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Foodomics – Fundamentals, State of the Art and Future Trends

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ABSTRACT

Foodomics is being consolidated in Food Science through the application and integration of a variety of omics tools (e.g., genomics/trascriptomics, proteomics, metabolomics) together with chemometrics and bioinformatics. Foodomics can greatly improve our understanding of the complex food – diet – individual interplay, involving different Food Science and Nutrition research areas dealing with food composition, food safety, quality and traceability issues, as well as the food impact on individual's health/illness status. Readers of the present chapter will get an overview of the fundamentals, the most recent advances and future perspectives in the different areas of Foodomics.

22 **X.1 Introduction**

23 Researchers in modern Food Science and Nutrition are moving from classical methodologies – traditionally used
24 e.g., to provide a descriptive view of raw food composition or to investigate functional and nutritional factors – to
25 more advanced and multi-disciplinary strategies. These new approaches adopt well-established methodologies in
26 medical, pharmacological, and/or biotechnological research, making use of advanced omics tools and
27 bioinformatics, along with *in-vitro*, *in-vivo* and/or clinical assays [1]. As a result of this trend, new interdisciplinary
28 research areas such as nutrigenomics, nutrigenetics, nutritional genomics, nutritranscriptomics, nutriproteomics,
29 nutrimetabolomics, microbiomics, toxicogenomics or systems biology have emerged.

30 The new omics technologies have the potential to widen the scope of traditional targeted analysis and opened up
31 impressive possibilities to explore formerly unanswered questions and problems relevant to Food Science and
32 Nutrition. They have become powerful tools to tackle the comprehensive assessment of food safety, the first
33 challenge for food researchers, that largely affects our health as consumers in a globalized market. Since many
34 products contain multiple and processed ingredients, very often shipped from different parts of the world, worldwide
35 movement of food and related raw materials are repeatedly demonstrated to undergo global contamination
36 episodes. Therefore, ensuring the safety, as well as the quality and traceability of food has never been more
37 complicated and necessary than today.

38 In this line, European Food Safety Authority (EFSA) has open a scientific debate on the integration of data produced
39 by omics in the risk assessment of food, including the safety assessment of transgenic or GM foods among others
40 [2,3].

41 Current trends in modern Food Science and Nutrition are increasingly focused on understanding the food and
42 health interplay. Food is now considered not only a source of energy but also an affordable way to prevent future
43 diseases, as many food components are potential sources of health-promoting compounds. The possibility to
44 account on food products tailored to promote the health and well-being of groups of population identified on the
45 basis of their individual genomes is an impressive opportunity opened by these new omics approaches. However,
46 to scientifically demonstrate the healthy effect of food and food ingredients, analytical strategies have to face
47 important difficulties derived, among others, from food complexity, the huge natural variability, the large number of
48 different nutrients and bioactive food compounds, their very different concentrations, their bioavailability and
49 transformation in the human tract, the numerous targets with different affinities and specificities that might exist in
50 the human body, etc. Thus, understanding the biochemical, molecular and cellular mechanisms that underlies the
51 beneficial or adverse effects of certain bioactive food components is currently a hot topic in food research
52 considered unapproachable few years ago.

53 In this context, it is understandable the need of innovative, high-throughput, multi-omics platforms able to provide
54 with the necessary data and information to offer real solutions and answers to the actual challenges in food science.
55 Foodomics emerge as an integrative framework that involves not only gathering data coming from the different

