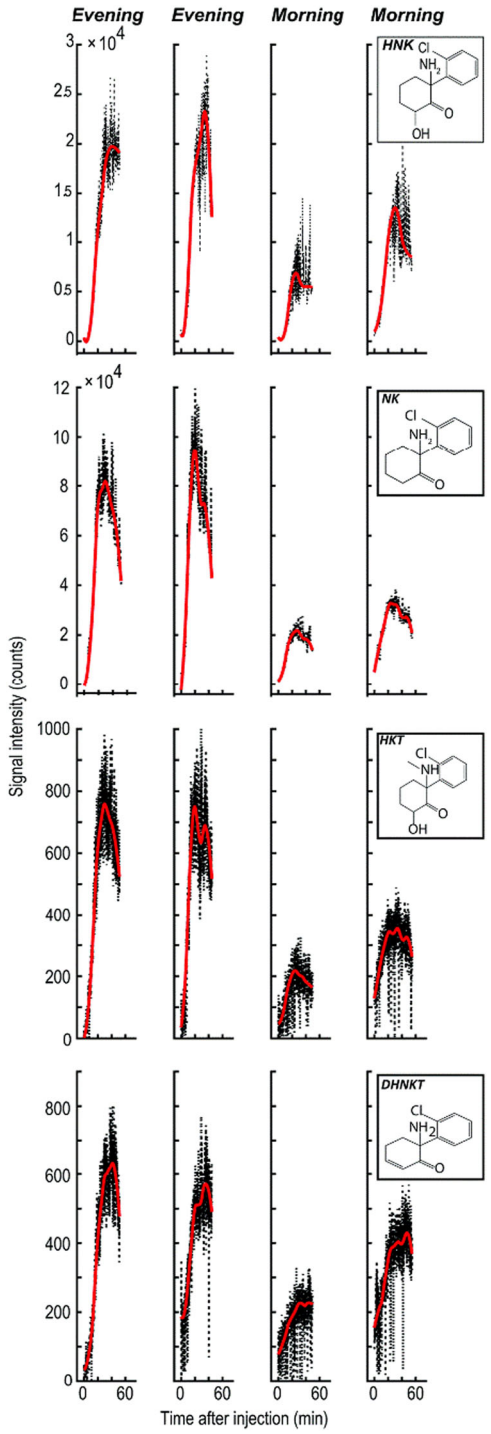

FIGURE 12 | SESI-MS measurement of Hydroxynorketamine (A) and Norketamine (B) for wild-type (WT) and knock-out (KO) mice, with the left half measured in the evening and the right half in the morning. The data suggests that the signal intensity of the two metabolites in the breath of WT mice is higher when injected in the evening compared to the morning, while KO mice did not exhibit injection time-dependent differences. Reprinted with permission from (Martinez-Lozano sinues et al. 2017). [Color figure can be viewed at wileyonlinelibrary.com]

phenomena among the microbes. The use of ^{2}H tracing enables the monitoring of short-chain fatty acids, which are the main products of gut microbiome activity (Arnold et al. 2022). Choueiry et al. further revealed the impact of the gut microbiota on host metabolism by monitoring the changes in the mouse volatilome (Choueiry et al. 2023b). In their experimental setup, significant differences in the volatilomes of mice with different gut microbiota compositions were observed, and the impact of microbes on host metabolism was confirmed through LC-MS analysis of mouse biological matrices. Pathway analysis of mouse VOCs revealed that lysine degradation and phenylalanine metabolism were disrupted in all experimental groups colonized with microbes, indicating the metabolic interplay between the gut microbiota and the host.

The aforementioned study demonstrates that: (1) the composition of the gut microbiota has a significant impact on the volatilome, (2) this influence originates both from substances released by the microbes and from alterations in host metabolism induced by the microbes, and (3) the volatilome obtained through SESI-HRMS can provide new insights into the study of the gut microbiota. It is worth noting that, the murine-derived VOCs detected from the container may originate from breath, body, fur, or even excrement. Future studies will need to clarify the sources of VOCs to further elucidate the mechanisms by which the gut microbiota influence the volatilome.

3.7 | Humans

Humans are the primary subjects of metabolomics studies based on SESI-MS. Analyzing human skin volatiles, exhaled breath, and other biofluids provides valuable insights into the body's metabolic dynamics and environmental exposure. Clearly, breath analysis is the most fascinating field among them, due to its potential as a noninvasive diagnostic tool. Therefore, the focus of this section will be on breath analysis.

