Chapter 5
Metabolomics of Food Systems

Sandip Kumar Patel, Bhawana George, Neeraj Jain, and Vineeta Rai

Abstract 'Food metabolomics' is an emerging area in metabolomics, enabling food processors and scientists to understand the biochemistry and composition of food with precision, speed, and efficiency. The approach is applied to identify food resources and nutrition biomarkers, organic and genetically modified food authentication, geographic origin screening, and elucidation of environmental stress feedback in food resources and livestock research, quantitate and quantify dietary intake and exposure, and provide insights into the molecular mechanisms underlying sensory and nutritional characteristics. Food metabolomics encompasses plant to human nutrition ranging from soil quality, food resources, food processing to human nutrition. Understanding the bioactive and nutritional content of the food is becoming an emerging area of metabolomics. Since it's an emerging area, there are several challenges: lack of optimized workflow, uncharacterized metabolites, and lack of databases. Typical food metabolomics workflow includes targeted and untargeted metabolomics analysis in conjunction with chemometric analysis. Food databases help to characterize 'unknown metabolites.' This book chapter describes the recent trends and application of food metabolomics.

S. K. Patel
Department of Biosciences and Bioengineering, Indian Institute of Technology Bombay,
Powai, Mumbai, Maharashtra, India

Buck Institute for Research on Aging, Novato, CA, USA

B. George
Department of Hematopathology, The University of Texas MD Anderson Cancer Center,
Houston, TX, USA

N. Jain
Department of Medical Oncology and Hematology, All India Institute of Medical Sciences,
Rishikesh, Uttarakhand, India

V. Rai (✉)
Department of Entomology & Plant Pathology, North Carolina State University,
Raleigh, NC, USA

Natural Product Chemistry, Bayer Crop Science, West Sacramento, CA, USA
e-mail: vineetaiitbombay@gmail.com

V. K. Yata et al. (eds.), *Sustainable Agriculture Reviews 59*, Sustainable
Agriculture Reviews 59, https://doi.org/10.1007/978-3-031-21630-5_5

Keywords Food metabolomics · Soil quality · Food resources · Food processing · Human nutrition

5.1 Introduction

Metabolomics deals with the systematic analysis of endogenous and exogenous small molecules (<1kD) involved in primary or secondary metabolic processes. Metabolomics is fascinating due to the vast diversity of the metabolites classified into amino acids, lipids, nucleotides, carbohydrates, organic acids, etc. The organism's metabolic repertoire changes consistently and significantly during growth and development and interactions with environmental factors. The metabolic shifts thus represent the physiological state of the organism and have a strong correlation to the phenotype. Metabolomics is applied to all arena of biological sciences ranging from human health to agriculture (Kim et al. 2016; Tian et al. 2016). Assessing food quality is a prime area of the food industry today since there is increasing awareness among consumers regarding food safety and composition. Food metabolomics is an emerging area in metabolomics, enabling food processors and scientists to understand the biochemistry and composition of food more quickly and efficiently. With the ever-increasing population, reduction in agricultural lands, climate change, and environmental pollutants, food metabolomics analysis is imperative for food security and human health. This chapter focuses on metabolomics workflows, applications, and challenges in agriculture, livestock, processed food, human nutrition, and plant resource food. New advances such as food metabolomics databases, the application of metabolomics to screen genetically modified (GM) crops, and organic food are also discussed. This chapter also highlights the challenges in the food metabolomics research, such as sample preparation, data analysis, identification of unknown compounds.

5.2 Metabolomics Analysis

5.2.1 Study Design

The study design of metabolomics analysis should be based on the biological question. Two different metabolomics approaches are employed based on the analysis requirement: untargeted and targeted (Fig. 5.1). If the research is hypothesis-driven, primarily to recognize the prior characterized and biochemically annotated metabolites, then a **targeted approach** is preferred. The analysis could be undertaken quantitatively or semi-quantitatively based on the standards. **Untargeted metabolomics** is ideal for hypothesis development, as it simultaneously identifies and quantifies several unknown/known metabolites. The identification of unknown

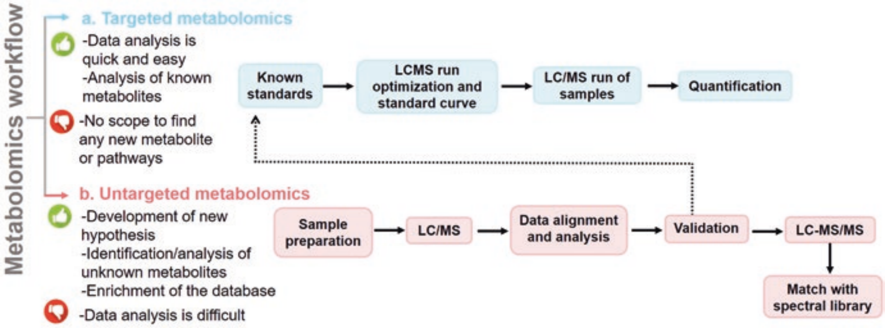

Fig. 5.1 Metabolomics workflows (**a**) targeted and (**b**) untargeted

features is performed by matching the metabolic MS/MS fingerprints with the public spectral library repository or standards, which leads to limited metabolite identification. Therefore, many potentially useful information in MS/MS data sets remains uncurated. Several *in silico* tools like Global Natural Product Social Molecular Networking (GNPS) could catalog the uncurated MS/MS data sets via a spectral correlation and visualization approach (Wang et al. 2016). Both methods have their advantages and limitations. There is no universal metabolomics workflow that is one-for-all due to vast metabolites complexity.

5.2.2 Sample Collection, Quenching, and Storage

Sample collection and storage are very critical. The metabolites are very dynamic; hence sampling time becomes essential, and samples should be collected systematically. Consistency is the key to sample collection, particularly for long-term experiments. Food habits, age, sex, social-economic status, geographic location, etc., should be considered for animal models or human subjects. Likewise, species, environmental factors like watering patterns, nutritional content, light, moisture, day-night cycles, and development stage should be accounted in plant study. The tissue/bacterial samples should be washed with buffer or water before storage to remove any media/external components. Likewise, for exometabolomics research, the samples should be filtered to remove any cells in the media. Further, samples may be spiked with the known concentration of metabolite “standard” to evaluate any degradation/change in the metabolite during storage. As soon as the samples are collected, they should be quenched with liquid nitrogen or solvents like methanol and stored at −80 °C until processed further.

5.2.3 *Workflow*

Typical metabolomics workflow (Fig. 5.2) includes
(i) **Study designing**, the most critical factor for any metabolomics study. Study design comprises but is not limited to asking the right question or hypothesis based on which sample size, controls, sampling time, metabolite extractions solvents/ methods, analytical tools, data analysis, etc., are decided.
(ii) **Metabolite extractions:** the intracellular metabolite extraction goals include separation of the small molecules from cell debris or other cellular biomolecules like protein, nucleic acids, etc. For the exometabolites, like the extraction of metabolites from the soil, the aim is to separate metabolites from the complex matrix. The metabolite extraction approaches should be consistent and minimize the losses due to biochemical/photochemical conversion or degradation. However, the biases are inevitable due to the wide dynamic range of metabolites and varying solubility quotient (Phapale et al. 2020). A wide range of solvent choices is available based on metabolite interest and chemistry. Apart from the solvent, temperature, pH, and desired molecular weight of the metabolite of interest should be considered. Monophasic and biphasic extraction approaches are employed based on the metabolites of interest. In monophasic extraction, only one solvent is used, while for biphasic extraction, a combination of polar and non-polar solvents are used to achieve a comprehensive metabolite coverage. Samples may be spiked with the known concentrations of standards to normalize for metabolite losses during extraction. Again, the standard spiked could be stable isotope-labeled (absolute standards) or pseudo standards that are primary or secondary metabolite not present in the experimental sample. For example, reserpine, curcumin (found exclusively in plants) could be spiked in serum/blood samples. Likewise, process control or negative control is vital to eliminate any contamination from leached pipette tips, centrifuge tubes or mass spec peak tubings, etc. Last but not least, sample homogenization should be considered; based on our information on the spatial localization of the metabolites, which suggests different regions of the tissue might have different concentrations or compositions of metabolites. The extracted metabolites should be aliquoted to prevent any metabolite degradation due to freeze-thaw.
(iii) **Sample complexity could be reduced on-line or off-line.** For on-line metabolite separation, liquid/gas chromatography (LC/GC), capillary electrophoresis (CE), and ion-mobility spectrometry (IMS) (Fig. 5.3) are attached to the mass spectrometry.

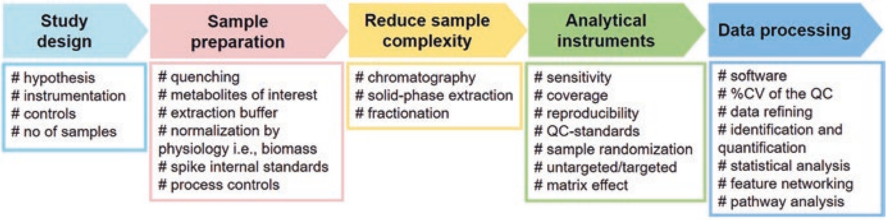

Fig. 5.2 Typical metabolomics workflow

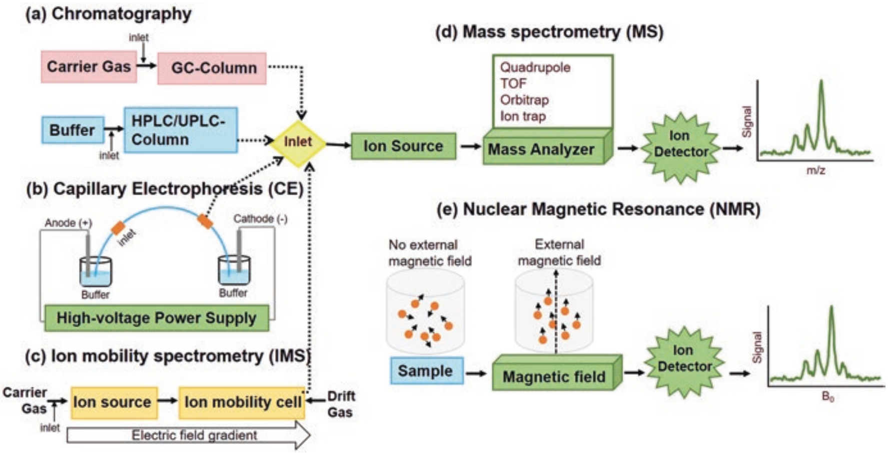

Fig. 5.3 (**a**) Chromatography, (**b**) capillary electrophoresis, (**c**) ion mobility spectrometry, (**d**) mass spectrometry, and nuclear magnetic resonance working principle

The most common off-line metabolite separation includes solid-phase extraction and LC-based fractionation based on the retention times. This step is essential in complex samples, where several masses co-elutes and make the data analysis challenging.
(iv) **Analytical instruments:** are selected based on experimental needs. For example, Gas-chromatography is employed to analyze the volatiles, or direct infusion mass spectrometry is used to analyze less complex metabolite extracts. GC uses gas (usually an inert gas or an unreactive gas) as a mobile phase and solid or liquid stationary phases. GC separation is highly robust as it separates metabolites based on vapourization temperatures. Thus, the technique is limited to the analysis (identification and semi-quantification) of molecules that are vaporized below 350–400 °C without decomposing or reacting with the GC components. Primarily to lower the vapor pressure, the metabolites are derivatized. LC uses liquid (acid, base, or neutral solvents) as a mobile phase and solid stationary phase. LC separation is highly variable and depends on the combination of mobile and solid phase, solvents, column properties like column material, length, diameter, pore size, temperature, etc. LC offers versatility and no or limited sample pre-processing requirement (Fig. 5.3a). CE separates ionized molecules in the liquid phase based on their electrophoretic mobility. The greater the electric field applied, the faster the mobility. Thus, the approach is inclusive for the analysis of ions (charged molecules) but not neutral species (Fig. 5.3b). IMS separates ionized molecules in the gas phase based on their mobility in a carrier buffer gas (Fig. 5.3c). Mass spectrometry (MS) measures the mass-to-charge ratio (*m/z*) of the ionized molecules. MS finds application in absolute or relative quantification of the metabolites, identify unknown molecules based on molecular weight and fragmentation patterns, a structure prediction. MS comprises three major components: ionization source, a mass analyzer, and an ion detector. The ionization source converts molecules to gas-phase ions, which could be negatively or positively charged. Hard and soft ionizations could be employed.

Hard ionization like Electron Impact ionization (EI) causes extensive fragmentation of the ions (ambiguous identification of the molecule weight) and is incompatible with LC, hence a method of choice for GC-MS. While soft ionization like electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), and matrix-assisted laser desorption ionization (MALDI) has gained popularity and increased the MS applications in metabolomics analysis. A mass analyzer sorts and separates the ionized molecules according to mass-to-charge (m/z) ratios. Quadrupole (Q), Time-of-flight (TOF), Ion trap, Orbitrap, etc., are few examples are mass analyzers that are interchangeably used for metabolomics analysis based on the prerequisites for sensitivity, precision, accuracy, or resolution. A detector detects the sorted ions, and a mass spectrum/chromatogram is generated representing the m/z ratio against intensity/relative abundance (Fig. 5.3d). Each technique has advantages and limitations (Johnson and Gonzalez 2012). To reduce the complexity of the analysis, lower the sample volume and minimize analytical variation, several separation-free MS techniques like direct infusion-MS, MALDI-MS, mass spectrometry imaging (MSI), and direct analysis in real-time (DART)-MS are gaining popularity. Mass spectrometry imaging (MSI) has revolutionized MS-based metabolomics by providing spatial resolution. MSI is operated in two modes: imaging (Stoeckli et al. 2001) to correlate with histology and profiling to know the overall metabolites (Cornett et al. 2006). MSI technique is applied in broad areas of plant biology, including development, defense, and responses to abiotic and biotic stress, and the developing field of spatial-temporal metabolomics. Nuclear Magnetic Resonance (NMR) relies on detecting the electromagnetic signals generated due to the perturbation of the nuclei in a weak oscillating magnetic field (Fig. 5.3e). NMR finds application in quantifying the known compounds or identifies unknown compounds based on the match against the spectral libraries, or infer the basic structures. Chromatography or reducing the metabolite complexity is essential to reduce the matrix effect, identify reteition time that adds third dimention to the MS data, and enhance the MS/MS data quality.

(v) **Data analysis:** the aim of the data analysis is to get rid of the aritifacts, contaminants and redundant peaks, identify/quantify biologically relevant peak and statistical and pathway analysis. Metabolomics data analyis could be performed using propriety tools like mass propessional profiler (MPP), compound discoverer, etc., or open source tools like mzMine or XCMS. Metabolomics data analysis pipeline is shown in Fig. 5.4.

5.3 Food Metabolomics

‘Food metabolomics‘is the application of metabolomics in food systems, including processes from agriculture-to-human nutrition: (a) soil quality, (b) food resource, (c) food processing, and (d) human nutrition (Fig. 5.5).

