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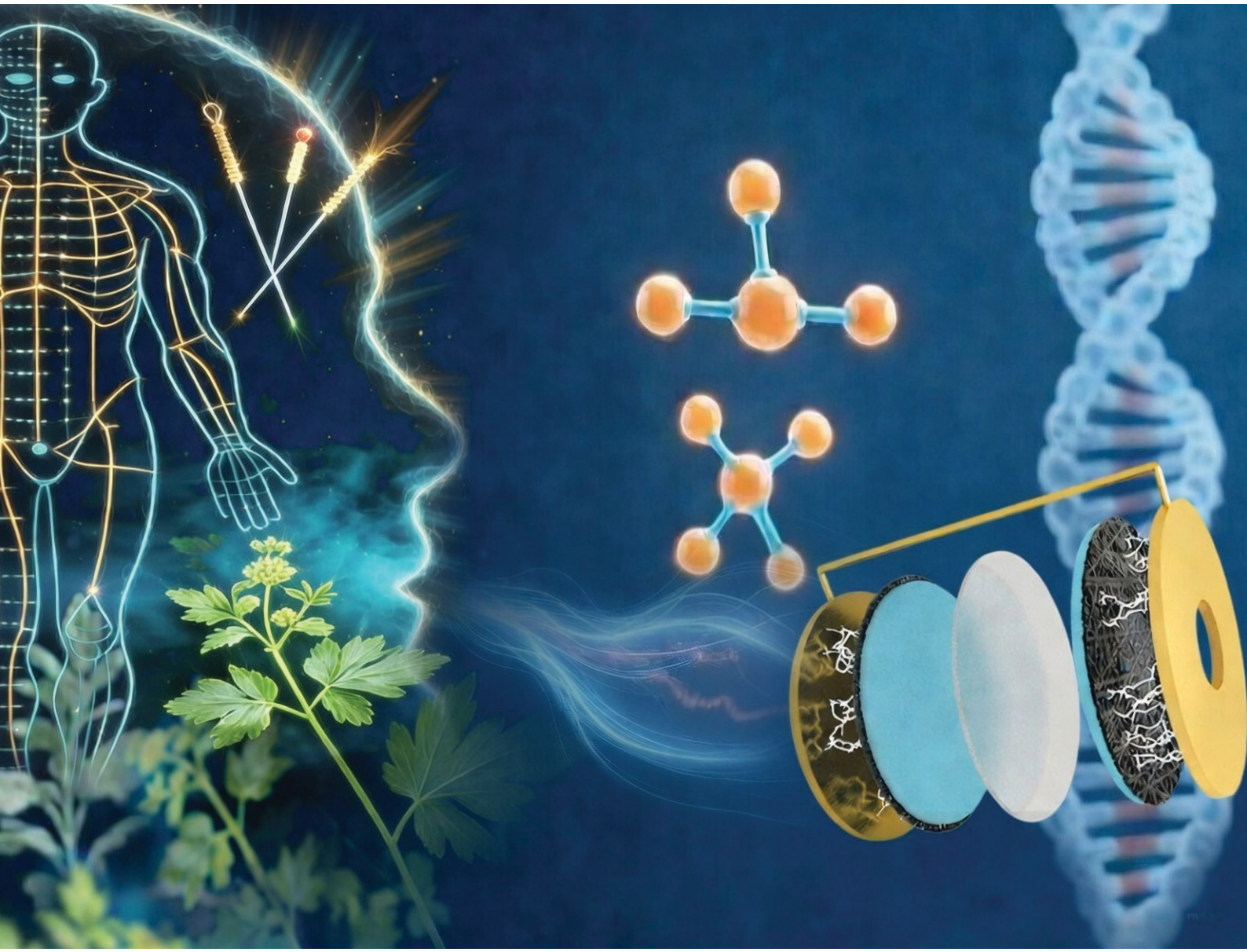

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CRITICAL REVIEW

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Molecular sensing transforms olfactory diagnosis in traditional Chinese medicine: a critical review

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Objectifying and standardizing diagnostic methods are essential steps toward the modernization and global recognition of traditional Chinese medicine (TCM). The "four diagnostic methods", namely, inspection, auscultation and olfaction, inquiry, and palpation, constitute the fundamental diagnostic framework of TCM, among which olfactory diagnosis plays a vital role. This method relies on identifying characteristic odors from the breath or secretions of a patient to guide syndrome differentiation (Bian Zheng). However, conventional olfactory diagnosis remains highly subjective depending on the practitioner's experience, which results in inconsistent outcomes and challenges in reproducibility and quantification. The integration of medical science with modern sensing and analytical technologies provides a transformative pathway to overcome these limitations. Recent studies have shown that exhaled breath contains a complex spectrum of volatile organic compounds (VOCs) that collectively form a personalized "breathprint", reflecting physiological and pathological states. Objective analysis of these VOCs enables quantifiable, evidence-based characterization of disease-related odors, thereby providing a scientific foundation for olfactory diagnostics in TCM. This review summarizes advancements in VOC detection methodologies, including gas chromatography-mass spectrometry (GC-MS) and electronic nose (e-nose) systems paired with data-driven analytical frameworks, to advance the transformation of traditional olfactory diagnosis in TCM into a standardized, evidence-based diagnostic paradigm.

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1. Introduction

Traditional Chinese medicine (TCM) embodies a holistic medical philosophy developed over millennia, emphasizing the dynamic balance between the human body and its environment. Central to TCM diagnostics are the "four diagnostic methods", namely, inspection, auscultation and olfaction, inquiry, and palpation, through which practitioners assess physiological and pathological conditions.[1] Among these, "olfactory diagnosis" (smelling diagnosis or "Wen Zhen") plays a vital yet often underappreciated role. It involves evaluating body odors, exhaled breath, and secretions to infer the internal state of organs, qi–blood circulation, and pathogenic transformations. However, traditional olfactory diagnosis relies heavily on the subjective experience and sensory acuity of practitioners, leading to variability between individuals and institutions. The absence of standardized evaluation metrics limits its clinical reliability, hindering its broader acceptance in modern healthcare systems.

Recent advances in analytical chemistry and sensing technologies have opened new opportunities for transforming this ancient diagnostic art into a scientific and quantifiable process.[2] Exhaled human breath is now recognized as a rich and non-invasive source of physiological information, containing hundreds of volatile organic compounds (VOCs) derived from endogenous metabolic activities, diet, and microbiome interactions.[3] These VOCs serve as biomarkers for various diseases, including diabetes, asthma, liver dysfunction, and certain cancers.[4] The VOC profile generated by an individual constitutes a unique metabolic signature, providing real-time insights into biochemical pathways and pathophysiological developments. The identification and analysis of VOC patterns make it possible to capture objective molecular correlates of what was historically described in TCM as "foul", "sweet", or "fishy" pathological odors. This convergence between VOC analytics and the TCM olfactory theory provides a scientific foundation for standardizing olfactory diagnosis (Fig. 1).