3.7.1 | Skin

Skin, being the largest organ of the body, envelops the entire external surface. It not only serves as an excretory route for numerous metabolites into the air but also often accumulates compounds from the external environment. Real-time analysis of compounds on the skin surface and those released into the surrounding air using SESI-MS provides insights into human metabolism and environmental exposure.

Chen et al. combined ND sampling method with SESI-MS for the analysis of human skin. This method can detected the metabolic characteristics from different regions of the skin and trace amounts of RDX (a typical explosive) accumulated on the skin (Chen et al. 2007d). When using an air-tight sampling device, the neutral sample plume generated by ND method can be transported over long distances (400 cm) along the sample line, achieving sub-femtogram detection of explosives on the skin surface (Chen et al. 2009). Martin et al. developed a split sampling method for skin VOC analysis. This method uses polydimethylsiloxane swabs for off-site collection of skin VOCs, which were then transported to the laboratory for analysis via TD-SESI-TOF-MS. Their study demonstrated that this approach could differentiate between skin VOCs from individuals with and without body odor (Martin et al. 2014).

Another commonly used sampling method is headspace sampling. This method directly samples the air around the skin, thereby detecting volatile substances released from the skin, such as fatty acids (Martínez-Lozano 2009) and amines (Martínez-Lozano and de la Mora 2009). In addition to the analysis of skin-released volatiles, SESI-MS has also been utilized to identify secondary organic compounds formed by the reaction of skin surface lipids with indoor air components (Zeng et al. 2020c), representing one of the research directions in indoor pollution sources.

3.7.2 | Breath

Human breath serves as a biological matrix containing a large number of metabolites produced by human metabolic processes (Martínez-Lozano and de la Mora 2007; Chen et al. 2007a; Martínez-Lozano and Fernández de la Mora 2008). Due to its noninvasive sampling nature, it has gained significant attention in the medical field. Human breath analysis is also the most researched area among SESI applications, typically employing metabolomics research strategies and often referred to as breath metabolomics or breathomics. In this field, researchers use SESI-MS as a tool for detecting metabolites in exhaled breath, aiming to identify biomarkers related to physiological states, diseases, and drug treatments, with the goal of clinical application. Based on research objectives, this section will explore the areas of standardization, physiological measurements, disease diagnosis, and therapeutic drug monitoring.

3.7.2.1 | Standardization. Standardization is a critical component in breathomics research, as it reduces human-induced and methodological errors, thereby facilitating the discovery of more reliable biomarkers. Currently, standardization practices primarily comprise instrumentation and standard operating procedures (SOP), as well as compound identification and quantification (Singh et al. 2018). Instruments are the cornerstone of standardization. However, the early application of SESI-MS typically requires some modifications to the front-end hardware of mass spectrometer, making it challenging to ensure the uniformity of the devices across various laboratories. This dilemma was effectively addressed since 2016 with the introduction of a commercial SESI source (Gaugg et al. 2016). The commercially available SESI sources in the market include Super SESI (FIT, Spain) (Singh et al. 2019; Semren et al. 2022), LF-SESI (SEADM, Spain) (Gaugg et al. 2016), and Helius-3000 (A-HealthX, China; Unpublished thesis). In 2019, following the development of the universal SESI source, Singh et al. proposed a first SOP for real-time breath analysis, utilizing Super SESI coupled to high-resolution (Orbitrap) MS (Singh et al. 2019). This SOP recommends various parameters for the mass spectrometer and ion source and introduces a real-time expiratory parameter monitor equipped with a display, enabling subjects to regulate their exhaled flow rate to a fixed value. When using a 92.7 ppb β-pinene standard gas as a reference, the system demonstrated high reproducibility, with a coefficient of variation (CV) of 2.9% within 1 h. In addition, the breath signal variability was assessed using the signals of 27 different aldehydes. The median CV values for intra-subject and inter-subject variability were 6.7% and 48.2%, respectively (Singh et al. 2019). Following the SOP, two studies were conducted under the framework of the "peppermint consortium." One focused on the identification of volatile compounds upon ingestion of a specific peppermint oil capsule (Gisler et al. 2020), while the other aimed at determining the washout kinetics of major peppermint oil compounds from human breath (Lan et al. 2021). These studies demonstrated the performance of SESI-HRMS and provided benchmark data comparable to other breath analysis techniques.

