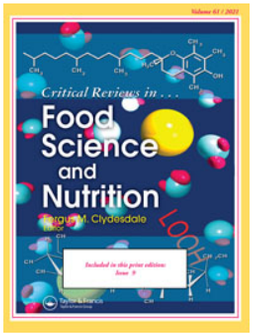

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

Recent advances in the application of metabolomics for food safety control and food quality analyses

Shubo Li, Yufeng Tian, Pingyingzi Jiang, Ying Lin, Xiaoling Liu & Hongshun Yang

To cite this article: Shubo Li, Yufeng Tian, Pingyingzi Jiang, Ying Lin, Xiaoling Liu & Hongshun Yang (2021) Recent advances in the application of metabolomics for food safety control and food quality analyses, Critical Reviews in Food Science and Nutrition, 61:9, 1448-1469, DOI: 10.1080/10408398.2020.1761287

To link to this article: https://doi.org/10.1080/10408398.2020.1761287

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
2021, VOL. 61, NO. 9, 1448–1469
https://doi.org/10.1080/10408398.2020.1761287

Taylor & Francis
Taylor & Francis Group

REVIEW

Recent advances in the application of metabolomics for food safety control and food quality analyses

Shubo Li[a], Yufeng Tian[a], Pingyingzi Jiang[a], Ying Lin[a], Xiaoling Liu[a], and Hongshun Yang[b]

[a]College of Light Industry and Food Engineering, Guangxi University, Nanning, China; [b]Department of Food Science & Technology, National University of Singapore, Singapore, Singapore

ABSTRACT

As one of the omics fields, metabolomics has unique advantages in facilitating the understanding of physiological and pathological activities in biology, physiology, pathology, and food science. In this review, based on developments in analytical chemistry tools, cheminformatics, and bioinformatics methods, we highlight the current applications of metabolomics in food safety, food authenticity and quality, and food traceability. Additionally, the combined use of metabolomics with other omics techniques for "foodomics" is comprehensively described. Finally, the latest developments and advances, practical challenges and limitations, and requirements related to the application of metabolomics are critically discussed, providing new insight into the application of metabolomics in food analysis.

KEYWORDS

Food analysis; food safety; mass spectrometry; metabolomics; nuclear magnetic resonance

Introduction

Food safety is being challenged by the global scale of food supply chains (Stewart et al. 2018), and most countries have created laws and regulations to guarantee food safety. However, with the globalization of food production and distribution, there are several risks of food pollution caused by environmental and anthropogenic sources (Akrami-Mohajeri et al. 2018, Derakhshan et al. 2018), including microbial organisms, organic and inorganic chemical pollutants, drugs, and physical hazards. Foodborne pathogens have become one of the major concerns in the food sector, but there has been no reduction in the incidence of foodborne diseases despite of advances in analytical tools and establishments of food laws (Havelaar et al. 2015). More importantly, with consumers making better-informed decisions on food products, there is considerable attention given to the biochemical composition of foods, the mechanisms by which they are affected during processing, transportation, and storage, and to methods for improving health through functional foods, functional ingredients, and nutraceuticals (Stewart et al. 2018). Therefore, endless efforts are required to improve the efficiency of current regulatory systems for ensuring public safety. In this manner, more sensitive, robust, efficient, and cost-effective analytical methods should be further developed to ensure the safety, quality, and traceability of foods without compromising nutritional, functional, and sensory characteristics according to legislation and consumers demands (Liu, Wu, and Chan 2019).

Recently, the growing interest on food-related topics, such as safety, sensorial profile, quality, traceability, and compliance with regulatory requirements, has accelerated the development and implementation of analytical techniques and statistical approaches to understand and predict these critical issues (Fallahzadeh et al. 2018). As an emerging field in the biological sciences, metabolomics focuses on small molecule metabolites of a particular system or organism at a specific time point (Raamsdonk et al. 2001). Until recently, metabolomics was an acceptable, reproducible platform technology, and most of the work was focused on molecular epidemiology, toxicity evaluation, functional and nutritional genomics, biomarker discovery and identification, drug exploitation, and personalized health care (Buescher et al. 2015, Doerr 2017). For example, metabolomics has already been successfully applied in various fields of food science, showing promise in maintaining food safety and food quality (Savolainen et al. 2017; Pinu 2016). Here, we briefly review various aspects of recent metabolomics approaches for the evaluation of food safety, food quality and authenticity, and food traceability. Moreover, the latest developments and advances, limitations, future evolution, and applications of metabolomics are also critically discussed, providing valuable insights for further research directions in food analysis.

Brief overview of metabolomics

Principle of metabolomics

With the introduction of high-resolution analytical equipment, especially nuclear magnetic resonance (NMR) and mass spectrometry (MS), sophisticated chromatography, clever isotope labeling strategies, and powerful software (Kamphorst and Lewis 2017), metabolomics has emerged to

CONTACT Hongshun Yang fstynghs@nus.edu.sg Department of Food Science & Technology, National University of Singapore, Singapore 117543, Singapore.

comprehensively analyze small molecules (metabolites with molecular weight <1500 Da) in a biological system, providing mechanistic insights on physiological and pathological activities in distinct scenarios (Patti, Yanes, and Siuzdak 2012). As one of the major omics tools, extensive metabolomics-based approach has achieved great success in addressing a series of issues in biological, biomedical, agricultural, and nutritional research, including drug discovery, disease diagnosis, and plant physiology, among others (Pinu, Goldansaz, et al. 2019).

As for modern food analysis, food metabolomics, which predominantly evaluates food ingredients, food quality, food processing, and food pathogens from farm to table, has been applied in food safety control (in the evaluation of microbial toxins, allergens, anti-nutritionals, foodborne pathogens, pesticides), food quality (organoleptic properties and nutritional value), food authenticity (adulterations and geographic origin), and food traceability (Pinu 2016; Cook and Nightingale 2018).

Aspects of measurement techniques in metabolomics

Analytical technologies of metabolomics

Using different analytical technologies, metabolomics analyzes a mass of compounds that belong to multiple categories with diverse physical and chemical characteristics and in a wide range of concentrations (Zhang, Liu, et al. 2016). Currently, the two main analytical technologies used in metabolomics are NMR and MS (Figure 1).

NMR spectroscopy. NMR spectroscopy is an extremely powerful and rapid analytical platform for elucidating the structure and conformation of both micro- and macromolecules with minimal sample preparation (Bouatra et al. 2013). In general, NMR can offer several unparalleled advantages, including selective isotope detection in complex mixtures, highly reproducible data, *de novo* determination of crucial structural parameters of unknown metabolites, accurate quantification without standards, and in situ analysis of pathway dynamics from cells to whole organisms without any destructive effects (Markley et al. 2017). Therefore, NMR, which provides a "holistic view" of metabolites under specified conditions, is an essential orthogonal analytical approach for metabolomics (Wishart 2019).

However, due to limited availability of quantitative methods and commercial software, NMR has some disadvantages, such as low sensitivity, poor spectral resolution, and poor time resolution (Bingol et al. 2016) (Table 1). Technical advances in high-field magnets, pulse sequences, and cryoprobe technology could effectively enhance the sensitivity and resolution of NMR (Markley et al. 2017). Currently, advances in NMR-related hardware, kit development, pulse sequence design, and software/databases have contributed to faster and more economical NMR-based metabolomics. For example, the pure shift (real-time BIRD) ^{1}H-^{13}C HSQC-SI has been optimized to simultaneously enhance the sensitivity and resolution in HSQC spectra without increasing detection time for typical conditions, such as aqueous solutions

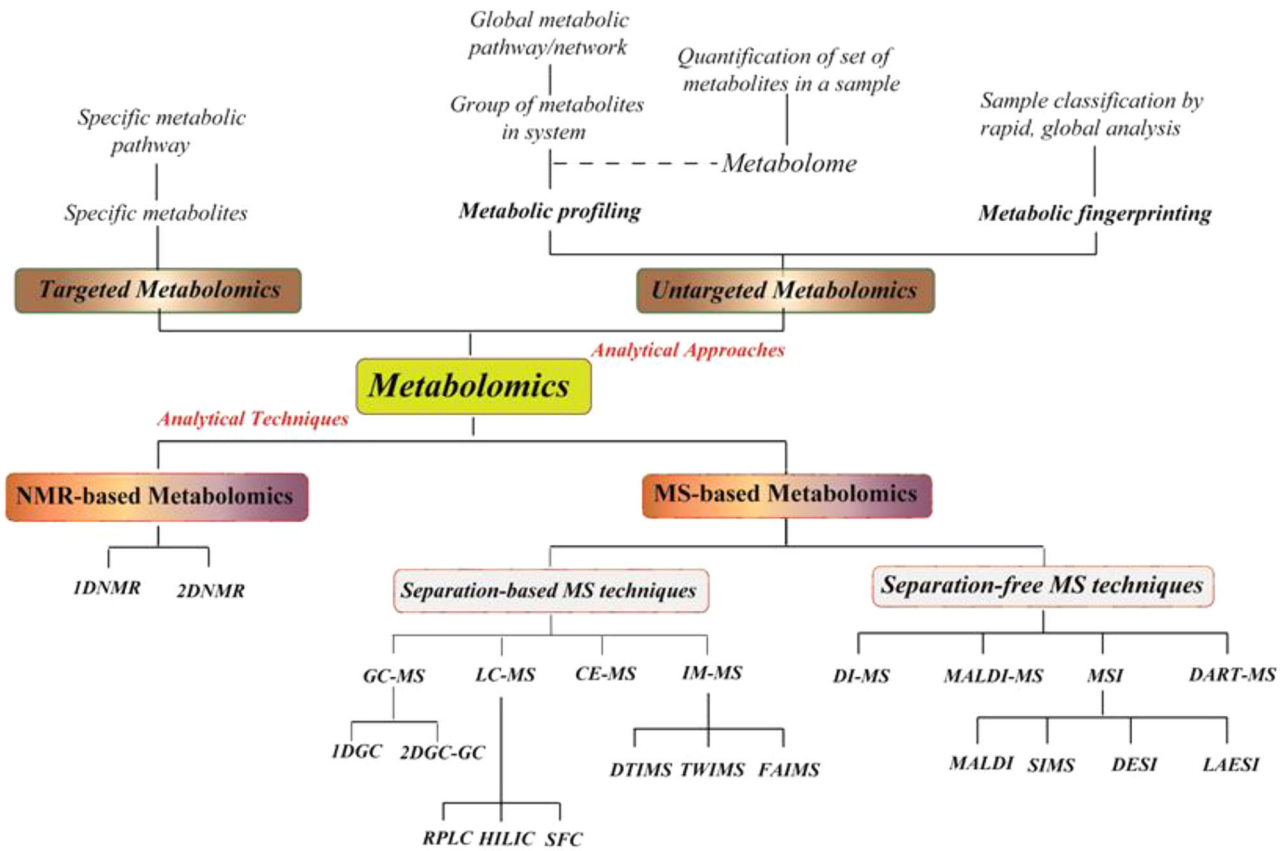

Figure 1. NMR/MS-based technologies used for targeted and untargeted metabolomics (adapted from Ren et al. 2018; Xu et al. 2014).

and high-field apparatus, providing the more effective and accurate way for identifying metabolites (Timári et al. 2019).

Mass spectrometry. Due to the high resolution instruments and compatibility with separation techniques, MS has gradually become the most widely used analytical platform for metabolomics with high sensitivity, speed, and throughput (Emwas et al. 2015). However, MS-based metabolomics has some disadvantages in the detection of trace-level metabolites including high technical variability, massive amounts of data processing, and limited identification and quantification of metabolites (Sampson et al. 2013) (Table 1). Therefore, to improve MS-based metabolomics, it is necessary to improve the analytical tools used in the detection, identification, and quantification of unknown metabolites, create standardized and freely available MS/MS spectral database for identifying unknown compounds, develop software tools to manage and process large quantities of raw metabolomics data, and design chemometric tools to extract information from the data (Wishart et al. 2018).

There have been significant advances in separation-based MS techniques including gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), capillary electrophoresis-mass spectrometry (CE-MS), ion mobility-mass spectrometry (IM-MS), separation-free MS techniques such as direct infusion-mass spectrometry (DI-MS), matrix-assisted laser desorption ionization-mass spectrometry (MALDI-MS), mass spectrometry imaging (MSI), and direct analysis in real time-mass spectrometry (DART-MS) (Ren et al. 2018) (Figure 1). Therefore, MS not only allows chemical information analysis of the extractive by LC-MS or DI-MS, but can also investigate intact tissue or cells and offer certain information on the location of specific metabolites when coupled with imaging methods. Among these imaging methods, LC-MS has become one of the most widely used instruments in metabolomics because of its high sensitivity, specificity, and throughput in data acquisition, and has been applied for both targeted and untargeted metabolic profiling (Cai and Zhu 2019). Twin derivatization-based LC-MS (TD-LC–MS) has significantly improved the sensitivity of LC-MS by 3.6- to 400-fold (Li, Zhang, and Xu 2018), while the chemical isotope labeling (CIL)-based LC-MS/MS has been applied to improve and cover a relatively large amount of metabolites to meet quantification requirements (Jang, Chen, and Rabinowitz 2018). Therefore, the higher selectivity and flexibility, and lower detection limits of MS together with its compatibility with various separation equipment and ability to generate qualitative and quantitative data make MS as an excellent tool in metabolomics applications.

Comparison and combination of MS and NMR for metabolomics. As shown in Table 1, NMR is a robust, quantitative, and reproducible method that requires simple sample preparation protocols and has a nondestructive nature (Dona et al. 2016). However, NMR has high maintenance costs, lacks sensitivity ($\geq 1\,\mu M$), and is limited in data acquisition and data processing (Wishart 2019). Comparatively, MS has higher sensitivity and throughput and can detect metabolites at very low concentrations with a higher resolution ($\sim 10^3$ to 10^4) and dynamic range ($\sim 10^3$ to 10^4) reliability. However, MS has lower absolute quantification (Kostidis et al. 2017) and reproducibility and greater ambiguity of associated spectral signatures (Bingol and Brüschweiler 2014) than NMR. Consequently, NMR and MS have obvious strengths and weaknesses and both uniquely avail metabolomics, but NMR and MS are highly complementary analytical methods (Boiteau et al. 2018).

NMR and MS could be combined in various ways: (1) by physically interfacing NMR and MS hardware, (2) by chemically modifying metabolites through derivatization, (3) by tracing stable isotopes with isotopically labeled metabolites, (4) by using combined cheminformatics techniques for a precise and rapid analysis, or (5) by implementing specific data processing and data mining techniques via multivariate statistical-based methods (Bingol et al. 2015). Therefore, the hybrid MS/NMR approach could significantly increase the coverage of metabolome and improve the accuracy of metabolite identification, thereby enhancing the quality and accuracy of metabolomics data (Bingol 2018).

Table 1. Comparing the main characteristics between NMR and MS-based metabolomics (Wishart 2019; Vignoli et al. 2019).

Technology	NMR	MS
Reproducibility	Excellent reproducibility	Moderate reproducibility
Sensitivity	Poor to moderate sensitivity (μM)	Excellent sensitivity (nM)
Sample preparation	Minimal or/and simple	Complex, generally requiring chromatographic separation and derivatization
Effect on sample	Nondestructive	Destructive
Volume of sample used	0.1–0.5 mL	0.01–0.2 mL
Coverage of metabolites detected	Modest metabolite coverage containing NMR active nuclei (e.g., amino acids, organic acids, keto acids, sugars, lipids and nucleotides)	Extensive metabolite coverage, such as most organic and some inorganic, e.g., amino acids, fatty acids, phosphates, sugars, steroids, nucleotides, sterols, glycerolipids, organic acids and metal ions
Types of experiments	All metabolites above detection limit are observed simultaneously	Several, tailored for specific chemical species
Characteristics of spectra	Spectra are predictable	Spectra not very predictable
Ambiguous/false identification	Inherently quantitative and precise structure determination	Not inherently quantitative and partial structure determination
Types of instruments	Robust instrumentation with easily automated workflow and minimal instrument downtime	Frail instrumentation with difficult-to-automate workflow and frequent instrument downtime
Characteristics of instruments	Very expensive instrumentation, high cost of maintaining, and large instrument footprint	Moderately expensive instrumentation, moderate cost of maintaining, and small instrument footprint
Types of detected results	Small spectral databases, and few software resources	Large spectral databases, and many software resources

Analytical approaches in metabolomics

Based on the coverage of metabolites, the analytical approaches for metabolomics could be further classified as targeted analysis and untargeted analysis (Chaleckis et al. 2019) (Figure 1). Targeted analysis, which is commonly performed with LC-MS/MS and NMR, focuses on a particular group of metabolites that require the identification and quantification of plenty of metabolites within the group and evaluates organismal response with respect to environmental perturbation, xenobiotic exposure, or disease pathology and diagnosis (An, Yamaguchi, and Fukusaki 2017; Cevallos-Cevallos et al. 2009). In contrast, untargeted analysis, which is generally carried out with LC-QTOF-MS/MS and LC-Orbitrap-MS/MS, attempts to simultaneously identify maximum coverage of metabolites in a particular system, obtaining patterns or fingerprints without identifying or quantifying specific compounds (Gallo and Ferranti 2016). Therefore, untargeted analysis, as an effective method for simultaneously determining and accurately quantifying a range of different chemical groups, is more suitable for discovering metabolites that change with respect to manipulation of a biological system (Bloszies and Fiehn 2018), becoming more important in the area of metabolomics. However, targeted and untargeted methods are highly complementary and are applied to identify metabolites that change in abundance between two or more conditions (Alonso, Marsal, and Julià 2015).