Considering the constant change and evolution in the food supply and the ever-increasing and continuous launch of new products and formulations into the marketplace, there is a need to keep track of the vital food metabolites. Moreover, raw

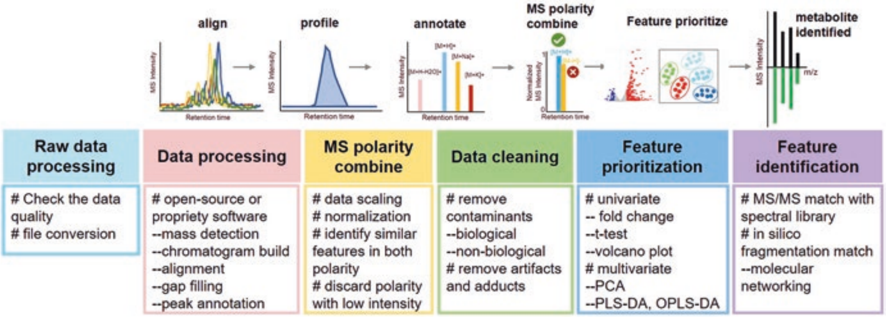

Fig. 5.4 Untargeted metabolomics data analysis workflow

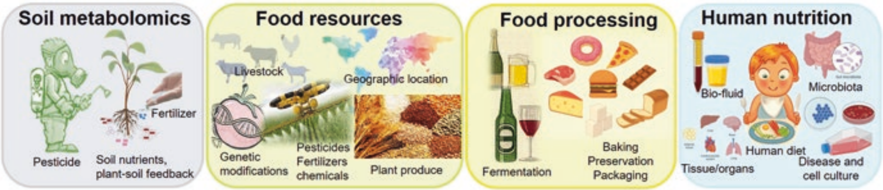

Fig. 5.5 Applications of food metabolomics

agricultural products, their composition like nutritional value, assimilated environmental contaminants, pesticides, etc., are also continually changing, leading researchers, nutritionists, and food policymakers to emphasize beyond single nutrients to develop holistic nutrition plans foods, food groups, and dietary patterns. Also, there is a growing urge for transparent and easily accessible information about nutrients and other food components. Typical workflow and challenges encountered to perform food metabolomics experiments are shown in Fig. 5.6.

Several natural and non-natural food metabolomics annotated databases are made available in the public domain (Table 5.1). Briefly, food databases are in place to get the list of possible metabolites, chemical and biological properties, structures, spectral data, related metabolic pathways, and their presence or concentration in food products based on the query m/z or elemental formula. Recently USDA launched an integrated, research-focused data system, ‘FoodData Central,’ that provides expanded data on nutrients and other food components and links to sources of related agricultural, food, dietary supplement, and additional information (https://fdc.nal.usda.gov/). The data in FoodData Central includes five data types, including Foundation Foods and Experimental Foods. In a similar effect, Dr. David Wishart Research Group at the University of Alberta annotated a comprehensive 28,000 food metabolite ‘FooDB’ (http://www.foodb.ca/) that comprises food constituents flavor, color, taste, texture, and aroma. Various European research groups have also taken the initiative to develop databases with tailored phytochemical components of the food metabolome. One such example is Phenol Explorer, which comprises 500

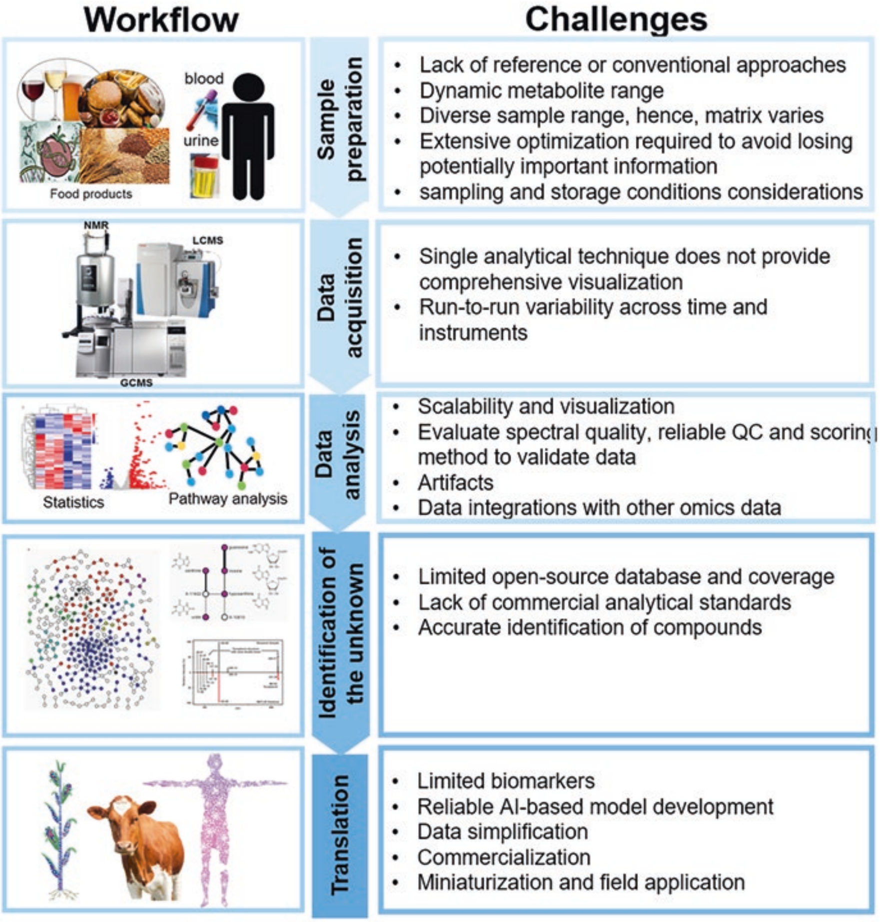

Fig. 5.6 Food metabolomics workflow and challanges

dietary polyphenols and their known human metabolites in over 400 foods (Rothwell et al. 2012). A similar ongoing project is PhytoHUB that will contain a comprehensive inventory of dietary phytochemicals and their human metabolites and structures either obtained from previous publications or predicted *in silico* (http://phytohub.eu/).

5.3.1 Soil Quality

Soil quality is one of the most critical factors determining plant health. The typical soil quality indicators are organic matter content, salinity, tilth, compaction, available nutrients, rooting depth, and microbial populations. Untargeted soil

Table 5.1 List of food metabolomics databases

#	Food metabolomics database	Information included	Public data
1	FoodData Central	Foods, compounds	Yes
2	FOODB	Foods, compounds	Yes
3	Exposome-Explorer	Foods, compounds, diseases	Yes
4	FoodComEx	Food compounds	Yes
5	PhytoHub	Food compounds	Yes
6	Phenol-Explorer	Polyphenol content in foods	
7	Human Metabolome Database (HMDB)	Small molecule metabolites	Yes
8	Chemical Entities of Biological Interest (ChEBI)	Small molecule metabolites	Yes
9	Dictionary of Food Compounds	Small molecule metabolites	No
10	KNApSAcK Core System	Plant metabolites	Yes
11	Dr. Duke's Phytochemical and Ethnobotanical Databases	Plant metabolites	Yes

metabolomics approaches are used to analyze extractable organic matter using LCMS (Swenson et al. 2015) and NMR (Johns et al. 2017) or discriminate the suppressive and non-suppressive soils for disease resistance (Rochfort et al. 2015). Soil metabolomics is also employed to assess the microbial (Boiteau et al. 2019; Rai et al. 2020) and plant metabolites (Petriacq et al. 2017; van Dam and Bouwmeester 2016) in soil.

Rai et al. has recently developed a high throughput method for the extraction and quantification of siderophores, highly specialized iron-chelating secondary metabolite, in the soil (Rai et al. 2020). Siderophores have ecological significance and find application as a biomarker for soil quality, the remedy of polluted sites, and improving nutrient metal uptake by crops or other plants. The detection and quantification of soil metabolites are challenging due to the complexity of soil matrix and metabolites' structural diversity. The workflow has the potentials to identify the soil biomarkers of plant health, as both plants and microbes secrete siderophores in response to iron limitation or cataloging soil-borne plant pathogens, a prerequisite for food security. On the other hand, identifying siderophores from beneficial rhizosphere bacteria can protect plants from pathogens and their virulence factors and keep them healthy. A yet another potential is discovering novel siderophores in the soil, which is obscure due to our inability to culture microbes in laboratory conditions. Microbes' critical need to sequester essential iron provides an achilles heel for new antibiotic development by utilizing the siderophore-based molecular recognition covalently attached to antimicrobial peptides. The unique metabolites of the soil-borne pathogens are used as biomarkers for plant diseases such as macrocarpa for *Rhizoctonia solani*-suppressive soil (Hayden et al. 2019) or siderophore of beneficial bacteria that promotes or inhibits *Ralstonia solanacearum* infections (Pollak and Cordero 2020). Metabolomics is also employed to investigate the impact of soil microbial population on the leaf metabolome and herbivore feeding behavior (Badri et al. 2013).

5.3.2 Food Resources

Environmental factors such as geographical origins, application of chemicals (fertilizers, pesticides, industrial wastes), stress (abiotic and biotic), and genetic factors, including genetically modified (GM) crops in agriculture, significantly influence food resource production (Kim et al. 2016). Advancements in the analytical tools and ease to analyze a wide variety of plant samples ranging with varying culture conditions, geographic locations, growing seasons, exposure to stress, etc., could lead to the assessment of food resource quality changes due to environmental and genetic factors.

5.3.2.1 Metabolomics to Screen Geographic Origin

Geographical origins of food resources affect the quality and the prices, and hence is becoming an important issue for consumers and producers due to increasing international trade. It is almost impossible to determine the geographical origins of food resources by their phenotypes. Metabolomics is thus employed as a tool to assess the legitimacy and source of specific food resources such as hazelnuts (Klockmann et al. 2017), tobacco (Zhao et al. 2015), coffee (Arana et al. 2015), green tea (Lee et al. 2015), Spanish Extra Virgin Olive Oils (Gil-Solsona et al. 2016), grape (Teixeira et al. 2014), wine (Amargianitaki and Spyros 2017), milk and dairy products (Brescia 2005; Renou et al. 2004), honey (Zhou et al. 2018b), fish, and seafood (Cubero-Leon et al. 2014), beef (Man et al. 2021) since the metabolite profiles differ depending on their geographical origins. NMR fingerprinting is used to differentiate coffee beans based on country of origin (Arana et al. 2015). Zhao et al. correlated metabolite changes of carbon and nitrogen pools in tobacco plants from two different locations due to climatic factors such as rainfall and temperature (Arana et al. 2015).

5.3.2.2 Metabolomics for Organic Food Authentication

There is an increasing demand for **organic products**, and hence organic food items are expensive. The lack of reliable chemical markers to discriminate between organic and conventional products makes them an attractive target for fraudulent malpractices. Metabolomics could solve this problem by precisely detecting and quantifying the chemicals like pesticides or fertilizers in food products. The ability of metabolomics to detect unknown targets is particularly beneficial to identify/detect new adulterants. A non-targeted metabolomics approach identifies food markers that discriminate between organic and conventional tomato crops (Martínez Bueno et al. 2018). Also, the presence of pesticides is determined in the amphibian liver (Van Meter et al. 2018), urine samples of healthy individuals (Reisdorph et al. 2020), and pregnant women (Sem et al. 2013). Growers sometimes apply growth promoter substances like testosterone, progesterone, auxin, and gibberellins beyond permissible limits to improve food resources quality and production yield. Metabolomics has recently been introduced as a new tool to detect illegal and excessive uses of growth promoters (Rodriguez-Celma et al. 2011; Šimura et al. 2018; Stephany 2010).

Organic agricultural systems rely on non-conventional soil fertilization techniques like the application of organic manures, biological pest controls, and multiannual crop rotation, including legumes and other green manure crops. In contrast, chemical plant protection products, including pesticides, are applied to protect plants in conventional agriculture. Organic production systems increase the susceptibility of the plants to pathogens, hence resulting in the accumulation of inducible protective secondary metabolites such as phenolics; chlorogenic acid (Malik et al. 2009; Novotná et al. 2012; Young et al. 2005), and flavonoids (Mitchell et al. 2007). Metabolomics studies distinguish conventionally and organically grown produces (Martínez Bueno et al. 2018; Novotná et al. 2012; Vallverdu-Queralt et al. 2011). Factors such as plant response, rhizosphere microbiome are accountable (Bradi et al. 2013).

5.3.2.3 Metabolomics to Screen Genetically Modified (GM) Crops

Genetically modified (GM) food crops are resistant to diseases, pests, and unfavorable environmental conditions, produce high-quality foods with less effort and lower costs; however, GM food resources continue to be a controversial issue due to their safety and relation to human health and the environment (Simo et al. 2014). Organization for Economic Co-operation and Development (OECD), comprising 37 member countries, is established to globally deal with GM food resources safety issues (Kearns et al. 2021). OECD and European Food Safety Authority (EFSA) has developed guidance and regulations for GM crops to evaluate their safety and nutritional value (Bedair and Glenn 2020). Metabolomics provides comprehensive information about GM food composition compared to their corresponding non-GM counterparts (Simo et al. 2014). Metabolomics is effectively employed to assess the safety of widely consumed GM maize by comparing plasma metabolome and fecal microbiota in GM maize and non-GM near-isogenic maize-fed rats (Mesnage et al. 2019). Metabolomics is also employed to evaluate and assess GM food resources such as soybean (Garcia-Villalba et al. 2008; Inaba et al. 2007), rice (Jiao et al. 2010; Zhou et al. 2009), maize (Frank et al. 2012; Piccioni et al. 2009), wheat (Baker et al. 2006), tomato (Kusano et al. 2011b; Noteborn et al. 2000), potato (Catchpole et al. 2005), poplar (Srivastava et al. 2013), carrot (Cubero-Leon et al.

2018), and barley (Kogel et al. 2010). A recent study of GM rice with *Cr1C* gene transformation showed no significant difference in metabolic profile than the parent line (Chang et al. 2021). Another study reported differential metabolite profiles between wild-type and *cryIAc* and *sck* genes; for improving insect resistance in GM rice (Zhou et al. 2009). Targeted quantitative metabolomics could provide additional information for safety and nutritional assessment for GM crops with traits known to modify metabolic pathways. Integrating metabolomics with other omics data provides more comprehensive knowledge about risk assessment of GM crops (Kok et al. 2019). Metabolomics application for the safety assessment of GM crops, which is ever-growing and introduced to the global market, provides relevant information regarding the associated metabolite alteration. The challenges faced in such metabolomics applications include chemical complexity, identification of unknown metabolites, matrix effect as each plant is different, and dynamic concentration range. One key hurdle in using data from omics studies with GM crops, including metabolomics, is the difficulty to assess whether there is any impact on safety in the observed differences amongst the 1000s of signals characterized by the untargeted profiling method(s) (Bedair and Glenn 2020). Application of metabolomics to screen GM crops is infancy, and to get a comprehensive understanding of the detected metabolite changes in a biological context, big-data generated needs to be analyzed together with other 'omics' data such as proteomics and transcriptomics as proposed by the new Foodomics strategy (Ibanez et al. 2012). The development of advanced tools and databases is essential for metabolomics studies.