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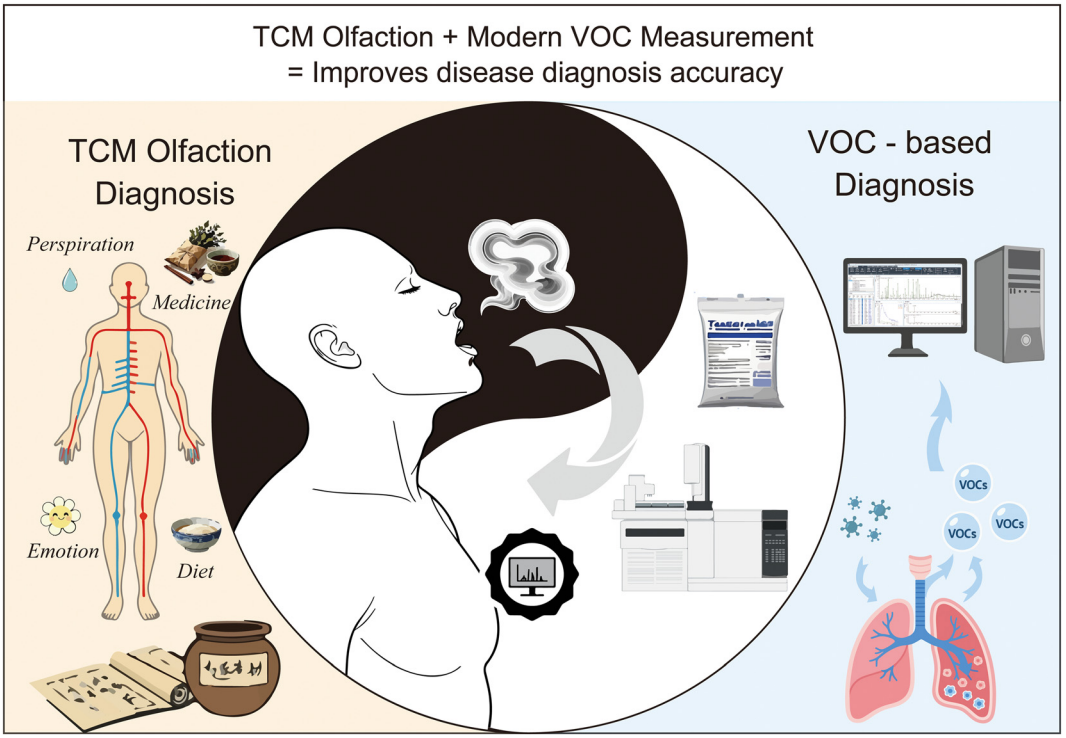

Fig. 1 The "TCM olfaction diagnosis" section on the left: as a traditional Chinese diagnostic method, it involves the detection of the odors of VOCs produced by the body's endogenous metabolism, including sweat secretion, drug metabolism, emotional fluctuations, and dietary intake. The "VOC-based diagnosis" section on the right: VOCs generated by the body's endogenous metabolism are transported to the lungs *via* the blood circulation and exhaled. By analyzing the chemical composition profiles of these VOCs in exhaled breath, disease diagnosis can be achieved. Middle section: the complementary integration of traditional Chinese olfactory perception (empirical diagnosis) and modern technological analysis (objective metabolic data analysis) enhances diagnostic accuracy and reliability.

Contemporary detection technologies such as gas chromatography-mass spectrometry (GC-MS) and electronic nose (e-nose) systems have markedly advanced VOC characterization. GC-MS enables precise compound identification and quantification,[5] whereas e-nose arrays enable rapid, pattern-based odor recognition, mimicking the human olfactory system.[6] Combined with emerging data-driven approaches—including machine learning, multivariate statistical analysis, and pattern recognition algorithms—these technologies facilitate efficient extraction of diagnostic features from complex VOC datasets. Consequently, they provide a powerful platform for mapping traditional TCM odor categories to measurable chemical signatures and disease-specific biomarkers. This review systematically discusses state-of-the-art VOC detection techniques, their integration with intelligent data processing, and their application in VOC profile correlation with TCM pattern identification. By bridging ancient diagnostic wisdom with modern sensing and analytical sciences, we aim to establish a comprehensive framework for the objectification, standardization, and modernization of TCM olfactory diagnosis—integrating advanced computational techniques with traditional sensory insights—to enable the development of intelligent, evidence-based diagnostic systems that harmonize ancient medical wisdom with modern scientific rigor.

2. Theory behind diagnosis by olfactory in TCM

The sophisticated correspondence between VOC patterns in exhaled breath and systemic metabolic conditions, as elucidated in TCM olfactory diagnostic principles, demonstrates striking congruence with contemporary biomedical evidence indicating that respiratory VOC signatures serve as dynamic biomarkers for organ-specific physiological and pathological alterations. This convergence provides a theoretical basis for combining the two approaches. This integration provides a basis for elucidating the scientific essence of olfactory diagnosis and paves the way for advancing TCM diagnosis from experiential perception to objective quantification. Furthermore, it establishes a solid basis for the subsequent exploration of the practical application of exhaled VOCs in disease pattern differentiation and clinical practice. Below, we will explore the theoretical basis of exhaled VOCs within the TCM olfactory diagnostic framework.

2.1 Origins of olfactory diagnosis in TCM

The TCM theory posits that odors emanating from the body can indicate dysfunction or imbalance of the internal organs. Within TCM diagnostics, olfactory examination, a component

of auscultation and olfaction, enables the identification of disease patterns and establishment of TCM syndromes by evaluating odors from the body, breath, secretions, and excretions. The *Huangdi Neijing: Suwen* (Inner Canon of Yellow Emperor: Basic Questions), particularly the *Jinkui Zhenyan Lun* (Essential Truths from the Golden Cabinet), delineates the correlations between the five zang organs (a core concept in TCM referring to the liver, heart, spleen, lung, and kidney) and their characteristic pathological odors: liver disease may manifest as a rancid odor, heart disease as a scorched or burnt smell, spleen disease as a fragrant or sweet scent, lung disease as a fishy stench, and kidney disease as a putrid or rotten stink. Chao Yuanfang, a physician of the Sui Dynasty, noted in his work *Zhu Bing Yuan Hou Lun* (General Treatise on the Causes and Manifestations of All Diseases) that the cold or heat nature of diseases can be discerned by evaluating the odor of the mouth and vomitus. Dai Tianzhang, a Qing Dynasty physician, emphasized in *Guang Wenyi Lun* (An Augmented Treatise on Warm Epidemics) that diagnosing cold damage requires five distinctions, the foremost being odor assessment, highlighting the critical role of olfactory examination in syndrome differentiation. By the modern Republic of China period, auscultation and olfaction had been further refined and secured a significant position among the four diagnostic methods of TCM.

