

BIOCHEMISTRY
AND MOLECULAR
BIOLOGY IN THE
POST GENOMIC ERA

METABOLOMICS *And* CLINICAL APPROACH

SEVGI DURNA DAŞTAN
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Biochemistry and Molecular Biology in the Post Genomic Era



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**Sevgi Durna Daştan
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Editors

Metabolomics and Clinical Approach



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DOI: <https://doi.org/10.52305/FZMO0355>

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Library of Congress Cataloging-in-Publication Data

Names: Durna Daştan, Sevgi, editor. | Daştan, Taner, editor.

Title: Metabolomics and clinical approach / Sevgi Durna Daştan, editor, Associate Professor, Department of Biology, Division of Molecular Biology, Faculty of Science, Sivas Cumhuriyet University, Sivas, Turkey, Taner Daştan, PhD, editor, Faculty of Science and Department of Biochemistry, Sivas Cumhuriyet University, Sivas, Turkey.

Description: New York : Nova Science Publishers, [2023] | Series: Biochemistry and molecular biology in the post genomic era | Includes bibliographical references and index. |

Identifiers: LCCN 2023041393 (print) | LCCN 2023041394 (ebook) | ISBN 9798891130951 (hardcover) | ISBN 9798891131811 (adobe pdf)

Subjects: LCSH: Metabolism. | Metabolites.

Classification: LCC QP171 .M48223 2023 (print) | LCC QP171 (ebook) | DDC 612.3/9--dc23/eng/20231010

LC record available at <https://lccn.loc.gov/2023041393>

LC ebook record available at <https://lccn.loc.gov/2023041394>

Published by Nova Science Publishers, Inc. † New York

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Chapter 20

Metabolomic Applications in Food Science and Nutrition

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Abstract

The definition of metabolomics encloses an efficient description of small molecule metabolites present in different biological matrices. Metabolomics has shown up as a prominent tool for various areas including health diseases, drug research, plant science, food science, and nutrition. The metabolomics has recently been used to investigate some parameters in particular for food quality, processing, and the safety of both raw materials and final products. Food metabolomics has also a position in human nutrition research. This book chapter focuses on the novel and potential applications of metabolomics in food science and nutrition by summarizing some metabolomic analysis of food components, metabolomics from the preferential, presumable, and informative approaches in food processing, food microbiology, food safety, food quality, and benefits of foodomics in human nutrition and related health diseases.

Keywords: metabolomics, foodomics, food science, food processing, food analyses, nutrition

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In: Metabolomics and Clinical Approach
Editors: Sevgi Durna Daştan and Taner Daştan
ISBN: 979-8-89113-095-1
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Introduction

Metabolomics is a discipline to explain the performances of metabolites by identifying, quantifying, and detailing their mechanisms of action. There are several advanced instruments and techniques to investigate the metabolomes of various samples, including fundamentally nuclear magnetic resonance (NMR), mass spectrometry (MS), and vibrational spectrometry (VS) or combinations of other techniques. Generally, all these instrumental techniques are aimed to isolate, determine, quantify, characterize structures, and explain their functions on the metabolic pathways. Since metabolomes are complex molecules, it is highly needed to conduct many of these techniques together to better understand the whole mechanism (Fraga-Corral et al., 2022; Zhang et al., 2012).

Metabolomics has great potential to figure out the major problems of food science. Moreover, metabolomics is considered as an effective technique for further agricultural needs (Green et al., 2007; Hall et al., 2008). The engagements of informative, discriminative, and predictive metabolomics have been used for food quality, process, nutrition, and food component analysis (Cevallos-Cevallos et al., 2009). This book chapter covers a review of current metabolomics applications in food quality, safety, microbiology, processing, and nutrition.

Metabolomics in Food Science

Analysis of Food Metabolomics

The analysis of food metabolomics has been used in food safety control, including foodborne pathogens, toxins, some allergens, pesticides, antibiotics, food quality (in terms of organoleptic properties and nutritional value), food authenticity, and food traceability (Cook and Nightingale, 2018).

There are six main steps for metabolomics analysis including sample preparation, metabolite extraction, derivatization, metabolite separation, detection, and data treatment. In general, the essential steps for metabolomics analysis are detection and data analysis. The steps could be selected according to the purpose of the study, sample type, instrument type, and detection method (Pinu, 2015). Some of the metabolomics studies related to different food samples are summarized in Table 1. Since the metabolomic analyses of foods are quite varied, most studies could be classified as discriminative. The

informative metabolomic analyses are mostly interested in the recognition and quantification of certain metabolites to obtain detailed information about the food sample. The untargeted metabolomics solely focuses on the identification of some groups of metabolites to obtain patterns or fingerprints, whereas targeted metabolomics demands higher purification and selective extraction stages (Alonso et al., 2015). Some metabolomics studies are predictive means that statistical models are constructed to estimate a variable that is difficult to quantify based on the metabolite profile and abundance (Table 1).