In recent years, researchers have focused on addressing the challenges encountered in clinical research. To investigate the reproducibility of SESI-HRMS in multi-center studies, Gisler et al. proposed an SOP for multicentric data acquisition and processing, which was tested in three independent laboratories located in Switzerland and China (Gisler et al. 2022). The comparison of multicenter data revealed a technical variability of the SESI-HRMS platform is approximately 20%, and nearly 850 common breath features are present across data from three laboratories, predominantly corresponding to amino acid, xenobiotic, and carbohydrate metabolic pathways (Gisler et al. 2022). This framework aids in the design and implementation of future large-scale multicentric clinical studies. Additionally, several studies have proposed offline breath collection and analysis protocols (Sola-Martínez et al. 2024; Berchtold et al. 2014). These offline methods were applicable to breath analysis in infants and patients who are unable to move (Decrue et al. 2021). However, challenges in clinical breath research also include interference from ambient air on breath composition (Berchtold et al. 2014; Weber et al. 2023a), batch effects in longitudinal breath data, and significant inter-individual breath variability (Singh et al. 2019; Chagovets et al. 2015), among others. There are still no satisfactory solutions to these issues.

Identification of breath metabolites is another crucial part of standardization. Due to the lack of chromatographic separation in real-time SESI-HRMS analysis, a complementary technique is required for this purpose. Moreover, on-line MS2 spectra need to be utilized for further confirming that the compounds are detected in real-time analysis. To address this issue, researchers have proposed an integrated compound identification workflow (García-Gómez et al. 2015a, 2015b, 2015c), comprising the following three steps: (1) Compounds were putatively assigned based on exact mass; (2) Perform real-time MS/MS analysis and identify compounds via their characteristic fragments in the tandem mass spectra (3) Perform HPLC-MS/MS analysis of exhaled breath condensate and chemical standards. It should be noted that the purpose of step 3 is to confirm that putative compounds are present in human breath and to provide reference spectra for step 2. Figure 13 demonstrates the workflow of this integrated approach used for identifying linear alkanedioic acids detected in real-time breath analysis. Preliminary identification results based on accurate mass were further confirmed through the matching of retention time and MS2 fragments with the standards (Gaugg et al. 2017a). Additionally, this method has been employed to identify furan derivatives (García-Gómez et al. 2015a), aldehydes (García-Gómez et al. 2015c), amino acids (García-Gómez et al. 2016b), tricarboxylic acid metabolites (Tejero Rioseras et al. 2018), and tryptophan metabolites (García-Gómez et al. 2016a) in human