In addition, according to the particular objective of analysis and data manipulation, metabolomics research may be (1) informative, which focuses on the identification and quantification of targeted or untargeted metabolites to generate sample intrinsic information (Cruickshank-Quinn et al. 2014); (2) discriminative, which identifies diversities between sample populations without necessarily establishing statistical models or assessing possible pathways (Ismail et al. 2017); or (3) predictive, which creates statistical models to predict class memberships (Cevallos-Cevallos et al. 2009).

Metabolomic analysis workflow: a brief overview

To achieve an accurate measurement of either metabolome or specific metabolites in targeted experiments, many analytical procedures (including sample preparation, instrumental analysis, data treatment and statistical analysis, and data interpretation) are involved in metabolomics research and directly impact the final results and biological interpretations (Lamichhane et al. 2015) (Figure 2). However, food is the complex matrices that involving a broad array of very different components, and even some natural compounds negatively impact the analysis of targeted compounds. Consequently, proper sample treatment methodologies (such as solid phase microextraction, extract and/or concentrate) and suitable analytical techniques are essential to successfully detect contaminants and other interesting compounds in very low amounts for food metabolomics (Markley et al. 2017; Reyes-Garcés and Gionfriddo 2019).

In addition, because of the size and complexity of metabolomics datasets, the identification of metabolites has become one of the foremost bottlenecks in the entire workflow (Li et al. 2013). Research efforts currently focus on improving chemometric methods and chemometric data analytical strategies in relation to data processing from high-throughput datasets in metabolomics (Yi et al. 2016). More importantly, several signals discovered in NMR and MS spectra belong to metabolites that are not present in metabolomics databases (Bingol et al. 2016), and the identification of "unknown" molecules significantly hinders the functional interpretation of high-throughput metabolomics (Gaudêncio and Pereira 2015). Therefore, newly discovered metabolites should be added into metabolomics databases, offering easy access for rapidly identifying a large number of metabolites in various biological conditions. Currently, various tools and resources (almost 50 databases) are available to assist metabolite identification or annotation, providing diverse and often complementary functionalities (Barupal, Fan, and Fiehn 2018; Marco-Ramell et al. 2018).

At present, there are no definitive or standardized operating procedures for every workflow step in metabolomics research. In principle, typical metabolomics research consists of several different parts or sections, which can be classified in four major steps depending on the type of research (untargeted or targeted), sample (solids, liquids, and gas), separation instrument (GC or LC), and inspection instrument (MS or NMR) (Cevallos-Cevallos et al. 2009). Furthermore, some challenges remain in sample preparation, data processing, and data interpretation (Gong et al. 2017), especially when analyzing identical samples using different analytical methods, which influence the data and potentially result in erroneous discovery and contradictory conclusions (Blaženović et al. 2018).

Applications of metabolomics in food analysis

Several food quality and safety issues, including emergence of novel food pathogens, adulteration of food, risk assessment of genetically modified foods, and detection of chemical contaminants/pollutants, have been gaining increased public attention to become one of the most important topics in food analysis (Pinu 2015). With the growing demand for high standards in food quality assurance, metabolomics has been developed to comprehensively assess quality and safety aspects of foods, providing valuable information for the quality and authenticity of food products (Aru et al. 2018) (Table 2).

Metabolomics in food safety control

During the critical steps of production, processing, transport, and storage, foods may be contaminated with a large number of foodborne causative agents, such as pathogens, biotoxins, man-made physical and chemical toxicants (e.g., pesticides and metals), thereby contributing to foodborne illnesses (Rešetar, Pavelić, and Josić 2015). According to the World Health Organization, unsafe foods may cause more than 200 diseases ranging from diarrhea to cancers, in which an estimated 600 million, i.e., almost 10% in the world, fall ill after consuming contaminated food and 420,000 die every year (Havelaar et al. 2015). However, due to the diversity of

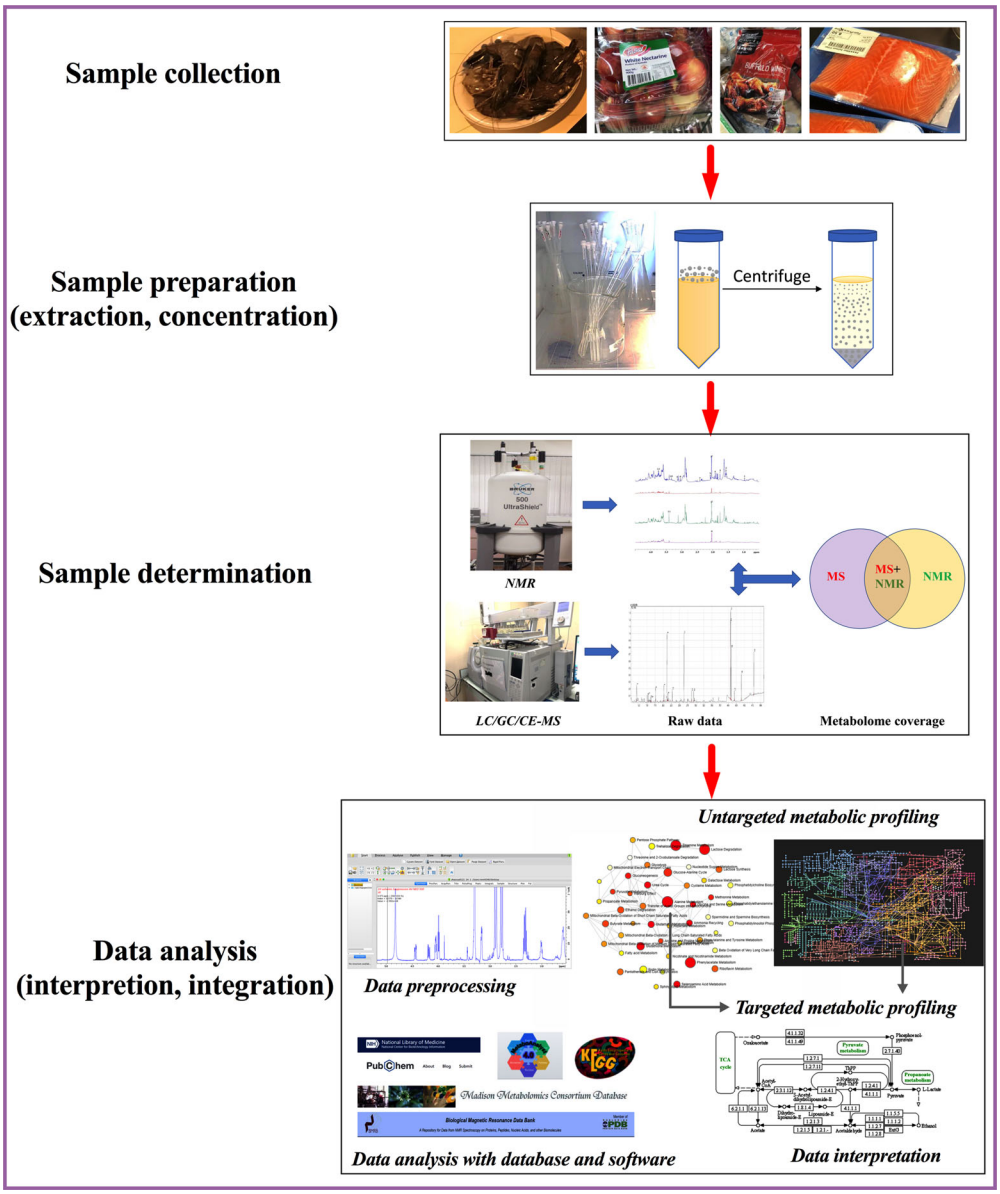

Figure 2. Schematic representation of metabolomics workflow for food analysis, which could be divided into four analytical procedures: sample collection, sample preparation, sample detection, and data analysis (adapted from Cevallos-Cevallos et al. 2009; Blaženović et al. 2018; Xu et al. 2014; Marshall and Powers 2017).

modern food components, the interconnected global food-chain, and the distinction of hazardous matters, traditional detection techniques commonly take weeks and need substantial biochemical analysis or may be inadequate in the detection of biological and chemical contaminants (Rešetar, Pavelić, and Josić 2015). MS/NMR-based metabolomics, which is preferred over standard approaches in modern food analysis, has become the most important technique in the detection and quantification of pathogens, environmental contaminants, banned external compounds, and natural toxins (Castro-Puyana et al. 2017).

Metabolomics in the detection of microbial contamination

Despite exceptional efforts by food handlers, the adaptation mechanisms of pathogens (e.g., spore formation, thermostable bacterial toxins and mycotoxins, and biofilm production) allow the survival and growth of foodborne pathogens that contaminate foods at any stage from food production to consumption (Rešetar, Pavelić, and Josić 2015). More importantly, foodborne pathogens and/or their toxins cannot dramatically change food flavor, texture, or appearance. Consequently, microbial-related contaminants have become the most frequently reported foodborne causative agents (Sugrue et al. 2019), and numerous foodborne outbreaks have highlighted the risks of foodborne diseases, resulting in the development and implementation of technologies and programs (e.g., HACCP systems) to rapidly and sensitively determine food pathogens and biotoxins (Anderson et al. 2014).

Detection of food pathogens and spoilage microorganism contaminants. With the globalization of food supply chain and changes in food consumption patterns, several foodborne pathogens (e.g., *Salmonella* spp., *Listeria monocytogenes*, *Campylobacter jejuni*, and *Shigella* spp.), spoilage microorganisms (such as *Pseudomonas* spp., *Acinetobacter*

Table 2. Summary of some recent metabolomics application for food analysis.

Food matrix	Purpose of analysis	Analytical technique/types	Main results	References
Food safety control				
Tea	The multi-residue determination of pesticides	GC-MS/MS/Targeted	162 pesticides were determined within the range of 70–120% in green tea, oolong tea, black tea and matcha	Saito-Shida, Nemoto, and Teshima (2015)
Wines	The multi-residue determination of pesticides	LC-MS/MS/Targeted	Providing a cost-effective and validated method for determining 172 pesticide residues in 27 commercial Cypriot wines	Christodoulou et al. (2015)
Meat	Determination of veterinary drug residues	HILIC-MS/MS/targeted	Providing a multi-residue/multiclass analytical method for simultaneously measuring 6 aminoglycosides and 70 other veterinary drugs and pharmaceuticals in bovine muscle tissue	Dasenaki, Michali, and Thomaidis (2016)
Food contact materials	Contaminants	UHPLC-ESI-QTOF-MS/ Untargeted/Targeted	Developing a step-by-step strategy for tentatively identifying substances, in which 15 were initially selected for determining in vitro, and 7 were commercially available and then quantitatively determined in vitro	Bengtström et al. (2016)
Shellfish	Analyzing the residue of banned veterinary drugs in shellfish	LC/GC-MS/MS/Targeted	Revealing 3.8 ng/g of chloramphenicol, 16.1–60.1 ng/g of pendimethalin, and 17.0 ng/g of mefenacet in various seafoods, suggesting that 19.1% of samples contained residues of banned veterinary drugs and pesticides	Chang, Chen, and Lin (2016)
Honey	Quantitative determination of pesticides, antibiotics and steroids	UHPLC-HRMS/Targeted	Providing a rapid and quantitative method for determining multi-xenobiotic residues in honey, making 157 compounds quantified in less than 15 min	Li et al. (2016)
Kale, salmon, pork, avocado	Analysis of 65 pesticides and 52 environmental contaminants (PAHs, PCBs, PBDEs, and FRs)	GC-MS/MS/Targeted	Developing a novel commercial EMR-Lipid (enhanced matrix removal of lipids) product with the QuEChERS approach for determining 117 contaminants	Han et al. (2016)
Rice, red pepper, mandarin	Measuring pesticides, including insecticides, fungicides and herbicides with QuEChERS -based methods	GC-MS/MS/Targeted	Developing a quantitative analytical method for determining 113 pesticides in brown rice, red pepper and mandarin orange	Cho et al. (2016)
Baby foods, oranges, tomato	The multi-residue determination of contaminants	UHPLC-HRMS/Targeted	Evaluating the performance for multiclass testing organic contaminants, such as pesticides, veterinary drugs and mycotoxins, using QuEChERS-based approach	Pérez-Ortega et al. (2016)
Wheat	Early detecting 57 mycotoxins according to an ISO 17025 accredited method in wheat	UHPLC-QTOF/untargeted	Developing a simplified workflow for measuring mycotoxins and plant-pathogen cross-talk; Exploiting (bio) monitoring markers for early detection of mycotoxins, and Fusarium disease	Rubert, Righetti, et al. (2017)
Lysogeny broth	Identification of volatile molecules produced by pathogenic bacterium *Klebsiella pneumoniae*	GC × GC-TOFMS/Untargeted	Providing an early-stage volatile metabolomic analysis of bacterial pathogen; Increasing the reported *K. pneumoniae*-associated volatile molecules from 77 to 150	Rees et al. (2017)
Raw coffee	Simultaneous determination of 117 pesticides and 30 mycotoxins	LC-ESI-MS/MS/Untargeted	Developing an acetonitrile based approach for simultaneously extracting and determing pesticides and mycotoxins	Reichert et al. (2018)
Planktonic and air-dried *E. coli*	Comparison of metabolic response between the planktonic and air-dried *E. coli* to electrolyzed water combined with ultrasound	NMR/Untargeted	A total of 43 metabolites were identified in two states of *E. coli*, including amino acids, organic acids, nucleotides and their derivatives	Zhao, Zhao, et al. (2019)
Assessment of food quality and authenticity				
Strawberry	Characterizing the primary metabolites of different strawberry cultivars	GC-MS (IT)/untargeted	Revealing changens in primary metabolites (such as sugars, organic acids and amino acids) between	Akhatou, González-Domínguez, and

(*continued*)

Table 2. Continued.

Food matrix	Purpose of analysis	Analytical technique/types	Main results	References
			three strawberry cultivars grown under different crop conditions,	Fernández-Recamales (2016)
Vinegar	Revealing comprehensive metabolite profile of vinegar	GC-MS; Untargeted	A total of 123 metabolites were determined, in which five volatile metabolites, including acetin, 2-methylpyrazine, 2-acetyl-1-pyroline, 4-anisidine and 1,3-diacetoxypropane, were first identified in vinegar	Pinu et al. (2016)
Meat	Identifying biomarkers for meat quality traits	GC-HRMS/HILIC-HRMS; Untargeted	Meat quality traits and color are impact by processes of energy metabolism, whereas drip loss is linked with lipid metabolism	Welzenbach et al. (2016)
Olive oil	Determination and classification of volatile components of olive oil	GC-HRMS (QTOF)/Untargeted	Developing a statistical model with an accuracy in oil classification of 70%, taking the official established method	Sales et al. (2017)
Honey	Discrimination of honeys with floral origin or bee	NMR/Untargeted	Revealing endogenous diacylglyceryl ether is the vital marker in Apis Mellifera honey	Zuccato et al. (2017)
Citrus fruits	Discrimination of authentic and adulterated citrus fruits/fruit juices	UHPLC-HRMS; LC-MS/MS Untargeted/Targeted	Ratios of limonin glucoside to hesperidin, narirutin, and didymin; narirutin to hesperidin and vicenin-2; didymin to hesperidin and narirutin; and vicenin-2 to didymin, were applied to evaluate the authenticity of Indian citrus fruits/fruit juices	Jandrić et al. (2017)
Fermented vegetable juice	Discriminating strain-dependent fermentation characteristics of lactic acid bacteria (LAB)	NMR/untargeted	Revealing the contribution of low-abundance metabolites, including acetoin, phenyllactic acid, hydroxyphenyllactic acid, glycerophosphocholine, and succinic acid, for homolactic fermentation; but ornithine, tyramine, and γ-aminobutyric acid (GABA) for heterolactic fermentation	Tomita et al. (2017)
Turmeric and curcuminoids	Quality evaluation of raw turmeric from different region	LC-HRMS; LC-QTRAP-MS/MS; Untargeted/Targeted	Developing a targeted curcuminoid profile for evaluating the the quality of turmeric from different regions in China and Myanmar	Jin et al. (2017)
Rice	Discrimination of geographical origins of rice	NMR; Untargeted	A total of 106 rice samples from nine different provinces of China were investigated; Linear Discriminant Analysis was used to extract the variables mainly responsible for separation, such as sucrose, fructose, polyphenols, trigonelline and asparagine	Huo et al. (2017)
Butia spp. (Arecaceae)	Discriminating among *Butia* species and geographical origins of *Butia odorata*	LC-ESI-qTOF-MS; Untargeted	Primary metabolites (such as sugars and organic acids) and specialized metabolites (such as tetrahydroxy-*trans*-stilbene and rutin) were used for species discrimination	Hoffmann et al. (2017)
Lettuce	Revealing metabolite variations between different lettuce varieties	GC $\times$ GC-TOF/MS; UPLC-IMS-QTOF/MS; Untargeted	Sixteen metabolites (such as phenolic acid derivatives, glycosylated flavonoids, and one iridoid) were identified with different levels in leaf and head type lettuces	Yang et al. (2018)
Coffees	Assessment of protected designation of origin for Colombian coffees	UHPLC-(Q)ToF MS/Untargeted	Providing a discrimination model to highlight the most differential compounds, in which thirteen compounds were used to distinguish green coffee according to origin	Ossa et al. (2018)
Carrots	Organic food authentication	LC-MS; Untargeted	Developing a statistical models for predicting organic food authentication with the correct classification rates from 76% to 100% without considering the harvest year	Cubero-Leon, De Rudder, and Maquet (2018)
Goji	Geographical Origin	NMR; Untargeted	Comparing morphological characteristics, sugar and polysaccharide concentration, antioxidant activity, and metabolites profiling of goji among climatic regions	Yao et al. (2018)