5.3.2.4 Metabolomics to Elucidate Environmental Stress Feedback in Food Resources

Environmental stress (biotic/abiotic) is a major limiting factor of agriculture production, affecting both yields and nutritional content. The early detection of stress symptoms could help reduce loss. Plant metabolomics has emerged as the most promising tool to decipher the metabolic changes caused by (a) climatic and seasonal variations, (b) biotic factors including pathogens and beneficial/symbiotic associations (Alseekh and Fernie 2018) for high-quality food resource production since the last decade.

Abiotic stress is responsible for global crop yield reduction ranging from 50% to 70% (Boyer 1982). Climate change and population growth have worsened the situation (Raza et al. 2019). Understanding plants' responses to such stressors to determine methods for improving crops quantitatively and qualitatively is inevitable. Abiotic stress in plants leads to the synthesis of phytohormones to impart stress resistance (Han et al. 2012; Rai et al. 2016); the oxidative stress disturbs the stomatal conductance and activates several signaling mechanisms and the dysregulated gene expression profiles (Rai et al. 2016). In particular, all essential plants' mechanisms from germination to maturity are severely affected by abiotic stresses. The major abiotic plant health stressors include drought, salinity, temperature extremes, waterlogging, heavy metal, and chilling. Metabolomics has been applied for probing unique metabolites that regulate the abiotic stress tolerance mechanism in crops with two prime objectives: (i) identification of biomarkers for abiotic stress and (ii) investigate metabolic variations under abiotic stresses to detect different metabolites that permit restoration of plant homeostasis and normalize metabolic modifications (Arbona et al. 2013). **Water deficit (drought)** caused by global climate changes seriously endangers plant survival and crop productivity (Lesk et al. 2016). Metabolic profiling of drought-stressed wheat (Michaletti et al. 2018), barley (Chmielewska et al. 2016), rice (Lawas et al. 2019), and soybean (Das et al. 2017) are carried out to elucidate vital metabolites/biomarkers for drought tolerance. Soil **Salinity** is rapidly increasing, and about 20% of irrigated land is salt-affected. Salinity stress causes >20% losses in crop plants (Food and Agriculture Organization 2015). The GC-MS-based metabolic profiling of two salt-sensitive (Sujala and MTU 7029) and tolerant varieties (Bhutnath, and Nonabokra) of indica rice showed accumulation of two signaling molecules, serotonin, and gentisic acid, which may serve as a biomarker to produced salt-tolerant rice varieties (Gupta and De 2017). Metabolomics is employed to study metabolic remodeling due to salinity stress in several other crop plants like tomato (Rouphael et al. 2018), millet (Pan et al. 2020), strawberry (Antunes et al. 2019). **Temperature stress,** including heat (Abdelrahman et al. 2020; Escandon et al. 2018; Raza 2020) or cold (Furtauer et al. 2019; Xu et al. 2020), disturbs the homeostasis and physiological mechanisms. Metabolomics analysis of temperature-stressed wheat (Qi et al. 2017; Thomason et al. 2018), tomato (Almeida et al. 2020; Paupiere et al. 2017; Zhang et al. 2019), and maize (Obata et al. 2015; Sun et al. 2016; Urrutia et al. 2021) are studied to identify the effect of temperature stress. **Heavy metal** stress has become a significant concern on various terrestrial ecosystems due to extensive industrialization (Guerrero et al. 2019; Shahid et al. 2015). Suboptimal concentrations of trace metals such as Zn, Cu, Mo, Mn, Co, Ni, As, Pb, Cd, Hg, Cr, and Al reduce crop metabolism, growth, and productivity (Tiwari and Lata 2018). Metabolomics analysis of high Zn and Cu treated beans (Jahangir et al. 2008), Zn-deficient tea plants (Zhang et al. 2017), heavy metal stressed (Cu, Fe, and Mn) Brassica rapa (Jahangir et al. 2008), Cr-toxicated sunflower (Gonzalez Ibarra et al. 2017) and Fe-toxicated rice (Turhadi et al. 2019) are performed. A better understanding of the **nutrient-limitation**, including macro- and micro-nutrients, would enhance the food/fodder nutritional contents. Metabolic changes due to macro-nutrient: nitrogen (Kusano et al. 2011a; Rai et al. 2017), phosphorus (Jones et al. 2018; Vance et al. 2003), and potassium (Zeng et al. 2018), deficiency has been studied in plants/microalgae using HPLC and enzymatic activities (Scheible et al. 2004; Tschoep et al. 2009), FT-ICR-MS (Hirai et al. 2004), LC-MS (Peng et al. 2008), GC-MS (Heyneke et al. 2017; Urbanczyk-Wochniak and Fernie 2005), CE-MS (Takahara et al. 2010; Takahashi et al. 2009), 1H-NMR (Broyart et al. 2010).

Plant-microbe (pathogenic/beneficial) interactions (**Biotic factors**) trigger a plethora of primary and secondary metabolites changes, which could be easily detected by metabolomics (Allwood et al. 2008; Castro-Moretti et al. 2020). A wide range of phytopathogens, including fungi, bacteria, viruses, viroids, mollicutes, parasitic higher plants, and protozoa, are known to cause plant disease. Metabolomics is an emerging tool to study plant-pathogen interactions (Castro-Moretti et al. 2020). An integrated metabolo-proteomic approach showed induced phenolic acid and phenylpropanoids in *Fusarium graminearum* infected wheat (Gunnaiah et al. 2012). NMR analysis indicated an increased accumulation of disease-resistant biomarkers (Sarrocco et al. 2016). Metabolomic analysis of the susceptible and resistant wheat cultivars infected with the fungal pathogen *Zymoseptoria tritici* showed that immune and defense-related metabolites in resistant and susceptible wheat cultivars using FT-ICR-MS (Seybold et al. 2020). Likewise, the metabolomics responses in wheat against viral infection; wheat streak mosaic virus (Farahbakhsh et al. 2019), rice against fungal infection; *Rhizoctonia solani* (Suharti et al. 2016), *Magnaporthe grisea* (Jones et al. 2010), insect attack; gall midge (Agarrwal et al. 2014), bacterial infection; *Xanthomonas oryzae* pv. oryzae (Sana et al. 2010), maize against fungal infection; *Fusarium graminearum* (Zhou et al. 2018a), southern corn leaf blight (Vasmatkar et al. 2019), and insect attack; *Ostrinia furnacalis* (Guo et al. 2019) are studied. Adverse environmental conditions, including temperature, soil fertility, light, water deficit, give an edge to the pathogens and increase disease severity. However, we have very little knowledge about these tripartite interactions, suggesting future investigations towards understanding the multi-dimensional nature of plant-pathogen interactions in changing climate conditions (Velásquez et al. 2018). Weeds are yet another problem that impacts crop productivity at multiple levels, such as competing for nutrients, reducing crop yields and nutritional content, interfering with harvest efficiency, and recurrence. Metabolomics analysis of the canola plant extracts detected allelopathic metabolites (3,5,6,7,8-pentahydroxy flavones, p-hydroxybenzoic acid, and sinapyl alcohol) that inhibit the rye root and shoot development (Asaduzzaman et al. 2015). Similarly, weed-suppressing metabolites in wheat and legume are investigated (Latif et al. 2019).

5.3.2.5 Metabolomics in Livestock Research

Traditional livestock analysis, such as feed consumption, is time-consuming, expensive, and requires specific equipment (Karisa et al. 2014). Reproductive trait measurements need animals to reach the maturity stage, while carcass trait evaluation requires animal slaughter which otherwise could have been used for breeding. Metabolomics has emerged as an efficient, cost-effective, non-invasive way to detect animal traits for livestock research and industry. Livestock metabolomics is instrumental in animal breeding farm trials for efficient and quicker quantitative phenotyping (Karisa et al. 2014; te Pas et al. 2017) and is primarily applied for biomarker identification for weight gain, milk quality (D’Auria et al. 2013), health (LeBlanc et al. 2005), fertility (Chapinal et al. 2012), etc. The metabolomic signatures associated with feed efficiency in beef cattle (Novais et al. 2019), dairy cow (Saleem et al. 2012) is studied. Also, metabolomics is employed to analyze antimicrobial resistance in livestock pathogens like *E. coli* (Campos and Zampieri 2019; Lin et al. 2019). Livestock metabolomics experimental design should take diet, diurnal variations, sex, and sampling time into consideration to reduce variability. Shortage of data resources makes data interpretation a challenge in livestock metabolomics Goldansaz et al. created a livestock metabolome database of more than 1000 metabolites detected in livestock metabolomic studies on cattle, sheep, goats, horses, and pigs (Goldansaz et al. 2017). Bovine Metabolome Database is a recent collection of more than 50,000 metabolites focusing on animal health which describes a healthy range of metabolites in bovine biofluids and tissues (Foroutan et al. 2020).

5.3.3 Food Processing

Our modern lifestyle and the ever-growing global population have caused increased food processing industry demands. Food processing can be defined as the physical and/or chemical manipulation of raw food to enhance nutritional and sensory quality and sustainability. Some of the food processes where metabolomics is applied include cheese (Afshari et al. 2020), tomato purees (Capanoglu et al. 2008), tinned vegetables, biscuits (Diez-Simon et al. 2019), alcoholic beverages (Álvarez-Fernández et al. 2015; Ichikawa et al. 2019), yogurt (Settachaimongkon et al. 2015) and milk (Rocchetti et al. 2020). Metabolomics finds its role in the **food processing** industry ranging from food preparation, packaging, and storage. For instance, food preparation processes like pasteurization, fermentation, etc., could affect the food's nutritional and sensory quality either beneficially (improved digestibility, nutrients bioavailability, foodborne pathogens/toxins inactivation) or detrimentally (vitamins and nutrient loss, toxic compounds formation, conferring adverse effects on flavor, aroma, texture or color), monitored by metabolomics. Another exciting application of metabolomics is identifying the chemical species that contribute to flavor, texture, taste, and color quality, which could be used to develop meat using plants, considering the growing demand for plant-based foods (https://www.impossiblefoods.com/food). Metabolomics is applied in **food safety** for rapid and reliable monitoring of food contaminants (i) pesticides and other chemical residues like furans, dioxins, dioxin-like polychlorinated biphenyls (PCBs), non-dioxin-like PCBs (Tengstrand et al. 2012; Zainudin et al. 2015), (ii) foodborne pathogens like *Salmonella* sp., *E. coli* (Cevallos-Cevallos et al. 2011) and *Listeria* sp. (Jadhav et al. 2015), with short-term and long-term health risks (Pinu 2016). Predicting the end of shelf life before apparent spoilage (expiry date or best before) and determining effects of food processing on the shelf life is another application of metabolomics. For instance, metabolic profiling showed a correlation between diphenylamine oxidation treatment and extended shelf-life during storage in apples (Leisso et al. 2013). Likewise, the shelf life of meat at various storage temperatures was studied (Argyri et al. 2015). A comprehensive understanding of food metabolite composition during processing and storage will improve preservation methods. Metabolomic assessment of **food packaging** types is performed to detect contaminants and spoilage in packaging materials (Makkliang et al. 2015). Also, metabolomics could expand our understanding of the biodegradable materials used for packaging (Kleeberg et al. 1998) and microbial and plant strain improvement for efficient production of eco-friendly packaging materials.

5.3.4 Human Nutrition

Diet/nutrition is linked to metabolic disorders, including obesity, diabetes, cardiovascular disease, and aging (Shlisky et al. 2017). The traditional way to evaluate beneficial or detrimental effects of foods based on volunteers filling the questionnaires has several limitations: misreporting, bias and measurement error, high cost and time consumption, and unreliability for populations with cognitive impairment (Fallaize et al. 2014). Metabolomics is a powerful tool to overcome such limitations, and hence dietary biomarkers are emerging as an objective and accurate measure of dietary intake and nutrient status (O'Gorman et al. 2013). Novel metabolic signatures are associated with juice and fruits (Liu et al. 2015), grain, fish (Hanhineva et al. 2015), wine (Urpi-Sarda et al. 2015), and diet patterns (western vs. prudent) (Bouchard-Mercier et al. 2013). Also, metabolomics is used to monitor diet-related metabolic diseases (Sebedio 2017). LC/MS-based metabolic profiling suggested green tea mediated stimulation of hepatic lipid metabolism associated with obesity prevention (Lee et al. 2015). Likewise, the anti-hyperlipidemia effect of curcumin was demonstrated using NMR and MS-based metabolomics (Li et al. 2015). A yet another hot area of metabolomics research is the human gut-microbiota study. Recent studies have suggested that the gut microbiome secretes metabolites that impact human health (Dore and Blottiere 2015). Moreover, the gut microbiome varies between individuals and is greatly affected by diet. Interestingly, diet changes can manipulate the gut microbiome, currently being studied for use as a potential therapy (Shoaie et al. 2015). Selected food metabolomics studies are listed in Table 5.2.

5.4 Challenges in Food Metabolomics

Despite its enormous potential, there are several dark areas of food metabolomics: (i) lack of optimized workflow for sample processing, normalization, and data analysis, (ii) run-to-run variability, (iii) substantial matrix effects, (iv) limited spectral library coverage, (iv) availability of open-source data analysis tools and databases, and (v) lack of comprehensive guidelines for biomarker prediction and validation for food resources. To overcome the challenges of experimental design, power calculation should be performed to determine the sample size required for statistically significant results and reduce variability, particularly for field samples. Cultivated varieties, geographical location, and fertilization schemes should be taken into consideration. Quality control samples should be included to determine run-to-run

Table 5.2 Comprehensive list of food metabolomics study

Food metabolomics	Treatments	Tissue	Sample	Primary/Secondary metabolites	Analytical platform	Reference
Plant food resources	Genetic lines	Fruit	Apple	Primary and secondary	GC-MS	Cuthbertson et al. (2012)
		Fruit	Grape	Primary and secondary	1H NMR	Fortes et al. (2011)
		Fruit	Melon	Primary and secondary	1H NMR, FIE-MS, SPMEGC-MS, GC-MS	Allwood et al. (2014) and Bernillon et al. (2012)
		Fruit	Tomato	Primary and secondary	GC-MS, LC-MS	Gomez-Romero et al. (2010) and Schauer et al. (2006)
		Fruit	Pepper	Primary and secondary	LC-MS, GC-MS	Wahyuni et al. (2013)
		Flower	Broccoli	Primary and secondary	LC-MS	Sun et al. (2015)
		Leaf and fruit	Tomato	Primary	GC-MS	Roessner-Tunali et al. (2003)
		Grain	Rice	Primary and secondary	1H NMR, GC-MS	Calingacion et al. (2011) and Lou et al. (2011)
		Tuber	Potato	Primary	GC-MS	Roessner et al. (2000)
	Natural accessions	Tuber	Potato	Primary	GC–MS	Carreno-Quintero et al. (2012)
		Grain	Maize	Secondary	LC-MS	Lipka et al. (2013) and Owens et al. (2014)
		Vegetable	Tomato	Metabolome	GC–MS	Sauvage et al. (2014)
		Kernel	Maize	Primary and secondary	LC–MS	Shen et al. (2013) and Wen et al. (2014)
	Doubled haploid lines	Flag leaf	Wheat	Metabolites	LC–ESI–MS, GC-MS	Hill et al. (2013, 2015)

(continued)

