Emerging applications of metabolomics in food science and future trends

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ABSTRACT

Metabolomics is a relatively new component in systems biology that focuses on the high-throughput characterization of small molecular metabolites in biological systems. It is widely used in several scientific fields, particularly in that of food. Due to its excellent detection and prediction capacities, metabolomics well suited to analyze such complex matrix. This review emphasizes the most commonly used food metabolomics analytical technologies with a focus on novel approaches that have emerged in recent years, highlighting their suitability for food samples analysis as aided by chemometric data visualization. A comparison is presented among different metabolomics platforms and their prioritization for which metabolite classes in food. Application of metabolomics are presented in the context of food composition analysis, food quality safety, and food traceability. Furthermore, the constraints and limitations of actual metabolomics applications are explored, bringing novel insights into metabolomics use in food science to maximize its application potential in that major industrial sector.

Introduction

Metabolomics (or metabonomics) was firstly proposed in 1999 (Nicholson, Lindon & Holmes, 1999), which has quickly emerged as a technology to explores the changes in the metabolic, response of organisms under the action of internal and external environments, it targets small molecule metabolites typically less than 1500 kDa (Lao, Jiang & Ypress, 2009; Kuehnbaum & Britz-Mckibbin, 2013). Owing to some features of metabolomics, such as predictability and non-targeted attribute, metabolomics can qualitatively and quantitatively reflect the influence of internal and external factors on organisms’ metabolism from the overall level. It is a comprehensive and systematic analysis method that shows potential in elucidating the mechanism of action of bioactive components, dietary intervention, screening of new biomarkers, and evaluation of metabolic disease prescription interventions. In recent years, with the development and progress of technologies, such as ultra-performance liquid chromatography (UPLC), capillary electrophoresis (CE), and matrix-assisted laser desorption/ionization (MALDI) (Chen et al., 2021), metabolomics has gradually increased in applications, especially in the field of food owing to its excellent detection or structural elucidation capacity of such complex metabolome (Fig. 1). By comparing database information, such as Fiehn library, Golm Metabolome Database, and Wiley Database, mass spectrometry (MS) can quickly identify relevant metabolites (Putri et al., 2022). In food industry analysis, search engines such as Request and Mascot can be used to analyze peptide segments and then match corresponding proteins. The SPINE database in the nuclear magnetic resonance (NMR) community also facilitates NMR analysis, it builds to support the product sample production and structure determination efforts (Fraga et al., 2022). In addition, there are a series of publicly shared comprehensive database platforms like Mass Bank (Go, 2010).

Food metabolites are typically affected by various factors such as species, environment, processing methods, and storage techniques. The changes of these metabolites will directly affect food safety and quality. The use of metabolomics technologies allows for the monitoring of metabolite changes during food processing, allowing for optimisation of

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processing procedures and better quality products (Farag et al., 2022). Potentially harmful components of food processing and production, such as food toxins and drug residues, can also be identified by metabolomics technology to ensure human health (Johanningsmeier, Harris, & Kle- vorn, 2016). With the improvement of science and technology in recent years, food counterfeiting through the addition of food additives or other substances has occurred frequently. There are also counterfeiting methods that use cheap ingredients of similar types to pass off as expensive foods. Traditional analytical methods usually have limitations such as long identification time and low identification accuracy, which make it difficult to solve these problems and bring impact to the food industry. By using advanced food metabolomics techniques, changes in food composition in terms of compositional analysis, food safety, food classification and traceability can be clearly shown, providing a new paradigm for answering questions in this field. This paper presents the main features of metabolomics-related technologies commonly used in food science in recent years, enumerating the applications of metabolomics technologies in the food industry, while highlighting future trends and areas for improvement.

Metabolomics technologies

Mass spectrometry (MS)

MS is currently one of the most widely used platforms for metabolomics analyses and whose principle is to ionize molecules to generate charged ions with different mass-to-charge ratio ($m/z$), which form ion beam under the action of accelerating electric field and enter the analyzer for separation and further detection. MS is equivalent to a "highly sensitive balance", which can directly weigh the atomic weight and molecular weight of substances, with high sensitivity, high resolution, fast analysis speed, and other advantages.

In recent years, different types of MS techniques have been constructed by improving ion sources and mass analyzers. Ion sources act as the heart of the mass spectrum, volatilizing and ionizing molecules into charged particle beams, determining the rate of $m/z$-based selective separation and identification, the extent of which determines the ability to detect and quantify the metabolome (Fraga-Corral et al., 2022). Ionization methods commonly used by ion sources include electron impact (EI), electrospray ionization (ESI), and atmospheric pressure chemical ionization (APCI) (Gowda & Djukovic, 2014). EI is a hard ionization method capable of destroying metabolites to produce sub-products, but can be detected with minimal matrix effects and is well suited for the detection of volatile and thermal stable compounds (Rigano et al., 2019). In contrast, ESI is a soft ionization technique in which ions are formed from liquids without significant fragmentation of their molecular ions. Therefore, ESI is more suited for analyzing ionic/polar compounds, refractory or thermally unstable compounds e.g., glycosides and alkaloids in foods. APCI, on the other hand, only forms single-charge ions and is generated in the gaseous state, which is appropriate to small molecular compounds with moderate or low polarity and certain volatility such as lipids.
The solvent is volatilized, the surface of the sample is purged into the gas phase by DESI, the height and angle of the nebulizer and detector from the sample can be adjusted for optimal imaging.