Almonds (*Prunus dulcis*)	Discrimination of almonds according to origin and variety	UHPLC-QTOF; Untargeted	Revealing the key marker compounds (including pyranosides, peptides or amino acids) for discrimination	Solsona et al. (2018)
Tea	Characterizing white tea subtypes by distinct chemical compositions	UHPLC-Q-TOF/MS; Untargeted	Developing a model for quality evaluation of diverse grades of Bai Mudan white tea; Identifying 93 metabolites, in which 21 low abundant metabolites were closely associated with tea grade variation	Yue et al. (2019)
Grapes and juices	Classifying volatile profiles of grape juices based on different fungal pathogens	GC-HRMS (TOF)/Untargeted	*B. cinerea* samples were higher in 1,5-dimethylnaphthalene and several unidentified sesquiterpenes, *A. niger* and *A. carbonarius* groups were higher in 2-carboxymethyl-3-hexylmaleic acid anhydride, while *P. expansum* groups were higher in γ- nonalactone and *m*-creso	Schueuermann et al. (2019)
Non-fermented teas	Characterizing primary and secondary metabolites to establish a standard model for classification	GC/LC–MS/Untargeted	Five hundred and ninety unique tea metabolites were identified and quantified in three types of teas; Building a partial least squares discriminant analysis model for classifying non-fermented teas	Zhang et al. (2019)
Saffron	Discrimination of adulterated and authentic saffron, and traceability of geographical origin	UHPLCESI/QTOF-MS; Untargeted	Anthocyanins and glycosidic flavonols were identified as the marker compounds for styles' adulteration; Other flavonoids, protocatechuic aldehyde and isomeric forms of hydroxybenzoic acid were identified as the markers for discrimining PDO vs non PDO saffron	Senizza et al. (2019)
Food traceability in food processing				
Soybean sprouts	Evaluating the relationship between germination and nutritional quality	GC-MS/MS; UHPLC-HRMS; Untargeted	Revealing fifty-eight metabolites, including macromolecular derivatives related to energy production, amino acids, myoinositol metabolites, phytosterols, antioxidants, isoflavones, and soya saponins, associated with health benefits and/or taste quality, increased with germination time	Gu et al. (2017)
Banana	Elucidating the metabolite changes during postharvest senescence	NMR; Untargeted	The principal metabolites, including valine, alanine, aspartic acid, choline, acetate, glucose, malic acid, gallic acid and dopamine, were responsible for postharvest senescence of banana; Salsolinol was generated from the conversion of dopamine, becoming the key marker for the postharvest senescence of banana fruit	Yuan et al. (2017)
Blueberries	Elucidating the impacts of baking, boiling and microwaving on polyphenols in blueberries	UHPLC-MS; Untargeted	Microwaving method was the highest losses of polyphenols when cooking blueberries	Zhao et al. (2017)
Apple fruit	Elucidating apple fruit responses to static and dynamic controlled atmosphere storage	NMR, GC–MS, HS-SPME-GC–MS; Untargeted	A total of 130 metabolites (volatiles and non-volatiles) were identified, in which 95 metabolites were much different between both cultivars, whereas 13 volatile compounds were specific for either GS or RD	Brizzolara et al. (2017)
Broccoli sprouts	Elucidating predominant changes in primary metabolites of broccoli sprouts in response to pre-harvest selenium treatment	GC-MS; Untargeted	The total sulfur concentration was slightly lower and the total selenium concentration was much higher in the selenate-treated sprouts; Serine, melezitose and tyrosine were up-regulated, but succinic acid and citric acid were down-regulated after selenate treatment	Tian et al. (2018)
Lettuce	Discovering early biomarkers to predict browning of fresh-cut lettuce	LC–MS; UPLC-MS-QTOF; Untargeted	The ratio ferulic acid methyl ester/caffeoyl quinic acid could be used to predict browning after 5 days of storage	García, Gil, and Tomas-Barberan (2018)

(*continued*)

Table 2. Continued.

Food matrix	Purpose of analysis	Analytical technique/types	Main results	References
Daylily	Revealing the chemical profile changes with different processing method after harvest	UHPLC-HRMS^n; Untargeted	The quercetin 3-O-rutinoside, 5-O-caffeoylquinic acids were higher in freeze-dried and steam-dried samples	Sun et al. (2018)
Strawberries	Physiological and metabolomic analysis of cold plasma treated fresh-cut strawberries	UPLC-MS; Untargeted	Plasma treatment could effectively improve the biosynthesis of metabolites in flavones and flavonol biosynthesis pathway and phenylpropanoids biosynthesis pathway	Li, Li, et al. (2019)
Organic mung bean	Elucidating the metabolomic changes of mung beans under different energy statuses	NMR; Untargeted	Identifying 42 metabolites, in which oleic, linoleic, and succinic acids and sugars were the featured compounds related to sprouting	Chen et al. (2019)

spp. and *Botrytis* spp.), and novel foodborne pathogens have emerged (Li and Zhu 2017). Traditional detection in laboratories is still mainly dependent on conventional microbiological methods with time-consuming culture-based techniques, molecular techniques, and proteomics-based approaches, which are expensive and labor-intensive (García-Cañas et al. 2012).

Considering the short shelf-life of food products, metabolomics-based methods have been applied to identify a mass of microbial biomarkers involving different levels of microbial contamination, showing a great potential in the rapid and reliable detection of microbial contamination during the early stages (Pinu 2016). For example, proton-transfer-reaction-MS (PTR-MS) was developed to determine microbial volatile organic compounds (MVOCs) with real-time analysis, providing a valuable tool for determining the real-time evolution of volatiles produced by microorganisms in food products (Alothman et al. 2017). In addition to MVOCs, other metabolites have been identified to detect pathogens. For instance, gas chromatography combined with mass spectrometry (GC-MS) has been applied to characterize three important foodborne pathogens, *E. coli* O157:H7, *L. monocytogenes*, and *S. enterica*, in which several potential pathogen-specific biomarkers were identified, leading to the rapid discrimination between clean (without interested pathogens) and contaminated (with interested pathogens) food samples (Jadhav 2019).

Microbial metabolomics may also be applied to elucidate the effect of environmental factors on complex biological systems (Xu et al. 2014; Chen, Zhao, Wu, Liu, et al. 2020). To comprehensively elucidate the inactivation mechanism of electrolyzed water, the metabolic profile changes of *E. coli* and *L. innocua* against electrolyzed water perturbations have been evaluated by multivariate data analysis of NMR data. Overall, 36 metabolic compounds involved in a wide range of biochemical pathways, including nucleotide and amino acid metabolism, energy-associated pathway, osmotic modification, fatty acid biosynthesis, glutamate decarboxylase (GAD) system, and the γ-aminobutyric acid (GABA) shunt have been characterized using NMR spectroscopy (Liu et al. 2017; Liu et al. 2018). Furthermore, following electrolyzed water and ultrasound treatments, the metabolomics variations of *E. coli* ATCC 25922 in planktonic and adherent states have been characterized by NMR spectroscopy. As a result, 43 significant variable metabolites, involving in various amino acids, organic acids, nucleotides and their derivatives, were detected in two states of *E. coli*. Further pathway analyses have shown that alanine, aspartate and glutamate metabolism, glycolysis, pyruvate metabolism, and TCA (tricarboxylic acid cycle) were markedly altered in planktonic culture, but to a less level in air-dried culture, in which some changes in GAD and some shunts involving in mixed acid fermentation and pentose phosphate pathway were found for maintaining metabolic balance (Zhao, Zhao, et al. 2019). Therefore, metabolomics is promising in identifying diverse metabolic shifts in various states of microorganism, providing important information on pathogen behavior.

However, because microbes are significantly different in terms of size, structure, and biochemical properties, it is

difficult to develop a universal method for disposing bacterial cultures during metabolomics analysis (Patejko, Jacyna, and Markuszewski 2017). Furthermore, microbial metabolites are generally complex, and the intracellular and extracellular metabolites are difficult to separate and identify. More importantly, metabolites are rather unstable and easily disturbed during sample handling and processing. Therefore, the current advance in microbial metabolomics is still not ideal, and highly sensitive and reproducible analytical instruments and proper sample treatment protocols are essential to analyze the complexity of metabolites for a successful metabolomics analysis (Markley et al. 2017).

Detection of microbial toxin contaminants. In general, foodborne biotoxins can be classified into two categories: (1) intrinsic foodborne biotoxins, associated with non-zoonotic, non-microbial food adulterations, such as amatoxins, lectins, and phytotoxins (Xu 2017) and (2) extrinsic foodborne biotoxins, in which bacterial endotoxins can be generated via cellular autolysis, external lysis, or phagocytic digestion, but bacterial exotoxins (such as enterotoxins, mycotoxins, neurotoxins, and hemolysins) are directly released into the extracellular space (Stoev 2015). Therefore, several toxins are secreted or released into the extracellular environment during pathogen growth, becoming the second most reported causative agent of foodborne outbreaks. To guarantee food safety, metabolomics has made great efforts in identifying toxins at the earliest stage, where MS could profile metabolites related to microbial contamination (Rodríguez-Carrasco et al. 2013) and NMR could directly determine microbial toxins (Kleigrewe et al. 2012).

However, considering that some natural toxins are extremely toxic (even lethal) at very low concentrations, preparation methods should be further improved to allow for a sensitive and high-throughput detection (Man et al. 2017). For example, prior to the application of HPLC-MS/MS, the multiple antibody immunoaffinity column was used to selectively extract seven toxins, increasing the linear range of the determination and decreasing the detection limit to μg/kg (Zhang, Hu, et al. 2016). Similarly, in the presence of diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*‴-pentaacetic acid (DTPA), detection limits as low as 0.38 fmol for saxitoxin in seafood could be achieved by employing capillary electrophoresis-inductively coupled plasma-MS (CE-ICP-MS) (He et al. 2017). Therefore, even though the maximum acceptable concentrations of some biotoxins in foods have been built, regulatory limits for new toxins in foods will continue to emerge (García-Cañas et al. 2014).

Metabolomics in the detection of chemical contaminants

As human-made substances, xenobiotics (e.g., fungicides, pesticides, antibiotics, and nanomaterials) can enter the food chain through the atmosphere, soil, and water and have adverse effects on living organisms even at low levels (Chen et al. 2018). To control the emergence of hazardous compounds, food safety laws have become a priority to sternly regulate food production, processing, storage, and permissible limits of xenobiotics. Metabolomics could quantitatively and sensitively detect diverse groups of xenobiotics in different food matrices in just one run (Castro-Puyana et al. 2017).

Metabolomics in the detection of veterinary drug residues. Generally, veterinary drug residues are discovered in animal tissue (meat or organs) or animal products (e.g., milk, eggs, etc.), causing side effects in humans upon consumption (Rath et al. 2019). However, there are rigorous policies and regulations on the acceptable levels of veterinary drug residues in foods (Alimentarius 2015). The use of illegal veterinary drugs has become a major concern. To this end, new detecting methods (e.g., metabolomics) have been developed to control the illegitimate use of unknown drugs or mixtures of veterinary drug residues in cattle by tracking changes of metabolites in biological tissues (Kaufmann et al. 2015). For example, in the assistance of a simple generic solid-liquid extraction step and ultrasonic-assisted extraction, liquid chromatography coupled with electrospray ionization and tandem mass spectrometry (LC-ESI-MS/MS) has been successfully used to quantify and identify 115 veterinary drug and pharmaceutical residues in animal-derived foods, such as milk powder, egg, and fish tissue (Dasenaki and Thomaidis 2015).

Furthermore, antibiotics are often used to treat inflammatory diseases or as growth promoters in cattle. Due to the detrimental effects on human health and the latent emergence of antibiotic resistant pathogens, the maximum residue limits (MRLs) of antibiotics in foods are strictly controlled in several nations by specific laws. Sensitive analytical instruments should be developed to supply credible detections of multiple antibiotics in foods. Tandem CE and MS has been applied to determine fluoroquinolones in bovine milk, in which ciprofloxacin, norfloxacin, and ofloxacin were quantified by coupling CE and off-line CE-MALDI-TOF spectrometry (Springer et al. 2015). Similarly, a targeted approach using two-dimensional LC has been successfully used to analyzed the presence of 20 antibiotic residues, including β-lactams, aminoglycosides, amphenicols, quinolones and sulfonamides, in dairy products such as powdered milk, commercial milk, and raw milk (Wang et al. 2001).

Metabolomics in the detection of pesticide residues. The wide use of pesticides or herbicides in agriculture has attracted considerable attention because the presence of residues in foods constitutes a health risk (Raina-Fulton 2014). "QuEChERS" (Quick, Easy, Cheap, Effective, Rugged, and Safe), as a two-step sample enrichment and desalting approach, has been commonly used in coupled with LC or GC for small molecules detection (González-Curbelo et al. 2015), in which the combination between QuEChERS with solid-phase-extraction (SPE) or solid-phase micro-extraction (SPME) has been successfully employed for multi-residue pesticide analyses in foods. For example, the QuEChERS approach was optimized for simultaneously determining mycotoxins and pesticides in coffee. As result, a total of 117 pesticides and 30 mycotoxins were simultaneously determined in raw coffee by LC-ESI-MS/MS without clean-up (Reichert et al. 2018). Similarly, CE-MS/MS could be applied to evaluate the presence of three phenyl urea herbicides,

namely monuron, monolinuron, and diuron, in yam (Daniel and do Lago 2019).

In addition, some banned substances, such as chemical raw materials, dyes, steroid hormones, nitrofurans, and other materials, are often applied in agriculture and food production and frequently detected in tainted foods. An UPLC-MS/MS approach with matrix solid-phase dispersion (MSPD) has been used to analyze 10 steroid hormones in foods of animal origin. The developed approach, which is highly sensitive and reproducible, can rapidly determine trace residues of steroid hormones in complicated food matrices with limits of detection of 0.01 μg/kg (Fan et al. 2014).

Metabolomics in the assessment of food quality and authenticity

Food quality and authenticity are closely related. While the objective of food quality is able to guarantee the appropriate organoleptic and appreciated characteristics of product, food authenticity is linked to the origin of valuable foods that exhibit special characteristics (Montero and Herrero 2019).

Metabolomics in the assessment of food quality

In general, the sensory perception of foodstuffs is a vital aspect of food quality. Because of the complex character of flavor components, several classified approaches, including principal component analysis (PCA), orthogonal projection to latent structures discriminant analysis (OPLS-DA), fisher discriminant analysis (FDA), and other stoichiometry methods, may be tedious and time consuming (Rosso et al. 2018). An automatic preparative approach coupling LC with solid phase extraction (SPE), i.e., HPLC-SPE HPLC, was developed for analyzing the taste-active compounds in sweet and licorice-like bitter tasting aniseed extracts. A total of 256 fractions were obtained, which were further investigated by ultra-high performance liquid chromatography coupling time-of-flight MS (UHPLC-TOF-MS) to identify the responsible sweet and bitter compounds in aniseed (Pickrahn, Sebald, and Hofmann 2014).

Additionally, food quality-related researches aim to assess the effects of food processes on food compounds. For example, two-dimensional LC was applied to compare the metabolic profile in different aged red wines, in which the concentrations of anthocyanins and other new related compounds in young and aged red wines were comprehensively assessed, detected, and identified (Willemse et al. 2015). Similarly, an untargeted metabolomics method was used to differentiate volatile profiles of grape juices based on the presence of diverse fungal pathogens, such as *Botrytis cinerea*, *Penicillium expansum*, *Aspergillus niger* or *A. carbonarius*. The findings showed that *B. cinerea* samples were relatively higher in 1,5-dimethylnaphthalene and some unknown sesquiterpenes, while *A. niger* and *A. carbonarius* samples were comparatively higher in 2-carboxymethyl-3-hexylmaleic acid anhydride and *P. expansum* samples were higher in γ-nonalactone and *m*-cresol (Schueuermann et al. 2019). Therefore, metabolomics methods have been extensively applied to assess the fingerprinting, chemical composition (Cossignani et al. 2014), and taste quality of foods and beverages such as white tea (Yue et al. 2019), green tea (Zhang, Wu, et al. 2019), set-yogurt (Palama et al. 2016), and red and white ginseng (Zhang, Jiang, et al. 2019).

Metabolomics in the evaluation of food authenticity

Adulteration of food masks quality defects by adding banned components or inferior quality products, resulting in a health risk for consumers (Cubero-Leon, Peñalver, and Maquet 2014). Therefore, food authenticity is of utmost importance for food industry, producers, distributors, and consumers in ensuring nutritional value, origin, and productive processes (Kendall et al. 2018). However, it is often challenging to differentiate between adulterated and pure products by using conventional sensory evaluation and quality indicators, such as iodine value and saponification value of edible oils (Consonni and Cagliani 2010). With developments in analytical techniques, metabolomics-based approaches could complement existing methodologies to effectively determine the discrimination potential between adulterated and authentic foods and to trace geographical origin (Hou et al. 2015). For example, metabolomics coupled with 2DLC has been used to analyze different types of added compounds in milk, in which the processing and quality parameters of milk powders were analyzed. The research findings showed that monosaccharides were present in various brands and types of milk powder (Ma et al. 2014). With separation techniques, high-resolution mass spectrometry (HRMS) was developed to investigate the authenticity of foods with significant improvements in resolving power, sensitivity, robustness, extended dynamic range, mass calibration, and tandem mass capabilities, making HRMS as an attractive, useful, and reliable tool for the food metabolomics community (Rubert, Zachariasova, and Hajslova 2015).