56 omics approaches but also the integration of all of them using advanced bioinformatics tools to be able to end up
57 with the whole picture of the food-biological system interaction [4].
58 In the following sections, the principles of Foodomics including the fundamental omic tools employed and its
59 implications in Food Science and Nutrition will be comprehensively described. Furthermore, an updated evaluation
60 of representative Foodomics applications in the field of foods safety, quality and traceability as well as in nutrition
61 and health research will be provided. At the end of the chapter, the future challenges and foreseen trends that will
62 face this promising discipline are discussed.
63
64 **X.2 Principles and fundamentals of Foodomics**
65 Foodomics, as defined in 2009 [5], is *a discipline that studies the food and nutrition domains through the application*
66 *and integration of advanced omics technologies to improve consumer's well-being, health, and confidence.*
67 Foodomics is, therefore, a broad discipline that integrates all the multidisciplinary approaches in modern food
68 science and nutrition (e.g. nutrigenomics, nutrigenetics, microbiomics, toxicogenomics, nutritranscriptomics,
69 nutriproteomics, nutrimetabolomics, etc). Considering the complexity of the foodome, defined as *the collection of*
70 *all compounds present in any investigated food sample and/or in any biological system interacting with the*
71 *investigated food at a given time* [6], the implementation of omics platforms such as transcriptomics, proteomics and
72 metabolomics is essential to conveniently characterize the mentioned foodome. The combination of these
73 techniques produces complementary analytical information, thus allowing a wider foodome coverage at different
74 molecular expression levels (transcripts, proteins and metabolites). A representation of the areas covered by
75 Foodomics and the tools usually employed can be seen in Figure X.1.
76
77 [Insert Figure X.1 here]
78
79 By taking advantage of the newest omics methodologies, Foodomics is continuously pushing the research in
80 different hot topics in Food Science and Nutrition. One of the main goals and interests in Foodomics is in line with
81 medicine and biosciences toward prevention of future diseases through adequate food intakes, and the
82 development of the so-called functional foods and nutraceuticals [7]. In this regard, Foodomics covers, for instance,
83 the investigation of the mechanisms that underlies the beneficial or adverse effects of certain bioactive food
84 components at biochemical, molecular and cellular level [8]; the gene-based differences among individuals in
85 response to a specific dietary pattern and the roadmap towards a personalized nutrition [9, 10]; the identity of the
86 genes involved in the previous stage to the onset of the disease, that can lead to the discovery of possible molecular
87 biomarkers; the global role and functions of gut microbiome and its impact on individuals health [11]. Furthermore,
88 Foodomics can also help to investigate and solve crucial topics in food science and nutrition such as global omics

89 strategies to explore food safety, quality and traceability [7, 12, 13]; the unintended effects in genetically modified crops
90 or the comprehension of the molecular basis of biological processes with agronomic interest and economic
91 relevance (interaction between crops and its pathogens, postharvest phenomena or physicochemical changes
92 during fruit ripening) among other issues [4, 14].
93 Since its origin, the interest in Foodomics has greatly increased, and many works have already shown the
94 tremendous possibilities of this approach to boost food science investigations [6]. A good example of the interest of
95 the scientific community in Foodomics is the number of publications that have appeared in the last decade (more
96 than 250 SCI papers). Some representative review papers on Foodomics are detailed in Table X.1, covering
97 aspects related to (i) food quality and traceability, (ii) food safety and (iii) food bioactivity and health. Despite the
98 growing number of papers dealing with applications in the Foodomics field, the number of research works showing
99 real experimental data integrating different omics technologies is still limited compared to opinions, comments and
100 review papers, demonstrating the complexity of these multi-omics approaches and the long way that we still have
101 to go.
102
103 [Insert Table X.1 here]
104