Table 5.2 (continued)

Food metabolomics	Treatments		Tissue	Sample	Primary/Secondary metabolites	Analytical platform	Reference
	Chromosomal segment substitution lines		Seed	Rice	Primary	LC-Q-TOF-MS	Matsuda et al. (2012)
	Introgression lines		Vegetable	Tomato	Primary and secondary	GC–MS, LC-MS	Alseekh et al. (2015), Perez-Fons et al. (2014), Schauer et al. (2008), Schauer et al. (2006), and Toubiana et al. (2012)
	Abiotic stress	Drought	Leaf	Rice	Primary and secondary	GC/EI-TOF-MS	Degenkolbe et al. (2013), Do et al. (2013), and Ma et al. (2016)
			Leaf	Soybean	Primary	1H NMR	Silvente et al. (2012)
			Leaf	Sorghum	Primary and secondary	FT-IR and GC/MS	Ogbaga et al. (2016)
			Leaf	Maize	Primary	GC/MS	Obata et al. (2015)
			Multiple tissues	Maize	Primary	GC-TOF-MS	Witt et al. (2012)
			Immature kernels	Maize	Primary	RP/UPLC -MS/MS	Yang et al. (2018)
			Root, shoot, leaf and flag leaf	Wheat	Primary and secondary	GC-MS	Guo et al. (2018), Kang et al. (2019), and Yadav et al. (2019)

		Salt	Leaf and root	Rice	Primary and secondary	GC/MS, NMR	Chang et al. (2019), Gupta and De (2017), and Ma et al. (2018)
			Seedling	Rice	Primary and secondary	GC/MS	Gayen et al. (2019)
			Leaf	Wheat	Primary and secondary	GC/MS	Che-Othman et al. (2020) and Guo et al. (2015)
			Leaf	Maize	Primary and secondary	GC-MS	Zorb et al. (2013)
			Roots	Barley	Primary and secondary	GC-MS	Shelden et al. (2016)
			Roots and shoots	Wheat	Primary and secondary	HPLC	Borrelli et al. (2018)
			Terminal leaflet	Tomato	Primary and secondary	UHPLC-ESI/ QTOF-MS	Rouphael et al. (2018)
		Heat	Filling grains	Wheat	Primary and secondary	LC-MS/MS HPLC	Wang et al. (2018)
			Flag leaves	Wheat	Primary and secondary	LC-HRMS	Thomason et al. (2018)
		Waterlogging	Root and leaf	Soybean	Primary and secondary	CE/MS, NMR	Coutinho et al. (2018) and Komatsu et al. (2014)
			Leaf	Rice	Primary and secondary	GC/MS, NMR	Barding Jr. et al. (2013) and Locke et al. (2018)
			Shoot	Wheat	Primary and secondary	GC/MS, LC/MS	Herzog et al. (2018)

(continued)

Table 5.2 (continued)

Food metabolomics	Treatments		Tissue	Sample	Primary/Secondary metabolites	Analytical platform	Reference
	Biotic stress	*Zymoseptoria tritici*, *Fusarium graminearum*, Wheat streak mosaic virus, *Triticum turgidum*	Leaf	Wheat	Primary and secondary	FT-ICR-MS, NMR, LC-MS	Cuperlovic-Culf et al. (2019), Farahbakhsh et al. (2019), Seybold et al. (2020), and Shavit et al. (2018)
		Fusarium graminearum	Rachis and spikelet	Wheat	Primary and secondary	NMR, LC-LTQ-Orbitrap	Cuperlovic-Culf et al. (2016) and Gunnaiah et al. (2012)
		Orseolia royzae, *Xanthomonas oryzae* pv. Oryzae, *Magnaporthe grisea*, *Rhizoctonia solani*, *Chilo suppressalis*, Nilaparvata lugens	Leaf	Rice	Primary and secondary	GC/MS, LC/MS, NMR, CE/TOF-MS	Agarrwal et al. (2014), Jones et al. (2010), Liu et al. (2016), Peng et al. (2016), Sana et al. (2010), and Suharti et al. (2016)
		Lolium perenne	Root and shoot	Rice	Primary and secondary	LC-QTOF-MS	Asaduzzaman et al. (2014)
		Bipolaris maydis, *Ostrinia furnacalis*	Leaf	Maize	Primary and secondary	FT-IR, NMR, LC-MS	Guo et al. (2019) and Vasmatkar et al. (2019)
		Fusarium graminearum	Roots	Maize	Primary and secondary	LC/MS	Zhou et al. (2019)
		Pseudomonas syringae pv	Leaf	Tomato	Primary and secondary	NMR and LC/MS	Lopez-Gresa et al. (2010)
	Organic vs. conventional		Grain	Wheat	Primary	GC-MS	Zorb et al. (2006)

Livestocks	Stored for different periods	Beef	Beef	Primary	1H NMR	Graham et al. (2010) and Savorani et al. (2010)
	Genetic lines	Fish	Gilthead sea bream	Primary	1H NMR	Savorani et al. (2010)
		Liver and white muscle	Salmon	Primary	1H NMR	Wagner et al. (2014)
		Meat	Pork	Primary	1H NMR	Straadt et al. (2014)
	Three different aquaculture systems	Meat	Gilthead sea bream	Primary	1H NMR	Savorani et al. (2010)
Processed food	Genetic lines	Oil	Olive oil	Secondary	LC-MS	Sanchez de Medina et al. (2014)
		Orange juice	Mandarin oranges	Primary	1H NMR	Zhang et al. (2012)
	Changes in food composition during postharvest handling, processing, and storage	Wine	Grapes	Primary and secondary	1H NMR, GC-MS	Pinu et al. (2013)
			Rice (Japanese sake)	Primary	CE-MS, LC-MS	Sugimoto et al. (2012)
		Grains	Barley	Primary and secondary	GC-MS	Frank et al. (2011)
		Edible part	Broccoli, tomato, and carrot	Primary and secondary	1H NMR, LC-MS, LC-MRM, GC-MS	Lopez-Sanchez et al. (2015)
		Tomato paste	Tomato	Primary and secondary	LC-MS	Capanoglu et al. (2008)
		Fruits	Peach	Primary and secondary	GC-MS	Lauxmann et al. (2014)
		Pasta	Semolina pasta	Primary and secondary	LC-MS, GC-MS	Beleggia et al. (2011)
		Soy sauce	Soybeans	Primary metabolites	1H NMR	Ko et al. (2009)

(continued)

Table 5.2 (continued)

Food metabolomics	Treatments		Tissue	Sample	Primary/Secondary metabolites	Analytical platform	Reference
	Storage temperature		Beer	Beer	Primary and secondary	LC-MS	Heuberger et al. (2012)
	Various Bacillus strains		Fermented soybean paste	Soybean	Primary	GC-MS	Baek et al. (2010)
	Foods based on characteristic metabolite profiles		Cheese	Mozzarella cheese	Primary	1H NMR	Mazzei and Piccolo (2012)
			Wine	Wine	Primary	1H NMR	Lopez-Rituerto et al. (2012)
	Organic vs. conventional		Puree	Ketchup	Primary and secondary	LC-MS	Vallverdu-Queralt et al. (2011)
Human nutrition	Uptake as food	Milk and meat	Serum and urine	Human	Primary and secondary	LCMS	Bertram et al. (2007)
		Dietary modulation	Urine	Human	Primary and secondary	1H NMR	Stella et al. (2006)
		Well-cooked chicken	Urine	Human	Primary and secondary	LCMS/MS	Kulp et al. (2004)
		Gelatin	Serum	Human	Primary and secondary	LCMS/MS	Ichikawa et al. (2010)
		Citrus	Urine	Human	Primary and secondary	1H NMR	Heinzmann et al. (2010)

variability; any data showing coefficient of variance higher than 20% should be discarded. The lack of external validation sets using samples, which are not part of the statistical models built for prediction, is a significant limitation in most studies published (Cubero-Leon et al. 2018). Matrix effects could to either eliminated by reducing the sample complexity or spiking the standards in the matrix. Absolute metabolite quantification workflows should be improved using a combination of different analytical tools. So far, targeted approaches are used for metabolite quantification, efforts for developing untargeted quantitative metabolomics methods are needed for efficient biomarker discovery. Further regulatory guidelines for biomarker discovery should be put in place for robust experimental design, data acquisition, validation, and translation. Extensive research is required for the instrument miniaturization, cost-effectiveness, accessibility, and ease-of-handing for the fieldable application of metabolomics in agriculture farms. This could be achieved by corroboration between farm workers, researchers, and engineers. Automated, user-friendly, and open-source metabolomics data analysis platforms should be developed for robust data interpretation.

5.5 Conclusion

With ever-increasing food demand, climate change, and the advent of food metabolomics in the past decade, the horizon of metabolomics application has increased from food resource production to food processing and human nutrition. Because of increased efficiency, cost-effectiveness, and accuracy, applications of food metabolomics are rapidly expanding, as discussed extensively in this chapter. Untargeted metabolomics is especially useful in detecting unknown adulterants or advancing food metabolomics research (Cubero-Leon et al. 2014). Food databases are handy in elucidating the unknown/novel metabolites (Table 5.1). Plant metabolite repertoire has a wide dynamic range and diverse chemical composition. With the current set-up, only ~10% of the metabolite are identified; hence there is enormous scope to explore the unknowns. Integrating the metabolomics information with other-omics (genomics, transcriptomics, and proteomics) and non-omics studies (physiological data), combined with reliable and broad-spectrum food metabolome databases and artificial intelligence technologies, could help identify and elucidate many 'unknowns' and monitor in real-time to predict dynamics and quality control for accelerating, automating and progressing production processing.

5.6 Perspective

Apart from the applications of food metabolomics discussed in this chapter, metabolomics could be employed in personalized nutrition, crop improvement, metabolic fingerprinting in livestock and plants. Metabolomics investigations have generated a plethora of information that will allow food manufacturers to develop nutritional and sensorial rich food. Metabolomics-assisted crop improvement could lead to high-yielding, stress-tolerant germplasm and create climate-smart crop varieties. However, deciphering a specific metabolite's function (metabolite-phenotype) and decoding the structure of metabolic networks remains a major hurdle in the third decade of plant metabolomics. Identifying biomarkers related to plant biotic/abiotic stress, genetically modified organisms (GMOs), organic vs. conventional produce, and human nutrition using metabolomics and its translation in the agricultural fields, food industry, and clinics could be a future application. Also, metabolomics allows the determination of nutrient enhancement or reduction due to food processing via detection chemical alteration, which could significantly alter human health. Fingerprinting metabolic phenotypes of livestock and plants in response to defined feeding/fertilizing patterns and compositions is another emerging application. Finally, the food waste generated as a by-product of agriculture, the food processing industry, or household could be used to extract high-value bioactive compounds and nutraceuticals. In the years to come, an innovative sequential approach could simultaneously use food resources for food processing and simultaneously extract specific bioactive compounds and nutraceuticals to be used as functional foods.

References

Abdelrahman M, Burritt DJ, Gupta A, Tsujimoto H, Tran LP (2020) Heat stress effects on source-sink relationships and metabolome dynamics in wheat. J Exp Bot 71(2):543–554

Afshari R, Pillidge CJ, Read E, Rochfort S, Dias DA, Osborn AM, Gill H (2020) New insights into cheddar cheese microbiota-metabolome relationships revealed by integrative analysis of multi-omics data. Sci Rep 10(1):3164

Agarrwal R, Bentur JS, Nair S (2014) Gas chromatography mass spectrometry based metabolic profiling reveals biomarkers involved in rice-gall midge interactions. J Integr Plant Biol 56(9):837–848

Allwood JW, Ellis DI, Goodacre R (2008) Metabolomic technologies and their application to the study of plants and plant-host interactions. Physiol Plant 132(2):117–135

Allwood JW, Cheung W, Xu Y, Mumm R, De Vos RC, Deborde C, Biais B, Maucourt M, Berger Y, Schaffer AA, Rolin D, Moing A, Hall RD, Goodacre R (2014) Metabolomics in melon: a new opportunity for aroma analysis. Phytochemistry 99:61–72

Almeida J, Perez-Fons L, Fraser PD (2020) A transcriptomic, metabolomic and cellular approach to the physiological adaptation of tomato fruit to high temperature. Plant Cell Environ 44(7):2211–2229

Alseekh S, Fernie AR (2018) Metabolomics 20 years on: what have we learned and what hurdles remain? Plant J 94(6):933–942

Alseekh S, Tohge T, Wendenberg R, Scossa F, Omranian N, Li J, Kleessen S, Giavalisco P, Pleban T, Mueller-Roeber B, Zamir D, Nikoloski Z, Fernie AR (2015) Identification and mode of inheritance of quantitative trait loci for secondary metabolite abundance in tomato. Plant Cell 27(3):485–512

Álvarez-Fernández MA, Cerezo AB, Cañete-Rodríguez AM, Troncoso AM, García-Parrilla MC (2015) Composition of nonanthocyanin polyphenols in alcoholic-fermented strawberry products using LC–MS (QTRAP), high-resolution MS (UHPLC-Orbitrap-MS), LC-DAD, and antioxidant activity. J Agric Food Chem 63(7):2041–2051

Amargianitaki M, Spyros A (2017) NMR-based metabolomics in wine quality control and authentication. Chem Biol Technol Agric 4(1):9

Antunes AC, Acunha TDS, Perin EC, Rombaldi CV, Galli V, Chaves FC (2019) Untargeted metabolomics of strawberry (Fragaria x ananassa 'Camarosa') fruit from plants grown under osmotic stress conditions. J Sci Food Agric 99(15):6973–6980

Arana VA, Medina J, Alarcon R, Moreno E, Heintz L, Schafer H, Wist J (2015) Coffee's country of origin determined by NMR: the Colombian case. Food Chem 175:500–506

Arbona V, Manzi M, Ollas C, Gomez-Cadenas A (2013) Metabolomics as a tool to investigate abiotic stress tolerance in plants. Int J Mol Sci 14(3):4885–4911

Argyri AA, Mallouchos A, Panagou EZ, Nychas G-JE (2015) The dynamics of the HS/SPME–GC/MS as a tool to assess the spoilage of minced beef stored under different packaging and temperature conditions. Int J Food Microbiol 193:51–58

Asaduzzaman M, Pratley JE, An M, Luckett DJ, Lemerle D (2014) Metabolomics differentiation of canola genotypes: toward an understanding of canola allelochemicals. Front Plant Sci 5:765

Asaduzzaman M, Pratley JE, An M, Luckett DJ, Lemerle D (2015) Metabolomics differentiation of canola genotypes: toward an understanding of canola allelochemicals. Front Plant Sci 5:765

Badri DV, Zolla G, Bakker MG, Manter DK, Vivanco JM (2013) Potential impact of soil microbiomes on the leaf metabolome and on herbivore feeding behavior. New Phytol 198(1):264–273

Baek JG, Shim SM, Kwon DY, Choi HK, Lee CH, Kim YS (2010) Metabolite profiling of Cheonggukjang, a fermented soybean paste, inoculated with various bacillus strains during fermentation. Biosci Biotechnol Biochem 74(9):1860–1868