In olfactory diagnosis, ancient Chinese physicians relied on "oral odor" to identify pathological conditions, as TCM believes that such odors stem from imbalances in the zang-fu organs. For example, an acidic taste in the mouth can be associated with a perceptible sour odor. The *Zhu Bing Yuan Hou Lun* noted that "An acrid taste indicates phlegm in the upper burner and chronic cold in the spleen and stomach, preventing proper digestion. Undigested food leads to distension and fullness, causing qi to reverse. This results in belching and sour breath". This theory posits that a sour taste in the mouth results from stomach coldness hindering food transformation. Regarding halitosis, *Danxi Shoujing* (Hand Mirror of Danxi), a foundational text in TCM authored by Zhu Zhenheng, recorded: "Appetite impairment (liver dysfunction affecting spleen qi) manifests as a distinctive foul odor resembling decaying fish, detectable prior to disease manifestation". These passages describe liver-related odors and their differential diagnosis in various liver conditions. Some patients with severe liver damage emit a distinctive odor reminiscent of mouse urine in their breath.[7] Many classical Chinese medical books describe body odors associated with diseases affecting different organs.

2.2 Correlation between auscultation–olfaction theory and exhaled VOC biomarkers in TCM

The rapid advancement of modern biomedicine, particularly in respiratory genomics, has provided novel scientific evidence supporting "odor" as a disease indicator. Modern research suggests that human-exhaled breath contains hundreds to thousands of trace VOCs, the metabolic patterns of which are closely associated with various pathophysiological states.[8] These VOCs encompass normal metabolic byproducts and disease-associated products, such as lipid peroxidation and amino acid degradation products.[9–11] Their compositional characteristics serve as indicators of systemic metabolic status.[12] Therefore, analysis of exhaled VOCs not only aids disease diagnosis and screening[13–16] but also enables monitoring of clinical changes in critically ill patients[17,18] during the perioperative period.[19–21] Advances in sensor-based detection technologies and chromatographic analysis have made objective, standardized analysis of human breath odors feasible.

The principle of applying exhaled VOCs to disease diagnosis shares profound conceptual similarities to the role of olfactory diagnosis in TCM. Although rooted in different theoretical paradigms, both serve as indicators of vital state through "odor". To investigate the modern scientific implications of this ancient wisdom linking the five zang organs to five odors, this review attempts to construct an integrative conceptual framework. It explores correlations between the organ theory of TCM and certain disease-associated VOCs currently identified (as shown in Table 1). It is crucial to emphasize that this framework does not aim to establish absolute one-to-one diagnostic relationships. Rather, it serves as an inspirational integrative model designed to provide new perspectives and directions for interdisciplinary research.

The above framework provides a modern biological perspective for understanding TCM theories; however, its application and interpretation require careful consideration due to the inherent complexity and limitations of TCM itself. First, the scientific evidence strength for the correlations between different elements in the framework significantly varies. For example, the links between "kidney-deficiency" and "putrid odor" (*via* ammonia) or "liver-qi stagnation" and "sulfurous odor" (*via* methyl mercaptan) are clinically recognized physical signs with well-established pathophysiological mechanisms, thereby providing a solid evidence base. However, the association between "heart-qi deficiency" and ketones/aldehydes is more of a highly speculative hypothesis derived from theories of myocardial energy metabolism and oxidative stress, with unclear olfactory correspondence. Moreover, these VOCs are more commonly found in other diseases, such as diabetes, exhibiting low specificity. Second, the non-specificity of VOCs is a universal challenge. Many compounds listed in the table, such as aldehydes and volatile alkanes, are general products of systemic oxidative stress or inflammation rather than exclusive biomarkers for specific zang-fu organ diseases. Therefore, future research should shift from searching for single biomarkers to constructing "VOC fingerprints" for specific TCM syndromes (*e.g.*, "spleen-insufficiency") or diseases, utilizing multivariate analysis patterns to enhance diagnostic accuracy. Finally, it is essential to recognize the fundamental paradigm differences between TCM and

Table 1 Modern interpretation framework of TCM five organs–five odors theory based on VOCs

Five zang organs and five odors	Modern systemic correlation	Generation and verification of VOCs			Ref.
		Core VOC	Generation process	Potential diagnostic value	
Liver-rancid	Neuroendocrine system	Methanethiol	Liver failure results in impaired methionine metabolism, leading to the production of methyl mercaptan by intestinal flora, which is exhaled through the lungs	Non-invasive screening for hepatic encephalopathy and assessment of cirrhosis severity	22–25
Heart-scorched	Circulatory, nervous system	Ketones (*e.g.*, acetone); aldehydes (*e.g.*, hexanal)	Myocardial ischemia or heart failure, on the one hand, causes energy metabolism disorders and incomplete fatty acid oxidation, producing ketones; on the other hand, oxidative stress leads to lipid peroxidation, generating volatile alkanes	Auxiliary diagnosis of myocardial ischemia and monitoring of heart failure progression	26–29
Spleen-fragrant	Digestive, immune, endocrine system	Short-chain fatty acids (*e.g.*, acetic acid); amines (*e.g.*, cadaverine)	Under normal physiological conditions, the spleen functions properly, and the mild "grain aroma" exhaled may be composed of short-chain fatty acids (*e.g.*, acetic acid) produced by normal intestinal flora metabolism and volatile components from grains themselves. Pathologically (spleen deficiency), impaired transportation leads to food stagnation, and abnormal bacterial fermentation produces cadaverine (an amine) and excessive acetic acid, mixing to form a putrid odor	Non-invasive evaluation of gastrointestinal function and auxiliary diagnosis of functional dyspepsia	30–32
Lung-fishy	Respiratory, immune system	Hydrogen sulfide; ammonia, volatile alkanes	In cases of lung infection, pathogens decompose proteins to produce hydrogen sulfide and amines; during tumor or inflammatory states, lipid peroxidation generates volatile alkanes	Auxiliary differentiation of pulmonary infection types and non-invasive screening for lung cancer	33–35
Kidney-putrid	Genitourinary, endocrine, reproductive system	Ammonia, trimethylamine	In renal failure, urea diffuses into the respiratory tract and skin *via* the bloodstream and is decomposed into ammonia by bacteria; trimethylamine originates from intestinal flora metabolism	Non-invasive monitoring of renal function and auxiliary diagnosis of uremia	36–40

modern medicine. The "five zang organs" in TCM are functional aggregates, whereas VOCs are specific chemical substances. Mapping the two is a beneficial simplification aimed at promoting interdisciplinary understanding; however, it cannot fully encompass the systematic and holistic connotations of TCM theories.

In conclusion, although the direct deterministic mechanism between "odor type" and "specific chemical components" has not been fully elucidated, investigation of the relationship between traditional medicine and modern odor chemistry can facilitate the transformation of traditional empirical knowledge into standardized, quantifiable modern medical systems, thereby providing innovative solutions for disease prevention, treatment, and health management.

3. Progress of technology for detecting VOCs in exhaled breath

To achieve the standardization of TCM diagnosis based on olfactory analysis, precise VOC detection and analysis are indispensable. Advances in analytical chemistry and precision instrument manufacturing facilitate the clinical adoption of exhaled-breath VOC detection methods. These methods are evolving toward portable devices and multimodal data fusion, offering significant potential to advance TCM olfactory diagnosis.