Furthermore, metabolomics has been used to evaluate the authenticity of protected designation of origin (PDO), granting food products with a particular quality, including geographical origin, processing, and attractive organoleptic characteristics. With LC-QTOF-MS, the adulteration of wine in the Bordeaux region of France was investigated, in which 46 compounds from 9322 extracted compounds and four major components of 39 wine samples were assessed to determine adulteration in wine regions (Lin et al. 2014). Subsequently, a prediction model was generated to accurately distinguish adulterated wines in terms of geographical origin (Lin et al. 2014). Similarly, an UHPLCESI/QTOF-MS-based method was applied to discriminate saffron authenticity and traceability and PDO vs. non-PDO saffron products based on chemical fingerprints. The results showed that anthocyanins and glycosidic flavonols were optimum adulteration indicators, while other flavonoids (principally free flavonols and flavones), protocatechuic aldehyde, and isomeric forms of hydroxybenzoic acid were used as indicators for discriminating PDO vs. non PDO saffron products (Senizza et al. 2019).

Metabolomics-based approaches have been widely used in verifying the labeled ingredients of fruits (Hoffmann et al. 2017), rice (Huo et al. 2017), and vegetables (Erban et al. 2019), elucidating diversities in organic vs. traditional production systems in wheat (Kessler et al. 2015), maize (Röhlig

and Engel 2010), peppers (Novotná et al. 2012), potatoes (Shepherd et al. 2014), and white cabbage (Mie et al. 2014), and assessing the origin of olive oil (Sales et al. 2017), vinegars (Chinnici, Durán-Guerrero, and Riponi 2016), wines (Díaz et al. 2016), almonds (*Prunus dulcis*) (Solsona et al. 2018), cocoa beans (Hori, Kiriyama, and Tsumura 2016), honey (Zuccato et al. 2017), coffee species (Souard et al. 2018), saffron (Senizza et al. 2019), and citrus fruit/fruit juices (Jandrić et al. 2017), among others.

Metabolomics in the risk assessment of genetically modified food

Genetically modified (GM) crops possess considerable potential in improving the quality of life and reducing environmental effect. For example, GM crops may need less herbicide and pesticide applications and less water consumption and contain various health-promoting compounds and nutrients. With the assistance of new genetic engineering tools (such as CRISPR/Cas systems), novel genetically engineered (GE) crops containing genomic modifications have been generated without introducing foreign transgenes, making the cultivation of GM crops significantly increased in developing countries (Gao 2018). However, the undiscovered health risks of GM foods remain a concern among consumers, and many countries do not allow GM foods (Chao and Krewski 2008). To protect consumer rights, it is important to assess the unidentified addition of GM foods and/or food ingredients into the food supply and evaluate the risk assessment of novel foods by using metabolomics technologies (Stewart et al. 2018). For example, metabolomics has been applied to investigate transgenic rice, where the levels of tryptophan, linolenic acid, 5-hydroxy-2-octadenoic acid, Pro-Met-Leu, and 2-(11Z-octadecenoyl)-rac-glycerol reduced by 15%, 6%, 30%, 21%, and 15%, respectively, and the levels of palmitic acid, LPE16:0, 9, 10, 13-TriHOME, and phytosphingosine increased by 16%, 44%, 25%, 50%, respectively, relative to those in native rice samples (Chang et al. 2012). Therefore, the differentiation between conventional foods, transgenic foods, and genetically modified organisms (GMOs) has become a controversial topic, in which untargeted metabolomics is routinely used to differentiate genetic modification for safety assessment in soybean (García-Villalba et al. 2008), potato (Shepherd et al. 2015), barley (Kogel 2010), and wheat (Shewry et al. 2007), providing reliable information on GMO composition (e.g., metabolites and proteins) (Zhu et al. 2018; Beale, Karpe, and Ahmed 2016).

Metabolomics in food traceability

Food traceability, defined as "from farm to fork," is a relevant topic in food analysis and closely linked to food quality, food safety, and human health (Kaufmann 2014). Consumers not only demand food quality and food safety, but also require food traceability, which is associated to the capacity to interrelate identifiable entities chronologically throughout the food chain. However, there is limited understanding of the temporal processes on food composition, and multivariate statistics are used to comprehensively assess chemical changes under different food treatments (e.g., heat treatment, fermentation, and storage) (Gauglitz et al. 2018). Metabolomics could differentiate food metabolite profiles acorrding to genotype and growing conditions (such as climate, soil composition, fertilization, and irrigation), and provide information on unintended effects during pretreatment and processing, such as changes in nutrient composition, degradation of health-related compounds, and formation of new compounds, supplying useful information on the origin, composition, processing, and authenticity of foods (Rubert, Zachariasova, and Hajslova 2015).

Currently, non-targeted analysis is the most common method to assess changes in the metabolic profiles of foods during food-processing, whereas targeted analysis is employed to evaluate metabolic changes attributed to different enviromental stresses or growth stages (Bündig et al. 2016). For example, the non-targeted UHPLC-QTOF-MS approach was applied to assess the phenolic profiles of three diverse processed tomato products. The findings showed that different processing methods could significantly affect the nutrition and health promoting potential of tomato products (Lucini et al. 2017). Similarly, NMR-based metabolomics was used to investigate and monitor the effects of vacuum impregnated fish gelatin (FG) and grape seed extract (GSE) on metabolites that determine fish quality during storage. A total of 42 metabolites were identified, in which 36 metabolites were quantified. Some metabolites, such as choline and trimethylamine oxide, were closely associated with freshness, while organic acids were related to spoilage. More importantly, the combination of FG and GSE could significantly reduce the formation of undesirable metabolites such as trimethylamine and histidine (Zhao, Zhao, et al. 2019).

Targeted and untargeted metabolomics have been applied to analyze the effects of industrial processing strategies on the metabolite composition of foods, including the effects of blending and heating on Tiger nut (*Cyperus esculentus L.*) milk (Rubert, Monforte, et al. 2017), carrot, tomato, and broccoli (Lopez-Sanchez et al. 2015), the effects of storage conditions on red wine (Arapitsas et al. 2016), fresh-cut lettuce (García, Gil, and Tomas-Barberan 2018), and banana (Chen, Zhao, Wu, He, et al. 2020), the effects of different energy levels on mung beans sprout (Chen et al. 2019), and the effects of thermal processing on Brassica vegetables (Hennig et al. 2014). Targeted and untargeted metabolomics provide valuable information that address some of the following specific topics in food process industry, (1) the mechanism by which the molecular composition of foods changes during ripening, (2) the method by which improper storage affects the molecular make-up (such as meat and vegetables), and (3) the effect of food processing, such as roasting type of coffee and brewing tea.

In summary, metabolomics approaches, especially non-targeted fingerprinting, combined with sophisticated bioinformatics analysis and mathematical modeling exhibit an extreme power in assessing food quality, safety, and traceability (Cavanna et al. 2018). However, the application of metabolomics in food analysis is still at an early stage due to the

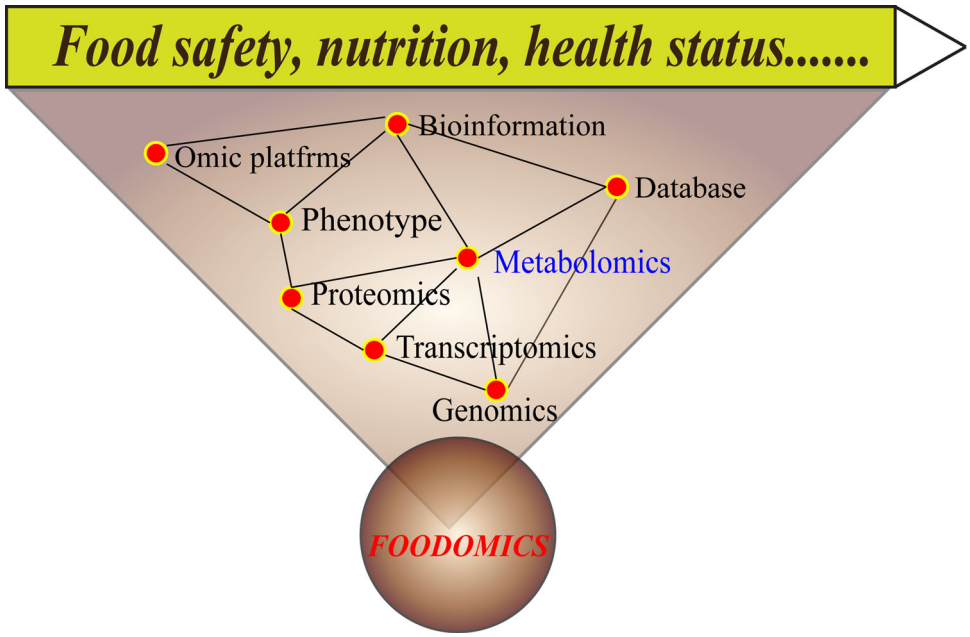

Figure 3. Application of foodomics in food analysis and nutrition research by integrating omics technologies and robust bioinformatics tools (adapted from Braconi et al. 2018; Vignoli et al. 2019).

limitation in technology and bioinformatics, and then the more robust, cheaper, and automated technologies, as well as larger food databases should be further improved to draw valid conclusions, therefore enlarging the application of food metabolomics (Cubero-Leon, De Rudder, and Maquet 2018).

Combined use of metabolomics with other omics

Compared with single omics approaches, integrated omics approaches have become increasingly popular in all aspects of life science (Pinu, Beale, et al. 2019), in which metabolomics can complement other omics methods (genomics, transcriptomics, and proteomics) to provide correlations between organismal response and phenotype at a given time point (Jaeger et al. 2017), offering a more holistic molecular perspective to comprehensively study biological systems. Recently, metabolomics coupled with genomics, transcriptomics, and proteomics has been applied to investigate food and nutrition domains, providing fast, accurate, and reliable tools to address problems inherent to food technology, such as food quality control and safety (Ferranti 2018), and the complexity of post-harvest fruit physiology (Nham et al. 2015).

Omics techniques for foodomics

Foodomics is a discipline that investigates food and nutrition domains as a whole to elucidate the connections among food components, food safety, diet, health, and diseases via integrating advanced omics technologies and biostatistics, chemometrics and bioinformatics tools to improve consumer's well-being, health, and knowledge (Figure 3) (Gilbert-Lopez, Mendiola, and Ibanez 2017; Cifuentes 2009; León, Cifuentes, and Valdés 2018). Currently, the main areas of foodomics could be summarized as follows, (1) human health, which can be further classified into food consumption monitoring research and treatment/prevention of diseases by improving human diet (Zotti et al. 2016), (2) food resources, which focus on analyzing the food composition of animal and plant origins and defined by climate, land, and cultural practices (Humpfer et al. 2015; Picone et al. 2019), and (3) food processing, which characterizes the effects of pre- and post-production processes on food products, such as growth conditions (such as feed, GMOs, chemicals and pesticides), packaging and storage strategies, and safety and authenticity control (Acunha et al. 2016; Martinović, Šrajer Gajdošik, and Josić 2018).

Foodomics for assessing the relationship between food bioactivity and health

Recently, foodomics has been applied to elucidate the complicated relationships between food, nutrition and human health at different molecular levels, and then provided information for developing "nutraceuticals" and "functional foods" (Li, Li, et al. 2019; Ibanez et al. 2013), or personalized therapeutic interventions through tailored manipulations of dietary interventions (Braconi et al. 2018; Montero and Herrero 2019). For example, to elucidate the in vitro gastrointestinal protective effects of Bee pollen (BP) against inflammatory bowel disease, metabolomics analysis by ultra-performance liquid chromatography tandem with quadrupole time of flight-mass spectrometry (UPLC-Q-TOF/MS) was performed to elucidate the regulatory mechanism of BP extract on protecting cellular metabolic pathways against DSS-induced Caco-2 cells metabolism disorders (Li, Li, et al. 2019). Similarly, a multi-omics approach, integrating transcriptomics and metabolomics, together with viability and cell cycle experiments, was applied to research the anti-proliferative potential of *Passiflora mollissima* seeds on HT-29 human colon cancer cells. As a result, the foodomics enabled the identification of genes, involving in polyamine and glutathione metabolism, or the inactivation

of NUPR1 transcription factor, that might be associated with the changes in intracellular ceramide concentations in response to endoplasmic reticulum stress (Ballesteros-Vivas et al. 2020).

Foodomics for elucidating food microbiota interactions

The complex ecosystem contains millions of commensal and pathogenic microorganisms (forming the "microbiota") (Greer et al. 2016), which dynamically interact with the diet and host, playing fundamental roles in fundamental physiological processes, such as immunity, skin disorders (Maguire and Maguire 2017), and neurodevelopmental alterations (Kelly et al. 2017). With respect to microbial communities, metabolites could be as mediators in nutrient and energy exchange, cell-to-cell communication, and antibiosis (Xu et al. 2019), allowing the scientific community to (1) elucidate the function of chemical exchange and communication among members by foodomics, (2) link microbial community structure, dynamics, interactions, and metabolic functions, (3) obtain answers on microbial diversity, output, resilience, and succession, and (4) further understand microbic response to abiotic and biotic stressors (Beale et al. 2017).

At present, meta-omics approach is conducive to consideration of microbiota ecosystem as a holistic population structure, and the genes, transcripts, proteins, and metabolites of microorganisms can be integrated via high-throughput global analysis (Rowland et al. 2018). Specifically, metagenomics is mainly used for comparing the composition of microbiota between healthy and diseased individuals; however, metatranscriptomics has not been frequently adopted in gut microbiota analysis due to difficulties in determination and extrapolation of short-term responses based on mRNAs. Metaproteomics provides the strategy to link proteins with given taxonomic groups, and metabolic profiling could generate a large number of information on metabolic phenotype by selecting endogenous (from the host) and exogenous (from the environment, such as microbiota and diet) molecules (Rowland et al. 2018).

Foodomics for investigating other food-associated issues

Furthermore, foodomics approaches have become valuable tools for investigating food microbiology and toxicology and for providing data on (1) viability, adaptation, and survival potential and mechanisms of detected bacteria, (2) real-time detection and tracking of high risk pathogen subtypes and microbiomes (Kovac 2019), and (3) qualitative and quantitative information for toxins in foods (Berthiller et al. 2017). For example, omics-based methods, e.g., proteomics with matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-ToFMS) and metabolomics with GC-MS, have been used to detect three red meat pathogens, including *L. monocytogenes*, *S. enterica*, and *E. coli* O157:H7. As a result, species-level identification could be obtained within 18 h for *S. enterica* and *E. coli* O157:H7 and 30 h for *L. monocytogenes*, providing a rapid detection method for some important foodborne pathogens (Jadhav et al. 2018). Therefore, omics-based techniques could provide improved screening and subtyping tools for both known and unknown pathogens (Forbes et al. 2017) and be useful in pathogen detection, foodborne illness outbreak detection, microbial source tracking analyses, antimicrobial resistance, and product shelf-life, providing a detailed information on how bacteria or pathogens survives in the environment and discovering new targets for limiting serious infections (Cook and Nightingale 2018).

Omics fusion for integrative analysis of omics data

However, due to the depth or coverage obtained from different omic technologies, it was difficult to integrate the different levels of information. For example, compared with the high amount of proteins, phosphorylation sites or genes obtained from proteomics, phosphoproteomics or transcriptomics analyses, low number of identified metabolites has been considered to be the key bottleneck for metabolomics. Furthermore, with the increase of available multiple omics data, data processing has become more and more important in understanding the biological mechanisms responsible for variations in the observed metabolomic profiles (Broadhurst and Kell 2007). To the end, it should be further improvements in computational techniques for effective storage, integration and utilization of prior information, identification and accurate quantification of metabolites, "multi-omics" data integration, and pathway visualization, in which various databases, software tools, and methods are now freely accessible to assist with integrating multi-omics data sets (Broadhurst and Kell 2007; Subramanian et al. 2020).

Currently, before the analysis and interpretation of different omics data, a series of specialized tools and approaches were developed to integrate different omics data sets (Kuo, Tian, and Tseng 2013), including: (1) statistical approaches, using orthogonal two-way projection to latent structures (O2PLS) and its variant (O*n*PLS) to analyze systematic variation (Trygg and Wold 2003; Löfstedt and Trygg 2011); (2) unsupervised methods, using machine learning algorithms to identify patterns without referring to known results (Noor, Cherkaoui, and Sauer 2019); (3) supervised machine learning, using a set of input attributes to predict the target value (Franzosa et al. 2019). Among of them, *Omics Fusion*, an extendible, web-based platform for comprehensively analyzing omics data from three classical fields, transcriptomics, proteomics, and metabolomics, has been developed to offer simple data administration, such as automated input of spreadsheets, together with connections to other platforms, such as EMMA (Dondrup et al. 2009), MeltDB (Kessler et al. 2013), or QuPE (Albaum et al. 2009). More importantly, *Omics Fusion* does not only focus on networks and pathways (e.g., Cytoscape (Shannon et al. 2003) or iPEAP (Sun et al. 2014)) or on a specific organism. *Omics Fusion* provides numerous visualization methods for single and multi-omics data and offers a collection of new and established tools and visualization approaches to extract omics data, validate results, and understand how to modify experiments to achieve new findings (Brink et al. 2016). However, because of inherent

data diversities, the integration of multi-omics platforms is still an ongoing challenge (Patt et al. 2019).

In summary, foodomics has become the most advanced methodology in food risk evaluation, security control, foodborne outbreak detection, bioactive compounds assessment on health, and health improvement through diet manipulation (Putignani and Dallapiccola 2016), but its rapid assessment and integration still prevented by technical and biological issues, including (1) the complex and heterogeneous of biological data, (2) the limited repeatability of the results of transcriptomics, proteomics, and metabolomics due to the heterogeneity of available analysis tools, (3) the absence of normal data formats for both omics data and metadata, and (4) the lack of effective softwares for omics data integration and interpretation (Cambiaghi, Ferrario, and Masseroli 2017). To obtain a deeper comprehension of how diet, microbiota, and interindividual variability effectively impact phenotypic alterations between health and disease, it is necessary to further develop harmonization and mormalizaiton of samplings, implement analysis techniques, establish standardized animal models, improve biological databases with functional annotations, and develop novel powerful exploiting tools (Braconi et al. 2018; Montero and Herrero 2019).