Fig. 2. MSI of food ingredients and ionization technique commonly used in MSI technology. (a) MSI enables a two-dimensional view of the distribution of ingredients in food. After the food is thinned, the components are analyzed by ionization methods, and then the mass spectral information of each area is integrated to form a two-dimensional image of the component distribution. (b) MALDI. For thermally sensitive samples, MALDI technology can be used for ionization, solid samples are covered with a matrix or liquid samples are proportionally diluted to fix the samples, under laser irradiation, the sample is instantly vaporized and ionized by the matrix, and then enters the detector. (c) SIMS. The sample is directly bombarded by the ion beam, and then the molecules on the surface of the sample are sputtered to become charged ions, which are detected and imaged by the detector. (d) DESI. DESI can directly process a solvent and then dripped onto the surface of the insulating material. After the solvent droplets surrounding the sample evaporate under the action of high-speed airflow, the sample enters the detector for detection and imaging. In DESI, the height and angle of the nebulizer and detector from the sample can be adjusted for optimal imaging.

With the development of the new generation mass analyzers, the quality resolution has been improved significantly. Currently, MS depending on its mass analyzers can be divided into Magnetic Sector MS, Quadrupole MS, Ion Trap MS, time of flight MS (TOF-MS), fourier transform Ion cyclotron resonance MS (FTICR-MS), with Orbitrap MS to emerge in recent years. Among these MS analyzers, TOF-MS, FTICR-MS, and Orbitrap MS are High Resolution Mass Spectrometer (HRMS) with resolution ≥ 10,000, which can be used for accurate qualitative and non-directional unknown screening in food samples (Kaufmann, 2012). In addition, it plays an unprecedented role in rapid detection of food composition because of its fast scanning time and positive/negative ion capability, as well as its ability to provide exact mass and possible elemental composition of precursor and fragment ions aiding in unknown compounds identification especially phytoneutrients.

Due to the diversity of analyzed samples and the difference of analysis requirements, the ionization methods and ionization mechanisms are also different, which leads to the difference of ionization sources and mass analyzers. In order to meet the requirements of multidirectional analysis, many different arrangements and system combinations can be constructed through some engineering work. Therefore, MS and HRMS can work with gas chromatography (GC), CE, TOF, and FTICR, among others. For example, GC−MS combines features of GC and MS to identify different chemicals in samples (Castro-Puyana et al., 2017; Cevallos-Cevallos et al., 2011), which has strong separation ability, resolution and sensitivity, is suitable for qualitative and quantitative evaluation of volatile and semi-volatile organic compounds (such as esters, short-chain fatty acids, and flavonoid aglycans), but to some extent requires derivatization and lengthy pretreatment steps. During the use of GC−MS, avoid sample components with too high boiling points. In addition, substances with strong polarity and substances containing carboxylic acid cannot be directly analyzed by GC−MS. CE is a separation technology based on mobility and distribution behavior, CE-MS is commonly used for efficient analysis of polar and charged metabolites, such as amino acids, peptides, organic acids, and nucleic acids (Granados-Chinchilla & Rodríguez, 2017; Sugimoto et al., 2017; Sugimoto et al., 2020). TOF-MS combines the acquisition speed with the ability to collect complete spectral information. Meanwhile, with the development of spatial focusing, reflector, and vertical acceleration technology, TOF-MS has extremely fast scanning speed and high sensitivity, with a mass accuracy of 10⁶ millimass units (mmu) and a resolution of more than 10,000 at present, allowing the detection of even minor peaks. Its quality accuracy can reach ppm level after strict correction, with the mass range of detected ions can reach hundreds of thousands of daltons. Currently, QMS combined with TOF-MS are widely used to analyze food samples (Farag et al., 2013). Compared with other types of MS, TOF-MS has a higher resolution and a wider range of ion quality detection, posing it as being suited for food profiling matrices. FTICR-MS is the highest resolution mass spectrometer among all HRMS, to reach 1,000,000 in accuracy while maintain acceptable sensitivity. Consequently, FTICR-MS is a powerful tool for molecular structure confirmation and molecular rearrangement reaction research in food compounds. However, its high price and complex operation limit its wide application in food testing especially in industry (Leavell et al., 2002). Linear ion trap electrostatic orbitrap combined MS (LTQ Orbitrap-MS) can parallel detection of ion trap and HRMS. The multi-stage MS of ion trap can obtain structural fragments and HRMS can obtain the molecular formula, providing comprehensive data for the identification of regioisomers and structural analogues (Eliuk & Makarov, 2015). In addition, UPLC quadrupole orbitrap MS (UPLC-Q-Orbitrap-MS) greatly improved both the sensitivity and specificity of analysis, achieving both accuracy, speed, and advantages of convenience (Zhang et al., 2018).