105 **X.2.1 Omics approaches in Foodomics**

106 To face the enormous challenges in different subdisciplines and applications, Foodomics involves the use of
107 multiple omics tools capable of providing molecular information on the different expression levels, i.e., gene,
108 transcript, protein, or metabolite. Thus, some fundamentals about the main omics approaches used in Foodomics,
109 namely transcriptomics, proteomics and metabolomics are provided below.
110 Gene expression profiling is a useful tool to understand the mechanisms of interaction between nutrient and genes.
111 Thus, two conceptually different transcriptomics approaches can be applied to identify and quantify changes in
112 mRNA expression levels of hundreds or thousands of genes. One of the approaches is based on gene expression
113 microarrays, whereas the other transcriptomic platform is based on massive sequencing of RNA (RNA-Seq), which
114 makes possible the analysis of thousands of transcribed sequences quickly and efficiently [15]. Afterwards, gene
115 validation, through quantitative polymerase chain reaction (qPCR), is normally employed to confirm the up- or
116 down-regulation of a selected number of genes [16], mostly after using microarrays. The fundamental goal of these
117 approaches is to identify differentially expressed genes (DEGs) in the condition of interest. The discovery of a large
118 number of non-coding RNAs (e.g., microRNA (miRNA), long non-coding RNA (lncRNA), pseudogenes) with
119 regulatory functions opens a new field of study for nutrient action and emphasizes the study of transcriptomics as
120 an end-point of regulatory control [17].

121 Traditionally, hybridization-based approaches such as gene expression microarray have been the standard gene
122 expression profiling technology in transcriptomic studies. This technique is based on specific nucleic acids
123 hybridization to measure the relative quantities of specific messenger RNAs (mRNAs) in two or more samples for
124 thousands of genes simultaneously. The experimental procedure involves RNA extraction from tissue, cells, or
125 other biological sample, labelling (e.g., fluorescent marker) and hybridization with their complementary genes-
126 specific probes on the microarray [3]. Despite the powerful performance, variability is one of the main drawbacks of
127 this technique, that can mask the biological signals of interest. The huge amount of data generated from microarray
128 experiments requires thorough data processing to extract biologically meaningful information [18]. In most
129 transcriptomics analysis, the tool of choice up to now is the microarray, and Affymetrix platforms are the most
130 preferred. Agilent, Illumina, Applied Biosystems, and home-made low-density arrays are also used. [17]
131 RNA-Seq technology has emerged as an attractive alternative to traditional microarray platforms for conducting
132 transcriptional profiling. The main difference between RNA-Seq and microarrays is that the former allows for full
133 sequencing of the whole transcriptome while the latter only profiles predefined transcripts/genes through
134 hybridization. In practice, RNA-Seq can help identifying more differentially modulated transcripts of relevance,
135 splice variants, and non-coding transcripts. However, the RNA-Seq approach has a few disadvantages compared
136 to microarrays, namely (1) a lack of optimized and standardized protocols for analysis in spite of the availability of
137 multiple computational tools and (2) the size of RNA-Seq files, which are considerably larger than microarray files.
138 Finally, RNA-Seq requires an extensive and more complex bioinformatics analysis, which results in highly intensive
139 and expensive computation infrastructure and analytics, as well as longer analysis times. However, these
140 limitations are gradually improving [19].
141
142 Proteomics represents a comprehensive scientific study of all expressed proteins or entire proteome at any given
143 time in an organism. Proteomics can provide details about the changes and comparisons in expression pattern of
144 proteins in a specific physiological or pathological condition. Protein profiling approaches can also be used to
145 analyze quality, origin, or adulterations of food [20].
146 The complexity in the proteome is mainly due to a large dynamic range, 6–10 orders of magnitude. In plasma, the
147 range is even higher than 10, which makes difficult to detect very-low abundant proteins. Proteomics deals with
148 other problems such as the alternative splicing and the post-translational modifications (PTM), which play crucial
149 roles in regulating the biology of the cell since they can change the physical or chemical properties, activity,
150 localization or stability of the proteins [8].
151 The analysis of the complex proteome has been boosted in recent years by the development and improvement of
152 high-resolving separation systems, along with the even more accurate high-resolution (HR) tandem mass
153 spectrometers. When working with complex food/biological sample most of protocols usually include depletion of
154 the most abundant interfering proteins, selective enrichment of the low abundance proteins of interest, or even