3.1 VOC detection technology

The electronic nose (e-nose) is one of several methods for VOC detection in exhaled breath and possesses unique advantages for TCM diagnosis through smell. Also known as an artificial olfactory system, it is designed to mimic the biological olfactory system;[6] the process of non-invasive respiratory detection *via* the electronic nose system is presented in Fig. 2. The core architecture of e-nose consists of three modules: a sensor array, signal processing circuits, and a pattern recognition unit. The sensor array is the core component, with common sensors including metal oxide semiconductors (MOS), conductive polymers, field-effect transistors (FETs), and quartz crystal microbalances (QCMs). Optimization of the structures and materials of these sensors enhances the ability to analyze complex gas mixtures. This technology closely aligns with the holistic, qi-based diagnostic paradigm of TCM by performing global pattern recognition on exhaled-breath VOC mixtures through an

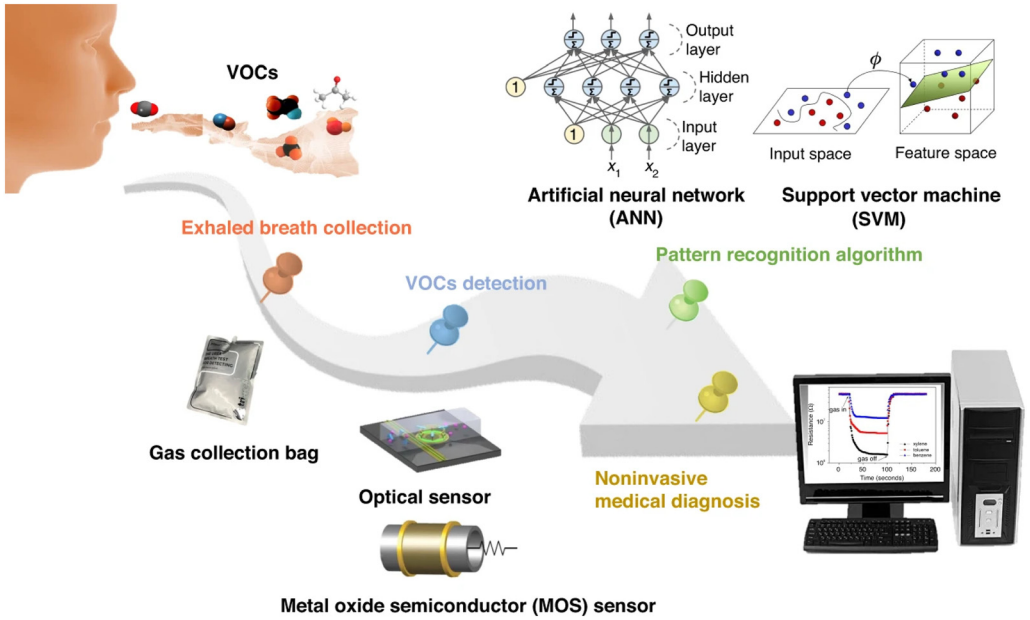

Fig. 2 The process of non-invasive respiratory detection *via* the electronic nose system. Figure reproduced from ref. 49 with permission from [Springer Nature], copyright [2023].

array of gas-sensitive sensors, rather than analyzing individual compounds in isolation. This non-destructive detection method avoids sample interference from complex pretreatment procedures, features rapid response times, and is user-friendly and compact, making it suitable for real-time disease monitoring in TCM clinical practice. Although current research on the translation of TCM syndrome characteristics and disease-specific VOCs into sensor response patterns remains exploratory, the multi-channel data fusion capabilities of e-noses provide a unique technical pathway for establishing "odor-syndrome" correlation models. The application of e-noses in TCM is an emerging field. The core innovation of this methodology lies in its capacity to systematize the holistic diagnostic patterns intrinsic to TCM, highlighting systemic pattern integration over isolated compound identification. E-noses have currently been applied in TCM syndrome differentiation studies for various conditions, including community-acquired pneumonia, type 2 diabetes, chronic gastritis, pulmonary nodules, and colorectal cancer.[41–48]

The electronic nose technology shows potential in the modernization of TCM olfaction diagnosis; however, its inherent technical limitations—including sensor drift, background noise elimination, and the non-linear interference of humidity with sensor responses—pose challenges to clinical VOC precision analysis and pathological mechanism interpretation. A primary bottleneck lies in the non-resolvable nature of features: mainstream sensors (*e.g.*, MOS, CP, QCM) rely on an "overall response pattern", where signals are superpositions of interactions from multiple gases, making it difficult to isolate the contribution of a single component from mixed responses.[50] In addition, the complexity of real-world application scenarios may introduce interference: environmental factors such as humidity, temperature, and exhaled background gases affect the stability and accuracy of discrimination.[51] With the improvement of electronic nose technology in recent years, issues such as humidity drift have been gradually addressed.[52] Therefore, electronic nose is more suitable for playing a role in rapid screening and auxiliary classification in TCM modernization research. In-depth biomarker discovery and pathological mechanism studies remain reliant on quantitative analysis techniques, such as high-resolution mass spectrometry.

Recent progress in gas analysis technologies has markedly enhanced the applicability of VOC detection in TCM olfactory diagnosis. Gas chromatography-mass spectrometry (GC-MS), while remaining the gold standard owing to its high sensitivity (detection limits down to ppt levels) and comprehensive standardized databases, faces practical limitations in clinical implementation.[53] These constraints primarily stem from its dependence on laboratory infrastructure, time-consuming sample protocols (the duration of routine analysis is up to 1 hour),[54] and bulk equipment size (weighing >50 kg), which collectively impede its deployment in point-of-care TCM diagnostic settings.[55]

Direct mass spectrometry techniques, exemplified by proton-transfer reaction mass spectrometry (PTR-MS) and extractive electrospray ionization mass spectrometry (EESI-MS), provide innovative solutions by circumventing traditional sample separation and derivatization steps.[56] However, technical challenges persist: PTR-MS exhibits susceptibility to water vapor interference and struggles with isomer differentiation,[57–61] whereas EESI-MS demonstrates limited sensitivity to nonpolar compounds and potential fragmentation of terpenoid VOCs in drift tubes, thereby complicating quantitative assessments.[62,63]

While spectroscopic techniques excel in real-time, non-invasive detection, they primarily target inorganic gases and demonstrate limited specificity for the complex VOC mixtures that define TCM olfactory signatures. This gap highlights the need for integrated sensor systems that synergistically combine electronic noses, optical spectroscopy (*e.g.*, Fourier transform infrared spectroscopy [FTIR]), and machine learning algorithms.[64–67] Recent progress in FTIR technology has enabled high-throughput detection of exhaled VOCs with high spectral resolution and rapid acquisition times, expanding its utility in clinical diagnostics and environmental monitoring. Separately, TCM diagnostic frameworks highlight the diagnostic value of VOC cluster patterns, driving demand for advanced multivariate analysis algorithms, such as partial least-squares discriminant analysis (PLS-DA), to interpret these patterns.[68–70] In sum, algorithmic optimizations, sensor miniaturization, and machine learning convergence are propelling next-generation TCM olfactory diagnostic systems from concept to practice.