Ion mobility spectroscopy mass spectroscopy (IMS-MS) identifies ions by measuring their mobility. The constant electric field in IMS-MS drives ions against the inert gas to fly over the drift tube, and the ions with high mobility first pass through the drift tube. Because the flight speed of ions is affected by their own cross-sectional area, they can also identify isotopic ions with different structures. By adjusting the length of IMS-MS drift tube or the flow rate of reverse inert gas, IMS-MS can obtain different resolutions for different scenes (Delafield et al., 2022; Eldrid & Thalassinos, 2020). Since the IMS system does not need to operate in a vacuum environment, its entire device is relatively small.
and more convenient to use. In addition, IMS-MS can provide rapid analysis at the millisecond level. IMS-MS has become an attractive technology for separating and detecting metabolites with similar structures (Burnum-Johnson et al., 2019).

**Mass spectrometry imaging (MSI)**

MSI is a two-dimensional analysis method that allows MSI to determine and visualize the spatial distribution of intact molecules in a tissue or tissue section based on the molecular weight or m/z value of a specific chemical component without the need for extraction steps, purification, and separation (Fig. 2). In MSI, different layers of the sample surface are scraped off using laser beam irradiation on the instrument platform for analysis. By collecting multiple spectra at specific coordinates on the sample surface, and compiling all spectra into one data, their spatial distribution can be described as an image (Yoshimura et al., 2016). The ionization methods of MSI usually include MALDI, secondary ion mass spectrometry (SIMS), and desorption electrospray ionization (DESI) (Fig. 2). Both MALDI and SIMS are performed on samples placed in a vacuum, which provides analysis with a sub-micron resolution scale (Pacholski & Winograd, 1999). Both MALDI and SIMS imaging instruments are more expensive, with debris or matrix interference in the SIMS and MALDI process coupled with sample preparation that results in slow analysis. Therefore, it is reasonable to use them when high-resolution spatial resolution is required (Burrell, Earnshaw & Cranch, 2007). Conversely, the spatial resolution required in food imaging applications is often lower, so less expensive methods (such as immuno-staining methods) are often used (Borges et al., 2006; Gorji et al., 2005).

In recent years, the emerging (Desorption electrospray ionization MS staining methods) are often used (Borges et al., 2006; Gorji et al., 2005). Conversely, the spatial resolution required in food imaging applications is often lower, so less expensive methods (such as immuno-staining methods) are often used (Borges et al., 2006; Gorji et al., 2005). In MSI-MSI has solved the problems of analysis speed and sample pretreatment, and its appropriate resolution has gradually become the first choice in the analysis of food metabolites (Cledinnen, Monge & Fernández, 2017).

Matrix-assisted laser desorption/ionization MS imaging (MALDI-MSI) is a non-targeted two-dimensional analysis method under vacuum conditions, which can directly and widely detect all ionized intact molecules in tissue sections. The spatial resolution of MALDI-MSI is between 5 and 200 μm, which is sufficient to obtain the molecular distribution of a single cell (Morisasa et al., 2019). MALDI-MSI can be performed on most food-related matrices, but fresh samples unaffected by chemicals should be preferred. Repeated freeze–thaw cycles should be avoided to prevent tissue degradation (Schwartz, Reyer & Caprioli, 2003). Remarkably, the fixation of the sample should be avoided to cause ionization of the embedding material to affect the detection. MALDI-MSI usually requires tissue sections of 5–20 μm thickness. In the case of analyzing high molecular weight molecules (3–21 kDa), thinner tissue sections of 2–5 μm thickness are recommended (Goodwin, Pennington & Pitt, 2008). Plant tissue can be analyzed using thicker tissue sections of 20–50 μm (Peukert et al., 2012; Yoshimura et al., 2012). Sections require tissue washing to remove salts that affect the spectral quality (Andersson et al., 2008; Deutskens, Yang & Caprioli, 2011; Franck et al., 2010; Groseclose et al., 2007), followed by tissue digestion and derivatization, which increase metabolites detection and ionization rates (Aerni, Cornett & Caprioli, 2006; Lemaire et al., 2007; Morita et al., 2010; Toue et al., 2014). In MALDI-MSI detection, the matrix ionized absorption laser beam energy uniformly applied to the tissue section is used to protect the intact molecules in the tissue from damage. The matrix used for MALDI-MSI usually includes sinapinic acid (SA), 3,5-dimethoxy-4-hydroxycinnamic acid (CHCA), DHB, and 9-aminoacridine (9-AA) (Karas & Hillenkamp, 1988; Kaletas et al., 2009).