Baker JM, Hawkins ND, Ward JL, Lovegrove A, Napier JA, Shewry PR, Beale MH (2006) A metabolomic study of substantial equivalence of field-grown genetically modified wheat. Plant Biotechnol J 4(4):381–392

Barding GA Jr, Beni S, Fukao T, Bailey-Serres J, Larive CK (2013) Comparison of GC-MS and NMR for metabolite profiling of rice subjected to submergence stress. J Proteome Res 12(2):898–909

Bedair M, Glenn KC (2020) Evaluation of the use of untargeted metabolomics in the safety assessment of genetically modified crops. Metabolomics 16(10):111

Beleggia R, Platani C, Papa R, Di Chio A, Barros E, Mashaba C, Wirth J, Fammartino A, Sautter C, Conner S, Rauscher J, Stewart D, Cattivelli L (2011) Metabolomics and food processing: from semolina to pasta. J Agric Food Chem 59(17):9366–9377

Bernillon S, Biais B, Deborde C, Maucourt M, Cabasson C, Gibon Y, Hansen TH, Husted S, de Vos RCH, Mumm R, Jonker H, Ward JL, Miller SJ, Baker JM, Burger J, Tadmor Ya, Beale MH, Schjoerring JK, Schaffer AA, Rolin D, Hall RD, Moing A (2012) Metabolomic and elemental profiling of melon fruit quality as affected by genotype and environment. Metabolomics 9(1):57–77

Bertram HC, Hoppe C, Petersen BO, Duus JO, Molgaard C, Michaelsen KF (2007) An NMR-based metabonomic investigation on effects of milk and meat protein diets given to 8-year-old boys. Br J Nutr 97(4):758–763

Boiteau RM, Fansler SJ, Farris Y, Shaw JB, Koppenaal DW, Pasa-Tolic L, Jansson JK (2019) Siderophore profiling of co-habitating soil bacteria by ultra-high resolution mass spectrometry. Metallomics 11(1):166–175

Borrelli GM, Fragasso M, Nigro F, Platani C, Papa R, Beleggia R, Trono D (2018) Analysis of metabolic and mineral changes in response to salt stress in durum wheat (Triticum turgidum ssp. durum) genotypes, which differ in salinity tolerance. Plant Physiol Biochem 133:57–70

Bouchard-Mercier A, Rudkowska I, Lemieux S, Couture P, Vohl MC (2013) The metabolic signature associated with the Western dietary pattern: a cross-sectional study. Nutr J 12:158

Boyer JS (1982) Plant productivity and environment. Science 218(4571):443–448

Bradi DV, Zolla G, Bakker MG, Manter DK, Vivanco JM (2013) Potential impact of soil microbiomes on the leaf metabolome and on herbivore feeding behavior. New Phytol 198:264–273

Brescia M (2005) Characterisation of the geographical origin of buffalo milk and mozzarella cheese by means of analytical and spectroscopic determinations. Food Chem 89(1):139–147

Broyart C, Fontaine JX, Molinie R, Cailleu D, Terce-Laforgue T, Dubois F, Hirel B, Mesnard F (2010) Metabolic profiling of maize mutants deficient for two glutamine synthetase isoenzymes using 1H-NMR-based metabolomics. Phytochem Anal 21(1):102–109

Calingacion MN, Boualaphanh C, Daygon VD, Anacleto R, Sackville Hamilton R, Biais B, Deborde C, Maucourt M, Moing A, Mumm R, de Vos RCH, Erban A, Kopka J, Hansen TH, Laursen KH, Schjoerring JK, Hall RD, Fitzgerald MA (2011) A genomics and multi-platform metabolomics approach to identify new traits of rice quality in traditional and improved varieties. Metabolomics 8(5):771–783

Campos AI, Zampieri M (2019) Metabolomics-driven exploration of the chemical drug space to predict combination antimicrobial therapies. Mol Cell 74(6):1291–1303.e6

Capanoglu E, Beekwilder J, Boyacioglu D, Hall R, de Vos R (2008) Changes in antioxidant and metabolite profiles during production of tomato paste. J Agric Food Chem 56(3):964–973

Carreno-Quintero N, Acharjee A, Maliepaard C, Bachem CW, Mumm R, Bouwmeester H, Visser RG, Keurentjes JJ (2012) Untargeted metabolic quantitative trait loci analyses reveal a relationship between primary metabolism and potato tuber quality. Plant Physiol 158(3):1306–1318

Castro-Moretti FR, Gentzel IN, Mackey D, Alonso AP (2020) Metabolomics as an emerging tool for the study of plant–pathogen interactions. Meta 10(2):52

Catchpole GS, Beckmann M, Enot DP, Mondhe M, Zywicki B, Taylor J, Hardy N, Smith A, King RD, Kell DB, Fiehn O, Draper J (2005) Hierarchical metabolomics demonstrates substantial compositional similarity between genetically modified and conventional potato crops. Proc Natl Acad Sci U S A 102(40):14458–14462

Cevallos-Cevallos JM, Danyluk MD, Reyes-De-Corcuera JI (2011) GC-MS based metabolomics for rapid simultaneous detection of Escherichia coli O157:H7, salmonella typhimurium, salmonella Muenchen, and salmonella Hartford in ground beef and chicken. J Food Sci 76(4):M238–M246

Chang J, Cheong BE, Natera S, Roessner U (2019) Morphological and metabolic responses to salt stress of rice (Oryza sativa L.) cultivars which differ in salinity tolerance. Plant Physiol Biochem 144:427–435

Chang X, Ning D, Mao L, Wang B, Fang Q, Yao H, Wang F, Ye G (2021) Metabolic analysis reveals Cry1C gene transformation does not affect the sensitivity of Rice to Rice dwarf virus. Meta 11(4):209

Chapinal N, Carson ME, LeBlanc SJ, Leslie KE, Godden S, Capel M, Santos JE, Overton MW, Duffield TF (2012) The association of serum metabolites in the transition period with milk production and early-lactation reproductive performance. J Dairy Sci 95(3):1301–1309

Che-Othman MH, Jacoby RP, Millar AH, Taylor NL (2020) Wheat mitochondrial respiration shifts from the tricarboxylic acid cycle to the GABA shunt under salt stress. New Phytol 225(3):1166–1180

Chmielewska K, Rodziewicz P, Swarcewicz B, Sawikowska A, Krajewski P, Marczak L, Ciesiolka D, Kuczynska A, Mikolajczak K, Ogrodowicz P, Krystkowiak K, Surma M, Adamski T, Bednarek P, Stobiecki M (2016) Analysis of drought-induced proteomic and Metabolomic changes in barley (Hordeum vulgare L.) leaves and roots unravels some aspects of biochemical mechanisms involved in drought tolerance. Front Plant Sci 7:1108

Cornett DS, Mobley JA, Dias EC, Andersson M, Arteaga CL, Sanders ME, Caprioli RM (2006) A novel histology-directed strategy for MALDI-MS tissue profiling that improves throughput and cellular specificity in human breast cancer. Mol Cell Proteomics 5(10):1975–1983

Coutinho ID, Henning LMM, Döpp SA, Nepomuceno A, Moraes LAC, Marcolino-Gomes J, Richter C, Schwalbe H, Colnago LA (2018) Flooded soybean metabolomic analysis reveals important primary and secondary metabolites involved in the hypoxia stress response and tolerance. Environ Exp Bot 153:176–187

Cubero-Leon E, Peñalver R, Maquet A (2014) Review on metabolomics for food authentication. Food Res Int 60:95–107

Cubero-Leon E, De Rudder O, Maquet A (2018) Metabolomics for organic food authentication: results from a long-term field study in carrots. Food Chem 239:760–770

Cuperlovic-Culf M, Wang L, Forseille L, Boyle K, Merkley N, Burton I, Fobert PR (2016) Metabolic biomarker panels of response to fusarium head blight infection in different wheat varieties. PLoS One 11(4):e0153642

Cuperlovic-Culf M, Vaughan MM, Vermillion K, Surendra A, Teresi J, McCormick SP (2019) Effects of atmospheric CO2 level on the metabolic response of resistant and susceptible wheat to fusarium graminearum infection. Mol Plant-Microbe Interact 32(4):379–391

Cuthbertson D, Andrews PK, Reganold JP, Davies NM, Lange BM (2012) Utility of metabolomics toward assessing the metabolic basis of quality traits in apple fruit with an emphasis on antioxidants. J Agric Food Chem 60(35):8552–8560

Das A, Rushton PJ, Rohila JS (2017) Metabolomic profiling of soybeans (Glycine max L.) reveals the importance of sugar and nitrogen metabolism under drought and heat stress. Plants (Basel) 6(2):21

D'Auria S, Melzer N, Wittenburg D, Repsilber D (2013) Integrating Milk metabolite profile information for the prediction of traditional Milk traits based on SNP information for Holstein cows. PLoS One 8(8):e70256

Degenkolbe T, Do PT, Kopka J, Zuther E, Hincha DK, Kohl KI (2013) Identification of drought tolerance markers in a diverse population of rice cultivars by expression and metabolite profiling. PLoS One 8(5):e63637

Diez-Simon C, Mumm R, Hall RD (2019) Mass spectrometry-based metabolomics of volatiles as a new tool for understanding aroma and flavour chemistry in processed food products. Metabolomics 15(3):41

Do PT, Degenkolbe T, Erban A, Heyer AG, Kopka J, Kohl KI, Hincha DK, Zuther E (2013) Dissecting rice polyamine metabolism under controlled long-term drought stress. PLoS One 8(4):e60325

Dore J, Blottiere H (2015) The influence of diet on the gut microbiota and its consequences for health. Curr Opin Biotechnol 32:195–199

Escandon M, Meijon M, Valledor L, Pascual J, Pinto G, Canal MJ (2018) Metabolome integrated analysis of high-temperature response in Pinus radiata. Front Plant Sci 9:485

Fallaize R, Forster H, Macready AL, Walsh MC, Mathers JC, Brennan L, Gibney ER, Gibney MJ, Lovegrove JA (2014) Online dietary intake estimation: reproducibility and validity of the Food4Me food frequency questionnaire against a 4-day weighed food record. J Med Internet Res 16(8):e190

Farahbakhsh F, Hamzehzarghani H, Massah A, Tortosa M, Yassaie M, Rodriguez VM (2019) Comparative metabolomics of temperature sensitive resistance to wheat streak mosaic virus (WSMV) in resistant and susceptible wheat cultivars. J Plant Physiol 237:30–42

Food and Agriculture Organization (2015) Status of the Worlds's Soil Resources (SWSR) – main report. Food and Agriculture Organization, Rome

Foroutan A, Fitzsimmons C, Mandal R, Piri-Moghadam H, Zheng J, Guo A, Li C, Guan LL, Wishart DS (2020) The bovine metabolome. Meta 10(6):233

Fortes AM, Agudelo-Romero P, Silva MS, Ali K, Sousa L, Maltese F, Choi YH, Grimplet J, Martinez-Zapater JM, Verpoorte R, Pais MS (2011) Transcript and metabolite analysis in Trincadeira cultivar reveals novel information regarding the dynamics of grape ripening. BMC Plant Biol 11:149

Frank T, Scholz B, Peter S, Engel K-H (2011) Metabolite profiling of barley: influence of the malting process. Food Chem 124(3):948–957

Frank T, Rohlig RM, Davies HV, Barros E, Engel KH (2012) Metabolite profiling of maize kernels--genetic modification versus environmental influence. J Agric Food Chem 60(12):3005–3012

Furtauer L, Weiszmann J, Weckwerth W, Nagele T (2019) Dynamics of plant metabolism during cold acclimation. Int J Mol Sci 20(21):5411

Garcia-Villalba R, Leon C, Dinelli G, Segura-Carretero A, Fernandez-Gutierrez A, Garcia-Canas V, Cifuentes A (2008) Comparative metabolomic study of transgenic versus conventional soybean using capillary electrophoresis-time-of-flight mass spectrometry. J Chromatogr A 1195(1–2):164–173

Gayen D, Barua P, Lande NV, Varshney S, Sengupta S, Chakraborty S, Chakraborty N (2019) Dehydration-responsive alterations in the chloroplast proteome and cell metabolomic profile of rice reveals key stress adaptation responses. Environ Exp Bot 160:12–24

Gil-Solsona R, Raro M, Sales C, Lacalle L, Díaz R, Ibáñez M, Beltran J, Sancho JV, Hernández FJ (2016) Metabolomic approach for extra virgin olive oil origin discrimination making use of ultra-high performance liquid chromatography – quadrupole time-of-flight mass spectrometry. Food Contrl 70:350–359

Goldansaz SA, Guo AC, Sajed T, Steele MA, Plastow GS, Wishart DS (2017) Livestock metabolomics and the livestock metabolome: a systematic review. PLoS One 12(5):e0177675

Gomez-Romero M, Segura-Carretero A, Fernandez-Gutierrez A (2010) Metabolite profiling and quantification of phenolic compounds in methanol extracts of tomato fruit. Phytochemistry 71(16):1848–1864

Gonzalez Ibarra AA, Wrobel K, Yanez Barrientos E, Corrales Escobosa AR, Gutierrez Corona JF, Enciso Donis I, Wrobel K (2017) Changes of Metabolomic profile in Helianthus annuus under exposure to chromium(VI) studied by capHPLC-ESI-QTOF-MS and MS/MS. J Anal Methods Chem 2017:3568621

Graham SF, Kennedy T, Chevallier O, Gordon A, Farmer L, Elliott C, Moss B (2010) The application of NMR to study changes in polar metabolite concentrations in beef longissimus dorsi stored for different periods post mortem. Metabolomics 6(3):395–404

Guerrero M, Hahne C, Rai V, Baars O (2019) Microbial exudate production in response to toxic metals in soils. In: ASA, CSSA and SSSA international annual meetings (2019). ASA-CSSA-SSSA, Raleigh

Gunnaiah R, Kushalappa AC, Duggavathi R, Fox S, Somers DJ (2012) Integrated metabolo-proteomic approach to decipher the mechanisms by which wheat QTL (Fhb1) contributes to resistance against Fusarium graminearum. PLoS One 7(7):e40695

Guo R, Yang Z, Li F, Yan C, Zhong X, Liu Q, Xia X, Li H, Zhao L (2015) Comparative metabolic responses and adaptive strategies of wheat (Triticum aestivum) to salt and alkali stress. BMC Plant Biol 15:170

Guo R, Shi L, Jiao Y, Li M, Zhong X, Gu F, Liu Q, Xia X, Li H (2018) Metabolic responses to drought stress in the tissues of drought-tolerant and drought-sensitive wheat genotype seedlings. AoB Plants 10(2):ply016

Guo J, Qi J, He K, Wu J, Bai S, Zhang T, Zhao J, Wang Z (2019) The Asian corn borerOstrinia furnacalisfeeding increases the direct and indirect defence of mid-whorl stage commercial maize in the field. Plant Biotechnol J 17(1):88–102

Gupta P, De B (2017) Metabolomics analysis of rice responses to salinity stress revealed elevation of serotonin, and gentisic acid levels in leaves of tolerant varieties. Plant Signal Behav 12(7):e1335845

Han Y, Li A, Li F, Zhao M, Wang W (2012) Characterization of a wheat (Triticum aestivum L.) expansin gene, TaEXPB23, involved in the abiotic stress response and phytohormone regulation. Plant Physiol Biochem 54:49–58