3.2 VOC data processing strategy

Data obtained from the analysis of VOCs in exhaled breath can significantly vary in their nature and attributes depending on the specific detection methodologies employed. These data typically encompass four hierarchical levels of information, namely, raw spectral data, peak identification, compound identification, and multi-sample datasets, as detailed in Table 2.

TCM syndrome patterns (Bian Zheng) are complex clinical phenotype entities that exhibit multidimensional, nonlinear, and multilevel characteristics. VOCs in exhaled breath can serve as biomarkers reflecting the internal metabolic states of the body and have been shown to be associated with specific TCM syndromes. To reveal and validate this association, analysis of VOC data typically requires sophisticated feature extraction, statistical modeling, and predictive validation. VOC data primarily originate from analytical techniques, such as GC-MS, PTR-MS, and selected-ion flow-tube mass spectrometry (SIFT-MS). The datasets generated by these techniques are typically high-dimensional and sparse and contain a high degree of noise. Therefore, comprehensive data preprocessing and normalization are required before modeling to ensure analytical quality and robustness. The data processing procedure is as follows: (1) data acquisition and preprocessing: the data collected by the instrument undergoes a series of preprocessing steps, including noise reduction, baseline correction, area normalization, smoothing filtering, and peak extraction, to ensure the accuracy and reliability of subsequent analyses.[76] (2) Feature extraction and selection: dimensionality reduction, structuring, denoising, and enhancing discriminability are crucial preprocessing steps before modeling. Utilizing various feature extraction methods, such as principal component analysis (PCA),[77] linear discriminant analysis (LDA),[78] orthogonal partial least-squares discriminant analysis (OPLS-DA),[79] t-distributed stochastic neighbor embedding (t-SNE), uniform manifold approximation and projection (UMAP), representative features are extracted from raw data to reduce dimensionality and enhance the accuracy of subsequent classification or quantitative analysis. (3) Data modelling and classification: the extracted VOC feature variables are used to construct classification models for predicting or distinguishing TCM syndromes. Common modelling approaches include *K*-nearest neighbor (KNN),[80] support vector machine (SVM),[81] logistic regression (LR), random forest (RF), XGBoost, artificial neural networks (ANN),[82] convolutional neural networks (CNN) in deep learning (DL),[83] recurrent neural networks (RNN),[84] deep neural network (DNN), convolutional neural network (CNN), and RNN, which are suitable for processing complex patterns or spectral structures but require a large sample size. In small-sample studies, they should be used with caution due to the risk of overfitting or performance degradation caused by data heterogeneity. Key optimization methods for small-sample scenarios include ridge regularization, L1/L2 regularization, dropout, sparse network architecture, spectral peak perturbation, and other data augmentation strategies to avoid inaccurate real-world performance owing to overfitting or data heterogeneity as well as other algorithms to establish correlation models between exhaled-breath data and specific diseases or physiological states. Subsequently, exhaled-breath data is classified, for instance, to distinguish between healthy individuals and patients or to differentiate between various diseases[85] or subjected to quantitative analysis, including disease severity assessment.[86] (4) Model evaluation and optimization: to ensure the clinical utility and robustness of the model, multidimensional assessment of the classification

Table 2 Types and characteristics of VOC detection in exhaled breath

Data type	Data content	Characteristic form	Example	References
Original spectrum data	Raw GC-MS/MS and TD-GC-MS[a] signals	Continuous signal curve	TIC,[c] EIC[d]	71, 72
Peak identification data	Retention time, area, height, and other semi-quantitative indicators	Numeric features	Peak area, peak height	72, 73
Compound identification data	Compound name, structure, CAS[b]	High-dimensional data matrix	Esters, aldehydes, ketones, alkanes, *etc.*	74, 75
Multi-sample data matrix	Two-dimensional table: samples × VOCs	Classification/structural indicators	N[e] × P[f] matrix	75

[a] TD-GC-MS, thermal desorption gas chromatography-mass spectrometry. [b] CAS, chemical abstracts service registry number. [c] TIC, total ion chromatogram. [d] EIC, extracted ion chromatogram. [e] N, sample number. [f] P, VOC type.

model is essential. For instance, model performance metrics, such as accuracy, sensitivity, specificity, F1 score, and receiver operating characteristic (ROC) curves, should be selected based on specific research objectives. Model optimization through methods such as cross-validation and external validation set assessment enhances classification accuracy and generalization ability.[87] When models are intended for clinical use, decision curve analysis (DCA) can be employed to evaluate their clinical utility. Moreover, VOC data in TCM syndrome research often originate from diverse hospitals, devices, and populations, exhibiting significant data heterogeneity with notable distribution differences across centers. Therefore, heterogeneous federated learning (HFL), as a critical approach to address sample scarcity and heterogeneity, enables cross-center collaborative modeling without sharing raw data. This not only expands the "virtual sample size" but also enhances the model's generalization ability in multi-region and multi-device scenarios, making it one of the key technologies for constructing high-trust VOC-based TCM syndrome models in the future. As illustrated in Fig. 3, the integrated analysis process of TCM olfactory diagnosis and exhaled-breath VOCs involves several specific steps.

In summary, using suitable detection methods, conducting systematic feature selection, selecting appropriate classification modeling approaches, and implementing rigorous model evaluation mechanisms enable the establishment of a robust correspondence between exhaled-breath VOCs and TCM syndrome patterns. This objective, quantitative approach offers a novel pathway for the differentiation of TCM syndromes.

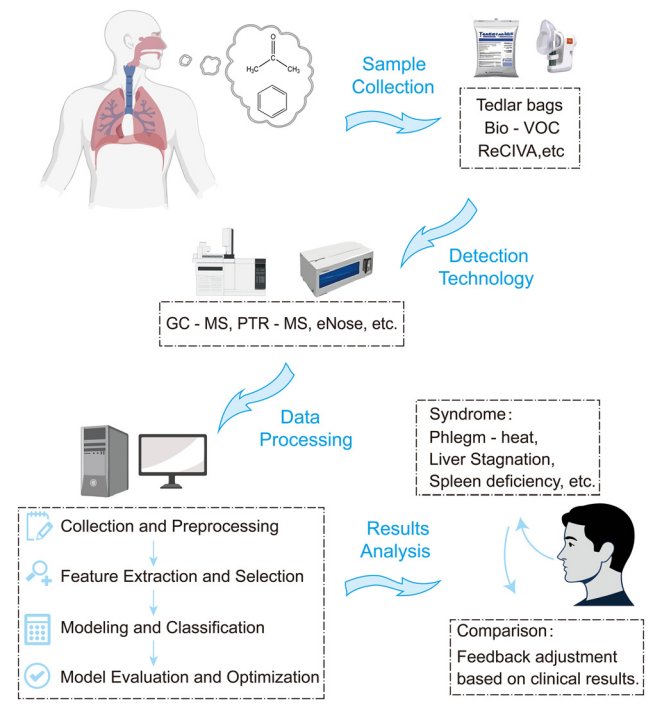

Fig. 3 Integrated analysis workflow of TCM olfactory diagnosis and exhaled-breath VOCs.