Conclusion and future outlooks

Corresponding to the fast development of analysis techniques, metabolomics has achieved great progress with exciting findings linking to biological systems and food analysis, in which it is possible to analyze more than 1000 metabolites in a single run or utilizing an integration of various analytical methods, showing great potential in diverse fields of life sciences. Like any other omics area, however, the application of metabolomics approaches in food security, food quality, and food traceability remains far from achieving its maximal potential (Pinu, Beale, et al. 2019) and suffers from some bottlenecks, including sensitivity and compound identification limitations (Pinu, Beale, et al. 2019), appropriate statistical approaches for the huge amount of data (Salari et al. 2018), and metabolite coverage and function (Alseekh and Fernie 2018). Furthermore, although the undeniable reliability of tools reviewed, metabolomics faces challenges in practical applications, mainly in the area of data integration, information database, and chemometrics to support a comprehensive assessment of experimental data and a deeper comprehension of how internal metabolic pathways or biological processes change in foods (Cambiaghi, Ferrario, and Masseroli 2017).

Consequently, it is essential to enhance the sensitivity and precision of instruments to enlarge the coverage of metabolites and increase data quality with the combination of different analytical methods and platforms (Begou et al. 2017). For example, the application of new technology as ion mobility separation (IMS) could provide a new dimension for chromatography and MS, allowing the monitoring of quality attributes during food processing through in situ automatic sampling and providing important information to assess losses of food characteristics and behavior of contaminants and toxic substances during food processing (López-Ruiz, Romero-González, and Frenich 2019). In addition, powerful statistical software tools should be further developed to handle large amounts of experimental data for effectively assessing the security of new or traditional processing technologies in food systems (Liu, Wu, and Chan 2019). As for targeted metabolomics, the automation, rapid, and accuracy of entire metabolite quantitation should be further improved. Metabolite libraries of MS/NMR software and web servers need to continually enlarge by adding more metabolites, establishing and recording more reliable standards, mining data from the literature, and elucidating structures of new metabolites (Bingol 2018). However, for untargeted metabolomics, several procedures should be further refined to control analytical data quality and develop standardization of protocols for meaningful, accurate, and precise management of untargeted studies in food analysis research (Dudzik et al. 2018).

Disclosure statement

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with this manuscript. We have no financial and personal relationships with other people or organizations that can inappropriately influence our work.

Funding

This work was funded by Key projects in Guangxi (2019GXNSFDA245008), Guangxi Natural Science Foundation (2017GXNSFAA198297), the "Bagui Young Scholars" Special Project, National Key R&D Program of China, and Natural Science Foundation of Jiangsu Province (BK20181184).

References

Acunha, T., C. Ibanez, V. Garcia-Canas, C. Simo, and A. Cifuentes. 2016. Recent advances in the application of capillary electromigration methods for food analysis and Foodomics. *Electrophoresis* 37 (1):111–41. doi: 10.1002/elps.201500291.

Akhatou, I., R. González-Domínguez, and Á. Fernández-Recamales. Á. 2016. Investigation of the effect of genotype and agronomic conditions on metabolomic profiles of selected strawberry cultivars with different sensitivity to environmental stress. *Plant Physiology and Biochemistry: PPB* 101:14–22. doi: 10.1016/j.plaphy.2016.01.016.

Akrami-Mohajeri, F., Z. Derakhshan, M. Ferrante, N. Hamidiyan, M. Soleymani, G. O. Conti, and R. D. Tafti. 2018. The prevalence and antimicrobial resistance of *Listeria* spp in raw milk and traditional dairy products delivered in Yazd, central Iran (2016). *Food and Chemical Toxicology* 114:141–4. doi: 10.1016/j.fct.2018.02.006.

Albaum, S. P., H. Neuweger, B. Fränzel, S. Lange, D. Mertens, C. Trötschel, D. Wolters, J. Kalinowski, T. W. Nattkemper, and A. Goesmann. 2009. Qupe-a Rich Internet Application to take a step forward in the analysis of mass spectrometry-based quantitative proteomics experiments . *Bioinformatics (Oxford, England)* 25 (23): 3128–34. doi: 10.1093/bioinformatics/btp568.

Alimentarius, C. 2015. Maximum residue limits (MRLs) and risk management recommendations (RMRs) for residues of veterinary drugs in foods. CAC/MRL 2-2015.

Alonso, A., S. Marsal, and A. Julià. 2015. Analytical methods in untargeted metabolomics: State of the art in 2015. *Frontiers in Bioengineering and Biotechnology* 3:23. doi: 10.3389/fbioe.2015.00023.

Alothman, M., K. A. Lusk, P. Silcock, and P. J. Bremer. 2017. Comparing PTR-MS profile of milk inoculated with pure or mixed cultures of spoilage bacteria. *Food Microbiology* 64:155–63. doi: 10.1016/j.fm.2017.01.001.

Alseekh, S., and A. R. Fernie. 2018. Metabolomics 20 years on: What have we learned and what hurdles remain? *The Plant Journal: For Cell and Molecular Biology* 94 (6):933–42. doi: 10.1111/tpj.13950.

An, P. N. T., M. Yamaguchi, and E. Fukusaki. 2017. Metabolic profiling of *Drosophila melanogaster* metamorphosis: A new insight into the central metabolic pathways. *Metabolomics* 13 (3):29. doi: 10.1007/s11306-017-1167-1.

Anderson, J., N. Bogart, A. Clarke, L. Nelson, B. Warren, and L. Jespersen. 2014. Food safety management in the global food supply chain. *Perspectives in Public Health* 134 (4):181.

Arapitsas, P., A. D. Corte, H. Gika, L. Narduzzi, F. Mattivi, and G. Theodoridis. 2016. Studying the effect of storage conditions on the metabolite content of red wine using HILIC LC–MS based metabolomics. *Food Chemistry* 197:1331–40. doi: 10.1016/j.foodchem.2015.09.084.

Aru, V., B. Khakimov, K. M. Sørensen, and S. B. Engelsen. 2018. The foodome of bivalve molluscs: From hedonic eating to healthy diet. *Journal of Food Composition and Analysis* 69:13–9. doi: 10.1016/j.jfca.2018.01.018.

Ballesteros-Vivas, D., G. Alvarez-Rivera, C. León, S. J. Morantes, E. Ibánez, F. Parada-Alfonso, A. Cifuentes, and A. Valdés. 2020. Foodomics evaluation of the anti-proliferative potential of *Passiflora mollissima* seeds. *Food Research International* 130:108938. doi: 10.1016/j.foodres.2019.108938.

Barupal, D. K., S. Fan, and O. Fiehn. 2018. Integrating bioinformatics approaches for a comprehensive interpretation of metabolomics datasets. *Current Opinion in Biotechnology* 54:1–9. doi: 10.1016/j.copbio.2018.01.010.

Beale, D. J., A. V. Karpe, and W. Ahmed. 2016. Beyond metabolomics: A review of multi-omic-based approaches. In *Microbial metabolomics*, ed. E. E. K. Baidoo, 289–312. Cham, Switzerland: Springer.

Beale, D. J., J. Crosswell, A. V. Karpe, W. Ahmed, M. Williams, P. D. Morrison, S. Metcalfe, C. Staley, M. J. Sadowsky, E. A. Palombo, et al. 2017. A multi-omics based ecological analysis of coastal marine sediments from Gladstone, in Australia's Central Queensland, and Heron Island, a nearby fringing platform reef. *The Science of the Total Environment* 609:842–53. doi: 10.1016/j.scitotenv.2017.07.184.

Begou, O., H. Gika, I. Wilson, and G. Theodoridis. 2017. Hyphenated MS-based targeted approaches in metabolomics. *The Analyst* 142 (17):3079–100. doi: 10.1039/c7an00812k.

Bengtström, L., A. K. Rosenmai, X. Trier, L. K. Jensen, K. Granby, A. M. Vinggaard, M. Driffield, and J. Højslev Petersen. 2016. Non-targeted screening for contaminants in paper and board food-contact materials using effect-directed analysis and accurate mass spectrometry. *Food Additives & Contaminants. Part A, Chemistry, Analysis, Control, Exposure & Risk Assessment* 33 (6):1080–93. doi: 10.1080/19440049.2016.1184941.

Berthiller, F., C. Brera, M. H. Iha, R. Krska, V. M. T. Lattanzio, S. MacDonald, R. J. Malone, C. Maragos, M. Solfrizzo, M. Stranska-Zachariasova, et al. 2017. Developments in mycotoxin analysis: An update for 2015-2016. *World Mycotoxin Journal* 10 (1):5–29. doi: 10.3920/WMJ2016.2138.

Bingol, K. 2018. Recent advances in targeted and untargeted metabolomics by NMR and MS/NMR methods. *High-Throughput* 7 (2):9. doi: 10.3390/ht7020009.

Bingol, K., L. Bruschweiler-Li, C. Yu, A. Somogyi, F. Zhang, and R. Brüschweiler. 2015. Metabolomics beyond spectroscopic databases: A combined MS/NMR strategy for the rapid identification of new metabolites in complex mixtures. *Analytical Chemistry* 87 (7):3864–70. doi: 10.1021/ac504633z.

Bingol, K., L. Bruschweiler-Li, D. Li, B. Zhang, M. Xie, and R. Brüschweiler. 2016. Emerging new strategies for successful metabolite identification in metabolomics. *Bioanalysis* 8 (6):557–73. doi: 10.4155/bio-2015-0004.

Bingol, K., and R. Brüschweiler. 2014. Multidimensional approaches to NMR-based metabolomics. *Analytical Chemistry* 86 (1):47–57. doi: 10.1021/ac403520j.

Blaženović, I., T. Kind, J. Ji, and O. Fiehn. 2018. Software tools and approaches for compound identification of LC-MS/MS data in metabolomics. *Metabolites* 8 (2):31. doi: 10.3390/metabo8020031.

Bloszies, C. S., and O. Fiehn. 2018. Using untargeted metabolomics for detecting exposome compounds. *Current Opinion in Toxicology* 8:87–92. doi: 10.1016/j.cotox.2018.03.002.

Boiteau, R., D. Hoyt, C. Nicora, H. Kinmonth-Schultz, J. Ward, and K. Bingol. 2018. Structure elucidation of unknown metabolites in metabolomics by combined NMR and MS/MS prediction. *Metabolites* 8 (1):8. doi: 10.3390/metabo8010008.

Bouatra, S., F. Aziat, R. Mandal, A. C. Guo, M. R. Wilson, C. Knox, T. C. Bjorndahl, R. Krishnamurthy, F. Saleem, P. Liu, et al. 2013. The human urine metabolome. *PLoS One* 8 (9):e73076. doi: 10.1371/journal.pone.0073076.

Braconi, D., G. Bernardini, L. Millucci, and A. Santucci. 2018. Foodomics for human health: Current status and perspectives. *Expert Review of Proteomics* 15 (2):153–64. doi: 10.1080/14789450.2018.1421072.

Brink, B. G., A. Seidel, N. Kleinbölting, T. W. Nattkemper, and S. P. Albaum. 2016. Omics fusion–a platform for integrative analysis of omics data. *Journal of Integrative Bioinformatics* 13 (4):43–46. doi: 10.1515/jib-2016-296.

Brizzolara, S., C. Santucci, L. Tenori, M. Hertog, B. Nicolai, S. Stürz, A. Zanella, and P. Tonutti. 2017. A metabolomics approach to elucidate apple fruit responses to static and dynamic controlled atmosphere storage. *Postharvest Biology and Technology* 127:76–87. doi: 10.1016/j.postharvbio.2017.01.008.

Broadhurst, D. I., and D. B. Kell. 2007. Statistical strategies for avoiding false discoveries in metabolomics and related experiments. *Metabolomics* 2 (4):171–96. doi: 10.1007/s11306-006-0037-z.

Buescher, J. M., M. R. Antoniewicz, L. G. Boros, S. C. Burgess, H. Brunengraber, C. B. Clish, R. J. DeBerardinis, O. Feron, C. Frezza, B. Ghesquiere, et al. 2015. A roadmap for interpreting (13)C metabolite labeling patterns from cells. *Current Opinion in Biotechnology* 34:189–201. doi: 10.1016/j.copbio.2015.02.003.

Bündig, C., C. Blume, C. Peterhänsel, and T. Winkelmann. 2016. Changed composition of metabolites in *Solanum tuberosum* subjected to osmotic stress in vitro: Is sorbitol taken up? *Plant Cell, Tissue and Organ Culture (PCTOC)* 127 (1):195–206. doi: 10.1007/s11240-016-1042-1.

Cai, Y., and Z.-J. Zhu. 2019. A high-throughput targeted metabolomics workflow for the detection of 200 polar metabolites in central carbon metabolism. In *Microbial metabolomics*, ed. E. E. K. Baidoo, 263–74. Totowa, NJ: Humana Press.

Cambiaghi, A., M. Ferrario, and M. Masseroli. 2017. Analysis of metabolomic data: Tools, current strategies and future challenges for omics data integration. *Briefings in Bioinformatics* 18 (3):498–510. doi: 10.1093/bib/bbw031.

Castro-Puyana, M., R. Pérez-Míguez, L. Montero, and M. Herrero. 2017. Reprint of: Application of mass spectrometry-based metabolomics approaches for food safety, quality and traceability. *TrAC Trends in Analytical Chemistry* 96:62–78. doi: 10.1016/j.trac.2017.08.007.

Cavanna, D., L. Righetti, C. Elliott, and M. Suman. 2018. The scientific challenges in moving from targeted to non-targeted mass spectrometric methods for food fraud analysis: A proposed validation workflow to bring about a harmonized approach. *TrAC Tends in Food Science & Technology* 80:223–41. doi: 10.1016/j.tifs.2018.08.007.

Cevallos-Cevallos, J. M., J. I. Reyes-De-Corcuera, E. Etxeberria, M. D. Danyluk, and G. E. Rodrick. 2009. Metabolomic analysis in food science: A review. *Trends in Food Science & Technology* 20 (11–12):557–66. doi: 10.1016/j.tifs.2009.07.002.

Chaleckis, R., I. Meister, P. Zhang, and C. E. Wheelock. 2019. Challenges, progress and promises of metabolite annotation for LC-MS-based metabolomics. *Current Opinion in Biotechnology* 55:44–50. doi: 10.1016/j.copbio.2018.07.010.

Chang, G.-R., H.-S. Chen, and F.-Y. Lin. 2016. Analysis of banned veterinary drugs and herbicide residues in shellfish by liquid chromatography-tandem mass spectrometry (LC/MS/MS) and gas chromatography-tandem mass spectrometry (GC/MS/MS). *Marine Pollution Bulletin* 113 (1–2):579–84. doi: 10.1016/j.marpolbul.2016.08.080.

Chang, Y., C. Zhao, Z. Zhu, Z. Wu, J. Zhou, Y. Zhao, X. Lu, and G. Xu. 2012. Metabolic profiling based on LC/MS to evaluate unintended effects of transgenic rice with *cry1Ac* and *sck* genes. *Plant Molecular Biology* 78 (4–5):477–87. doi: 10.1007/s11103-012-9876-3.

Chao, E., and D. Krewski. 2008. A risk-based classification scheme for genetically modified foods II: Graded testing. *Regulatory Toxicology and Pharmacology: RTP* 52 (3):223–34. doi: 10.1016/j.yrtph.2008.08.002.

Chen, J., K. Li, X. C. Le, and L. Zhu. 2018. Metabolomic analysis of two rice (*Oryza sativa*) varieties exposed to 2,2′,4,4′-tetrabromodiphenyl ether. *Environmental Pollution (Barking, Essex: 1987)* 237:308–17. doi: 10.1016/j.envpol.2018.02.027.

Chen, L., J. Wu, Z. Li, Q. Liu, X. Zhao, and H. Yang. 2019. Metabolomic analysis of energy regulated germination and sprouting of organic mung bean (*Vigna radiata*) using NMR spectroscopy. *Food Chemistry* 286:87–97. doi: 10.1016/j.foodchem.2019.01.183.

Chen, L., X. Zhao, J. Wu, Q. Liu, X. Pang, and H. Yang. 2020. Metabolic characterization of eight *Escherichia coli* strains and acidic responses of selected strains revealed by NMR spectroscopy. *Food Microbiology* 88:103399. doi: 10.1016/j.fm.2019.103399.

Chen, L., X. Zhao, J. Wu, Y. He, and H. Yang. 2020. Metabolic analysis of salicylic acid-induced chilling tolerance of banana using NMR. *Food Research International* 128:108796.

Chinnici, F., E. Durán-Guerrero, and C. Riponi. 2016. Discrimination of some European vinegars with protected denomination of origin as a function of their amino acid and biogenic amine content. *Journal of the Science of Food and Agriculture* 96 (11):3762–71. doi: 10.1002/jsfa.7566.

Cho, J., J. Lee, C.-U. Lim, and J. Ahn. 2016. Quantification of pesticides in food crops using QuEChERS approaches and GC-MS/MS. *Food Additives & Contaminants Part A: Chemistry, Analysis, Control, Exposure & Risk Assessment* 33 (12):1803–16. doi: 10.1080/19440049.2016.1235800.

Christodoulou, D. L., P. Kanari, P. Hadjiloizou, and P. Constantinou. 2015. Pesticide residues analysis in wine by liquid chromatography--tandem mass spectrometry and using ethyl acetate extraction method: Validation and pilot survey in real samples. *Journal of Wine Research* 26 (2):81–98. doi: 10.1080/09571264.2015.1022255.