155 partial purification of the target proteins. Before the final analysis in the mass spectrometer, further separation is
156 performed at protein and/or peptide level, typically based on two dimensional gel electrophoresis (2-DE, gel-based
157 approach) and/or liquid chromatography (LC, gel-free approach) [21]. Subsequent analysis of the isolated proteins
158 or peptides is mainly based on mass spectrometry (MS) detection, using soft ionization methods, mainly matrix-
159 assisted laser desorption/ionization (MALDI) and electrospray ionization (ESI). To avoid interferences in the
160 ionization source, the sample clean-up is critical to remove salts, stabilizers, and/or detergents used in the
161 extraction prior to MS analysis. [8].
162
163 Two different MS-based proteomic workflows can be followed, depending on whether the MS analysis is carried
164 out on the peptide fragments (bottom-up) or on the corresponding intact proteins (top-down). The most widely used
165 strategy is the bottom-up approach, characterized by the proteolytic digestion of the proteins prior to the MS
166 analysis. Proteins can be firstly separated by using gel-based approaches such as 2-DE or sodium dodecyl sulfate
167 polyacrylamide gel electrophoresis (SDS-PAGE), and subsequently submitted to an in-gel digestion. After
168 separation, the spots of interest are excised from the gel and submitted to analysis by MS. Alternatively, the protein
169 can be enzymatically digested, and separation of the peptides in on-line combination of various chromatographic
170 and/or electrokinetic separation methods, coupled with MS, following the so-called "shotgun" proteomic approach.
171 The identification of the original protein is carried out by comparison of the experimental mass spectra of the
172 peptides obtained in the digestion, with their corresponding theoretical masses stored in databases. A broad variety
173 of databases for proteins and peptides can be found: NCBI, SwePep, Erop-Moscow, PeptideDB, Peptidome, Pep-
174 Bank, IPI human protein database, BioPep or BioPD, among others. In addition, different search engines software
175 have been developed to facilitate this task, such as MASCOT, SEQUEST, Andromeda, and X!Tandem. Moreover,
176 advances in bioinformatics have enabled the development and the combination of computational tools for *in silico*
177 prediction and discovery of functional peptides information from the genome sequence (known as "reverse-genome
178 engineering") [22].
179 In the top-down approach, the intact proteins isolated from a previous fractionation or purification step, via 2-DE or
180 LC, are directly infused to a HRMS. The proteins are studied through measurement of their intact mass and further
181 fragmentation inside the mass spectrometer. Typical instruments used for top-down Proteomics are MALDI-time-
182 of-flight/time-of-flight (TOF/TOF), ESI-quadrupole(Q)/TOF, ESI-ion trap (IT), Orbitrap and the classical HRMS
183 instrumentation Fourier transform ion cyclotron resonance (FTICR) MS; the latter one offering the highest mass
184 resolution, resolving power, accuracy and sensitivity. This approach allows to characterize the post-transcriptional
185 modifications present in proteins and differentiate biomolecules with a high degree of sequence identity. However,
186 top-down Proteomics approaches are usually limited to simple protein mixtures since multiple charged proteins
187 generate very complex spectra. [20].
188