4. Use of exhaled VOC detection tech in TCM diagnosis

As a core component of syndrome differentiation and treatment in TCM, olfactory-based diagnosis has critically shifted toward standardization to transcend the limitations of traditional empirical practice. Conventional diagnostic methods depend on practitioners' subjective perception, resulting in inter-rater variability in syndrome differentiation. In contrast, microscopic syndrome differentiation provides material evidence for the essence of syndromes by analyzing biomarkers such as VOCs in exhaled breath.

Current research on VOCs for disease screening, diagnosis, and metabolic abnormality monitoring has made considerable progress in the international breathomics field. Teams from the UK, the Netherlands, Israel, and other countries have formed multi-center, large-sample research systems for lung cancer, infectious diseases, metabolic syndrome, and inflammatory diseases, accumulating extensive experience in sampling standardization, validation of the generalization ability of machine learning models, and cross-platform consistency. In contrast, VOC research conducted under the context of TCM, particularly studies aimed at syndrome differentiation, is primarily driven by a few domestic research teams. There are still significant differences from international breathomics research in terms of sample size, research design, model selection, and syndrome annotation systems. Most domestic studies focus on the VOC fingerprint characteristics of specific syndromes (*e.g.*, phlegm–dampness, qi deficiency, phlegm–blood stasis); however, due to limitations such as single-center data, small sample sizes, and subjective syndrome annotation, the cross-population reproducibility and universality of the results still need further verification. The following content will focus on elaborating the application of VOCs in TCM syndrome differentiation.

4.1 Research on the pathogenicity of exhaled VOCs in diseases

Heat, cold, deficiency, and excess patterns are common clinical patterns and constitute a vital component of the Eight Principles of syndrome differentiation in TCM. Accurate syndrome differentiation is the foundation of treatment. According to the principles of TCM, the intensity of odors corresponds to the nature of cold or heat in diseases. In pathological states, specific olfactory perceptions are indicative of bodily imbalances. Putrid or foul-smelling odors are often associated with excess heat or heat-toxin, whereas faint or slightly fishy odors are frequently associated with deficiency cold. Consequently, heat and cold syndromes across various diseases exhibit distinctive olfactory characteristics.

The research team of professor Lin Xuejuan used a custom-built TCM e-nose to analyze the oral breath odor profiles of patients, thereby unveiling substantial disparities in odor characteristics between those diagnosed with exterior

heat syndrome and those diagnosed with exterior cold syndrome.[43,88] Patients suffering from chronic gastritis also demonstrated distinct odor profiles based on their cold or heat pattern.[42] Subsequent research has shown that patients diagnosed with heat syndromes generally exhibit more pronounced olfactory signals. This finding led to the formulation of a hypothesis proposing a correlation between odor intensity and patterns of cold heat and deficiency excess. This hypothesis provides a significant foundation for the objective validation of TCM olfactory diagnosis.

The e-nose is aligned with the TCM diagnostic principle of "inferring the internal from the external" by capturing "overall odor patterns" rather than individual compounds. Its core advantage is translating experiential aspects of traditional olfactory diagnosis, such as "concentration, intensity, coldness, and heat", into quantifiable sensor parameters. This provides an objective tool for the eight principles diagnosis. Despite the need for further optimization to enhance the identification of complex syndromes, the efficacy of this approach in identifying heat syndromes and distinguishing between excess and deficiency syndromes has shown considerable clinical potential. This development indicates a pivotal shift in the transformation of TCM diagnosis, moving from an empirical, descriptive model to a data-driven paradigm.

The research team of professor Ren Yifeng has categorized pathological syndrome factors of pulmonary nodules into the following: yin deficiency, phlegm, dampness, qi impediment, and blood deficiency, among others. The integration of the Cyranose 320 electronic nose with a suitable model facilitates precise identification, contingent upon distinct pathological conditions, thereby substantiating its high specificity and sensitivity.[48] The research team of professor Zhu Jie employed the Cyranose 320 electronic nose to explore the distribution characteristics of TCM pattern elements in colorectal cancer and pulmonary nodules, conducting odor spectrum identification[46,47] to effectively distinguish disease patterns. Li Yuan *et al.*[89] employed gas chromatography coupled with surface acoustic wave (SAW) sensor technology to analyze exhaled breath from patients with spleen–stomach dysfunction. This method effectively identified patterns such as spleen qi deficiency pattern, damp heat in the spleen and stomach pattern, yang deficiency of the spleen and stomach pattern, stomach yin deficiency pattern, and stomach fire pattern, among others.

Research on electronic noses and odor spectrum analysis has provided substantial evidence for the objectification of TCM pattern classifications, such as cold, heat, deficiency, and excess. The conventional diagnostic paradigm, predicated on the notion that "the intensity and character of odors reflect cold, heat, deficiency, and excess", has been translated into quantifiable pattern features through the application of modern sensor technology. This development has yielded high levels of accuracy and clinical relevance across a range of diseases and TCM patterns. This advancement not only promotes the modernization and digitization of TCM olfactory diagnosis but also establishes a methodological foundation for the objectification of eight-principles syndrome differentiation. However, further optimization for discriminating complex patterns and large-scale validation studies are still warranted.

4.2 Research on disease localization through exhaled VOCs

According to the principles of TCM, the presence of abnormal oral odors can indicate pathological changes within the internal organs. Odor alterations can therefore be viewed as a marker of shifts in organ function. It is evident that the TCM theory is in alignment with contemporary medical research. Contemporary medicine has identified that disease states frequently result in abnormal blood metabolic processes. The composition of oral breath varies among patients with different diseases. For instance, patients with diabetes exhibit elevated levels of ketone bodies in their oral breath in comparison with healthy individuals,[90,91] whereas patients with lung cancer have increased levels of alkanes and benzene derivatives in their oral breath.[92] Consequently, the identification of distinct olfactory characteristics is instrumental in the precise localization of the disease site.

The research team of professor Lin Xuejuan has completed a study on the identification of exhalation patterns associated with various disease locations in conditions including community-acquired pneumonia, type 2 diabetes, and chronic gastritis.[41,42,44,45] The findings indicated that the primary disease locations in patients with chronic gastritis involve the stomach, spleen, and liver, each exhibiting distinct odor characteristics.[93] Patients with chronic gastritis and qi stagnation syndrome showed a distinct oral breath odor spectrum compared with those with disease locations identified as stomach, spleen–stomach, or liver–spleen–stomach. In patients with heat syndrome, prevalent disease locations included the stomach, lung, spleen, and liver. The olfactory spectrum varied among patients sharing the same disease location, and the electronic nose effectively differentiated odor profiles across these locations.[43] Furthermore, the team developed advanced models for odor spectrum recognition in diabetes research. These models were used to stage type 2 diabetes mellitus (T2DM), distinguishing between pre-diabetic and diabetic states, and to identify common disease locations, such as the liver, kidneys, and spleen. The study showed T2DM disease location patterns: the pre-diabetic stage primarily involved the liver and kidney (liver 19.67%), whereas the diabetic stage predominantly involved the kidney and liver (kidney 66.67%). These findings indicate that odor changes are associated with organ function, providing biological relevance to the observed odor profiles. The research employed multi-algorithm comparisons (DT/RF/SVM/DNN) and ROC curve analysis, which rigorously enhanced the accuracy of the deep neural network (DNN) models. In a related study, the research team of professor Ren Yifeng used the Cyranose 320 electronic nose combined with a specific model to identify common TCM syndromes in pulmonary