Cifuentes, A. 2009. Food analysis and Foodomics. *Journal of Chromatography A* 1216 (43):7109. doi: 10.1016/j.chroma.2009.09.018.

Consonni, R., and L. Cagliani. 2010. Nuclear magnetic resonance and chemometrics to assess geographical origin and quality of traditional food products. In *Advances in food and nutrition research*, Vol. 59, 87–165. Cambridge, MA: Academic Press.

Cook, P. W., and K. K. Nightingale. 2018. Use of omics methods for the advancement of food quality and food safety. *Animal Frontiers: The Review Magazine of Animal Agriculture* 8 (4):33–41. doi: 10.1093/af/vfy024.

Cossignani, L., E. Urbani, M. S. Simonetti, A. Maurizi, C. Chiesi, and F. Blasi. 2014. Characterisation of secondary metabolites in saffron from central Italy (*Cascia, Umbria*). *Food Chemistry* 143:446–51. doi: 10.1016/j.foodchem.2013.08.020.

Cruickshank-Quinn, C., K. D. Quinn, R. Powell, Y. Yang, M. Armstrong, S. Mahaffey, R. Reisdorph, and N. Reisdorph. 2014. Multi-step preparation technique to recover multiple metabolite compound classes for in-depth and informative metabolomic analysis. *Journal of Visualized Experiments* 89:e51670. doi: 10.3791/51670.

Cubero-Leon, E., O. De Rudder, and A. Maquet. 2018. Metabolomics for organic food authentication: Results from a long-term field study in carrots. *Food Chemistry* 239:760–70. doi: 10.1016/j.foodchem.2017.06.161.

Cubero-Leon, E., R. Peñalver, and A. Maquet. 2014. Review on metabolomics for food authentication. *Food Research International* 60:95–107. doi: 10.1016/j.foodres.2013.11.041.

Daniel, D., and C. L. do Lago. 2019. Determination of multiclass pesticides residues in corn by QuEChERS and capillary electrophoresis tandem mass spectrometry. *Food Analytical Methods* 12:1684–92.

Dasenaki, M. E., and N. S. Thomaidis. 2015. Multi-residue determination of 115 veterinary drugs and pharmaceutical residues in milk powder, butter, fish tissue and eggs using liquid chromatography-tandem mass spectrometry. *Analytica Chimica Acta* 880:103–21. doi: 10.1016/j.aca.2015.04.013.

Dasenaki, M. E., C. S. Michali, and N. S. Thomaidis. 2016. Analysis of 76 veterinary pharmaceuticals from 13 classes including aminoglycosides in bovine muscle by hydrophilic interaction liquid chromatography-tandem mass spectrometry. *Journal of Chromatography A* 1452:67–80. doi: 10.1016/j.chroma.2016.05.031.

Derakhshan, Z., G. Oliveri Conti, A. Heydari, M. S. Hosseini, F. A. Mohajeri, H. Gheisari, S. Kargar, E. Karimi, and M. Ferrante. 2018. Survey on the effects of electron beam irradiation on chemical quality and sensory properties on quail meat. *Food and Chemical Toxicology* 112:416–20. doi: 10.1016/j.fct.2017.12.015.

Díaz, R., H. Gallart-Ayala, J. V. Sancho, O. Nuñez, T. Zamora, C. P. B. Martins, F. Hernández, S. Hernández-Cassou, J. Saurina, and A. Checa. 2016. Told through the wine: A liquid chromatography-mass spectrometry interplatform comparison reveals the influence of the global approach on the final annotated metabolites in non-targeted metabolomics. *Journal of Chromatography A* 1433:90–7. doi: 10.1016/j.chroma.2016.01.010.

Doerr, A. 2017. Global metabolomics. *Nature Methods* 14 (1):32. doi: 10.1038/nmeth.4112.

Dona, A. C., M. Kyriakides, F. Scott, E. A. Shephard, D. Varshavi, K. Veselkov, and J. R. Everett. 2016. A guide to the identification of metabolites in NMR-based metabonomics/metabolomics experiments. *Computational and Structural Biotechnology Journal* 14:135–53. doi: 10.1016/j.csbj.2016.02.005.

Dondrup, M., S. P. Albaum, T. Griebel, K. Henckel, S. Jünemann, T. Kahlke, C. K. Kleindt, H. Küster, B. Linke, D. Mertens, et al. 2009. EMMA 2-a MAGE-compliant system for the collaborative analysis and integration of microarray data. *BMC Bioinformatics* 10:50. doi: 10.1186/1471-2105-10-50.

Dudzik, D., C. Barbas-Bernardos, A. García, and C. Barbas. 2018. Quality assurance procedures for mass spectrometry untargeted metabolomics. A review. *Journal of Pharmaceutical and Biomedical Analysis* 147:149–73. doi: 10.1016/j.jpba.2017.07.044.

Emwas, A.-H., C. Luchinat, P. Turano, L. Tenori, R. Roy, R. M. Salek, D. Ryan, J. S. Merzaban, R. Kaddurah-Daouk, A. C. Zeri, et al. 2015. Standardizing the experimental conditions for using urine in NMR-based metabolomic studies with a particular focus on diagnostic studies: A review. *Metabolomics* 11 (4):872–94. doi: 10.1007/s11306-014-0746-7.

Erban, A., I. Fehrle, F. Martinez-Seidel, F. Brigante, A. L. Más, V. Baroni, D. Wunderlin, and J. Kopka. 2019. Discovery of food identity markers by metabolomics and machine learning technology. *Scientific Reports* 9 (1):9697. doi: 10.1038/s41598-019-46113-y.

Fallahzadeh, R. A., R. Khosravi, B. Dehdashti, E. Ghahramani, F. Omidi, A. Adli, and M. Miri. 2018. Spatial distribution variation and probabilistic risk assessment of exposure to chromium in ground water supplies; a case study in the east of Iran. *Food and Chemical Toxicology* 115:260–6. doi: 10.1016/j.fct.2018.03.019.

Fan, Y-b, Y.-M. Yin, W.-B. Jiang, Y.-P. Chen, J.-W. Yang, J. Wu, and M.-X. Xie. 2014. Simultaneous determination of ten steroid hormones in animal origin food by matrix solid-phase dispersion and liquid chromatography-electrospray tandem mass spectrometry. *Food Chemistry* 142:170–7. doi: 10.1016/j.foodchem.2013.06.104.

Ferranti, P. 2018. The future of analytical chemistry in foodomics. *Current Opinion in Food Science* 22:102–8. doi: 10.1016/j.cofs.2018.02.005.

Forbes, J. D., N. C. Knox, J. Ronholm, F. Pagotto, and A. Reimer. 2017. Metagenomics: The next culture-independent game Changer. *Frontiers in Microbiology* 8:1069. doi: 10.3389/fmicb.2017.01069.

Franzosa, E. A., A. Sirota-Madi, J. Avila-Pacheco, N. Fornelos, H. J. Haiser, S. Reinker, T. Vatanen, A. B. Hall, H. Mallick, L. J. McIver, et al. 2019. Gut microbiome structure and metabolic activity in inflammatory bowel disease. *Nature Microbiology* 4 (2):293–305.

Gallo, M., and P. Ferranti. 2016. The evolution of analytical chemistry methods in foodomics. *Journal of Chromatography A* 1428:3–15. doi: 10.1016/j.chroma.2015.09.007.

Gao, C. 2018. The future of CRISPR technologies in agriculture. *Nature Reviews Molecular Cell Biology* 19 (5):275–6. doi: 10.1038/nrm.2018.2.

García, C. J., M. I. Gil, and F. A. Tomas-Barberan. 2018. LC–MS untargeted metabolomics reveals early biomarkers to predict browning of fresh-cut lettuce. *Postharvest Biology and Technology* 146:9–17. doi: 10.1016/j.postharvbio.2018.07.011.

García-Cañas, V., C. Simó, M. Castro-Puyana, and A. Cifuentes. 2014. Recent advances in the application of capillary electromigration methods for food analysis and foodomics. *Electrophoresis* 35 (1): 147–69. doi: 10.1002/elps.201300315.

García-Cañas, V., C. Simó, M. Herrero, E. Ibáñez, and A. Cifuentes. 2012. Present and Future Challenges in Food Analysis: Foodomics. *Analytical Chemistry* 84:10150–159.

García-Villalba, R., C. León, G. Dinelli, A. Segura-Carretero, A. Fernández-Gutiérrez, V. Garcia-Cañas, and A. Cifuentes. 2008. Comparative metabolomic study of transgenic versus conventional soybean using capillary electrophoresis-time-of-flight mass spectrometry . *Journal of Chromatography A* 1195 (1–2):164–73. doi: 10.1016/j.chroma.2008.05.018.

Gaudêncio, S. P., and F. Pereira. 2015. Dereplication: Racing to speed up the natural products discovery process. *Natural Product Reports* 32 (6):779–810. doi: 10.1039/c4np00134f.

Gauglitz, J. M., C. M. Aceves, A. A. Aksenov, G. Aleti, J. Almaliti, A. Bouslimani, E. A. Brown, A. Campeau, A. M. Caraballo-Rodríguez, R. Chaar, et al. 2018. Untargeted mass spectrometry-based metabolomics tracks molecular changes in raw and processed foods and beverages. BioRxiv:347716.

Gilbert-Lopez, B., J. A. Mendiola, and E. Ibanez. 2017. Green foodomics. Towards a cleaner scientific discipline. *TrAC Trends in Analytical Chemistry* 96:31–41. doi: 10.1016/j.trac.2017.06.013.

Gong, Z.-G., J. Hu, X. Wu, and Y.-J. Xu. 2017. The recent developments in sample preparation for mass spectrometry-based metabolomics. *Critical Reviews in Analytical Chemistry* 47 (4):325–31. doi: 10.1080/10408347.2017.1289836.

González-Curbelo, M. Á., B. Socas-Rodríguez, A. V. Herrera-Herrera, J. González-Sálamo, J. Hernández-Borges, and M. Á. Rodríguez-Delgado. 2015. Evolution and applications of the QuEChERS method. *TrAC Trends in Analytical Chemistry* 71:169–85. doi: 10.1016/j.trac.2015.04.012.

Greer, R., X. Dong, A. Morgun, and N. Shulzhenko. 2016. Investigating a holobiont: Microbiota perturbations and transkingdom networks. *Gut Microbes* 7 (2):126–35. doi: 10.1080/19490976.2015.1128625.

Gu, E.-J., D. W. Kim, G.-J. Jang, S. H. Song, J.-I. Lee, S. B. Lee, B.-M. Kim, Y. Cho, H.-J. Lee, H.-J. Kim, et al. 2017. Mass-based metabolomic analysis of soybean sprouts during germination. *Food Chemistry* 217:311–9. doi: 10.1016/j.foodchem.2016.08.113.

Han, L., J. Matarrita, Y. Sapozhnikova, and S. J. Lehotay. 2016. Evaluation of a recent product to remove lipids and other matrix co-extractives in the analysis of pesticide residues and environmental contaminants in foods. *Journal of Chromatography A* 1449:17–29. doi: 10.1016/j.chroma.2016.04.052.

Havelaar, A. H., M. D. Kirk, P. R. Torgerson, H. J. Gibb, T. Hald, R. J. Lake, N. Praet, D. C. Bellinger, N. R. de Silva, N. Gargouri, et al. 2015. World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010. *PLoS Medicine* 12 (12):e1001923. doi: 10.1371/journal.pmed.1001923.

He, Y., F. Mo, D. Chen, L. Xu, Y. Wu, and FFu Fu. 2017. Capillary electrophoresis inductively coupled plasma mass spectrometry combined with metal tag for ultrasensitively determining trace saxitoxin in seafood. *Electrophoresis* 38 (3–4):469–76. doi: 10.1002/elps.201600411.

Hennig, K., R. C. H. de Vos, C. Maliepaard, M. Dekker, R. Verkerk, and G. Bonnema. 2014. A metabolomics approach to identify factors influencing glucosinolate thermal degradation rates in Brassica vegetables. *Food Chemistry* 155:287–97. doi: 10.1016/j.foodchem.2014.01.062.

Hoffmann, J. F., I. R. Carvalho, R. L. Barbieri, C. V. Rombaldi, and F. C. Chaves. 2017. Butia spp. (*Arecaceae*) LC-MS-based metabolomics for species and geographical origin discrimination . *Journal of Agricultural and Food Chemistry* 65 (2):523–32. doi: 10.1021/acs.jafc.6b03203.

Hori, K., T. Kiriyama, and K. Tsumura. 2016. A liquid chromatography time-of-flight mass spectrometry-based metabolomics approach for the discrimination of cocoa beans from different growing regions. *Food Analytical Methods* 9 (3):738–43. doi: 10.1007/s12161-015-0245-0.

Hou, X., J. Ma, X. He, L. Chen, S. Wang, and L. He. 2015. A stop-flow two-dimensional liquid chromatography method for determination of food additives in yogurt. *Analytical Methods* 7 (5):2141–8. doi: 10.1039/C4AY02855D.

Humpfer, E., B. Schütz, F. Fang, C. Cannet, M. Mörtter, H. Schäfer, and M. Spraul. 2015. Food NMR optimized for industrial use – An NMR platform concept. In *Magnetic resonance in food science: Defining food by magnetic resonance*, eds. F. Capozzi, L. Laghi, and P. S. Belton, 77. Cambridge, UK: RSC Publications.

Huo, Y., G. M. Kamal, J. Wang, H. Liu, G. Zhang, Z. Hu, F. Anwar, and H. Du. 2017. 1H NMR-based metabolomics for discrimination of rice from different geographical origins of China. *Journal of Cereal Science* 76:243–52. doi: 10.1016/j.jcs.2017.07.002.

Ibanez, C., C. Simo, V. Garcia-Canas, A. Cifuentes, and M. Castro-Puyana. 2013. Metabolomics, peptidomics and proteomics applications of capillary electrophoresis-mass spectrometry in foodomics: A review. *Analytica Chimica Acta* 802:1–13. doi: 10.1016/j.aca.2013.07.042.

Ismail, S., M. Maulidiani, M. Akhtar, F. Abas, I. Ismail, A. Khatib, N. Ali, and K. Shaari. 2017. Discriminative analysis of different grades of gaharu (*Aquilaria malaccensis Lamk.*) via 1H-NMR-based metabolomics using PLS-DA and random forests classification models. *Molecules* 22 (10):1612. doi: 10.3390/molecules22101612.

Jadhav, S. R. 2019. Identification of putative biomarkers specific to foodborne pathogens using metabolomics. In *Foodborne bacterial pathogens*, ed. A. Bridier, 149–64. Totowa, NJ: Humana Press.

Jadhav, S. R., R. M. Shah, A. V. Karpe, P. D. Morrison, K. Kouremenos, D. J. Beale, and E. A. Palombo. 2018. Detection of foodborne pathogens using proteomics and metabolomics-based approaches. *Frontiers in Microbiology* 9:3132. doi: 10.3389/fmicb.2018.03132.

Jaeger, D., A. Winkler, J. H. Mussgnug, J. Kalinowski, A. Goesmann, and O. Kruse. 2017. Time-resolved transcriptome analysis and lipid pathway reconstruction of the oleaginous green microalga *Monoraphidium neglectum* reveal a model for triacylglycerol and lipid hyperaccumulation. *Biotechnology for Biofuels* 10:197. doi: 10.1186/s13068-017-0882-1.

Jandrić, Z., M. Islam, D. Singh, and A. Cannavan. 2017. Authentication of Indian citrus fruit/fruit juices by untargeted and targeted metabolomics. *Food Control* 72:181–8. doi: 10.1016/j.foodcont.2015.10.044.

Jang, C., L. Chen, and J. D. Rabinowitz. 2018. Metabolomics and isotope tracing. *Cell* 173 (4):822–37. doi: 10.1016/j.cell.2018.03.055.

Jin, S., C. Song, S. Jia, S. Li, Y. Zhang, C. Chen, Y. Feng, Y. Xu, C. Xiong, Y. Xiang, et al. 2017. An integrated strategy for establishment of curcuminoid profile in turmeric using two LC-MS/MS platforms. *Journal of Pharmaceutical and Biomedical Analysis* 132:93–102. doi: 10.1016/j.jpba.2016.09.039.

Kamphorst, J. J., and I. A. Lewis. 2017. Editorial overview: Recent innovations in the metabolomics revolution. *Current Opinion in Biotechnology* 43:iv–vii. doi: 10.1016/j.copbio.2017.01.005.

Kaufmann, A. 2014. Combining UHPLC and high-resolution MS: A viable approach for the analysis of complex samples? *TrAC Trends in Analytical Chemistry*63:113–28. doi: 10.1016/j.trac.2014.06.025.

Kaufmann, A., P. Butcher, K. Maden, S. Walker, and M. Widmer. 2015. Reliability of veterinary drug residue confirmation: High resolution mass spectrometry versus tandem mass spectrometry. *Analytica Chimica Acta* 856:54–67. doi: 10.1016/j.aca.2014.11.034.

Kelly, J. R., C. Minuto, J. F. Cryan, G. Clarke, and T. G. Dinan. 2017. Cross talk: The microbiota and neurodevelopmental disorders. *Frontiers in Neuroscience* 11:490. doi: 10.3389/fnins.2017.00490.

Kendall, H., P. Naughton, S. Kuznesof, M. Raley, M. Dean, B. Clark, H. Stolz, R. Home, M. Y. Chan, Q. Zhong, et al. 2018. Food fraud and the perceived integrity of European food imports into China. *PLoS One* 13 (5):e0195817. doi: 10.1371/journal.pone.0195817.