SIMS imaging is an ultra-high vacuum technique that uses an ion beam to strike a detection target, generating and using secondary ions to image solid surfaces, during the bombardment of the ion beam, the chemical bonds and structures of some molecules may be destroyed, resulting in the introduction of impurity ions in the detection process to interfere with the accuracy (Hand, Ranasinghe, & Cooks, 1993). This detection is limited to the uppermost layer of the sample, the primary ion beam can be focused to a spot of tens of nanometers with a resolution of 5–200 μm, and its spectral characteristics are mainly used for the targeted detection of elemental ions and small fragment ions (Fletcher, 2009). In the later development, SIMS imaging has become the mainstream technology in detection through the combination of TOF. TOF-SIMS imaging with high ion utilization, high mass resolution, and good sensitivity can obtain the full spectrum of the mass range with one ion pulse, high ion utilization, high mass resolution, and good sensitivity. In principle, the detection mass range of TOF-SIMS imaging can be unlimited by controlling the rered frequency of the pulses (Amaral et al., 1998).

DESI-MSI is developed by Takáts et al. (2004) compared to technologies such as MALDI and SIMS, which requires more arbitrary environmental conditions, and does not require harsh vacuum conditions, and prior sample processing. DESI-MSI can analyze solid, liquid, frozen, and gaseous samples in multiple states, while MALDI and SIMS are limited to solid samples analysis (DeMian et al., 2007). Since DESI-MSI does not require the addition of a matrix to the sample, there will be no matrix-related ions that are likely to interfere with sample detection. In DESI-MSI, to realize inhalation detection, pneumatically assisted electrosprays charged droplets onto the surface of the sample to be tested, then the spray droplets collide with a solvent film and splash secondary ions containing dissolved analytes into the air for detection (Cooks et al., 2006; Musah et al., 2012). The resolution of DESI-MSI is usually between 50 and 200 μm (Laskin et al., 2012).

**Nuclear magnetic resonance (NMR)**

NMR is a technology that uses radio frequency pulses to excite atomic nuclei with zero spin quantum number, causing the nuclear resonance to absorb energy and emit radio signals at a specific frequency, and then use a receiver to receive the signal and obtain data through computer processing, and is one of the most used analytical tools in metabolomics fingerprint and analysis (Marcone et al., 2013; Wishart, 2019; Yu et al., 2020). In the industrial production process of food, the producer needs to extract a certain percentage of products from each batch for food testing. For traditional invasive detection methods, such as probe or profile detection, food becomes incomplete after detection and is discarded. In order to ensure that the possibility of testing is appropriate, a considerable number of products need to be carried out. This type of invasive testing can be very wasteful when there are many production batches or when food ingredients are more expensive. NMR has intense penetration and is convenient for heterogeneous and complex food systems. It is also commonly used on solid and liquid substrates as a non-destructive approach well suited for the recovery of analyzed food samples compared MS techniques (Cao et al., 2018; Marcone et al., 2013). At the same time, it can monitor a variety of analytes/markers, providing unique structural information about metabolites, especially considering its strong structural elucidation power when coupled to two dimensional NMR (2D NMR) techniques even from crude matrix e.g., 2D 1H–1H correlation spectroscopy (COSY), Heteronuclear single Quantum Coherence (HSQC) and Heteronuclear Multiple Bond Correlations (HMBC) (Mahrous & Farag, 2015). Particularly, NMR based on isotopes is developed and applied to food analysis, mainly using hydrogen spectrum (1H NMR), carbon spectrum (13C NMR), or phosphorus spectrum (31P NMR), among which 1H NMR is the most widely used (Cao et al., 2021).

Hydrogen NMR spectrum (1H NMR) is a technology that uses magnetic nuclei with different energy levels in the static magnetic field to irradiate samples with electromagnetic waves of specific frequency. When electromagnetic wave energy is equal to energy level difference, the nuclei absorbs electromagnetic energy transition to generate resonance absorption signal and records the spectrum automatically using the recorder. 1H NMR spectroscopy is not only high throughput, of good
reproducibility, easy to operate, and rich in structural information, but also can quantitatively identify and detect metabolic components. These advantages result in application like food composition analysis, adulteration test, and geographical traceability. However, NMR is relatively sophisticated and has many parameters, which requires personnel with relevant professional knowledge to operate and then greatly limits its application coverage in industry. In addition, NMR detection time is long and the price is relatively expensive, which also brings certain restrictions on use.