189 As one of the most recent post-genomic disciplines, metabolomics has experienced a notable progress in the last
190 decade, as a result of the development of analytical platforms (mainly chromatography, nuclear magnetic
191 resonance (NMR) and, mostly, MS-based techniques) and software programs to process the large amount of
192 generated analytical data sets [23]. Metabolomics focuses on the full set of endogenous and small molecules with a
193 relative molecular weight of less than 1000 Da (metabolites), and the small pathway motifs that are present in any
194 biological system (cell, tissue, organ, organism or species). Unlike nucleic acid or protein-based omics techniques,
195 focused on the determination of a single chemical class of compounds, the huge number of compounds and broad
196 physicochemical diversity of the metabolome (e.g., sugars, amino acids, small peptides, organic acids, lipids and
197 nucleic acid) entails important analytical challenges. In addition, the relative concentration of metabolites in the
198 biological sample can vary from millimolar level (or higher) to picomolar, exceeding in most cases the linear range
199 of the analytical techniques employed [3].
200 Due the chemical diversity of the metabolome, no single analytical methodology or platform is applicable to detect,
201 quantify, and identify all metabolites in a certain sample. A group of well-established analytical techniques, mainly
202 based on NMR and MS, are the most frequently used in metabolic profiling and fingerprinting applications in
203 metabolomics. These techniques are used either as standalone or, most commonly, combined with different
204 separation techniques (LC-NMR, gas chromatography (GC)-MS, LC-MS, and capillary electrophoresis (CE)-MS).
205 The combination of techniques produces complementary analytical information, thus allowing a wider metabolome
206 coverage.
207 The typical workflow in metabolomics research involves experimental design, sampling and storage (the
208 metabolome must remain undamaged), sample preparation, sample analysis, data processing, biomarkers
209 selection/annotation and metabolic pathway analysis for data interpretation. The success of a metabolomics study
210 highly depends on the overall experimental design, which includes the careful consideration of the hypothesis and
211 experimental strategies according to the goal of the study. In this regard, two different types of metabolomics
212 studies can be carried out: 'metabolic fingerprinting' and 'metabolic profiling'. The metabolic fingerprinting approach
213 aims to compare patterns of metabolites that change in response to the cellular environment. In this approach, a
214 generic sample preparation and determination methodology is normally applied for not to miss any metabolite that
215 can be important for sample classification. Meanwhile, metabolic profiling focuses on the study of a group of related
216 metabolites or a specific metabolic pathway, which includes a more specific extraction procedure, as well as
217 chromatographic separation/detection. Metabolic profiles of a cell give a more accurate description of a phenotype
218 [24].
219 Considering the complexity of the metabolomics data matrices, containing thousands of m/z features, data
220 processing and data pre-treatment, including noise filtering, overlapping the peak resolution, peak alignment, peak
221 matching and normalization, is an essential requirement to allow the identification of significant metabolites.
222 Subsequent multivariate data analysis for pattern recognition usually involves unsupervised models and supervised

223 classification tools. Unsupervised models including principal component analysis (PCA), cluster analysis (HCA)
224 and nonlinear mapping (NLM) are used as first step in the data analysis to detect sample clustering in the measured
225 data. Afterwards, supervisory models such as linear discriminant analysis (LDA), partial least discriminant analysis
226 (PLS-DA) or orthogonal partial least discriminant analysis (OPLS-DA) can be used as statistical model validation
227 in order to find differences between the known groups, and to detect the differential metabolites [23]. Finally,
228 annotation of the significant markers is mainly based on search against HRMS or MS/MS fragmentation databases
229 (e.g., METLIN, Human Metabolome Database (HMBD), MassBank, NIST database, Fiehn Lib, mzCloud), that have
230 been continuously growing during the last decade, both in coverage and chemical diversity[25].
231 According to Chemical Analysis Working Group of the Metabolomics Standards Initiative (MSI), the identification
232 reliability of a metabolite can be classified in four different levels: 'identified metabolite' (level 1), 'Putatively
233 annotated compounds' (level 2), 'Putatively characterized compounds classes' (level 3) and 'Unknown' (level 4).
234 However, confident metabolites identification continuous to be a bottleneck in the metabolomics process. For this
235 reason, a combination of approaches is required, including new analytical strategies, computational algorithms and
236 database resources, as well as a joint effort of the metabolomics community, as recognised with the formation of
237 a scientific task group of the international Metabolomics Society to enhance the characterisation of metabolomes
238 by initially focusing on a few model organisms [26].
239
240 Considering the enormous amount of data generated by different omics platforms, the development of
241 bioinformatics tools is necessary in Foodomics in order to integrate the complex raw data obtained into useful
242 information. Many tools are available in order to build and visually explore genes, proteins and metabolites
243 interaction networks according to regularly updated databases. Most of these algorithms, such as Ingenuity
244 Pathway Analysis (IPA), Cytoscape or Pathway Studio, work on the basis of a web page where the list of interesting
245 genes, proteins or metabolites can be uploaded and searched for their annotations in databases (in-house built
246 databases or publicly available databases such as Gene Ontology (GO), KEGG or BIND) and mapping them to
247 known biological pathways [21].
248
249
250