Kessler, N., A. Bonte, S. P. Albaum, P. Mäder, M. Messmer, A. Goesmann, K. Niehaus, G. Langenkämper, and T. W. Nattkemper. 2015. Learning to classify organic and conventional wheat – A machine learning driven approach using the MeltDB 2.0 metabolomics analysis platform. *Frontiers in Bioengineering and Biotechnology* 3:35. doi: 10.3389/fbioe.2015.00035.

Kessler, N., H. Neuweger, A. Bonte, G. Langenkämper, K. Niehaus, T. W. Nattkemper, and A. Goesmann. 2013. MeltDB 2.0-advances of the metabolomics software system. *Bioinformatics (Oxford, England)* 29 (19):2452–9. doi: 10.1093/bioinformatics/btt414.

Kleigrewe, K., F. Aydin, K. Hogrefe, P. Piecuch, K. Bergander, E.-U. Würthwein, and H.-U. Humpf. 2012. Structure elucidation of new fusarins revealing insights in the rearrangement mechanisms of the *Fusarium* mycotoxin fusarin C. *Journal of Agricultural and Food Chemistry* 60 (21):5497–505. doi: 10.1021/jf3009469.

Kogel, K.-H. 2010. Transcriptome and metabolome profiling of field-grown transgenic barley lack induced differences but show cultivar-specific variances. *Proceedings of the National Academy of Sciences* 107:6198–203.

Kostidis, S., R. D. Addie, H. Morreau, O. A. Mayboroda, and M. Giera. 2017. Quantitative NMR analysis of intra- and extracellular metabolism of mammalian cells: A tutorial. *Analytica Chimica Acta* 980: 1–24. doi: 10.1016/j.aca.2017.05.011.

Kovac, J. 2019. Precision food safety: A paradigm shift in detection and control of foodborne pathogens. *mSystems* 4 (3):e00164-00119. doi: 10.1128/mSystems.00164-19.

Kuo, T. C., T. F. Tian, and Y. J. Tseng. 2013. 3Omics: A web-based systems biology tool for analysis, integration and visualization of human transcriptomic, proteomic and metabolomic data. *BMC Systems Biology* 7:64. doi: 10.1186/1752-0509-7-64.

Lamichhane, S., C. C. Yde, M. S. Schmedes, H. M. Jensen, S. Meier, and H. C. Bertram. 2015. Strategy for nuclear-magnetic-resonance-based metabolomics of human feces. *Analytical Chemistry* 87 (12): 5930–7. doi: 10.1021/acs.analchem.5b00977.

León, C., A. Cifuentes, and A. Valdés. 2018. Foodomics applications. In *Comprehensive analytical chemistry*, eds. J. Jaumot, C. Bedia, and R. Tauler, Vol. 82, 643–85. New York, NY: Elsevier.

Li, H., and J. Zhu. 2017. Targeted metabolic profiling rapidly differentiates *Escherichia coli* and *Staphylococcus aureus* at species and strain level. *Rapid Communications in Mass Spectrometry: RCM* 31 (19): 1669–76. doi: 10.1002/rcm.7949.

Li, M., X. Li, C. Han, N. Ji, P. Jin, and Y. Zheng. 2019. Physiological and metabolomic analysis of cold plasma treated fresh-cut strawberries. *Journal of Agricultural and Food Chemistry* 67 (14):4043–53. doi: 10.1021/acs.jafc.9b00656.

Li, Q., X. Liang, N. Guo, L. Hu, M. P. E, Y. Wu, X. Xue, L. Wu, and K. Wang. 2019. Protective effects of Bee pollen extract on the Caco-2 intestinal barrier dysfunctions induced by dextran sulfate sodium. *Biomedicine and Pharmacotherapy* 117:109200.

Li, S., Y. Park, S. Duraisingham, F. H. Strobel, N. Khan, Q. A. Soltow, D. P. Jones, and B. Pulendran. 2013. Predicting network activity from high throughput metabolomics. *PLoS Computational Biology* 9 (7):e1003123. doi: 10.1371/journal.pcbi.1003123.

Li, W., Z. J. Zhang, and F. G. Xu. 2018. Twins derivatization-based LC-MS: a promising quantitative tool for metabolomic analysis. *Bioanalysis* 10:1161–63.

Li, Y., J. Zhang, Y. Jin, L. Wang, W. Zhao, W. Zhang, L. Zhai, Y. Zhang, Y. Zhang, J. Zhou, et al. 2016. Hybrid quadrupole-orbitrap mass spectrometry analysis with accurate-mass database and parallel reaction monitoring for high-throughput screening and quantification of multi-xenobiotics in honey. *Journal of Chromatography A* 1429:119–26. doi: 10.1016/j.chroma.2015.11.075.

Lin, L., X. U. Dun-Ming, X. H. Shen, Z. G. Zhang, L. P. Chen, and C. X. Wang. 2014. Traceability of the wine in Bordeaux region from France based on liquid chromatography-quadrupole-time of flight tandem mass spectrometry. *Journal of Food Safety and Quality* 5: 2649–56.

Liu, Q., J. Wu, Z. Y. Lim, A. Aggarwal, H. Yang, and S. Wang. 2017. Evaluation of the metabolic response of *Escherichia coli* to electrolysed water by 1H NMR spectroscopy. *LWT - Food Science and Technology* 79:428–36. doi: 10.1016/j.lwt.2017.01.066.

Liu, Q., J. Wu, Z. Y. Lim, S. Lai, N. Lee, and H. Yang. 2018. Metabolite profiling of *Listeria innocua* for unravelling the inactivation mechanism of electrolysed water by nuclear magnetic resonance spectroscopy. *International Journal of Food Microbiology* 271:24–32. doi: 10.1016/j.ijfoodmicro.2018.02.014.

Liu, S. J., Y. N. Wu, and L. Chan. 2019. Application of metabonomics approach in food safety research – A review. *Food Reviews International*. doi: 10.1080/87559129.2019.1655571.

Löfstedt, T., and J. Trygg. 2011. OnPLS—A novel multiblock method for the modelling of predictive and orthogonal variation. *Journal of Chemometrics* 25:441–55. doi: 10.1002/cem.1388.

López-Ruiz, R., R. Romero-González, and A. G. Frenich. 2019. Metabolomics approaches for the determination of multiple contaminants in food. *Current Opinion in Food Science* 28:49–57. doi: 10.1016/j.cofs.2019.08.006.

Lopez-Sanchez, P., R. C. H. de Vos, H. H. Jonker, R. Mumm, R. D. Hall, L. Bialek, R. Leenman, K. Strassburg, R. Vreeken, T. Hankemeier, et al. 2015. Comprehensive metabolomics to evaluate the impact of industrial processing on the phytochemical composition of vegetable purees. *Food Chemistry* 168:348–55. doi: 10.1016/j.foodchem.2014.07.076.

Lucini, L., G. Rocchetti, D. Kane, and M. Trevisan. 2017. Phenolic fingerprint allows discriminating processed tomato products and tracing different processing sites. *Food Control* 73:696–703. doi: 10.1016/j.foodcont.2016.09.020.

Ma, J., X. Hou, B. Zhang, Y. Wang, and L. He. 2014. The analysis of carbohydrates in milk powder by a new "heart-cutting" two-dimensional liquid chromatography method. *Journal of Pharmaceutical and Biomedical Analysis* 91:24–31. doi: 10.1016/j.jpba.2013.11.006.

Maguire, M., and G. Maguire. 2017. The role of microbiota, and probiotics and prebiotics in skin health. *Archives of Dermatological Research* 309 (6):411–21. doi: 10.1007/s00403-017-1750-3.

Man, Y., G. Liang, A. Li, and L. Pan. 2017. Analytical methods for the determination of *Alternaria* mycotoxins. *Chromatographia* 80 (1): 9–22. doi: 10.1007/s10337-016-3186-x.

Marco-Ramell, A., M. Palau-Rodriguez, A. Alay, S. Tulipani, M. Urpi-Sarda, A. Sanchez-Pla, and C. Andres-Lacueva. 2018. Evaluation and comparison of bioinformatic tools for the enrichment analysis of metabolomics data. *BMC Bioinformatics* 19 (1):1. doi: 10.1186/s12859-017-2006-0.

Markley, J. L., R. Brüschweiler, A. S. Edison, H. R. Eghbalnia, R. Powers, D. Raftery, and D. S. Wishart. 2017. The future of NMR-based metabolomics. *Current Opinion in Biotechnology* 43:34–40. doi: 10.1016/j.copbio.2016.08.001.

Marshall, D. D., and R. Powers. 2017. Beyond the paradigm: Combining mass spectrometry and nuclear magnetic resonance for metabolomics. *Progress in Nuclear Magnetic Resonance Spectroscopy* 100:1–16. doi: 10.1016/j.pnmrs.2017.01.001.

Martinović, T., M. Šrajer Gajdošik, and D. Josić. 2018. Sample preparation in foodomic analyses. *Electrophoresis* 39 (13):1527–42. doi: 10.1002/elps.201800029.

Mie, A., K. H. Laursen, K. M. Åberg, J. Forshed, A. Lindahl, K. Thorup-Kristensen, M. Olsson, P. Knuthsen, E. H. Larsen, and S. Husted. 2014. Discrimination of conventional and organic white cabbage from a long-term field trial study using untargeted LC-MS-based metabolomics. *Analytical and Bioanalytical Chemistry* 406 (12):2885–97. doi: 10.1007/s00216-014-7704-0.

Montero, L., and M. Herrero. 2019. Two-dimensional liquid chromatography approaches in Foodomics - A review. *Analytica Chimica Acta* 1083:1–18. doi: 10.1016/j.aca.2019.07.036.

Nham, N. T., S. T. de Freitas, A. J. Macnish, K. M. Carr, T. Kietikul, A. J. Guilatco, C.-Z. Jiang, F. Zakharov, and E. J. Mitcham. 2015. A transcriptome approach towards understanding the development of ripening capacity in 'Bartlett' pears (*Pyrus communis* L.) . *BMC Genomics* 16:762. doi: 10.1186/s12864-015-1939-9.

Noor, E., S. Cherkaoui, and U. Sauer. 2019. Biological insights through omics data integration. *Current Opinion in Systems Biology* 15: 39–47. doi: 10.1016/j.coisb.2019.03.007.

Novotná, H., O. Kmiecik, M. Gałązka, V. Krtková, A. Hurajová, V. Schulzová, E. Hallmann, E. Rembiałkowska, and J. Hajšlová. 2012. Metabolomic fingerprinting employing DART-TOFMS for authentication of tomatoes and peppers from organic and conventional farming. *Food Additives & Contaminants: Part A* 29 (9):1335–46. doi: 10.1080/19440049.2012.690348.

Ossa, D. E. H., R. Gil-Solsona, G. A. Peñuela, J. V. Sancho, and F. J. Hernández. 2018. Assessment of protected designation of origin for Colombian coffees based on HRMS-based metabolomics. *Food Chemistry* 250:89–97. doi: 10.1016/j.foodchem.2018.01.038.

Palama, T. L., I. Canard, G. J. P. Rautureau, C. Mirande, S. Chatellier, and B. Elena-Herrmann. 2016. Identification of bacterial species by untargeted NMR spectroscopy of the exo-metabolome. *The Analyst* 141 (15):4558–61. doi: 10.1039/c6an00393a.

Patejko, M., J. Jacyna, and M. J. Markuszewski. 2017. Sample preparation procedures utilized in microbial metabolomics: An overview. *Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences* 1043:150–7. doi: 10.1016/j.jchromb.2016.09.029.

Patt, A., J. Siddiqui, B. Zhang, and E. Mathé. 2019. Integration of metabolomics and transcriptomics to identify gene-metabolite relationships specific to phenotype. In *Cancer metabolism*, ed. M. Haznadar, 441–68. Totowa, NJ: Humana Press.

Patti, G. J., O. Yanes, and G. Siuzdak. 2012. Innovation: Metabolomics: The apogee of the omics trilogy. *Nature Reviews. Molecular Cell Biology* 13 (4):263–9. doi: 10.1038/nrm3314.

Pérez-Ortega, P., F. J. Lara-Ortega, J. F. García-Reyes, B. Gilbert-López, M. Trojanowicz, and A. Molina-Díaz. 2016. A feasibility study of UHPLC-HRMS accurate-mass screening methods for multiclass testing of organic contaminants in food. *Talanta* 160:704–12. doi: 10.1016/j.talanta.2016.08.002.

Pickrahn, S., K. Sebald, and T. Hofmann. 2014. Application of 2D-HPLC/taste dilution analysis on taste compounds in aniseed (*Pimpinella anisum L.*). *Journal of Agricultural and Food Chemistry* 62 (38):9239–45. doi: 10.1021/jf502896n.

Picone, G., I. De Noni, P. Ferranti, M. A. Nicolai, C. Alamprese, A. Trimigno, A. Brodkorb, R. Portmann, A. Pihlanto, S. N. El, et al. 2019. Monitoring molecular composition and digestibility of ripened bresaola through a combined foodomics approach. *Food Research International* 115:360–8. doi: 10.1016/j.foodres.2018.11.021.

Pinu, F. R. 2015. Metabolomics—The new frontier in food safety and quality research. *Food Research International* 72:80–1. doi: 10.1016/j.foodres.2015.03.028.

Pinu, F. R. 2016. Early detection of food pathogens and food spoilage microorganisms: Application of metabolomics. *Trends in Food Science & Technology* 54:213–5. doi: 10.1016/j.tifs.2016.05.018.

Pinu, F. R., D. J. Beale, A. M. Paten, K. Kouremenos, S. Swarup, H. J. Schirra, and D. Wishart. 2019. Systems biology and multi-omics integration: Viewpoints from the metabolomics research community. *Metabolites* 9 (4):76. doi: 10.3390/metabo9040076.

Pinu, F. R., S. A. Goldansaz, and J. Jaine. 2019. Translational metabolomics: Current challenges and future opportunities. *Metabolites* 9 (6): 108. doi: 10.3390/metabo9060108.

Pinu, F. R., S. de Carvalho-Silva, A. Trovatti Uetanabaro, and S. Villas-Boas. 2016. Vinegar metabolomics: An explorative study of commercial balsamic vinegars using gas chromatography-mass spectrometry. *Metabolites* 6 (3):22. doi: 10.3390/metabo6030022.

Putignani, L., and B. Dallapiccola. 2016. Foodomics as part of the host-microbiota-exposome interplay. *Journal of Proteomics* 147:3–20. doi: 10.1016/j.jprot.2016.04.033.

Raamsdonk, L. M., B. Teusink, D. Broadhurst, N. Zhang, A. Hayes, M. C. Walsh, J. A. Berden, K. M. Brindle, D. B. Kell, J. J. Rowland, et al. 2001. A functional genomics strategy that uses metabolome data to reveal the phenotype of silent mutations. *Nature Biotechnology* 19 (1):45–50. doi: 10.1038/83496.

Raina-Fulton, R. 2014. A review of methods for the analysis of orphan and difficult pesticides: Glyphosate, glufosinate, quaternary ammonium and phenoxy acid herbicides, and dithiocarbamate and phthalimide fungicides. *Journal of AOAC International* 97 (4):965–77. doi: 10.5740/jaoacint.sgeraina-fulton.

Rath, S., A. H. Fostier, L. A. Pereira, A. C. Dioniso, F. de Oliveira Ferreira, K. M. Doretto, L. Maniero Peruchi, A. Viera, O. F. de Oliveira Neto, S. M. Dal Bosco, et al. 2019. Sorption behaviors of antimicrobial and antiparasitic veterinary drugs on subtropical soils. *Chemosphere* 214:111–22. doi: 10.1016/j.chemosphere.2018.09.083.

Rees, C., F. Franchina, K. Nordick, P. Kim, and J. Hill. 2017. Expanding the *Klebsiella pneumoniae* volatile metabolome using advanced analytical instrumentation for the detection of novel metabolites. *Journal of Applied Microbiology* 122 (3):785–95. doi: 10.1111/jam.13372.

Reichert, B., A. de Kok, I. R. Pizzutti, J. Scholten, C. D. Cardoso, and M. Spanjer. 2018. Simultaneous determination of 117 pesticides and 30 mycotoxins in raw coffee, without clean-up, by LC-ESI-MS/MS analysis. *Analytica Chimica Acta* 1004:40–50. doi: 10.1016/j.aca.2017.11.077.

Ren, J.-L., A.-H. Zhang, L. Kong, and X.-J. Wang. 2018. Advances in mass spectrometry-based metabolomics for investigation of metabolites. *RSC Advances* 8 (40):22335–50. doi: 10.1039/C8RA01574K.

Rešetar, D., S. K. Pavelić, and D. Josić. 2015. Foodomics for investigations of food toxins. *Current Opinion in Food Science* 4:86–91. doi: 10.1016/j.cofs.2015.05.004.

Reyes-Garcés, N., and E. Gionfriddo. 2019. Recent developments and applications of solid phase microextraction as a sample preparation approach for mass-spectrometry-based metabolomics and lipidomics. *TrAC Tends in Analytical Chemistry* 113:172–81.

Rodríguez-Carrasco, Y., G. Font, J. Mañes, and H. Berrada. 2013. Determination of mycotoxins in bee pollen by gas chromatography–tandem mass spectrometry. *Journal of Agricultural and Food Chemistry* 61 (8):1999–2005. doi: 10.1021/jf400256f.

Röhlig, R. M., and K.-H. Engel. 2010. Influence of the input system (conventional versus organic farming) on metabolite profiles of maize (*Zea mays*) kernels. *Journal of Agricultural and Food Chemistry* 58 (5):3022–30. doi: 10.1021/jf904101g.