Table 1. The metabolomics studies of different food samples

Sample and purpose	Analysis Type	Instrumentation	Data Analysis	Reference
Blueberries: polyphenol composition	Untargeted/informative	UHPLC-MS	Principal Component Analysis (PCA)	Zhao et al., 2017
Cheese: Production control	Untargeted/informative	IMS	Compound identification	Vautz et al., 2006
Honey: determinations of residues	Untargeted/discriminative/predictive	NMR	Partial Least Square (PLS)	Li et al., 2016
Meat: quality/safety	Targeted/discriminative	HILIC-MS/MS	MRL Validation	Dasenaki et al., 2016
Olive oil: classification	Untargeted/predictive	GC-HRMS	Orthogonal partial least squares discriminant analysis (OPLS-DA)	Sales et al., 2017
Maize: GMO identification	Untargeted/discriminative	CE-TOF-MS	PCA	Levandi et al., 2008
Vinegar: Metabolic profile	Untargeted/discriminative	GC-MS	Hierarchical cluster analysis (HCA)	Pinu et al., 2016
Fermented vegetable juice: monitoring metabolites	Untargeted/discriminative/predictive	NMR	PCA OPLS-DA	Tomita et al., 2017
Coffee: determination of product origin	Untargeted/predictive/discriminative	UHPLC-(Q)ToF MS	PCA PLS-DA	Ossa et al., 2018
Almonds: discrimination	Untargeted/discriminative/predictive	UHPLC-(Q)ToF	PCA PLS-DA	Solsona et al., 2018
Tea	Targeted	GC-MS	MRL Validation	Saito-Shida et al., 2015
Shellfish: drug residue	Targeted	LC/GC-MS-MS	Compound identification	Chang et al., 2016
Wheat	Untargeted	UHPLC-(Q)ToF	PCA OPLS-DA	Rubert et al., 2017a

Metabolomics in Food Quality

The main target of food quality states is to ensure the appropriate organoleptic and desired characteristics of the product. The research related to food quality aims to evaluate the impacts of food processes on food compounds. The improvement in metabolomic techniques has allowed the monitoring of some quality parameters of foods during processing. The metabolomics methods have been commonly employed to identify the chemical composition of food products (Cossignani et al., 2014). The taste quality of white tea was evaluated by non-targeted metabolomics in combination with multivariate analysis (Yue et al., 2019). A metabolomic data-based prediction model was constructed which could separate green, yellow, and white teas according to unique tea metabolites (Zhang et al., 2019). The two-dimensional liquid chromatography was utilized in the determination of anthocyanins of different aged red wines and also to make the comparison of metabolites of aged red wines (Willemse et al., 2015). An untargeted metabolomics technique was used to distinguish the volatile compounds of grape juices according to various fungal infections performed by *Botrytis cinerea*, *Penicillium expansum*, *Aspergillus niger*, or *A. carbonarius* (Schueuermann et al., 2019).

Food authenticity and quality are closely related to each other. Food adulteration exposes defects in quality by incorporating prohibited ingredients or poor products, causing a health threat to customers. Therefore, food authenticity has great importance in the food industry for maintaining nutritional benefits, origin, and production standards. The metabolomics-based methods effectively specify the discrimination potential between adulterated and authentic foods. Moreover, metabolomics has been used to define the protected designation of origin (PDO) of food products. A prediction model was performed to discriminate adulterated Bordeaux wine in terms of geographical origin with LC-QTOF-MS (Lin et al., 2014). The different ingredients of the milk powders were analyzed by metabolomics coupled with 2DLC and monosaccharides were found in various trademarks and types of milk powder (Ma et al., 2014).

Metabolomics-based methods have been extensively used in examining the ingredients stated on the label of fruits, rice, and different vegetables (potatoes, peppers, white cabbage), clarifying differences in established production systems of wheat and maize, detecting the origin of olive oil, vinegar, wine, almonds, cocoa beans, honey, coffee species, saffron, and citrus fruit juices (Li et al., 2021).

Metabolomics in Food Microbiology

The foodborne pathogens, particularly *Salmonella spp.*, *Listeria monocytogenes*, *Campylobacter jejuni*, and *Shigella spp.*, spoilage microorganisms (such as *Pseudomonas spp.*, *Acinetobacter spp.*, and *Botrytis spp.*), and currently emerging pathogens have appeared as a result of the internationalization of the food supply chain and food consumption trends (Li and Zhu, 2017). Traditional laboratory techniques are primarily time-consuming and labor-intensive. A large number of microbial biomarkers with varying levels of microbial contamination have been identified using metabolomics-based methods. These methods have demonstrated significant promise in the early detection of microbial contamination. The GC-MS has been used to characterize three prominent foodborne pathogens, *E. coli O157:H7*, *L. monocytogenes*, and *S. enterica*. Several potential pathogen-specific biomarkers were discovered, allowing the rapid differentiation of food samples containing pathogens (Jadhav et al., 2019). Furthermore, metabolomics has the ability to determine some antimicrobial compounds responsible for the antimicrobial characteristics of foods (Cevallos-Cevallos et al., 2009).