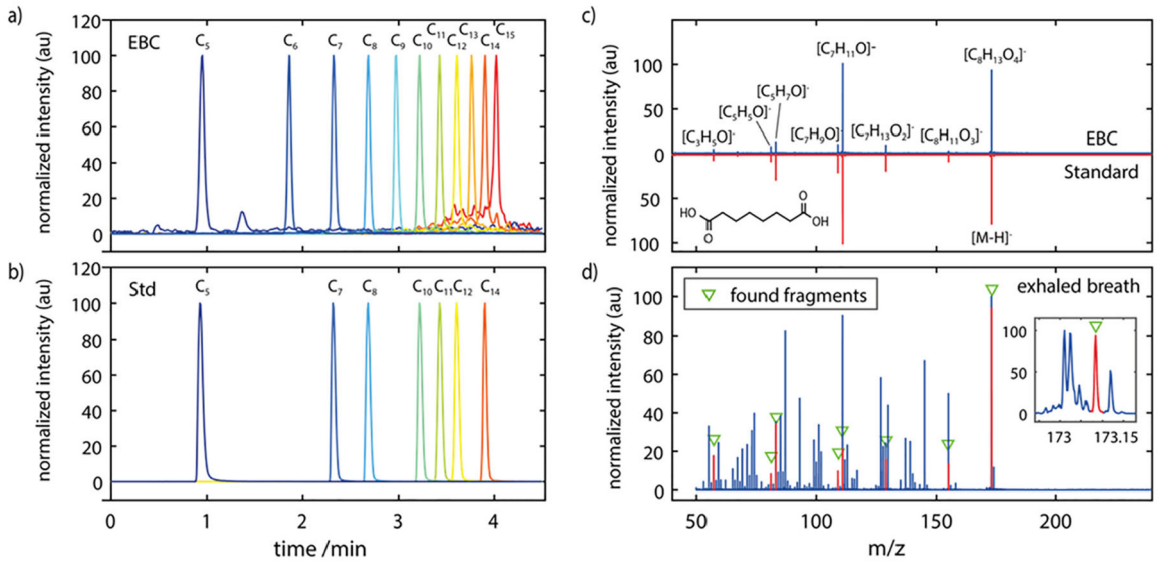

FIGURE 13 | Extracted ion chromatograms of the $[M-H]^-$ ions of linear, saturated dicarboxylic acids with chain lengths of 5–15, obtained from an UHPLC-MS analysis of EBC (A) and commercial standards (Std; B). (C) Head-to-tail plot of the base-peak normalized MS2 spectrum of octanedioic acid in EBC (top) and standard (bottom). (D) Base-peak normalized online MS2 spectrum of exhaled breath (precursor: 173.1 ± 0.35 Da). The inset shows a zoom of the precursor mass. All fragments of octanedioic acid have been identified (marked in green), supporting the presence of this compound in the breath. Reprinted with permission from (Gaugg et al. 2017a). Copyright 2017 American Chemical Society. [Color figure can be viewed at wileyonlinelibrary.com]

breath. It should be noted that recent studies have indicated that only 25% of the breath features detected in EBC overlap with those in online SESI-HRMS (Wüthrich et al. 2024a). Compounds with insufficient identification evidence should be assigned to a lower confidence level, and the criteria proposed by Bruderer et al. (2019) may serve as a reference.

Currently, the detection of breath metabolites in SESI-MS relies on semi-quantification, which is achieved by establishing calibration curves using standard gas (Streckenbach et al. 2023; Liu et al. 2021). To address the limited availability of commercial standard gases, researchers have developed a liquid-phase standards generator (Wüthrich et al. 2023), offering more options for reference compounds. Notably, the external calibration method neglects ion suppression effects present in breath samples, thereby introducing bias into quantitative results. In a recent study, researchers have attempted to apply the standard addition method for quantifying exhaled breath metabolites. This method involves introducing gaseous standards at gradient concentrations into online breath samples and extrapolating calibration curves to determine the concentration of target compounds in breath samples (Wüthrich et al. 2024b). This method accounts for matrix effects but relies on the accurate identification of compounds.

3.7.2.2 | Physiological Measurements. SESI-MS is employed in physiological state monitoring via nontargeted measurement of exhaled breath to capture the 'breathprint'. Existing studies have demonstrated that 'breathprints' are unique across different physiological states and among individuals. For example, Sinues et al. utilized SESI-TOF MS to analyze the exhaled breath of six subjects over 11 days, with a 4-month interval, revealing statistically recognizable differences in individual breathprint, and demonstrating that the breathprint for a given subject remains relatively stable over time (Martínez-Lozano et al. 2011). Further study involving 11 subjects over 9 days (Martinez-Lozano Sinues et al. 2013) showed that PCA and canonical variate analysis were able to discerned distinct breathprints, achieving a 76% classification accuracy. These results confirm the existence of individual signatures in the composition of exhaled breath. Currently, Sasiene et al. have utilized SESI-Orbitrap MS to measure 189 breath samples from 31 healthy volunteers, ultimately creating a healthy human "profile" that consists of 48 compounds (Sasiene et al. 2024). These compounds appear in at least 20% of the samples and have been putatively annotated. Additionally, the study identified certain breath features that are significantly associated with individual participants, gender, and the time of day the samples were collected (morning, afternoon, evening). These studies have all demonstrated that individual metabolic phenotypes can be determined by SESI-MS breath analysis. The next step is to expand the sample size and sampling period to identify more representative markers, and to explore how individual exhaled breath profiles can assist in personalized medicine.

The diurnal changes in human breath also can be monitored by SESI-MS, providing a novel insight into internal body time. In the proof-of-principle study, Sinues et al. monitored the diurnal variations of the breath composition of 12 individuals during 9 days (Sinues et al. 2013). They observed that the breathprints reveal a clear temporal evolution common to all subjects within a day, and this pattern is repeated on different dates. Furthermore, the time slot at which the breath samples were analyzed could be correctly predicted in 84% of the cases (Sinues et al. 2013). Another study conducted hourly breath measurements on 3 healthy volunteers for a full 24-h period (Sinues et al. 2014). And the results revealed that among the 111 coexisting breath features, about 40% exhibited significant circadian modulation, indicating the impact of the circadian clock

on breath metabolome. The aforementioned studies indicate that some composition in human breath is related to circadian rhythms, and the relationship between these composition and metabolic changes needs to be further revealed in future research.

In recent years, some researchers have evaluated the impact of daily activities on the breath metabolome. Metabolic pathways and metabolites that change significantly related to different sleep stages (Nowak et al. 2021a), exercise (Osswald et al. 2021), and postprandial states (Martínez-Lozano et al. 2011; Wüthrich et al. 2022) have also been characterized using real-time breath analysis by SESI-MS.