nodules.[48] This approach enabled precise identification of single-site lesions in the liver, lungs, or kidneys, demonstrating high specificity and sensitivity. The research team of professor Zhu Jie used an electronic nose to identify odor profiles associated with the pathological locations of colorectal cancer and pulmonary nodules.[46,47] The study focused on the TCM pathological locations for both diseases. The pathological location patterns for colorectal cancer patients primarily included the large intestine as well as the spleen, liver, stomach, and kidneys. Contrarily, the patterns for pulmonary nodules involved the liver, lungs, kidneys, and spleen. The research showed distinct differences in exhalation profile characteristics across different pathological locations. Sensor data processing using five algorithms—RF, KNN, LR, SVM, and XGBoost—achieved accuracies exceeding 80% for all methods. Among these, random forest demonstrated the highest recognition accuracy. However, due to the limitations of small sample sizes and high-dimensional data characteristics in TCM clinical research, the application of DNN and CNN models often leads to overfitting (excellent performance during model training but failure in external validation), resulting in diagnostic errors in clinical practice. In future related research, it is necessary to introduce standardized data processing workflows, feature engineering strategies, model optimization approaches, heterogeneous federated learning (HFL) architectures, and explainable artificial intelligence (XAI) tools to ensure the usability, generalizability, and reliability of AI in TCM olfaction research.

Research on VOCs in exhaled breath provides a novel objective method for identifying disease locations. The electronic nose technology and associated spectral analysis can effectively reveal odor differences associated with distinct organ systems, whereas multi-algorithm modeling markedly enhances the accuracy of disease localization. These findings not only validate the TCM theory that 'disease locations can be reflected by odors' but also provide biological interpretability for odor spectra.

In summary, research on exhaled VOCs provides an objective method for identifying disease patterns and locations in TCM, which fully demonstrates the modern application potential of "olfactory diagnosis". By capturing holistic VOC profiles, electronic noses transform traditional empirical concepts, such as "cold, heat, deficiency, excess, and pattern differentiation of zang fu organs", into quantifiable parameters and have shown high accuracy and clinical value across multiple diseases. Furthermore, multi-algorithm modeling enhances identification efficacy and provides clear biological interpretations for odor changes. However, most current studies remain constrained to the qualitative analysis provided by electronic noses, which hinders the separation and identification of individual VOC components and constrains the in-depth exploration of specific biomarkers. The future incorporation of precision detection technologies, such as chromatography and mass spectrometry, has the potential to enhance the differentiation and treatment of TCM syndromes. Such an integration is expected to facilitate a shift from macro-level experiential practice to micro-level mechanistic understanding, thereby achieving greater precision and standardization in TCM therapy. Despite the preliminary research foundation established by domestic teams in TCM syndrome-VOC correlation, future efforts still rely on more standardized sampling protocols, stricter syndrome annotation systems, and multicenter collaborative studies. These measures are aimed at constructing a high-quality evidence system capable of engaging in dialogue with international breathomics research and enhancing the reliability, interpretability, and international recognition of TCM syndrome-related VOC biomarkers.

4.3 Research on using AI for olfactory diagnosis

Over the past decade, artificial intelligence (AI) has undergone significant transformation, particularly with the rapid advancement of large language models. AI technology has had a profound impact on global human production and daily life in various fields. Artificial intelligence (AI)-driven advancements have markedly enhanced olfactory analysis capabilities, providing powerful tools for interpreting complex sensory information.[94] Before the integration of AI, olfactory analysis primarily relied on traditional statistical methods and heuristic approaches. Techniques such as gas chromatography (GC), mass spectrometry (MS), and principal component analysis (PCA) were widely employed for feature profile analysis. Although effective in controlled environments, these methods often required manual feature selection and struggled to adapt to different sample types and experimental conditions. Early rule-based electronic nose systems also suffered from nonlinearity, sensor drift, and background noise, which impaired their practical application. The introduction of AI has addressed these challenges through data-driven modeling as well as improved generalization ability and the capacity to uncover complex patterns in high-dimensional olfactory datasets, providing researchers with a more robust, scalable, and context-aware analytical tool. The integration of TCM and AI is driving major innovation and transformation in the field of medicine. The concepts of 'AI + TCM' and 'AI + digital' healthcare have ushered in an era of intelligent TCM medicine. Enabling AI to perform TCM syndrome differentiation and treatment hinges on standardizing, systematizing, digitizing and intellectualizing the four diagnostic methods of TCM. Current research has applied e-nose technology combined with pattern recognition algorithms to olfactomics-based diagnostic methodology, enabling VOC identification as well as disease progression staging and pathological site localization in patients with type 2 diabetes.[45] Zhou Fu *et al.*[95] used an electronic nose integrated with artificial neural networks to identify odor spectrum characteristics from different pathological sites in patients with community-acquired pneumonia (CAP), offering a novel approach to CAP localization diagnosis.

The AI-based identification and analysis of auscultation and palpation is a crucial step in the modernization of the four diagnostic methods of TCM. Future integrated, intelligent

diagnostic systems for the four diagnostic methods will represent a major application of AI in TCM syndrome differentiation. These systems combine multi-label classification and deep learning technologies to automate the complex task of TCM pattern differentiation. Treating information gathered from the four examinations as a unified dataset for analysis through multi-label and deep learning models enables these systems to more effectively handle the intricate relationships between diverse symptom characteristics and syndromes, thereby enhancing diagnostic accuracy.[96,97]

5. Challenges of VOCs in TCM olfactory diagnosis

The modernization of TCM urgently requires deep integration with modern technology. Building upon the preceding discussion of interdisciplinary research between TCM diagnostic theory and exhaled breathomics, this review proposes that characteristic VOC profiles captured in exhaled breath using devices such as electronic noses enable an objective diagnosis of TCM syndromes. These profiles can also provide quantitative evidence to differentiate the nature and location of diseases (*e.g. qizhi* or *xuexu* in the liver, lungs or kidneys) through mapping of the association between these profiles and TCM syndrome characteristics. Although progress has been made in the application of VOCs to TCM diagnosis, multiple challenges still need to be addressed before true clinical translation can be achieved. These challenges encompass technical standardization issues and the inherent complexity and diagnostic uncertainty of the TCM pattern differentiation system itself.