251 **X.3 Foodomics and Food Safety**

252 According to the World Health Organization, food contaminated with bacteria, viruses, toxins or chemicals is
253 responsible for more than 200 diseases, from diarrhea to cancers, affecting more than 600 million people worldwide
254 (10% of the population) [44]. Therefore, one of the main goals of food analysis has always been to guarantee food
255 safety. However, traditional analytical methods are frequently slow and inadequate for the detection of

256 contaminants in complex and diverse food matrices. Foodomics is a perfect tool when applied to this task as it can
257 help to overcome some of the challenges that lay ahead of food safety, such as the fast, multiple and simultaneous
258 detection of allergens and contaminants in complex food matrices[1]. The applications of Foodomics to food safety
259 encompass the discovery of biomarkers related to unsafe products and the development of analytical methods for
260 their quick detection. These biomarkers can be metabolites, proteins, peptides or polynucleotides that allow the
261 identification of potential microbial infections, toxins, allergens, veterinary drug or pesticide residues[32].

262

263 The global food market together with novel nutritional trends, like the increasing consumption of exotic, fresh and
264 sometimes raw food, are a risk for the appearance of allergies or new food pathogens, as for example the outbreak
265 of food poisoning that occurred in Germany and France in 2011 caused by the ingestion of Shiga-toxin producing
266 *E.coli* from organic Greek sprouts [45]. Other global problems such as the increase in pollution and sea microplastics,
267 or global warming may originate new toxic compounds which could raise more food safety concerns that should
268 be approached from a Foodomics perspective. Furthermore, Foodomic tools could be used to warrant food safety
269 in all the different steps of the food chain, from the analysis of raw materials, to food processing, distribution and
270 consumption. It is consequently necessary to develop more efficient, sensitive and cost-effective analytical
271 methods that ensure food safety in accordance with consumer and regulatory demands [46].

272

273 The use of genomics, transcriptomics, proteomics or metabolomics tools for the detection of pathogen biomarkers
274 in food has been increasingly gaining importance, as have been reviewed in several publications in recent years
275 [47-50]. In genomics and transcriptomics, the application of PCR or qPCR methods, microarrays and Next Generation
276 Sequencing (NGS) technologies together with bioinformatics approaches allows the identification and
277 quantification of microbial organisms. Also, the massive analysis of cellular gene expression enables the study of
278 foodborne pathogens survival strategies or their response to food preservation technologies or additives [50]. Figure
279 X.2 shows the main gene groups modified in the transcriptomic response of different foodborne pathogens to
280 environmental changes during the food chain. Some examples are the use of RNA-Seq for the determination of
281 the transcriptomic response of different strains of *E.coli* to prolonged cold stress[51] or to acidic pH[52], the response
282 of *S. aureus* to the antibacterial peptide nisin[53] and the adaptation mechanisms of *L. monocytogenes* to vacuum
283 packaging[54] or to the addition of sodium lactate and sodium diacetate[55]. As for other applications of NGS related
284 to food safety it is also interesting to mention the use of metagenomics for the characterization of the diversity of
285 microbial communities and their ecological interactions within food or to monitor the appearance and evolution of
286 microbiomes in food storage conditions[49].