3.7.2.3 | Disease Diagnosis. In the field of disease diagnosis, researchers employ nontargeted metabolomics strategies to identify discriminative metabolites between patients and healthy individuals. Current studies primarily focus on respiratory diseases. In the first proof-of-principle study, Sinues et al (Martinez-Lozano Sinues et al. 2014). examined the breath of 25 chronic obstructive pulmonary disease (COPD) patients and 36 healthy individuals, identifying a panel of discriminating breath features that could differentiate between COPD patients and control groups. A subsequent study involving 22 COPD patients and 14 healthy individuals identified 301 breath features with significant differences. Figure 14 (left box) shows that one of the differential breath features, 2-hydroxyisubutyric acid, has a higher intensity in the exhaled breath of COPD patients. Figure 14 (right box) highlights the intergroup differences in 2-hydroxyisubutyric acid (Bregy et al. 2018). Moreover, a study on the breath of COPD exacerbations patients have shown that frequent exacerbators exhibit reduced levels of omega-oxidation products and elevated levels of nitro-aromatic compounds (Gaugg et al. 2019a).

Obstructive sleep apnea (OSA) is a common sleep disorder associated with serious metabolic and cardiovascular issues. Researchers have conducted a series of studies on breath diagnostics for OSA and identified several robust breath markers. Schwarz et al. analyzed the breath of 26 OSA patients, of whom 13 received continuous positive airway pressure therapy while the other half did not. They identified 62 breath features that enabled differentiation between treated and untreated OSA patients with a sensitivity of 92.9% and a specificity of 84.6% (Schwarz et al. 2016). Building on this, Nowak et al. conducted a validation study in a cohort comprising 51 OSA patients and 33 controls. They developed a classification model using breath features associated with OSA in the previous study and discriminative features identified in this new cohort. The validation data set achieved an area under the curve (AUC) of 0.66 (Nowak et al. 2021b). Streckenbach et al. further validated previous studies in another independent cohort consisting of treated and untreated OSA patients as well as control subjects without OSA (Streckenbach et al. 2022). Based on a set of 42 out of 78 previously validated OSA features, the AUC for distinguishing treated and untreated OSA was 0.80, while the AUC for distinguishing untreated OSA and controls was 0.60. As several breath markers were clearly found to be repeatable and robust in this independent validation study, these results underscore the clinical potential of breath analysis for OSA diagnostics and monitoring. Schmidt et al. extended this study, suggesting that SESI-MS could discover the vigilance-state-dependent metabolic disruptions in OSA patients (Schmidt et al. 2022). However, a large fraction of the OSA biomarkers validated in the aforementioned studies has not yet been ambiguously identified. Future research should employ the comprehensive methods mentioned earlier to identify breath features and conduct multicenter studies.

Cystic fibrosis (CF) lung disease is a consequence of a vicious circle of early and often subclinical pulmonary infection and inflammation resulting in irreversible lung damage (Weber et al. 2020). Gaisl et al. revealed a potential predictive accuracy of 77.1% for CF based on a support vector machine model that utilized two features out of the 49 significantly altered breath features (Gaisl et al. 2018). Certain compounds were linked to oxidative stress, and among these, 11 features correlated with the mucus concentration of *Stenotrophomonas maltophilia*