Rosso, M. C., E. Liberto, N. Spigolon, M. Fontana, M. Somenzi, C. Bicchi, and C. Cordero. 2018. Evolution of potent odorants within the volatile metabolome of high-quality hazelnuts (*Corylus avellana L.*): Evaluation by comprehensive two-dimensional gas chromatography coupled with mass spectrometry. *Analytical and Bioanalytical Chemistry* 410 (15):3491–506. doi: 10.1007/s00216-017-0832-6.

Rowland, I., G. Gibson, A. Heinken, K. Scott, J. Swann, I. Thiele, and K. Tuohy. 2018. Gut microbiota functions: Metabolism of nutrients and other food components. *European Journal of Nutrition* 57 (1): 1–24. doi: 10.1007/s00394-017-1445-8.

Rubert, J., A. Monforte, K. Hurkova, G. Pérez-Martínez, J. Blesa, J. L. Navarro, M. Stranka, J. M. Soriano, and J. Hajslova. 2017. Untargeted metabolomics of fresh and heat treatment Tiger nut (*Cyperus esculentus L.*) milks reveals further insight into food quality and nutrition. *Journal of Chromatography A* 1514:80–7. doi: 10.1016/j.chroma.2017.07.071.

Rubert, J., L. Righetti, M. Stranska-Zachariasova, Z. Dzuman, J. Chrpova, C. Dall'Asta, and J. Hajslova. 2017. Untargeted metabolomics based on ultra-high-performance liquid chromatography-high-resolution mass spectrometry merged with chemometrics: A new predictable tool for an early detection of mycotoxins . *Food Chemistry* 224:423–31. doi: 10.1016/j.foodchem.2016.11.132.

Rubert, J., M. Zachariasova, and J. Hajslova. 2015. Advances in high-resolution mass spectrometry based on metabolomics studies for food – A review. *Food Additives & Contaminants: Part A* 32 (10): 1685–708. doi: 10.1080/19440049.2015.1084539.

Saito-Shida, S., S. Nemoto, and R. Teshima. 2015. Multiresidue determination of pesticides in tea by gas chromatography-tandem mass

spectrometry. *Journal of Environmental Science and Health, Part B* 50 (11):760–76. doi: 10.1080/03601234.2015.1058092.

Salari, M., E. Salami Shahid, S. H. Afzali, M. Ehteshami, G. O. Conti, Z. Derakhshan, and S. N. Sheibani. 2018. Quality assessment and artificial neural networks modeling for characterization of chemical and physical parameters of potable water. *Food and Chemical Toxicology* 118:212–9. doi: 10.1016/j.fct.2018.04.036.

Sales, C., M. I. Cervera, R. Gil, T. Portolés, E. Pitarch, and J. Beltran. 2017. Quality classification of Spanish olive oils by untargeted gas chromatography coupled to hybrid quadrupole-time of flight mass spectrometry with atmospheric pressure chemical ionization and metabolomics-based statistical approach. *Food Chemistry* 216: 365–73. doi: 10.1016/j.foodchem.2016.08.033.

Sampson, J. N., S. M. Boca, X. O. Shu, R. Z. Stolzenberg-Solomon, C. E. Matthews, A. W. Hsing, Y. T. Tan, B.-T. Ji, W.-H. Chow, Q. Cai, et al. 2013. Metabolomics in epidemiology: Sources of variability in metabolite measurements and implications. *Cancer Epidemiology, Biomarkers & Prevention* 22 (4):631–40. doi: 10.1158/1055-9965.EPI-12-1109.

Savolainen, O., M. V. Lind, G. Bergström, B. Fagerberg, A. S. Sandberg, and A. Ross. 2017. Biomarkers of food intake and nutrient status are associated with glucose tolerance status and development of type 2 diabetes in older Swedish women. *The American Journal of Clinical Nutrition* 106:1302–10.

Schueuermann, C., C. C. Steel, J. W. Blackman, A. C. Clark, L. J. Schwarz, J. Moraga, I. G. Collado, and L. M. Schmidtke. 2019. A GC-MS untargeted metabolomics approach for the classification of chemical differences in grape juices based on fungal pathogen. *Food Chemistry* 270:375–84. doi: 10.1016/j.foodchem.2018.07.057.

Senizza, B., G. Rocchetti, S. Ghisoni, M. Busconi, M. De Los Mozos Pascual, J. A. Fernandez, L. Lucini, and M. Trevisan. 2019. Identification of phenolic markers for saffron authenticity and origin: An untargeted metabolomics approach. *Food Research International* 126:108584. doi: 10.1016/j.foodres.2019.108584.

Shannon, P., A. Markiel, O. Ozier, N. S. Baliga, J. T. Wang, D. Ramage, N. Amin, B. Schwikowski, and T. Ideker. 2003. Cytoscape: A software environment for integrated models of biomolecular interaction networks. *Genome Research* 13 (11):2498–504. doi: 10.1101/gr.1239303.

Shepherd, L. V. T., C. A. Hackett, C. J. Alexander, J. A. Sungurtas, S. D. A. Pont, D. Stewart, J. W. McNicol, S. J. Wilcockson, C. Leifert, and H. V. Davies. 2014. Effect of agricultural production systems on the potato metabolome. *Metabolomics* 10 (2):212–24. doi: 10.1007/s11306-013-0573-2.

Shepherd, L. V. T., C. A. Hackett, C. J. Alexander, J. W. McNicol, J. A. Sungurtas, D. Stewart, K. F. McCue, W. R. Belknap, and H. V. Davies. 2015. Modifying glycoalkaloid content in transgenic potato – Metabolome impacts. *Food Chemistry* 187:437–43. doi: 10.1016/j.foodchem.2015.04.111.

Shewry, P. R., M. Baudo, A. Lovegrove, S. Powers, J. A. Napier, J. L. Ward, J. M. Baker, and M. H. Beale. 2007. Are GM and conventionally bred cereals really different? *TrAC Tends in Food Science & Technology* 18 (4):201–9. doi: 10.1016/j.tifs.2006.12.010.

Solsona, G., R. Boix, C. Ibáñez, and M. Sancho. 2018. The classification of almonds (*Prunus dulcis*) by country and variety using UHPLC-HRMS-based untargeted metabolomics. *Food Additives and Contaminants: Part A* 35:395–403.

Souard, F., C. Delporte, P. Stoffelen, E. A. Thévenot, N. Noret, B. Dauvergne, J.-M. Kauffmann, P. Van Antwerpen, and C. Stévigny. 2018. Metabolomics fingerprint of coffee species determined by untargeted-profiling study using LC-HRMS. *Food Chemistry* 245: 603–12. doi: 10.1016/j.foodchem.2017.10.022.

Springer, V., J. Jacksén, P. Ek, A. G. Lista, and Å. Emmer. Å. 2015. Capillary electrophoretic determination of fluoroquinolones in bovine milk followed by off-line MALDI-TOF-MS analysis. *Chromatographia* 78 (3–4):285–90. doi: 10.1007/s10337-014-2823-5.

Stewart, D., L. V. Shepherd, R. D. Hall, and P. D. Fraser. 2018. Crops and tasty, nutritious food – How can metabolomics help? *Annual Plant Reviews Online* 43:181–217.

Stoev, S. D. 2015. Foodborne mycotoxicoses, risk assessment and underestimated hazard of masked mycotoxins and joint mycotoxin effects or interaction. *Environmental Toxicology and Pharmacology* 39 (2):794–809. doi: 10.1016/j.etap.2015.01.022.

Subramanian, I., S. Verma, S. Kumar, A. Jere, and K. Anamika. 2020. Multi-omics data integration, interpretation, and its application. *Bioinformatics and Biology Insights* 14:1177932219899051.

Sugrue, I., C. Tobin, R. P. Ross, C. Stanton, and C. Hill. 2019. *Raw milk*, eds. L. Nero and A. F. De Carvalho, 259–72. Cambridge, MA: Academic Press.

Sun, H., H. Wang, R. Zhu, K. Tang, Q. Gong, J. Cui, Z. Cao, and Q. Liu. 2014. iPEAP: Integrating multiple omics and genetic data for pathway enrichment analysis. *Bioinformatics (Oxford, England)* 30 (5):737–9. doi: 10.1093/bioinformatics/btt576.

Sun, J., W. Liu, M. Zhang, P. Geng, Y. Shan, G. Li, Y. Zhao, and P. Chen. 2018. The analysis of phenolic compounds in daylily using UHPLC-HRMSn and evaluation of drying processing method by fingerprinting and metabolomic approaches. *Journal of Food Processing and Preservation* 42 (1):e13325. doi: 10.1111/jfpp.13325.

Tian, M., X. Xu, F. Liu, X. Fan, and S. Pan. 2018. Untargeted metabolomics reveals predominant alterations in primary metabolites of broccoli sprouts in response to pre-harvest selenium treatment. *Food Research International* 111:205–11. doi: 10.1016/j.foodres.2018.04.020.

Timári, I., C. Wang, A. L. Hansen, G. Costa Dos Santos, S. O. Yoon, L. Bruschweiler-Li, and R. Brüschweiler. 2019. Real-time pure shift HSQC NMR for untargeted metabolomics. *Analytical Chemistry* 91 (3):2304–11. doi: 10.1021/acs.analchem.8b04928.

Tomita, S., K. Saito, T. Nakamura, Y. Sekiyama, and J. Kikuchi. 2017. Rapid discrimination of strain-dependent fermentation characteristics among *Lactobacillus* strains by NMR-based metabolomics of fermented vegetable juice. *PLoS One* 12 (7):e0182229. doi: 10.1371/journal.pone.0182229.

Trygg, J., and S. Wold. 2003. O2-PLS, a two-block (X–Y) latent variable regression (LVR) method with an integral OSC filter. *Journal of Chemometrics* 17 (1):53–64. doi: 10.1002/cem.775.

Vignoli, A., V. Ghini, G. Meoni, C. Licari, P. G. Takis, L. Tenori, P. Turano, and C. Luchinat. 2019. High-throughput metabolomics by 1D NMR. *Angewandte Chemie (International ed. in English)* 58 (4): 968–94. doi: 10.1002/anie.201804736.

Wang, L., B. Yang, X. Zhang, and H. Zheng. 2001. Novel two-dimensional liquid chromatography–tandem mass spectrometry for the analysis of twenty antibiotics residues in dairy products. *Food Analytical Methods* 10:2010–17.

Welzenbach, J., C. Neuhoff, C. Looft, K. Schellander, E. Tholen, and C. Große-Brinkhaus. 2016. Different statistical approaches to investigate porcine muscle metabolome profiles to highlight new biomarkers for pork quality assessment. *PLoS One* 11 (2):e0149758. doi: 10.1371/journal.pone.0149758.

Willemse, C. M., M. A. Stander, J. Vestner, A. G. Tredoux, and A. de Villiers. 2015. Comprehensive two-dimensional hydrophilic interaction chromatography (HILIC) × reversed-phase liquid chromatography coupled to high-resolution mass spectrometry (RP-LC-UV-MS) analysis of anthocyanins and derived pigments in red wine. *Analytical Chemistry* 87 (24):12006–15. doi: 10.1021/acs.analchem.5b03615.

Wishart, D. S. 2019. NMR metabolomics: A look ahead. *Journal of Magnetic Resonance* 306:155–61. doi: 10.1016/j.jmr.2019.07.013.

Wishart, D. S., Y. D. Feunang, A. Marcu, A. C. Guo, K. Liang, R. Vázquez-Fresno, T. Sajed, D. Johnson, C. Li, N. Karu, et al. 2018. HMDB 4.0: The human metabolome database for 2018. *Nucleic Acids Research* 46 (D1):D608–17. doi: 10.1093/nar/gkx1089.

Havelaar A. H., M. D. Kirk, P. R. Torgerson, H. J. Gibb, T. Hald, R. J. Lake, N. Praet, D. C. Bellinger, N. R. de Silva, N. Gargouri, et al. World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010. *PLoS Medicine* 12:e1001923.

Xu, C., S. P. Couvillion, R. L. Sontag, N. G. Isern, Y. Maezato, S. R. Lindemann, T. R. Chowdhury, R. Zhao, B. R. Morton, R. J. Moore, et al. 2019. MetFish: A metabolomics platform for studying

microbial communities in chemically extreme environments. BioRxiv:518647.

Xu, Y.-J. 2017. Foodomics: A novel approach for food microbiology. *TrAC Trends in Analytical Chemistry* 96:14–21. doi: 10.1016/j.trac.2017.05.012.

Xu, Y.-J., C. Wang, W. E. Ho, and C. N. Ong. 2014. Recent developments and applications of metabolomics in microbiological investigations. *TrAC Trends in Analytical Chemistry* 56:37–48. doi: 10.1016/j.trac.2013.12.009.

Yang, X., S. Wei, B. Liu, D. Guo, B. Zheng, L. Feng, Y. Liu, F. A. Tomás-Barberán, L. Luo, D. Huang, et al. 2018. A novel integrated non-targeted metabolomic analysis reveals significant metabolite variations between different lettuce (*Lactuca sativa*. L) varieties. *Horticulture Research* 5:33. doi: 10.1038/s41438-018-0050-1.

Yao, R., M. Heinrich, Y. Zou, E. Reich, X. Zhang, Y. Chen, and C. S. Weckerle. 2018. Quality variation of Goji (fruits of *Lycium spp.*) in China: A comparative morphological and metabolomic analysis. *Frontiers in Pharmacology* 9:151. doi: 10.3389/fphar.2018.00151.

Yi, L., N. Dong, Y. Yun, B. Deng, D. Ren, S. Liu, and Y. Liang. 2016. Chemometric methods in data processing of mass spectrometry-based metabolomics: A review. *Analytica Chimica Acta* 914:17–34. doi: 10.1016/j.aca.2016.02.001.

Yuan, Y., Y. Zhao, J. Yang, Y. Jiang, F. Lu, Y. Jia, and B. Yang. 2017. Metabolomic analyses of banana during postharvest senescence by 1H-high resolution-NMR. *Food Chemistry* 218:406–12. doi: 10.1016/j.foodchem.2016.09.080.

Yue, W., W. Sun, R. S. P. Rao, N. Ye, Z. Yang, and M. Chen. 2019. Non-targeted metabolomics reveals distinct chemical compositions among different grades of Bai Mudan white tea. *Food Chemistry* 277:289–97. doi: 10.1016/j.foodchem.2018.10.113.

Zhang, A., Q. Liu, H. Zhao, X. Zhou, H. Sun, Y. Nan, S. Zou, C. W. Ma, and X. Wang. 2016. Phenotypic characterization of nanshi oral liquid alters metabolic signatures during disease prevention. *Scientific Reports* 6:19333. doi: 10.1038/srep19333.

Zhang, H., J.-M. Jiang, D. Zheng, M. Yuan, Z.-Y. Wang, H.-M. Zhang, C.-W. Zheng, L.-B. Xiao, and H.-X. Xu. 2019. A multidimensional analytical approach based on time-decoupled online comprehensive two-dimensional liquid chromatography coupled with ion mobility quadrupole time-of-flight mass spectrometry for the analysis of ginsenosides from white and red ginsengs. *Journal of Pharmaceutical and Biomedical Analysis* 163:24–33. doi: 10.1016/j.jpba.2018.09.036.

Zhang, Q., S. Wu, Y. Li, M. Liu, K. Ni, X. Yi, Y. Shi, L. Ma, L. Willmitzer, and J. Ruan. 2019. Characterization of three different classes of non-fermented teas using untargeted metabolomics. *Food Research International* 121:697–704. doi: 10.1016/j.foodres.2018.12.042.

Zhang, Z., X. Hu, Q. Zhang, and P. Li. 2016. Determination for multiple mycotoxins in agricultural products using HPLC-MS/MS via a multiple antibody immunoaffinity column. *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences* 1021:145–52. doi: 10.1016/j.jchromb.2016.02.035.

Zhao, L., X. Zhao, Je Wu, X. Lou, and H. Yang. 2019. Comparison of metabolic response between the planktonic and air-dried *Escherichia coli* to electrolysed water combined with ultrasound by 1H NMR spectroscopy. *Food Research International* 125:108607. doi: 10.1016/j.foodres.2019.108607.

Zhao, X., Je Wu, L. Chen, and H. Yang. 2019. Effect of vacuum impregnated fish gelatin and grape seed extract on metabolite profiles of tilapia (*Oreochromis niloticus*) fillets during storage. *Food Chemistry* 293:418–28. doi: 10.1016/j.foodchem.2019.05.001.

Zhao, Y., X. Wu, L. Yu, and P. Chen. 2017. Retention of polyphenols in blueberries (*Vaccinium corymbosum*) after different cooking methods, using UHPLC–DAD–MS based metabolomics. *Journal of Food Composition and Analysis* 56:55–66. doi: 10.1016/j.jfca.2016.12.003.

Zhu, G., S. Wang, Z. Huang, S. Zhang, Q. Liao, C. Zhang, T. Lin, M. Qin, M. Peng, C. Yang, et al. 2018. Rewiring of the fruit metabolome in tomato breeding. *Cell* 172 (1–2):249–61.e2. doi: 10.1016/j.cell.2017.12.019.

Zotti, M., L. D. Coco, S. A. D. Pascali, D. Migoni, S. Vizzini, G. Mancinelli, and F. P. Fanizzi. 2016. Comparative analysis of the proximate and elemental composition of the blue crab Callinectes sapidus, the warty crab Eriphia verrucosa, and the edible crab Cancer pagurus. *Heliyon* 2 (2):e00075. doi: 10.1016/j.heliyon.2016.e00075.

Zuccato, V., C. Finotello, I. Menegazzo, G. Peccolo, and E. Schievano. 2017. Entomological authentication of stingless bee honey by 1H NMR-based metabolomics approach. *Food Control* 82:145–53. doi: 10.1016/j.foodcont.2017.06.024.