Indeed, quantitative NMR can provide quantification of all resolved peaks in spectra using one spiked standard and contrary to MS in which response factor limit the application of one standard for quantification of all peaks (Farag et al., 2019). Special acquisition parameters should be considered i.e., relaxation delay, to ensure full relaxation of targeted nuclei to be quantitative. Although sensitivity reasons make the $^1$H nucleus the most utilized nucleus, other nuclei such as $^{13}$C have also recently gained popularity for their ability to solve specific problems in food science. The $^{13}$C NMR is the same as that of $^1$H, with the chemical shift range of $^{13}$C spectrum is 20–30 times that of $^1$H spectrum. Consequently, $^{13}$C spectrum has more information than $^1$H spectrum, in addition to its the ability to resolve overlapped peaks in $^1$H NMR spectra along the carbon dimension (Truzzi et al., 2021). The low sensitivity towards $^{13}$C detection can be overcome by using two dimensional NMR experiments such as HSQC and HMBC in which carbon resonance is acquired from the proton channel (Mahrous & Farag, 2015). In recent years, $^{31}$P NMR has become a tool for analyzing food and studying factors that affect food quality because of its selectivity to phosphorus-containing compounds such as nucleotides, coupled with the increasing sensitivity and analytical power of modern NMR spectrometers. It is widely used to detect low levels of content of monoglycerides and diglycerides in milk and dairy products, meat, fruits, and vegetables, cereals, lipids and oils. Quantitative $^{31}$P NMR spectra can be extended to quantify the components of functional groups with unstable protons (Spyros & Dais, 2000).

Fig. 3. The principle of NIR variety identification. First, it is necessary to use NIR to take a certain number of samples of each variety (such as 10 grapes of three different varieties of S1, S2, and S3) for spectral identification, and then calculate the average of 10 pieces of data for each of the three varieties to establish the model data of each variety is used for feature location (feature peaks). After the model data is established, NIR is used to determine the spectral data of the unknown variety samples, and chemometric tool is compared with the model data to find the most similar model data, and then the variety of the sample to be tested can be determined with better accuracy.
Near infrared spectroscopy (NIR)

NIR is a convenient and fast non-destructive testing technique that requires little tedious sample preparation, and its detection range is usually in the 780–2500 nm electromagnetic spectrum (Nicolai et al., 2007). It scans the near-infrared spectrum of the sample to obtain the characteristic information of hydrogen-containing groups (OH, NH, CH) in the organic matter, and compares it with the established calibration model to predict the organic matter in the sample (Li et al., 2017; Pojić & Mastilović, 2013). However, the bands of these hydrogen-containing groups are usually very wide, and the chemical bonds are numerous and complex in structure, making it difficult to impart certain characteristics to specific chemical components, such as in case of NMR. The development of chemometric tools has further aided NIR technology to be more accurately applied towards the prediction and analysis of food, and has become an important part of auxiliary NIR (Qu et al., 2015). These methods usually include partial least squares (PLS), linear discriminant analysis (LDA), principal component analysis (PCA), etc. (Cen & He, 2007). By establishing standard data for model samples, and combining chemometrics models for comparative analysis. NIR can be used to evaluate phenols, terpenes, alkaloids, carbohydrates, sulfur compounds, and other secondary metabolites in food. And it can be widely used in food adulteration, food classification, and identification of food varieties and origins (Fig. 3). With the development and application of NIR technology, portable NIR was also developed and appears to be more suited for applications in the food industry. Such portable and the cheaper device is more popular for researchers than desktop NIR and to expand upon the application of NIR in food industry. For a comprehensive review on IR applications in food analysis, please refer to the study of Nagy, Wang & Farag (2022).

Applications of metabolomics in food analysis

Traditional analysis techniques usually only analyse the macro-nutrients of food, such as sugars, lipids or proteins (Liang et al., 2022). The components within food products are complex and highly susceptible to transformation. The analysis of macro-nutrients is no longer sufficient to meet the needs of the current food industry.

**Fig. 4.** Comparison of the application of major metabolomics techniques in the detection of food components highlighting their advantages and or limitations.
Metabolomics techniques enable the analysis of changes in composition during food processing and storage, this is highly beneficial for quality control in the processing or storage of food products (Cao et al., 2021; Zhao et al., 2019). In addition, MSI-like imaging techniques can provide a good insight into the spatial distribution of metabolites in food. This facilitates the analysis of the nutritional profile of different parts of the food and provides principles and mechanisms for determining the functionality of the food. The use of metabolomics techniques allows for the rapid quantification or localisation of certain types of substances in foods, which is a very convenient method in food composition studies. Based on this same principle, toxins, hormones, pesticides or drug residues in food can be identified for the purpose of food safety control (Yan et al., 2022). Flavour components of food products are also a popular research topic. Most flavour substances are usually secondary metabolites of food components and are characterised by their small molecular weight, low concentration and volatility. By using metabolomics methods, the composition and concentration of these volatile substances can be well analysed, so that the production and processing of food products can be optimised to obtain better flavoured products (Liu et al., 2019; Farghal et al., 2022). It is also possible to analyse the main volatile flavour substances in food products and provide ideas for the development of natural food additives.