Hanhineva K, Lankinen MA, Pedret A, Schwab U, Kolehmainen M, Paananen J, de Mello V, Sola R, Lehtonen M, Poutanen K, Uusitupa M, Mykkanen H (2015) Nontargeted metabolite profiling discriminates diet-specific biomarkers for consumption of whole grains, fatty fish, and bilberries in a randomized controlled trial. J Nutr 145(1):7–17

Hayden HL, Rochfort SJ, Ezernieks V, Savin KW, Mele PM (2019) Metabolomics approaches for the discrimination of disease suppressive soils for Rhizoctonia solani AG8 in cereal crops using 1H NMR and LC-MS. Sci Total Environ 651:1627–1638

Heinzmann SS, Brown IJ, Chan Q, Bictash M, Dumas ME, Kochhar S, Stamler J, Holmes E, Elliott P, Nicholson JK (2010) Metabolic profiling strategy for discovery of nutritional biomarkers: proline betaine as a marker of citrus consumption. Am J Clin Nutr 92(2):436–443

Herzog M, Fukao T, Winkel A, Konnerup D, Lamichhane S, Alpuerto JB, Hasler-Sheetal H, Pedersen O (2018) Physiology, gene expression, and metabolome of two wheat cultivars with contrasting submergence tolerance. Plant Cell Environ 41(7):1632–1644

Heuberger AL, Broeckling CD, Lewis MR, Salazar L, Bouckaert P, Prenni JE (2012) Metabolomic profiling of beer reveals effect of temperature on non-volatile small molecules during short-term storage. Food Chem 135(3):1284–1289

Heyneke E, Watanabe M, Erban A, Duan G, Buchner P, Walther D, Kopka J, Hawkesford MJ, Hoefgen R (2017) Characterization of the wheat leaf metabolome during grain filling and under varied N-supply. Front Plant Sci 8:2048

Hill CB, Taylor JD, Edwards J, Mather D, Bacic A, Langridge P, Roessner U (2013) Whole-genome mapping of agronomic and metabolic traits to identify novel quantitative trait Loci in bread wheat grown in a water-limited environment. Plant Physiol 162(3):1266–1281

Hill CB, Taylor JD, Edwards J, Mather D, Langridge P, Bacic A, Roessner U (2015) Detection of QTL for metabolic and agronomic traits in wheat with adjustments for variation at genetic loci that affect plant phenology. Plant Sci 233:143–154

Hirai MY, Yano M, Goodenowe DB, Kanaya S, Kimura T, Awazuhara M, Arita M, Fujiwara T, Saito K (2004) Integration of transcriptomics and metabolomics for understanding of global responses to nutritional stresses in Arabidopsis thaliana. Proc Natl Acad Sci U S A 101(27):10205–10210

Ibanez C, Valdes A, Garcia-Canas V, Simo C, Celebier M, Rocamora-Reverte L, Gomez-Martinez A, Herrero M, Castro-Puyana M, Segura-Carretero A, Ibanez E, Ferragut JA, Cifuentes A (2012) Global Foodomics strategy to investigate the health benefits of dietary constituents. J Chromatogr A 1248:139–153

Ichikawa S, Morifuji M, Ohara H, Matsumoto H, Takeuchi Y, Sato K (2010) Hydroxyproline-containing dipeptides and tripeptides quantified at high concentration in human blood after oral administration of gelatin hydrolysate. Int J Food Sci Nutr 61(1):52–60

Ichikawa E, Hirata S, Hata Y, Yazawa H, Tamura H, Kaneoke M, Iwashita K, Hirata D (2019) Analysis of metabolites in Japanese alcoholic beverage sake made from the sake rice Koshitanrei. Biosci Biotechnol Biochem 83(8):1570–1582

Inaba Y, Brotherton JE, Ulanov A, Widholm JM (2007) Expression of a feedback insensitive anthranilate synthase gene from tobacco increases free tryptophan in soybean plants. Plant Cell Rep 26(10):1763–1771

Jadhav S, Gulati V, Fox EM, Karpe A, Beale DJ, Sevior D, Bhave M, Palombo EA (2015) Rapid identification and source-tracking of Listeria monocytogenes using MALDI-TOF mass spectrometry. Int J Food Microbiol 202:1–9

Jahangir M, Abdel-Farid IB, Choi YH, Verpoorte R (2008) Metal ion-inducing metabolite accumulation in Brassica rapa. J Plant Physiol 165(14):1429–1437

Jiao Z, Si XX, Li GK, Zhang ZM, Xu XP (2010) Unintended compositional changes in transgenic rice seeds (Oryza sativa L.) studied by spectral and chromatographic analysis coupled with chemometrics methods. J Agric Food Chem 58(3):1746–1754

Johns CW, Lee AB, Springer TI, Rosskopf EN, Hong JC, Turechek W, Kokalis-Burelle N, Finley NL (2017) Using NMR-based metabolomics to monitor the biochemical composition of agricultural soils: a pilot study. Eur J Soil Biol 83:98–105

Johnson CH, Gonzalez FJ (2012) Challenges and opportunities of metabolomics. J Cell Physiol 227(8):2975–2981

Jones OAH, Maguire ML, Griffin JL, Jung Y-H, Shibato J, Rakwal R, Agrawal GK, Jwa N-S (2010) Using metabolic profiling to assess plant-pathogen interactions: an example using rice (Oryza sativa) and the blast pathogen Magnaporthe grisea. Eur J Plant Pathol 129(4):539–554

Jones C, Hatier JH, Cao M, Fraser K, Rasmussen S (2018) Metabolomics of plant phosphorus-starvation response. In: Plaxton WC, Lambers H (eds) Annual plant reviews book series: phosphorus metabolism in plants, vol 48. Wiley

Kang Z, Babar MA, Khan N, Guo J, Khan J, Islam S, Shrestha S, Shahi D (2019) Comparative metabolomic profiling in the roots and leaves in contrasting genotypes reveals complex mechanisms involved in post-anthesis drought tolerance in wheat. PLoS One 14(3):e0213502

Karisa BK, Thomson J, Wang Z, Li C, Montanholi YR, Miller SP, Moore SS, Plastow GS (2014) Plasma metabolites associated with residual feed intake and other productivity performance traits in beef cattle. Livest Sci 165:200–211

Kearns PWE, Kleter GA, Bergmans HEN, Kuiper HA (2021) Biotechnology and biosafety policy at OECD: future trends. Trends Biotechnol 39(10):965–969

Kim S, Kim J, Yun EJ, Kim KH (2016) Food metabolomics: from farm to human. Curr Opin Biotechnol 37:16–23

Kleeberg I, Hetz C, Kroppenstedt RM, Muller RJ, Deckwer WD (1998) Biodegradation of aliphatic-aromatic copolyesters by Thermomonospora fusca and other thermophilic compost isolates. Appl Environ Microbiol 64(5):1731–1735

Klockmann S, Reiner E, Cain N, Fischer M (2017) Food targeting: geographical origin determination of hazelnuts (Corylus avellana) by LC-QqQ-MS/MS-based targeted metabolomics application. J Agric Food Chem 65(7):1456–1465

Ko BK, Ahn HJ, van den Berg F, Lee CH, Hong YS (2009) Metabolomic insight into soy sauce through (1)H NMR spectroscopy. J Agric Food Chem 57(15):6862–6870

Kogel KH, Voll LM, Schafer P, Jansen C, Wu Y, Langen G, Imani J, Hofmann J, Schmiedl A, Sonnewald S, von Wettstein D, Cook RJ, Sonnewald U (2010) Transcriptome and metabolome profiling of field-grown transgenic barley lack induced differences but show cultivar-specific variances. Proc Natl Acad Sci U S A 107(14):6198–6203

Kok E, van Dijk J, Voorhuijzen M, Staats M, Slot M, Lommen A, Venema D, Pla M, Corujo M, Barros E, Hutten R, Jansen J, van der Voet H (2019) Omics analyses of potato plant materials using an improved one-class classification tool to identify aberrant compositional profiles in risk assessment procedures. Food Chem 292:350–358

Komatsu S, Nakamura T, Sugimoto Y, Sakamoto K (2014) Proteomic and metabolomic analyses of soybean root tips under flooding stress. Protein Pept Lett 21(9):865–884

Kulp KS, Knize MG, Fowler ND, Salmon CP, Felton JS (2004) PhIP metabolites in human urine after consumption of well-cooked chicken. J Chromatogr B Analyt Technol Biomed Life Sci 802(1):143–153

Kusano M, Fukushima A, Redestig H, Saito K (2011a) Metabolomic approaches toward understanding nitrogen metabolism in plants. J Exp Bot 62(4):1439–1453

Kusano M, Redestig H, Hirai T, Oikawa A, Matsuda F, Fukushima A, Arita M, Watanabe S, Yano M, Hiwasa-Tanase K, Ezura H, Saito K (2011b) Covering chemical diversity of genetically-modified tomatoes using metabolomics for objective substantial equivalence assessment. PLoS One 6(2):e16989

Latif S, Gurusinghe S, Weston PA, Quinn JC, Piltz JW, Weston LA (2019) Metabolomic approaches for the identification of flavonoids associated with weed suppression in selected Hardseeded annual pasture legumes. Plant Soil 447(1–2):199–218

Lauxmann MA, Borsani J, Osorio S, Lombardo VA, Budde CO, Bustamante CA, Monti LL, Andreo CS, Fernie AR, Drincovich MF, Lara MV (2014) Deciphering the metabolic pathways influencing heat and cold responses during post-harvest physiology of peach fruit. Plant Cell Environ 37(3):601–616

Lawas LMF, Li X, Erban A, Kopka J, Jagadish SVK, Zuther E, Hincha DK (2019) Metabolic responses of rice cultivars with different tolerance to combined drought and heat stress under field conditions. Gigascience 8(5):giz050

LeBlanc SJ, Leslie KE, Duffield TF (2005) Metabolic predictors of displaced abomasum in dairy cattle. J Dairy Sci 88(1):159–170

Lee LS, Choi JH, Sung MJ, Hur JY, Hur HJ, Park JD, Kim YC, Gu EJ, Min B, Kim HJ (2015) Green tea changes serum and liver metabolomic profiles in mice with high-fat diet-induced obesity. Mol Nutr Food Res 59(4):784–794

Leisso R, Buchanan D, Lee J, Mattheis J, Rudell D (2013) Cell Wall, cell membrane, and volatile metabolism are altered by antioxidant treatment, temperature shifts, and Peel necrosis during apple fruit storage. J Agric Food Chem 61(6):1373–1387

Lesk C, Rowhani P, Ramankutty N (2016) Influence of extreme weather disasters on global crop production. Nature 529(7584):84–87

Li ZY, Ding LL, Li JM, Xu BL, Yang L, Bi KS, Wang ZT (2015) (1)H-NMR and MS based metabolomics study of the intervention effect of curcumin on hyperlipidemia mice induced by high-fat diet. PLoS One 10(3):e0120950

Lin Y, Li W, Sun L, Lin Z, Jiang Y, Ling Y, Lin X (2019) Comparative metabolomics shows the metabolic profiles fluctuate in multi-drug resistant Escherichia coli strains. J Proteome 207:103468

Lipka AE, Gore MA, Magallanes-Lundback M, Mesberg A, Lin H, Tiede T, Chen C, Buell CR, Buckler ES, Rocheford T, DellaPenna D (2013) Genome-wide association study and pathway-level analysis of tocochromanol levels in maize grain. G3 (Bethesda) 3(8):1287–1299

Liu H, Tayyari F, Khoo C, Gu L (2015) A 1H NMR-based approach to investigate metabolomic differences in the plasma and urine of young women after cranberry juice or apple juice consumption. J Funct Foods 14:76–86

Liu Q, Wang X, Tzin V, Romeis J, Peng Y, Li Y (2016) Combined transcriptome and metabolome analyses to understand the dynamic responses of rice plants to attack by the rice stem borer Chilo suppressalis (Lepidoptera: Crambidae). BMC Plant Biol 16(1):259

Locke AM, Barding GA Jr, Sathnur S, Larive CK, Bailey-Serres J (2018) Rice SUB1A constrains remodelling of the transcriptome and metabolome during submergence to facilitate post-submergence recovery. Plant Cell Environ 41(4):721–736

Lopez-Gresa MP, Maltese F, Belles JM, Conejero V, Kim HK, Choi YH, Verpoorte R (2010) Metabolic response of tomato leaves upon different plant-pathogen interactions. Phytochem Anal 21(1):89–94

Lopez-Rituerto E, Savorani F, Avenoza A, Busto JH, Peregrina JM, Engelsen SB (2012) Investigations of La Rioja terroir for wine production using 1H NMR metabolomics. J Agric Food Chem 60(13):3452–3461

Lopez-Sanchez P, de Vos RC, Jonker HH, Mumm R, Hall RD, Bialek L, Leenman R, Strassburg K, Vreeken R, Hankemeier T, Schumm S, van Duynhoven J (2015) Comprehensive metabolomics to evaluate the impact of industrial processing on the phytochemical composition of vegetable purees. Food Chem 168:348–355

Lou Q, Ma C, Wen W, Zhou J, Chen L, Feng F, Xu X, Lu X, Luo L, Mei H, Xu G (2011) Profiling and association mapping of grain metabolites in a subset of the core collection of Chinese rice germplasm (Oryza sativa L.). J Agric Food Chem 59(17):9257–9264

Ma X, Xia H, Liu Y, Wei H, Zheng X, Song C, Chen L, Liu H, Luo L (2016) Transcriptomic and Metabolomic studies disclose key metabolism pathways contributing to well-maintained photosynthesis under the drought and the consequent drought-tolerance in rice. Front Plant Sci 7:1886

Ma NL, Che Lah WA, Abd Kadir N, Mustaqim M, Rahmat Z, Ahmad A, Lam SD, Ismail MR (2018) Susceptibility and tolerance of rice crop to salt threat: physiological and metabolic inspections. PLoS One 13(2):e0192732

Makkliang F, Kanatharana P, Thavarungkul P, Thammakhet C (2015) Development of magnetic micro-solid phase extraction for analysis of phthalate esters in packaged food. Food Chem 166:275–282

Malik NSA, Perez JL, Lombardini L, Cornacchia R, Cisneros-Zevallos L, Braford J (2009) Phenolic compounds and fatty acid composition of organic and conventional grown pecan kernels. J Sci Food Agric 89(13):2207–2213

Man KY, Chan CO, Tang HH, Dong NP, Capozzi F, Wong KH, Kwok KWH, Chan HM, Mok DK (2021) Mass spectrometry-based untargeted metabolomics approach for differentiation of beef of different geographic origins. Food Chem 338:127847

Martínez Bueno MJ, Díaz-Galiano FJ, Rajski Ł, Cutillas V, Fernández-Alba AR (2018) A non-targeted metabolomic approach to identify food markers to support discrimination between organic and conventional tomato crops. J Chromatogr A 1546:66–76

Matsuda F, Okazaki Y, Oikawa A, Kusano M, Nakabayashi R, Kikuchi J, Yonemaru J, Ebana K, Yano M, Saito K (2012) Dissection of genotype-phenotype associations in rice grains using metabolome quantitative trait loci analysis. Plant J 70(4):624–636