Despite the fact that this technique is promising in identifying metabolic shifts in different stages of microorganisms and providing important information on pathogen microorganisms, it is challenging to develop a universal method for removing bacterial cultures during metabolomics research. The extracellular and intracellular metabolites of microorganisms are typically difficult to distinguish from each other and also to identify. Moreover, metabolites are relatively unstable and could be quickly degraded during the handling and processing of samples. The current improvements in microbial metabolomics are not optimal. Therefore, more sensitive and reproducible analytical tools, as well as appropriate sample treatment techniques, are required to successfully determine the complexity of metabolites for metabolomics analysis (Li et al., 2021). Metabolomics in Food Safety

The foods could be contaminated with foodborne causative agents (pathogens and biotoxins), and some physical and chemical materials (pesticides and metals) which cause to foodborne illnesses throughout the critical steps of food processes. Metabolomics is able to evaluate the safety conditions of foods during processing and pre- and post-harvest periods and storage. Generally, untargeted discriminative analysis has been used for food safety. The MS/NMR-based metabolomics analysis is superior for the

detection and quantification of pathogens, chemical contaminants, prohibition compounds, and natural toxins (Rešetar et al., 2015).

Foodborne pathogens and their toxins do not remarkably the change characteristic properties (flavor, texture, or appearance) of foods. As a result, microbial contaminants are the most frequently reported foodborne causative agents. Microbial metabolomics may also be used to explain how environmental factors affect complex biological systems (Anderson et al., 2014). The metabolomic applications for food microbiology are discussed in the previous section.

Foodborne biotoxins are classified into two groups: intrinsic foodborne biotoxins and extrinsic foodborne biotoxins. These toxins are synthesized and released into the environment during pathogen growth and cause common foodborne outbreaks. Metabolomics is able to detect toxins in the early stages to ensure food safety. Mass spectroscopy, in particular, could profile metabolites associated with microbial contamination, and NMR could also directly define microbial toxins (Kleigrewe et al., 2012). Some natural toxins are known to be lethal since they are extremely toxic at lower concentrations. As a result, preparation methods should be improved to provide sensitive and high-throughput detection. For example, the addition of multiple antibody immunoaffinity columns prior to HPLC-MS/MS was selectively determined different toxins with a reduction in the detection limit (Zhang et al., 2016).

Fungicides, pesticides, antibiotics, and nanomaterials are examples of xenobiotics that can contaminate food via the atmosphere, soil, and water. These xenobiotics negatively affect whole living organisms even at low levels. Metabolomics can detect various groups of xenobiotics in various food matrices (Li et al., 2021).

The metabolomics methods have been developed to control veterinary drug residues and antibiotics in animals following alterations in metabolites in biological tissues (Kaufmann et al., 2015). Liquid chromatography combined with electrospray ionization and tandem mass spectrometry (LC-ESI-MS/MS) has been utilized in the quantification and identification of 115 different veterinary drug and pharmaceutical residues in milk powder, egg, and fish tissue (Dasenaki and Thomaidis, 2015). A targeted analysis has been performed by investigating 20 different antibiotic residues in dairy products including powdered milk, commercial milk, and raw milk (Wang et al., 2017).

The pesticides are widely used in agricultural productions. Pesticides are receiving much more attention since the presence of residues in foods involves health risks. For multi-residue pesticide analyses in various foods, the combination of QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and

Safe) with solid-phase extraction (SPE) or solid-phase micro-extraction (SPME) has been achieved. The QuEChERS approach was optimized for the determination of mycotoxins and pesticides in coffee. It was observed that 117 pesticides and 30 mycotoxins were present in raw coffee (González-Curbelo et al., 2015; Reichert et al., 2018).

The new genetic engineering developments and genetically engineered (GE) crops with genomic modifications have been produced and allowed for the cultivation of genetically modified (GM) crops. The unknown health threat of GM foods is a source of health concerns among consumers, and they have been restricted in many countries. It is critical to estimate the addition of genetically modified foods and/or food ingredients to the food supply and to evaluate risk parameters using metabolomics techniques. Untargeted metabolomics is routinely involved in the differentiation of conventional foods, transgenic foods, and genetically modified foods (Cevallos-Cevallos et al., 2009; Li et al., 2021). There have been comprehensive researches related to wheat (Shewry et al., 2007), soybean (García-Villalba et al., 2008), barley (Kogel, 2010) and potato (Shepherd et al., 2015) differentiate genetic modification for food safety.