Falsification of origin and food adulteration is another major problem in the food industry. The high degree of consistency between substances often makes it difficult to distinguish such subtle differences using conventional analytical methods. Different substances have different metabolite compositions and concentrations from one another, and each variety of food can be fingerprinted independently using its own metabolite properties. By using this method, it is possible to directly compare the differences between the metabolite profiles of the food to be tested and the target food, for the purposes of adulteration identification, food classification and food traceability, and even to determine when the food was produced. The application of chemometric or statistical tools helps to compare and analyse the differences between the normal model and the substance under test to determine if differences exist. In addition, traditional food traceability tools often use blockchain technology, barcodes or traceable packaging to prove the origin of a food product, but with the growth of the transportation industry, the same batch of food ingredients may come from multiple regions of the world (Assis et al., 2022). The mixture of food properties from multiple regions makes it difficult to clearly trace multiple sources with traditional traceability tools, in which case the creation of individual source properties through the use of metabolomics of the database. In this case, the use of metabolomics to create a database of component

### Table 1

| Platform         | Sample                     | Result/Objective                                                                 | References                  |
|------------------|----------------------------|---------------------------------------------------------------------------------|----------------------------|
| LC-MS            | Legumes                    | Be able to differentiate between lentils, white beans and chickpeas.            | Llorach et al. (2019)      |
| LC-MS/MS         | Almond                     | It can simultaneously determine various aflatoxin in almond. Without purification, high sensitivity (0.34–0.5 μg/kg) | Ouakhssase et al. (2021)   |
| GC-MS            | Black tea                  | To monitor the dynamic changes of metabolites during the processing.            | Wu et al. (2019)           |
| GC-MS            | Saffron                    | Ketosiphorone and safranal identified as freshness versus and ageing marker. Safranal was identified as a marker to identify saffron adulteration. | Farag et al. (2020)        |
| GC/GC/TOF-MS     | Rice                       | Non targeted analysis of volatile metabolic compounds released during rice cooking. | Daygon et al. (2016)       |
| HPLC-QTOF-MS/MS  | Plantago depressa          | Effective exploration of polyphenol spectrum of complex natural products.       | Xu et al. (2020)           |
| UPLC-Q/TOF-MS    | Fish sauce                 | 46 metabolites were identified as the key chemical components of fish sauce flavor. | Wang et al. (2019)         |
| UPLC-QTOF/MALDI-MS | Pomegranate juice          | It can detect 1% apple juice and grape juice mixed in pomegranate juice.        | Dasekani et al. (2019)     |
| UPLC-ESI-MS/MS   | Pork                       | Determine the source of pork by using more than 100 lipid metabolites.          | Mi et al. (2019)           |
| DESI-MSI 3D imaging | Beef                      | Beef tissue can be directly tested for steroid ester injections.                | De Rijke et al. (2013)     |
| DESI-MSI         | Potato                     | Clarification of the distribution of the potato toxins α-chacomin and α-lonokin, based on m/z 852 and m/z 868. | Cabral et al. (2013)       |
| ESI/MS/MS imaging | Coffee bean                | Simultaneous determination of pesticides and mycotoxins in green coffee beans. | Reichert et al. (2018)     |
| TOF-SIMS Imaging | Chicken                   | Higher concentrations of vitamin E were found in the fat of chickens fed soybean oil and flaxseed oil. | Marzec et al. (2016)      |
| MALDI-MSI        | Chocolate                  | Differentiate between different chocolate producers and cocoa varieties.       | De Oliveira et al. (2018)  |
| MALDI-MSI        | Strawberry                 | The distribution of flavan-3-ols, organic acids, anthocyanins and ellagic glycosides in strawberry was found. | Enomoto et al. (2020); Enomoto (2021) |
| MALDI-MSI        | Pork                       | Phosphatidylcarnosine is most widely distributed in the spine and lumbar muscles. | Enomoto et al. (2021)     |
| MALDI-MSI        | Persimmon epimedium        | During the drying, the concentration of vitamin A1 increased, the vitamins B1 and B6 unchanged. | Shikano et al. (2020)     |
| MALDI-MSI        | Rice                       | The molecular types of lysophosphatidylcholine and the distribution of unsaturated fatty acids in rice were explored, and it was found that the content of lysophosphatidylcholine would affect the flavor of rice wine. | Zaima et al. (2014)       |
| NMR              | Chicken breast             | Differentiation of Korean Chicken Breast with Free Amino Acids.                | Kim, Ko & Jo (2021)       |
| H NMR            | Celery                     | Identification of the origin of celery using amino acids, organic acids and manniitol. | Lau et al. (2020)          |
| H NMR            | Milk powder                | Use of low molecular weight metabolites to differentiate between milk powder types. | Zhao et al. (2017)        |
| H NMR            | Olive oils                 | Differentiation of olive oils from different regions by fatty acid.            | Ūn & Ok (2018)            |
| H NMR            | Rice                       | Comparison of multiple metabolite levels to distinguish the origin of Chinese rice. | Huo et al. (2017)         |
| H NMR            | Olive oil                  | Fatty acyl is an important metabolite marker that can aid to determine shelf life of olive oil. | Ūn & Ok (2018)            |
| H NMR            | Duck breast                | Aserine, aspartic acid, and carnosine were correlated with quality, and nicotinamide with cooking degree. | Wang et al. (2020)        |
| 13C NMR          | Essential oils             | Identification of impurities such as vegetable oil.                           | Truzzi et al. (2021)      |
| FT-IR and NMR    | Saffron                    | Proposed some metabolomics markers for product shelf life, authenticity and quality of saffron. | Consomni et al. (2016)    |
| NIR              | Honey                      | Determination of hydroxybenzoic acid in honey.                                | Tahir et al. (2020)       |
| NIR              | Fruits                     | Qualitative and quantitative analysis of anthocyanins.                        | Teng et al. (2020)        |
| NIR              | Cantaloupe                 | Distinguish different varieties of cantaloupe with 100 % accuracy.            | Nemeth et al. (2019)      |
| NIR              | Truffle                    | Identification of adulteration of cheap truffle raw materials.               | Segelke et al. (2020)     |
| NIR              | Hungarian honey            | Identifying the botanical origin of Hungarian honey with 99 % accuracy.        | Bodor et al. (2021)       |
| NIR              | Beef                       | 100 % probability of detecting the presence of adulterants such as pork, fat and offal. | Morris & Sun (2013)       |
| NIR              | Rice                       | Capable of detecting more than 5 % of other rice.                             | Liu et al. (2020)         |
characteristics for each source can be a good solution. In this process, it is also necessary to use chemometrics to visualise the data and avoid over-fitting models. More awareness of model validation has been reported in such studies, especially in supervised data analysis (e.g. OPLS and PLS). This study by Biancolillo & Marini (2018) can be as the guidelines on chemometric modelling of spectroscopic datasets. A recent update on metabolomics studies in Meat Quality Analysis and Authentication has been made (Zhang et al., 2021). Currently, with improved analytical methods, classification and traceability can be achieved with an accuracy of over 95 %. Metabolomics has been applied to the food industry as a powerful analytical tool. Some works have been done using metabolomics techniques for food composition analysis, food adulteration and food traceability (Table 1). It can be argued that the use of metabolomics tools optimises food processing and storage techniques and facilitates the development of the food industry. The introduction of food metabolite profiling has accelerated the identification of food adulteration and improved the accuracy of food traceability.