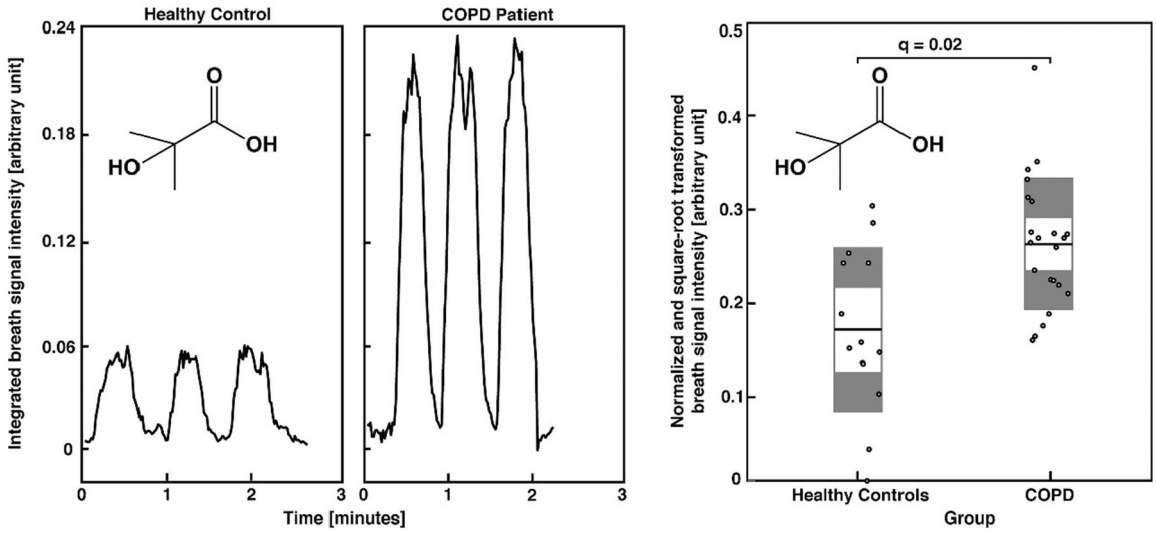

FIGURE 14 | Left boxes: breath signal time traces of 2-hydroxyisubutyric acid for a healthy control and a COPD Patient. Signal intensity from patient was enhanced in comparison to the ones from the healthy control. Right box (between-group comparison): the plot shows mean intensity of 2-Hydroxyisubutyric acid in all study participants, highlighting a distinct difference (q = 0.02) between groups (Gaugg et al. 2019a).

bacteria in CF patients. Another study focused on children with cystic fibrosis identified 171 discriminative VOCs (Weber et al. 2020). Among these, 46 compounds were putatively identified based on online MS2 spectra and literature comparison. A group of compounds, including glycolic acid, glyceric acid, and xanthine, were found to be elevated in the cystic fibrosis group. Conversely, a large group of acylcarnitines and aldehydes were observed to be decreased in cystic fibrosis (Weber et al. 2022). Other respiratory diseases, including idiopathic pulmonary fibrosis (Gaugg et al. 2019b) and allergic asthma (Weber et al. 2023b), have also had their potential biomarkers discovered by SESI-MS.

In addition to respiratory diseases, researchers have studied the breath of patients with severe conditions, such as cancer and liver failure. Sinues et al. established an 8-compound model that is able to discriminate exhaled breath from breast cancer patients versus healthy individuals, with both sensitivity and specificity above 0.9 (Martinez-Lozano Sinues et al. 2015). In a longitudinal study, Herth et al. analyzed the exhaled breath of 29 treatment-naive patients with lung cancer before and after surgery (Herth et al. 2024). Although 515 features with significant differences were identified, the small sample size generated a false positive rate of 0.71, indicating the need for a larger cohort to substantiate these findings (Herth et al. 2024). By utilizing modified SESI-MS, differences in exhaled metabolites between patients with liver failure and those with chronic hepatitis B or healthy controls were also discovered (Wu et al. 2021b). When combined with an off-line sampling method using air bags, SESI-HRMS also offers a new perspective for the noninvasive monitoring of diabetic ketoacidosisin the ICU environment (Awchi et al. 2024).

Although the aforementioned studies have identified a series of breath features with disease diagnostic potential, they have not yet transitioned into clinical practice. On one hand, these potential biomarkers lack validation through multicenter studies. On the other hand, and more critically, these features are primarily *m/z* values without being identified as specific compounds, hindering their mechanistic interpretation in molecular biology contexts.

3.7.2.4 | Therapeutic Drug Monitoring. Currently, there is a limited number of studies that utilize SESI-MS for TDM in human breath, with existing research primarily focusing on valproic acid, a medication used for the treatment of epilepsy. In the initial study carried out by Gamez and colleagues, they discovered a novel VPA marker, 4-OH-VPA-γ-lactone (or 5-OH-VPA-δ-lactone), which demonstrated a strong linear correlation between the signal intensity in exhaled breath and the free fraction of VPA in blood ($R^2 = 0.89$, $p \ll 0.01$) (Gamez et al. 2011). Singh et al. further developed a model based on 11 VPA-related breath metabolites to predict the total and free serum VPA concentrations, with concordance correlation coefficients of 0.63 and 0.66, respectively (Singh et al. 2021). And they found significant differences in breath metabolite abundance across multiple metabolic pathways for both (i) patients who do not respond to their antiseizure medications compared to those who do, and (ii) patients experiencing side effects compared to responders. The results indicate that these drug-modulated metabolites could potentially be used to predict side-effect and drug-response scores. Ultimately, based on the ability to predict serum drug concentrations and estimate risks through breath analysis, they proposed a clinical decision-making workflow as depicted in Figure 15. It should be noted that in the study, metabolites were assigned based on accurate mass. However, the six amino acids—γ-Aminobutyric acid (GABA), 5-Oxoproline (Oxo-Pro), L-Aspartic acid (Asp), L-Glutamine (Gln), L-Glutamic acid (Glu), and L-Tyrosine (Tyr)—that were found to be upregulated in measurements with side effects were confirmed through subsequent LC-MS/MS analyses (Awchi et al. 2023a). Recently, the previously discussed TDM method has been extended to the analysis of off-line breath samples, demonstrating good concordance with real-time breath analysis. The success of this study has led to the development of the DBI-EPIbreath, an IVD CE-certified breath test, which is commercialized by Deep Breath Intelligence AG (Awchi et al. 2023b).