Metabolomics in Food Processing

Food processing comprises the all over changes in physical and chemical structure that are created by components of foods that could be detected by metabolomics. Informative metabolomics is able to determine undesired effects pre-processing and during processing including degradation of compounds and nutrients, and synthesis of new compounds like toxins (Cevallos-Cevallos et al., 2009). The fermentation process of cheonggukjang has been monitored by informative and discriminative untargeted analysis by using nuclear magnetic resonance, and the final products were separated according to the fermentation time (Choi et al., 2007). Metabolomics could also be used to decide the suitability of raw materials for a certain process. While some potato varieties are favored for frying, others are used in the baking industry. The flow infusion electrospray-ionization mass spectrometry (FI-ESI-MS) and compound identification were aided by GC-MS to determine the differences between potato varieties (Beckmann et al., 2007).

Targeted and untargeted metabolomics have been widely used to measure the effects of process parameters on the metabolite composition of foods. There are several metabolomics studies related to different food processes; the

effects of storage conditions on red wine (Arapitsas et al., 2016), the influences of blending and heating on Tiger nut milk (Rubert et al., 2017b), carrot, tomato, broccoli (Lopez-Sanchez et al., 2015), and banana (Chen et al., 2020), the impacts of energy stages on mung beans sprout (Chen et al., 2019), and the consequences of heat processing on Brassica vegetables (Hennig et al., 2014).

Metabolomics for Nutrition

Foodomics is a discipline that focuses on food and nutrition to explain the relationship between ingredients of food with quality and safety, daily diet, health, and diseases via developed omics technologies and chemometrics, bioinformatics, and biostatistics to enhance consumer's beneficence, health, and knowledge. The main subjects of foodomics could be summarized into three groups;

1. Human health (food consumption related to human health)
2. Food resources (plant and animal origin of food)
3. Food Processing (Picone et al., 2019; Zotti et al., 2016).

Nowadays, foodomics is used to better understand the molecular connections between human health, nutrition, and food. In particular, foodomics has been used for developing novel nutraceutical and functional foods. The effects of bee pollen (BP) on inflammatory bowel disease were investigated utilizing metabolomics analysis by using ultra-performance liquid chromatography in tandem with quadrupole time of flight-mass spectrometry (UPLC-Q-TOF/MS). It was discovered that the BP extract's regulatory mechanism protects cellular metabolic pathways from DSS-induced Caco-2 cell metabolism disorders (Li et al., 2019). The metabolomic methods were used to assess the anti-proliferative potential of *Passiflora mollissima* seeds on HT-29 human colon cancer cells. The results confirm that foodomics enabled the identification of genes, comprising polyamine and glutathione metabolism, or the inactivation of NUPR1 transcription could be involved in fluctuations in intracellular ceramide concentrations (Ballesteros-Vivas et al., 2020).

One of the most important and challenging aspects of nutrition is the monitoring food consumption of consumers. It is a simple way to precisely control the health of consumers by monitoring the food that a person has

consumed. The food frequency questionnaires (FFQs) fill out by consumers revealed some findings on the positive or negative effects of certain foods or diets. It has also been observed that FFQ recall for retrospective diet studies is not good enough. Moreover, FFQ does not provide direct information about plasma levels of circulating nutrients or micronutrients (Wishart, 2008). Food consumption monitoring combined with metabolomics provides detailed knowledge of blood, urine, or saliva from volunteers in diet intervention studies. Foods are complex molecules and have many more components and metabolites. Food-specific biomarkers could be found in either blood or urine. The presence of these biomarkers proves the consumption of a certain food or the amount of the compound increases significantly over a period of time. It is known that the substantial difference between urine and blood is the percentages of metabolites to non-metabolites. Generally, urine has a significantly higher proportion of non-metabolites than blood. In a study on biomarkers of onion consumption, 11 relatively high abundance quercetin metabolites were discovered in urine, whereas only 5 lower abundance quercetin metabolites were found in the blood (Mullen et al., 2004). Therefore, metabolomic studies could be a solution to the problems of food consumption questionnaires used in probable diet objection or food interference studies.

Conclusion

Metabolomics has achieved great progress, with exciting findings associated with food analysis through the development of analytical techniques. The application of metabolomics in food processing, food quality control, and food safety is satisfactory with appropriate statistical analyses. Furthermore, targeted metabolomics should be improved with the automation, fast, and precision of entire metabolite quantitation. The untargeted metabolomics should be refined to control analytical data quality and develop a more reliable standardization of protocols. Comprehensive attention should be paid to food microbiology and nutrition for future aspects.

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