PCA, principal component analysis; PLS-DA, partial least squares-discriminant analysis; ANOVA, analysis of variance; LDA, linear discriminant analysis; SVM, support vector machines.

Future trends and applications

Metabolomics has become a powerful tool in food research such as food analysis, food safety testing, and food traceability. A summary of metabolomics new applications in food analysis with future trends is presented in Fig. 5. GC/MS is a powerful used platform to unravel volatiles behind unique food aroma, which are mainly generated during processing such as roasting in coffee, or fermentation in dairy products. Other analytical platforms, including NMR and LC/MS appears more suited for the profiling of non-volatile polar phytonutrients such as phenolics, glycosides to more contribute to food health benefits warranting for the employment of comparative metabolomics approaches to assess food metabolome more holistically. Compared to hyphenated techniques, direct spectroscopic measurement i.e., NIR appears more suited for these industrial food applications especially for monitoring consistency among food batches as routinely performed in drug analysis aided by chemometric tools. In recent years, with the development and popularization of MSI, portable NIR and other related analysis and detection technologies and instruments has facilitated metabolomics applications as industrial level. However, the accuracy and sensitivity of metabolomics-related technologies need to be improved. Many technologies are difficult to distinguish substances of the same masses or isomers, in addition to difficulty in detection of some metabolites with low content as in contaminants e.g., aflatoxins and small molecular weight. The database of food-related metabolites is not comprehensive enough, and the data processing technology and statistical methods have not been unified and standard initiatives can be developed to allow for comparison among different experimental setups and devices. In addition, metabolomics research can typically only analyze the output chemical, and it is difficult to characterize the production pathways and action mechanisms of metabolites by metabolomics-related technologies. For such goal, it can be combined with other omics technologies such as genomics, proteomics and other omics technologies for joint analysis.