Mazzei P, Piccolo A (2012) (1)H HRMAS-NMR metabolomic to assess quality and traceability of mozzarella cheese from Campania buffalo milk. Food Chem 132(3):1620–1627

Mesnage R, Le Roy CI, Biserni M, Salles B, Antoniou MN (2019) Relationship between faecal microbiota and plasma metabolome in rats fed NK603 and MON810 GM maize from the GMO90+ study. Food Chem Toxicol 131:110547

Michaletti A, Naghavi MR, Toorchi M, Zolla L, Rinalducci S (2018) Metabolomics and proteomics reveal drought-stress responses of leaf tissues from spring-wheat. Sci Rep 8(1):5710

Mitchell AE, Hong Y-J, Koh E, Barrett DM, Bryant DE, Denison RF, Kaffka S (2007) Ten-year comparison of the influence of organic and conventional crop management practices on the content of flavonoids in tomatoes. J Agric Food Chem 55(15):6154–6159

Noteborn HP, Lommen A, van der Jagt RC, Weseman JM (2000) Chemical fingerprinting for the evaluation of unintended secondary metabolic changes in transgenic food crops. J Biotechnol 77(1):103–114

Novais FJ, Pires PRL, Alexandre PA, Dromms RA, Iglesias AH, Ferraz JBS, Styczynski MP, Fukumasu H (2019) Identification of a metabolomic signature associated with feed efficiency in beef cattle. BMC Genomics 20(1):8

Novotná H, Kmiecik O, Gałązka M, Krtková V, Hurajová A, Schulzová V, Hallmann E, Rembiałkowska E, Hajšlová J (2012) Metabolomic fingerprinting employing DART-TOFMS for authentication of tomatoes and peppers from organic and conventional farming. Food Addit Contam Part A 29(9):1335–1346

Obata T, Witt S, Lisec J, Palacios-Rojas N, Florez-Sarasa I, Yousfi S, Araus JL, Cairns JE, Fernie AR (2015) Metabolite profiles of maize leaves in drought, heat, and combined stress field trials reveal the relationship between metabolism and grain yield. Plant Physiol 169(4):2665–2683

Ogbaga CC, Stepien P, Dyson BC, Rattray NJ, Ellis DI, Goodacre R, Johnson GN (2016) Biochemical analyses of sorghum varieties reveal differential responses to drought. PLoS One 11(5):e0154423

O'Gorman A, Gibbons H, Brennan L (2013) Metabolomics in the identification of biomarkers of dietary intake. Comput Struct Biotechnol J 4:e201301004

Owens BF, Lipka AE, Magallanes-Lundback M, Tiede T, Diepenbrock CH, Kandianis CB, Kim E, Cepela J, Mateos-Hernandez M, Buell CR, Buckler ES, DellaPenna D, Gore MA, Rocheford T (2014) A foundation for provitamin A biofortification of maize: genome-wide association and genomic prediction models of carotenoid levels. Genetics 198(4):1699–1716

Pan J, Li Z, Dai S, Ding H, Wang Q, Li X, Ding G, Wang P, Guan Y, Liu W (2020) Integrative analyses of transcriptomics and metabolomics upon seed germination of foxtail millet in response to salinity. Sci Rep 10(1):13660

Paupiere MJ, Muller F, Li H, Rieu I, Tikunov YM, Visser RGF, Bovy AG (2017) Untargeted metabolomic analysis of tomato pollen development and heat stress response. Plant Reprod 30(2):81–94

Peng M, Hudson D, Schofield A, Tsao R, Yang R, Gu H, Bi YM, Rothstein SJ (2008) Adaptation of Arabidopsis to nitrogen limitation involves induction of anthocyanin synthesis which is controlled by the NLA gene. J Exp Bot 59(11):2933–2944

Peng L, Zhao Y, Wang H, Zhang J, Song C, Shangguan X, Zhu L, He G (2016) Comparative metabolomics of the interaction between rice and the brown planthopper. Metabolomics 12(8):62

Perez-Fons L, Wells T, Corol DI, Ward JL, Gerrish C, Beale MH, Seymour GB, Bramley PM, Fraser PD (2014) A genome-wide metabolomic resource for tomato fruit from Solanum pennellii. Sci Rep 4:3859

Petriacq P, Williams A, Cotton A, McFarlane AE, Rolfe SA, Ton J (2017) Metabolite profiling of non-sterile rhizosphere soil. Plant J 92(1):147–162

Phapale P, Rai V, Mohanty AK, Srivastava S (2020) Untargeted metabolomics workshop report: quality control considerations from sample preparation to data analysis. J Am Soc Mass Spectrom 31(9):2006–2010

Piccioni F, Capitani D, Zolla L, Mannina L (2009) NMR metabolic profiling of transgenic maize with the Cry1Ab gene. J Agric Food Chem 57(14):6041–6049

Pinu FR (2016) Metabolomics: applications to food safety and quality research. In: Microbial metabolomics. Springer, pp 225–259

Pinu FR, Edwards PJB, Jouanneau S, Kilmartin PA, Gardner RC, Villas-Boas SG (2013) Sauvignon blanc metabolomics: grape juice metabolites affecting the development of varietal thiols and other aroma compounds in wines. Metabolomics 10(4):556–573

Pollak S, Cordero OX (2020) Rhizobiome shields plants from infection. Nat Microbiol 5(8):978–979

Qi X, Xu W, Zhang J, Guo R, Zhao M, Hu L, Wang H, Dong H, Li Y (2017) Physiological characteristics and metabolomics of transgenic wheat containing the maize C4 phosphoenolpyruvate carboxylase (PEPC) gene under high temperature stress. Protoplasma 254(2):1017–1030

Rai V, Sarkar S, Satpati S, Dey N (2016) Overexpression of human peroxisomal enoyl-CoA delta isomerase2 HsPECI2, an ortholog of bamboo expressed during gregarious flowering alters salinity stress responses and polar lipid content in tobacco. Funct Plant Biol 43(3):232–243

Rai V, Muthuraj M, Gandhi MN, Das D, Srivastava S (2017) Real-time iTRAQ-based proteome profiling revealed the central metabolism involved in nitrogen starvation induced lipid accumulation in microalgae. Sci Rep 7:45732

Rai V, Fisher N, Duckworth OW, Baars O (2020) Extraction and detection of structurally diverse Siderophores in soil. Front Microbiol 11:581508

Raza A (2020) Metabolomics: a systems biology approach for enhancing heat stress tolerance in plants. Plant Cell Rep 41(3):741–763

Raza A, Razzaq A, Mehmood SS, Zou X, Zhang X, Lv Y, Xu J (2019) Impact of climate change on crops adaptation and strategies to tackle its outcome: a review. Plants (Basel) 8(2):34

Reisdorph NA, Hendricks AE, Tang M, Doenges KA, Reisdorph RM, Tooker BC, Quinn K, Borengasser SJ, Nkrumah-Elie Y, Frank DN, Campbell WW, Krebs NF (2020) Nutrimetabolomics reveals food-specific compounds in urine of adults consuming a DASH-style diet. Sci Rep 10(1):1157

Renou J-P, Deponge C, Gachon P, Bonnefoy J-C, Coulon J-B, Garel J-P, Vérité R, Ritz P (2004) Characterization of animal products according to geographic origin and feeding diet using nuclear magnetic resonance and isotope ratio mass spectrometry: cow milk. Food Chem 85(1):63–66

Rocchetti G, Gallo A, Nocetti M, Lucini L, Masoero F (2020) Milk metabolomics based on ultra-high-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry to discriminate different cows feeding regimens. Food Res Int 134:109279

Rochfort S, Ezernieks V, Mele P, Kitching M (2015) NMR metabolomics for soil analysis provide complementary, orthogonal data to MIR and traditional soil chemistry approaches - a land use study. Magn Reson Chem 53(9):719–725

Rodriguez-Celma J, Vazquez-Reina S, Orduna J, Abadia A, Abadia J, Alvarez-Fernandez A, Lopez-Millan AF (2011) Characterization of flavins in roots of Fe-deficient strategy I plants, with a focus on Medicago truncatula. Plant Cell Physiol 52(12):2173–2189

Roessner U, Wagner C, Kopka J, Trethewey RN, Willmitzer L (2000) Technical advance: simultaneous analysis of metabolites in potato tuber by gas chromatography-mass spectrometry. Plant J 23(1):131–142

Roessner-Tunali U, Hegemann B, Lytovchenko A, Carrari F, Bruedigam C, Granot D, Fernie AR (2003) Metabolic profiling of transgenic tomato plants overexpressing hexokinase reveals that the influence of hexose phosphorylation diminishes during fruit development. Plant Physiol 133(1):84–99

Rothwell JA, Urpi-Sarda M, Boto-Ordonez M, Knox C, Llorach R, Eisner R, Cruz J, Neveu V, Wishart D, Manach C, Andres-Lacueva C, Scalbert A (2012) Phenol-Explorer 2.0: a major update of the Phenol-Explorer database integrating data on polyphenol metabolism and pharmacokinetics in humans and experimental animals. Database (Oxford) 2012:bas031

Rouphael Y, Raimondi G, Lucini L, Carillo P, Kyriacou MC, Colla G, Cirillo V, Pannico A, El-Nakhel C, De Pascale S (2018) Physiological and metabolic responses triggered by omeprazole improve tomato plant tolerance to NaCl stress. Front Plant Sci 9:249

Saleem F, Ametaj BN, Bouatra S, Mandal R, Zebeli Q, Dunn SM, Wishart DS (2012) A metabolomics approach to uncover the effects of grain diets on rumen health in dairy cows. J Dairy Sci 95(11):6606–6623

Sana TR, Fischer S, Wohlgemuth G, Katrekar A, Jung K-H, Ronald PC, Fiehn O (2010) Metabolomic and transcriptomic analysis of the rice response to the bacterial blight pathogen Xanthomonas oryzae pv. oryzae. Metabolomics 6(3):451–465

Sanchez de Medina V, Calderon-Santiago M, El Riachy M, Priego-Capote F, Luque de Castro MD (2014) High-resolution mass spectrometry to evaluate the influence of cross-breeding segregating populations on the phenolic profile of virgin olive oils. J Sci Food Agric 94(15):3100–3109

Sarrocco S, Cuperlovic-Culf M, Wang L, Forseille L, Boyle K, Merkley N, Burton I, Fobert PR (2016) Metabolic biomarker panels of response to fusarium head blight infection in different wheat varieties. PLoS One 11(4):e0153642

Sauvage C, Segura V, Bauchet G, Stevens R, Do PT, Nikoloski Z, Fernie AR, Causse M (2014) Genome-wide Association in Tomato Reveals 44 candidate loci for fruit metabolic traits. Plant Physiol 165(3):1120–1132

Savorani F, Picone G, Badiani A, Fagioli P, Capozzi F, Engelsen SB (2010) Metabolic profiling and aquaculture differentiation of gilthead sea bream by 1H NMR metabonomics. Food Chem 120(3):907–914

Schauer N, Semel Y, Roessner U, Gur A, Balbo I, Carrari F, Pleban T, Perez-Melis A, Bruedigam C, Kopka J, Willmitzer L, Zamir D, Fernie AR (2006) Comprehensive metabolic profiling and phenotyping of interspecific introgression lines for tomato improvement. Nat Biotechnol 24(4):447–454

Schauer N, Semel Y, Balbo I, Steinfath M, Repsilber D, Selbig J, Pleban T, Zamir D, Fernie AR (2008) Mode of inheritance of primary metabolic traits in tomato. Plant Cell 20(3):509–523

Scheible WR, Morcuende R, Czechowski T, Fritz C, Osuna D, Palacios-Rojas N, Schindelasch D, Thimm O, Udvardi MK, Stitt M (2004) Genome-wide reprogramming of primary and secondary metabolism, protein synthesis, cellular growth processes, and the regulatory infrastructure of Arabidopsis in response to nitrogen. Plant Physiol 136(1):2483–2499

Sebedio JL (2017) Metabolomics, nutrition, and potential biomarkers of food quality, intake, and health status. Adv Food Nutr Res 82:83–116

Sem DS, Bonvallot N, Tremblay-Franco M, Chevrier C, Canlet C, Warembourg C, Cravedi J-P, Cordier S (2013) Metabolomics tools for describing complex pesticide exposure in pregnant women in Brittany (France). PLoS One 8(5):e64433

Settachaimongkon S, van Valenberg HJF, Winata V, Wang X, Nout MJR, van Hooijdonk TCM, Zwietering MH, Smid EJ (2015) Effect of sublethal preculturing on the survival of probiotics and metabolite formation in set-yoghurt. Food Microbiol 49:104–115

Seybold H, Demetrowitsch TJ, Hassani MA, Szymczak S, Reim E, Haueisen J, Lubbers L, Ruhlemann M, Franke A, Schwarz K, Stukenbrock EH (2020) A fungal pathogen induces systemic susceptibility and systemic shifts in wheat metabolome and microbiome composition. Nat Commun 11(1):1910

Shahid M, Khalid S, Abbas G, Shahid N, Nadeem M, Sabir M et al (2015) Heavy metal stress and crop productivity. In: Hakeem KR (ed) Crop production and global environmental issues. Springer, Cham, pp 1–25

Shavit R, Batyrshina ZS, Dotan N, Tzin V (2018) Cereal aphids differently affect benzoxazinoid levels in durum wheat. PLoS One 13(12):e0208103

Shelden MC, Dias DA, Jayasinghe NS, Bacic A, Roessner U (2016) Root spatial metabolite profiling of two genotypes of barley (Hordeum vulgare L.) reveals differences in response to short-term salt stress. J Exp Bot 67(12):3731–3745

Shen M, Broeckling CD, Chu EY, Ziegler G, Baxter IR, Prenni JE, Hoekenga OA (2013) Leveraging non-targeted metabolite profiling via statistical genomics. PLoS One 8(2):e57667

Shlisky J, Bloom DE, Beaudreault AR, Tucker KL, Keller HH, Freund-Levi Y, Fielding RA, Cheng FW, Jensen GL, Wu D, Meydani SN (2017) Nutritional considerations for healthy aging and reduction in age-related chronic disease. Adv Nutr Int Rev J 8(1):17–26

Shoaie S, Ghaffari P, Kovatcheva-Datchary P, Mardinoglu A, Sen P, Pujos-Guillot E, de Wouters T, Juste C, Rizkalla S, Chilloux J, Hoyles L, Nicholson JK, Consortium MI-O, Dore J, Dumas ME, Clement K, Backhed F, Nielsen J (2015) Quantifying diet-induced metabolic changes of the human gut microbiome. Cell Metab 22(2):320–331

Silvente S, Sobolev AP, Lara M (2012) Metabolite adjustments in drought tolerant and sensitive soybean genotypes in response to water stress. PLoS One 7(6):e38554

Simo C, Ibanez C, Valdes A, Cifuentes A, Garcia-Canas V (2014) Metabolomics of genetically modified crops. Int J Mol Sci 15(10):18941–18966

Šimura J, Antoniadi I, Široká J, Tarkowská D, Strnad M, Ljung K, Novák O (2018) Plant Hormonomics: multiple Phytohormone profiling by targeted metabolomics. Plant Physiol 177(2):476–489