In addition to valproic acid, the metabolic effects of salbutamol (a kind of short-acting bronchodilator) were analyzed via SESI-Q-TOF, identifying both drug-related and drug-regulated metabolites (Gaugg et al. 2017b). These studies suggest that such real-time breath analysis method is a useful tool for noninvasive therapeutic drug monitoring.

3.7.3 | Other Biofluids

SESI-MS has also been extended to the study of other biofluids, but with a limited number. Research employing SESI-MS headspace analysis has demonstrated significantly higher levels of periodontal pathogen-related compounds in the saliva of periodontitis patients when compared to healthy controls (Bregy et al. 2019a). The changes in volatile metabolites in the saliva headspace of patients during periodontitis therapy can also be characterized by SESI-MS (Bregy et al. 2019b). These results indicate that SESI-MS has the potential to become a valuable tool for rapid diagnosis and monitoring therapy for periodontal diseases. Some studies have utilized urine as a biological matrix to establish quantitative detection methods for 1-hydroxypyrene (Li et al. 2013), atrazine (Zhou et al. 2007), and creatinine (Devenport et al. 2014; Liang et al. 2015; Li et al. 2012b), and the detection of creatinine in serum (Huang et al. 2016). However, for the detection of creatinine, reliable quantitative detection methods are already available in clinical settings, making the SESI-MS method difficult to achieve clinical translation.

4 | Conclusions and Perspectives

Since the early discovery on the ability of electrospray plumes to ionize volatile species for subsequent mass analysis (Whitehouse et al. 1986; Fuerstenau 1994; Fuerstenau et al. 1999; Chen et al. 1994; Wu et al. 2000), SESI-MS has evolved from a pure subject of academic study to an advanced analytical technique used to detect and analyze trace amounts of VOCs and other analytes in complex matrices. Its ability to provide real-time, high-sensitivity detection of trace compounds makes it an invaluable tool in research. In this review, we