In the future, as metabolomics develops more efficiently and comprehensive analysis coverage of food-related metabolites in the database, it will be more conducive to elucidate the functions and mechanisms of related metabolites in food either raw or in response to different processing methods such as fermentation, roasting, sprouting etc. Application of metabolomics to optimize for such food processes can help ensure best parameters leading to desired chemical output using such untargeted analyses. Compared to the extensive reports on the application of metabolomics in food of plant origin classification and

Fig. 5. A layout of metabolomics novel trends and future perspective in food analysis.
origin traceability, animal based products especially fish and sea type are much less explored and needs future attention especially considering their different matrix type from that of plant based food. It seems that it is difficult for a single food metabolism analysis technology to provide completely reliable analysis results. Spectral fusion technology can combine multiple data sources, and comprehensively analyze the changes of trace components in food through a combination of multiple data changes and calculations, which can make the analysis results more reliable. In addition, the computing power and efficiency of traditional computers based on electronic computing are relatively low, and the mature application of quantum computing in the future may speed up reliable. In addition, the computing power and efficiency of traditional technology.

**Declaration of Competing Interest**

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

**Data availability**

Data will be made available on request.

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**References**

Aerni, H. R., Cornett, D. S., & Caprioli, R. M. (2006). Automated acoustic matrix deposition for MALDI sample preparation. Analytical Chemistry, 78(3), 827–834. https://doi.org/10.1021/ac051534v

Amaral, A., Galle, P., Escraia, F., Cossonnet, C., Henge-Napolé, M. H., Ansoberio, E., & Zhang, L. (1998). The use of SIMS for uranium localization in biological research. Journal of Alloys and Compounds, 237, 19–24. https://doi.org/10.1016/S0925-8388(98)00164-9

Andersson, M., Groescole, M. R., Deutch, A. Y., & Caprioli, R. M. (2008). Imaging mass spectrometry of proteins and peptides: 3D volume reconstruction. Nature Methods, 5(1), 101–108. https://doi.org/10.1038/nmeth1145

Aste, M. T. Q. M., Lucas, M. R., & Rainho, M. J. M. (2022). A meta-analysis on the trust in agri-food supply chains. Food Frontiers, 3, 413–427. https://doi.org/10.1002/frz.2137

Biancolillo, A., & Marinis, F. (2018). Chemometric methods for spectroscopy-based pharmaceutical analysis. Frontiers in Chemistry, 6, 576. https://doi.org/10.3390/fchem.2018.00076

Bodor, Z., Kovacs, Z., Benedek, C., Hikta, G., & Behling, H. (2021). Origin identification of hungarian honey using meliponindolysis, physicochemical analysis, and infrared spectrospe. Molecules, 26(23), 7274. https://doi.org/10.3390/molecules26237274

Borges, J. P., Jaunené, A., Brüel, C., Culierrier, R., Barre, A., Didier, A., & Rouge, P. (2006). The lipid transfer protein (LTP) essentially concentrate in the skin of Rosaceae fruits as cell surface exposed allergens. Plant Physiology and Biochemistry, 44(10), 535–542. https://doi.org/10.1016/j.plaphy.2006.09.018

Burnum-Johnson, K. E., Zheng, X., Dodd, J. N., Ash, J., Fourches, D., Nicola, C. D., Wendler, J. P., Metz, T. O., Waters, K. M., Jansson, J. K., Smith, R. D., & Baker, E. S. (2019). Ion mobility spectrometry and the omics: Distinguishing isomers, molecular classes and contaminant ions in complex samples. Trends in Analytical Chemistry, 116, 292–299. https://doi.org/10.1016/j.trac.2019.04.022

Burrell, M., Earnshaw, C., & Grench, M. (2007). Imaging matrix assisted laser desorption ionization mass spectrometry: A technique to map plant metabolites within tissues at high spatial resolution. Journal of Experimental Botany, 58(4), 757–763. https://doi.org/10.1093/jxb/erm139

Cabral, E. C., Mirelli, M. F., Perez, C. J., & Iba, D. R. (2013). Blotting assisted by heating and solvent extraction for DESI-MS imaging. Journal of the American Society for Mass Spectrometry, 24(6), 956–965. https://doi.org/10.1016/j.jasms.2013.01.016-y

Cao, H., Sarooghi, D., Karagad, A., Dianconese, Z., Zoccatelli, G., Conte-Junior, C. A., González-Aguilar, G. A., Ou, J., Bui, W., Zamaroli, C. M., Fretzis, L. A. P., Shipigelan, A., Campelo, P. H., Capanoglu, E., Hii, C. L., Jafari, S. M., Qi, Y., Liao, P., Wang, M., Zou, L., Bourke, P., Simal-Gandara, J., & Xiao, J. (2021). Available technologies on improving the stability of polyphenols in food processing. Food Frontiers, 2, 109–139. https://doi.org/10.1002/frz.65