Srivastava V, Obudulu O, Bygdell J, Lofstedt T, Ryden P, Nilsson R, Ahnlund M, Johansson A, Jonsson P, Freyhult E, Qvarnstrom J, Karlsson J, Melzer M, Moritz T, Trygg J, Hvidsten TR, Wingsle G (2013) OnPLS integration of transcriptomic, proteomic and metabolomic data shows multi-level oxidative stress responses in the cambium of transgenic hipI- superoxide dismutase Populus plants. BMC Genomics 14:893

Stella C, Beckwith-Hall B, Cloarec O, Holmes E, Lindon JC, Powell J, van der Ouderaa F, Bingham S, Cross AJ, Nicholson JK (2006) Susceptibility of human metabolic phenotypes to dietary modulation. J Proteome Res 5(10):2780–2788

Stephany RW (2010) Hormonal growth promoting agents in food producing animals. Handb Exp Pharmacol (195):355–367. https://doi.org/10.1007/978-3-540-79088-4_16, https://pubmed.ncbi.nlm.nih.gov/20020373/

Stoeckli M, Chaurand P, Hallahan DE, Caprioli RM (2001) Imaging mass spectrometry: a new technology for the analysis of protein expression in mammalian tissues. Nat Med 7(4):493–496

Straadt IK, Aaslyng MD, Bertram HC (2014) An NMR-based metabolomics study of pork from different crossbreeds and relation to sensory perception. Meat Sci 96(2 Pt A):719–728

Sugimoto M, Kaneko M, Onuma H, Sakaguchi Y, Mori M, Abe S, Soga T, Tomita M (2012) Changes in the charged metabolite and sugar profiles of pasteurized and unpasteurized Japanese sake with storage. J Agric Food Chem 60(10):2586–2593

Suharti WS, Nose A, Zheng S-H (2016) Metabolomic study of two rice lines infected by Rhizoctonia solani in negative ion mode by CE/TOF-MS. J Plant Physiol 206:13–24

Sun J, Kou L, Geng P, Huang H, Yang T, Luo Y, Chen P (2015) Metabolomic assessment reveals an elevated level of glucosinolate content in CaCl(2) treated broccoli microgreens. J Agric Food Chem 63(6):1863–1868

Sun CX, Gao XX, Li MQ, Fu JQ, Zhang YL (2016) Plastic responses in the metabolome and functional traits of maize plants to temperature variations. Plant Biol (Stuttg) 18(2):249–261

Swenson TL, Jenkins S, Bowen BP, Northen TR (2015) Untargeted soil metabolomics methods for analysis of extractable organic matter. Soil Biol Biochem 80:189–198

Takahara K, Kasajima I, Takahashi H, Hashida SN, Itami T, Onodera H, Toki S, Yanagisawa S, Kawai-Yamada M, Uchimiya H (2010) Metabolome and photochemical analysis of rice plants overexpressing Arabidopsis NAD kinase gene. Plant Physiol 152(4):1863–1873

Takahashi H, Takahara K, Hashida SN, Hirabayashi T, Fujimori T, Kawai-Yamada M, Yamaya T, Yanagisawa S, Uchimiya H (2009) Pleiotropic modulation of carbon and nitrogen metabolism in Arabidopsis plants overexpressing the NAD kinase2 gene. Plant Physiol 151(1):100–113

te Pas MFW, Goldansaz SA, Guo AC, Sajed T, Steele MA, Plastow GS, Wishart DS (2017) Livestock metabolomics and the livestock metabolome: a systematic review. PLoS One 12(5):e0177675

Teixeira A, Martins V, Noronha H, Eiras-Dias J, Geros H (2014) The first insight into the metabolite profiling of grapes from three Vitis vinifera L. cultivars of two controlled appellation (DOC) regions. Int J Mol Sci 15(3):4237–4254

Tengstrand E, Rosén J, Hellenäs K-E, Åberg KM (2012) A concept study on non-targeted screening for chemical contaminants in food using liquid chromatography–mass spectrometry in combination with a metabolomics approach. Anal Bioanal Chem 405(4):1237–1243

Thomason K, Babar MA, Erickson JE, Mulvaney M, Beecher C, MacDonald G (2018) Comparative physiological and metabolomics analysis of wheat (Triticum aestivum L.) following post-anthesis heat stress. PLoS One 13(6):e0197919

Tian H, Lam SM, Shui G (2016) Metabolomics, a powerful tool for agricultural research. Int J Mol Sci 17(11):1871

Tiwari S, Lata C (2018) Heavy metal stress, signaling, and tolerance due to plant-associated microbes: An overview. Front Plant Sci 9:452

Toubiana D, Semel Y, Tohge T, Beleggia R, Cattivelli L, Rosental L, Nikoloski Z, Zamir D, Fernie AR, Fait A (2012) Metabolic profiling of a mapping population exposes new insights in the regulation of seed metabolism and seed, fruit, and plant relations. PLoS Genet 8(3):e1002612

Tschoep H, Gibon Y, Carillo P, Armengaud P, Szecowka M, Nunes-Nesi A, Fernie AR, Koehl K, Stitt M (2009) Adjustment of growth and central metabolism to a mild but sustained nitrogen-limitation in Arabidopsis. Plant Cell Environ 32(3):300–318

Turhadi T, Hamim H, Ghulamahdi M, Miftahudin M (2019) Iron toxicity-induced physiological and metabolite profile variations among tolerant and sensitive rice varieties. Plant Signal Behav 14(12):1682829

Urbanczyk-Wochniak E, Fernie AR (2005) Metabolic profiling reveals altered nitrogen nutrient regimes have diverse effects on the metabolism of hydroponically-grown tomato (Solanum lycopersicum) plants. J Exp Bot 56(410):309–321

Urpi-Sarda M, Boto-Ordonez M, Queipo-Ortuno MI, Tulipani S, Corella D, Estruch R, Tinahones FJ, Andres-Lacueva C (2015) Phenolic and microbial-targeted metabolomics to discovering and evaluating wine intake biomarkers in human urine and plasma. Electrophoresis 36(18):2259–2268

Urrutia M, Blein-Nicolas M, Prigent S, Bernillon S, Deborde C, Balliau T, Maucourt M, Jacob D, Ballias P, Benard C, Sellier H, Gibon Y, Giauffret C, Zivy M, Moing A (2021) Maize metabolome and proteome responses to controlled cold stress partly mimic early-sowing effects in the field and differ from those of Arabidopsis. Plant Cell Environ 44:1504–1521

Vallverdu-Queralt A, Medina-Remon A, Casals-Ribes I, Amat M, Lamuela-Raventos RM (2011) A metabolomic approach differentiates between conventional and organic ketchups. J Agric Food Chem 59(21):11703–11710

van Dam NM, Bouwmeester HJ (2016) Metabolomics in the rhizosphere: tapping into below-ground chemical communication. Trends Plant Sci 21(3):256–265

Van Meter RJ, Glinski DA, Purucker ST, Henderson WM (2018) Influence of exposure to pesticide mixtures on the metabolomic profile in post-metamorphic green frogs (Lithobates clamitans). Sci Total Environ 624:1348–1359

Vance CP, Uhde-Stone C, Allan DL (2003) Phosphorus acquisition and use: critical adaptations by plants for securing a nonrenewable resource. New Phytol 157(3):423–447

Vasmatkar P, Kaur K, Pannu PPS, Kaur G, Kaur H (2019) Unraveling the metabolite signatures of maize genotypes showing differential response towards southern corn leaf blight by 1H-NMR and FTIR spectroscopy. Physiol Mol Plant Pathol 108:101441

Velásquez AC, Castroverde CDM, He SY (2018) Plant–pathogen warfare under changing climate conditions. Curr Biol 28(10):R619–R634

Wagner L, Trattner S, Pickova J, Gomez-Requeni P, Moazzami AA (2014) (1)H NMR-based metabolomics studies on the effect of sesamin in Atlantic salmon (Salmo salar). Food Chem 147:98–105

Wahyuni Y, Ballester AR, Tikunov Y, de Vos RC, Pelgrom KT, Maharijaya A, Sudarmonowati E, Bino RJ, Bovy AG (2013) Metabolomics and molecular marker analysis to explore pepper (capsicum sp.) biodiversity. Metabolomics 9(1):130–144

Wang M, Carver JJ, Phelan VV, Sanchez LM, Garg N, Peng Y, Nguyen DD, Watrous J, Kapono CA, Luzzatto-Knaan T, Porto C, Bouslimani A, Melnik AV, Meehan MJ, Liu WT, Crusemann M, Boudreau PD, Esquenazi E, Sandoval-Calderon M, Kersten RD, Pace LA, Quinn RA, Duncan KR, Hsu CC, Floros DJ, Gavilan RG, Kleigrewe K, Northen T, Dutton RJ, Parrot D, Carlson EE, Aigle B, Michelsen CF, Jelsbak L, Sohlenkamp C, Pevzner P, Edlund A, McLean J, Piel J, Murphy BT, Gerwick L, Liaw CC, Yang YL, Humpf HU, Maansson M, Keyzers RA, Sims AC, Johnson AR, Sidebottom AM, Sedio BE, Klitgaard A, Larson CB, CAB P, Torres-Mendoza D, Gonzalez DJ, Silva DB, Marques LM, Demarque DP, Pociute E, O'Neill EC, Briand E, Helfrich EJN, Granatosky EA, Glukhov E, Ryffel F, Houson H, Mohimani H, Kharbush JJ, Zeng Y, Vorholt JA, Kurita KL, Charusanti P, McPhail KL, Nielsen KF, Vuong L, Elfeki M, Traxler MF, Engene N, Koyama N, Vining OB, Baric R, Silva RR, Mascuch SJ, Tomasi S, Jenkins S, Macherla V, Hoffman T, Agarwal V, Williams PG, Dai J, Neupane R, Gurr J, Rodriguez AMC, Lamsa A, Zhang C, Dorrestein K, Duggan BM, Almaliti J, Allard PM, Phapale P et al (2016) Sharing and community curation of mass spectrometry data with Global Natural Products Social Molecular Networking. Nat Biotechnol 34(8):828–837

Wang X, Hou L, Lu Y, Wu B, Gong X, Liu M, Wang J, Sun Q, Vierling E, Xu S (2018) Metabolic adaptation of wheat grain contributes to a stable filling rate under heat stress. J Exp Bot 69(22):5531–5545

Wen W, Li D, Li X, Gao Y, Li W, Li H, Liu J, Liu H, Chen W, Luo J, Yan J (2014) Metabolome-based genome-wide association study of maize kernel leads to novel biochemical insights. Nat Commun 5:3438

Witt S, Galicia L, Lisec J, Cairns J, Tiessen A, Araus JL, Palacios-Rojas N, Fernie AR (2012) Metabolic and phenotypic responses of greenhouse-grown maize hybrids to experimentally controlled drought stress. Mol Plant 5(2):401–417

Xu J, Chen Z, Wang F, Jia W, Xu Z (2020) Combined transcriptomic and metabolomic analyses uncover rearranged gene expression and metabolite metabolism in tobacco during cold acclimation. Sci Rep 10(1):5242

Yadav AK, Carroll AJ, Estavillo GM, Rebetzke GJ, Pogson BJ (2019) Wheat drought tolerance in the field is predicted by amino acid responses to glasshouse-imposed drought. J Exp Bot 70(18):4931–4948

Yang L, Fountain JC, Ji P, Ni X, Chen S, Lee RD, Kemerait RC, Guo B (2018) Deciphering drought-induced metabolic responses and regulation in developing maize kernels. Plant Biotechnol J 16(9):1616–1628

Young JE, Zhao X, Carey EE, Welti R, Yang S-S, Wang W (2005) Phytochemical phenolics in organically grown vegetables. Mol Nutr Food Res 49(12):1136–1142

Zainudin BH, Salleh S, Mohamed R, Yap KC, Muhamad H (2015) Development, validation and determination of multiclass pesticide residues in cocoa beans using gas chromatography and liquid chromatography tandem mass spectrometry. Food Chem 172:585–595

Zeng J, Quan X, He X, Cai S, Ye Z, Chen G, Zhang G (2018) Root and leaf metabolite profiles analysis reveals the adaptive strategies to low potassium stress in barley. BMC Plant Biol 18(1):187

Zhang X, Breksa AP 3rd, Mishchuk DO, Fake CE, O'Mahony MA, Slupsky CM (2012) Fertilisation and pesticides affect mandarin orange nutrient composition. Food Chem 134(2):1020–1024

Zhang Y, Wang Y, Ding Z, Wang H, Song L, Jia S, Ma D (2017) Zinc stress affects ionome and metabolome in tea plants. Plant Physiol Biochem 111:318–328

Zhang WF, Gong ZH, Wu MB, Chan H, Yuan YJ, Tang N, Zhang Q, Miao MJ, Chang W, Li Z, Li ZG, Jin L, Deng W (2019) Integrative comparative analyses of metabolite and transcript profiles uncovers complex regulatory network in tomato (Solanum lycopersicum L.) fruit undergoing chilling injury. Sci Rep 9(1):4470

Zhao Y, Zhao J, Zhao C, Zhou H, Li Y, Zhang J, Li L, Hu C, Li W, Peng X, Lu X, Lin F, Xu G (2015) A metabolomics study delineating geographical location-associated primary metabolic changes in the leaves of growing tobacco plants by GC-MS and CE-MS. Sci Rep 5:16346

Zhou J, Ma C, Xu H, Yuan K, Lu X, Zhu Z, Wu Y, Xu G (2009) Metabolic profiling of transgenic rice with cryIAc and sck genes: an evaluation of unintended effects at metabolic level by using GC-FID and GC-MS. J Chromatogr B Analyt Technol Biomed Life Sci 877(8–9):725–732

Zhou S, Zhang YK, Kremling KA, Ding Y, Bennett JS, Bae JS, Kim DK, Ackerman HH, Kolomiets MV, Schmelz EA, Schroeder FC, Buckler ES, Jander G (2018a) Ethylene signaling regulates natural variation in the abundance of antifungal acetylated diferuloylsucroses and Fusarium graminearum resistance in maize seedling roots. New Phytol 221(4):2096–2111

Zhou X, Taylor MP, Salouros H, Prasad S (2018b) Authenticity and geographic origin of global honeys determined using carbon isotope ratios and trace elements. Sci Rep 8(1):14639

Zhou S, Zhang YK, Kremling KA, Ding Y, Bennett JS, Bae JS, Kim DK, Ackerman HH, Kolomiets MV, Schmelz EA, Schroeder FC, Buckler ES, Jander G (2019) Ethylene signaling regulates natural variation in the abundance of antifungal acetylated diferuloylsucroses and Fusarium graminearum resistance in maize seedling roots. New Phytol 221(4):2096–2111

Zorb C, Langenkamper G, Betsche T, Niehaus K, Barsch A (2006) Metabolite profiling of wheat grains (Triticum aestivum L.) from organic and conventional agriculture. J Agric Food Chem 54(21):8301–8306

Zorb C, Geilfus CM, Muhling KH, Ludwig-Muller J (2013) The influence of salt stress on ABA and auxin concentrations in two maize cultivars differing in salt resistance. J Plant Physiol 170(2):220–224