5.1 The lack of standardization in exhaled-breath sampling and data processing

At present, there are no unified operating procedures for the sampling and analysis of VOCs in TCM olfaction diagnosis. Different studies use whole exhalation or alveolar air as sample types. Whole exhalation collection is simple and requires no additional equipment; however, the exhaled air from the front dead space dilutes the concentration of VOCs in the exhaled breath, and exogenous VOCs can introduce contaminants. Contrarily, alveolar air has lower concentrations of exogenous VOCs, and its endogenous VOC concentration is 2–3 times higher than that in mixed exhaled breath.[98] For whole exhalation, collection can be performed using containers such as gas bags (*e.g.*, Tedlar, Mylar, Flexfoil, and Nalophan bags), chemically inert and low-radioactivity plastic containers (*e.g.*, syringes), glass bottles, and stainless-steel containers or glass tubes with adsorbents (adsorption traps). Among these, gas bag collection is the most commonly used method.[99] Among various gas bags, Tedlar sampling bags are widely used in exhaled-breath analysis as their overall performance (*e.g.*, background emissions, storage time, and reusability) is superior to other materials.[100] Beauchamp *et al.* compared the stability of volatile organic compounds in exhaled-breath samples stored in Tedlar bags for 10 and 70 hours. The results indicated that over 80% of the compounds in the samples remained stable within 10 hours, but the recovery rate within 70 hours could not meet the requirements for subsequent analysis.[101] Evidently, various factors, including bag design, material, and sampling process (*e.g.*, sampling time, pre-sampling rinsing, number of exhalations, and duration of each exhalation), significantly affect the test results. Therefore, it is urgently needed to establish unified standards and operating procedures for exhaled-breath sampling to improve the repeatability and comparability of research, thereby providing a more accurate and reliable basis for clinical diagnosis and disease prediction.

Data processing technology is a crucial part of exhaled-breath detection. Owing to the complex composition of exhaled breath, untargeted full-spectrum analysis often detects massive metabolite information. To effectively identify these potential biomarkers, researchers must employ a series of data analysis methods for in-depth exploration. The combined application of basic statistical methods and machine learning (ML) has become the mainstream data analysis method in the field of exhaled-breath analysis in recent years. It integrates the rigor of statistics and the intelligence of algorithms, thereby enabling more precise revelation of biochemical information in exhaled breath and enhancing the accuracy of data analysis. The data processing of exhaled-breath signals mainly includes data acquisition, preprocessing, feature extraction, selection, modeling, classification, as well as model evaluation and optimization. In these steps, improper preprocessing may remove valid spectra and introduce additional errors and uncertainties. The quality of data preprocessing and feature extraction directly affects model performance. If the data is not comprehensive or biased, the accuracy of model predictions will be affected. Existing ML models and algorithms may not be applicable to all types of exhaled-breath samples, particularly those with significant individual differences or complex matrices. To address these problems, the amount of high-quality training data can be increased to ensure data diversity and representativeness, reduce bias, and improve model generalization ability. In summary, with the rapid development of artificial intelligence, continuous research and optimization of existing algorithms, as well as continuous introduction of the latest ML and DL (deep learning) technologies, is the best choice to promote the innovative development of data analysis in current digital-intelligent TCM olfaction diagnosis.

5.2 The dilemma of TCM syndrome differentiation

One of the most challenging contradictions in current research is the mapping of objective VOC indicators to subjective TCM syndrome patterns. The prevailing approach in TCM syndrome differentiation involves a considerable

degree of subjectivity and diagnostic variability. This stems from the reliance on practitioners' individual perception and experiential judgment of odors, tongue manifestations, pulse conditions, and other factors. Conversely, a single modern medical disease may correspond to multiple TCM syndromes, and *vice versa*. The indistinct boundaries and considerable overlap between syndromes complicate the establishment of a one-to-one relationship between VOCs and specific syndromes. Future research should prioritize the development of more objective and standardized syndrome classification systems through expert consensus or data-driven clustering methods (*e.g.*, factor analysis, cluster analysis). This approach could enhance diagnostic consistency and biological interpretability in VOC-based syndrome research.

5.3 The importance of integrating multimodal diagnostic information

Olfactory diagnosis is only one component of an integrated diagnostic approach fundamental to TCM, which is based on observation, listening and smelling, inquiry, and palpation. Isolated analysis of VOCs is insufficient to comprehensively reflect the overall pathophysiological status of patients. The integration of tongue manifestation analysis, pulse parameter measurements, symptom inquiry data, and VOC features would help establish a more comprehensive evaluation system that is better aligned with TCM principles. TCM is guided by a "holistic philosophy" and "treatment based on syndrome differentiation". Recent advancements in technologies such as digital tongue imaging, pulse wave analysis, and electronic diagnostic questionnaires have provided data support for research on multimodal TCM syndrome differentiation. Future research should focus on multimodal fusion at the feature or decision-making levels to enhance model accuracy and diagnostic capabilities.

5.4 The potential of AI and machine learning

In the context of high-dimensional and complex VOC data, machine learning (ML) and AI technologies show great potential. The efficacy of methodologies such as support vector machines (SVM), random forests, XGBoost, and neural networks has been demonstrated in the field of disease VOC research, and these techniques show great promise for extension to TCM syndrome identification. Nevertheless, incomplete or biased data can compromise the accuracy of model predictions. Existing ML models and algorithms may not be suitable for all types of exhaled-breath samples, particularly those exhibiting significant individual variability or complex matrix effects (*e.g.*, from diet, medication, or environmental background). Future efforts should concentrate on increasing the volume of high-quality training data, mitigating bias, and enhancing the models' generalization capabilities and reliability.

6. Conclusion

Modern analytical chemistry and sensing technologies are profoundly reshaping olfactory diagnosis in TCM. By integrating VOC analysis, GC-MS, and e-nose systems, traditional subjective olfactory diagnosis is transforming into an objective, quantifiable scientific practice. When combined with AI and data science, these technologies enable the construction of a "VOC-biomarker-syndrome" association database, which not only bridges classical TCM theory with modern biomedical understanding but also lays a solid technical foundation for the development of intelligent, non-invasive diagnostic platforms. However, the journey from subjective experience to objective science faces multiple challenges. First, human VOC emissions are highly susceptible to interference from diet, environment, and other complex factors, making data standardization and signal-to-noise ratio improvement top priorities. Second, the macroscopic and complex nature of TCM syndromes means that single or few VOC biomarkers cannot accurately correspond to syndromes, risking oversimplification in diagnostic models. Third, the lack of large-scale, high-quality, and accurately annotated "VOC-syndrome" databases considerably limits the training and validation of AI models. In addition, the high cost and complex operation of high-end analytical equipment hinder their widespread clinical application. Looking ahead, research efforts will focus on these bottlenecks. Technologically, the development of more precise and low-cost sensing technologies and establishment of strict data collection and preprocessing standards are essential. Theoretically, deepening multi-omics integration, combining metabolomics, microbiomics, and other cutting-edge fields, will systematically elucidate the underlying biomedical mechanisms of the "VOC-syndrome" association. Ultimately, these efforts will converge into next-generation diagnostic platforms that integrate intelligent algorithms, real-time monitoring, and non-invasiveness, thereby realizing the standardization, normalization, and internationalization of TCM olfactory diagnosis and promoting its role in modern health management.

Conflicts of interest

There are no conflicts to declare.

Data availability

Data availability is not applicable to this article as no new data were created or analyzed in this study.

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