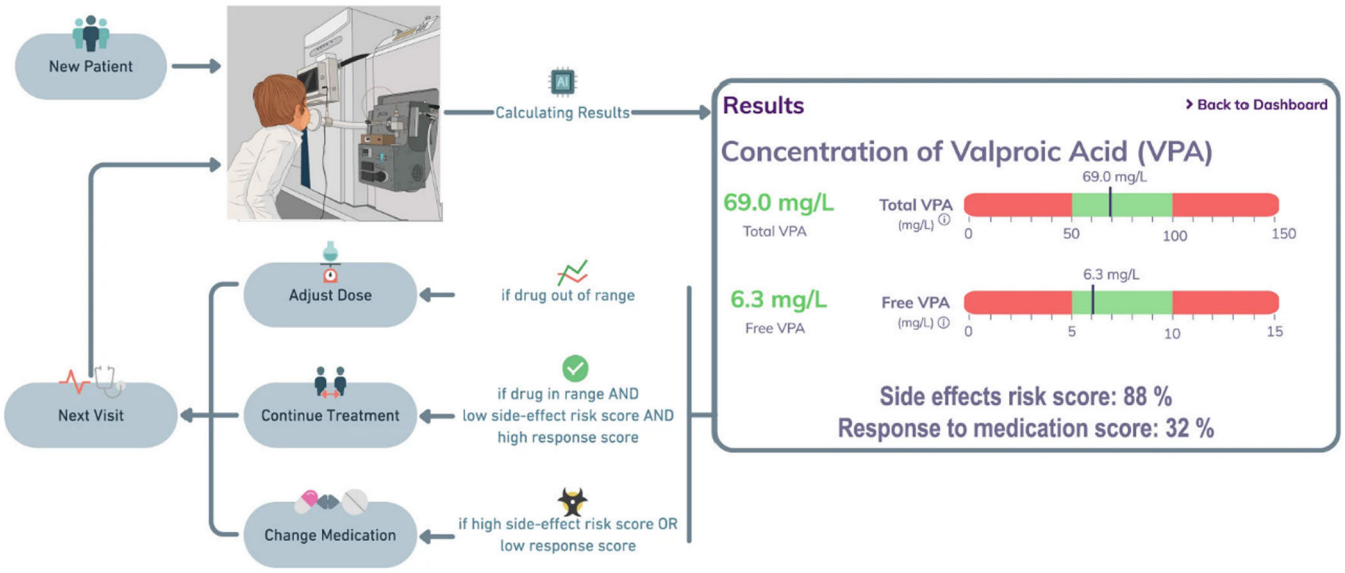

FIGURE 15 | The envisioned workflow for applying current breath-based TDM methods in future clinical practice. The steps are as follows: (i) Measuring the exhaled breath of a new patient requiring TDM; (ii) Predicting drug serum concentrations based on drug-related metabolites, while using drug-modulated metabolites to estimate side effects and drug-response scores; (iii) Based on the available information, the responsible clinician decides whether to continue the treatment, adjust the dose, or change the medication; (iv) Once the decision is made and implemented, the patient's breath metabolome is reassessed during the next visit to repeat the entire process. Reprinted with permission from (Singh et al. 2021). [Color figure can be viewed at wileyonlinelibrary.com]

provide a comprehensive overview of the broad range of SESI-MS applications, which includes areas from environmental monitoring to metabolomics, being breath analysis the branch that experienced its greatest development. Given the progress and persisting challenges in SESI applications across diverse fields, future research efforts should prioritize the following directions:

1. Full characterization of SESI mechanism, which will unlock the possibility of enabling absolute gas-phase quantification.
2. Establish SESI-MS fingerprint databases for diverse fields such as food authentication, bacterial volatiles, and human breathprints. This will support the development of standardized nontargeted identification methods and accelerate their translation to industrial and clinical applications. Additionally, it is worthwhile to explore the use of machine learning algorithms to compare reference fingerprints with experimental fingerprints to enhance classification performance.
3. Investigate the application of isotope tracing methods in biological sample analysis (Tejero Rioseras et al. 2017; Arnold et al. 2022), extending to human breath analysis. This approach will facilitate metabolite identification and metabolic pathway tracking, ultimately providing mechanistic insights into potential biomarkers at the molecular level.
4. Investigate the use of dopants. There are no robust solutions to address matrix effects currently. However, the application of dopants has demonstrated efficacy to enhance selectivity in targeted analysis. As demonstrated by Wüthrich et al. (2024c) in their untargeted breath analysis by SESI-Orbitrap MS, adding $AgNO_3$ to the electrospray solvent detected twice as many breath m/z signals compared to the conventional use of formic acid. This suggests that $AgNO_3$ could be explored as a supplementary dopant in future studies.

Author Contributions

Xin Luo: conceptualization, writing — original draft, writing — review and editing, **Huiling Wang:** writing — original draft; **Xiaolan Hu:** writing — review and editing, **Sasho Gligorovsk:** writing—review and editing, **Xue Li:** funding acquisition, project administration, supervision, **Pablo Sinues:** conceptualization, funding acquisition, project administration, supervision, writing — original draft, writing — review and editing.

Acknowledgments

PS received funding from Fondation Botnar (Switzerland) and the Swiss National Science Foundation (PCEGP3_181300). XL received funding from National Natural Science Foundation of China (No. 22122603), Guangdong Provincial International Science and Technology Cooperation Project (No. 2022A0505050044), Guangdong Major Project of Basic and Applied Basic Research (No. 2023B0303000013) and Research Fund Program of Guangdong Provincial Key Laboratory of Speed Capability Research (2023B1212010008). PS and XL extend their gratitude to Prof. Renato Zenobi for providing the opportunity to engage in this exciting research within his laboratory at ETH Zurich. Our time in his lab shaped our own scientific careers. His contributions to the field over the past 30 years have been profound and far-reaching.

Conflicts of Interest

PS is a cofounder of Deep Breath Intelligence AG (Switzerland), which develops breath-based diagnostic tools. XL is a cofounder of Guangdong A-HealthX Technologies Co. Ltd (China), which develops hardware and

software related to breath analysis. The remaining authors declare that they have no conflicts of interest.

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