287

288 [Insert Figure X.2 here]

289

290 NMR metabolomics as well as different MS-based approaches in both proteomics and metabolomics have become 291 widely used for the determination and quantification of pathogens, toxins, allergens and chemical contaminants in 292 food matrices as well as their interactions with the food components and their mechanisms of action[56]. Examples 293 of these applications in proteomics are the use of MALDI-TOF/TOF MS/MS to identify subtypes of Shiga toxin- 294 producing *E.coli* or 2-DE coupled with MS for protein spots identification to detect allergens in fish, rice or breast 295 milk[47]. Due to the short shelf-life of food products, there is a necessity for faster and non-labor-intensive pathogen 296 detection methods. In this regard, metabolomics has shown a great potential, as for example with the use of proton- 297 transfer-reaction MS for the real-time determination of the evolution of organic volatile compounds produced by 298 microorganisms in spoiled milk[57]. Both targeted and untargeted GC and LC-MS/MS metabolomics or lipidomics 299 approaches have also been widely used for the determination of chemicals from pesticide or antibiotic residues in 300 tea, wine, meat, coffee or honey[58].

301 The integration of different omics technologies not only improves the screening of bacteria in complex food 302 matrices, but also provides a better understanding of the molecular mechanisms behind pathogen survival and 303 niche adaptation, antimicrobial resistance, effects of pesticides in gut microbiota and discovery of new targets for 304 infection treatment[58]. An example is the use of MALDI-TOF proteomics together with GC-MS metabolomics 305 approaches for the fast and simultaneous detection of *E. coli*, *L. monocytogenes* and *S. enterica* in red meat[59]. 306 Also, Mesnage et al. used the combination of shotgun metagenomics and reverse phase UPLC-MS/MS 307 metabolomics to assess the effect of the pesticide glyphosate in the rat gut microbiota, showing alterations in the 308 caecum microbial community structure and dysregulation of metabolites related to redox balance[60]. Omics 309 integration paired with modern bioinformatics approaches such as docking may have a revolutionary impact in food 310 safety, for example in the elucidation of functional sites of novel natural food preservatives or antimicrobial 311 molecules[61].

312 Finally, the enormous amount of data produced by all these technologies is expected to perform a paradigm change 313 in future food safety concepts, and perhaps bring what is termed as "precision food safety" which will include the 314 use of different omics together with bioinformatics, phenotypic and epidemiological data to improve evidence- 315 supported food safety risk assessment for the implementation of new policies and procedures[48].

316

317 **X.4 Foodomics for Food Quality and Traceability**

318 The assessment of food quality needs to consider multiple aspects, involving the composition, nutritional properties,
319 flavor, origin and appearance of food. These factors are the ones preferentially used by consumers in order to
320 evaluate food attributes[4]. It is also of great importance to accurately track the source of possible food spoilages in
321 order to determine if it is the result of a sporadic event or a recurrent one and prevent future contaminations[49].
322 Furthermore, it is very interesting not only for consumers but also regulatory agencies to prevent food fraud and
323 warrant food authenticity. Foodomics can be perfectly applied to meet some of the challenges faced by food science
324 in terms of food authentication, traceability and quality.

325 The applications of Foodomics to prevent and control food adulteration have been reviewed [62-65]. The most
326 common issues related to food authenticity are the substitution of species for one of a lower quality and price, fraud
327 related to protected designation of origin and mislabeling of organically produced food products or GM organisms.
328 Genomics, proteomics, metabolomics and lipidomics have a great potential to reduce food fraud. For example, the
329 use of ambient MS ionization methods such as direct analysis in real time (DART) or desorption electrospray
330 ionization (DESI) is especially interesting in this field, as they require minimal sample preparation and pose a great
331 potential for on-site real-time analysis[66]. Also, novel genomic techniques such as DNA barcoding together with
332 droplet digital PCR and NGS may revolutionize this area as new species are constantly incorporated to DNA
333 barcode libraries and NGS has the capability to analyze the entire composition of a food product[64]. Figure X.3
334 shows a diagram of the proteomic MS approaches to face food authenticity challenges.

335 [Insert Figure X.3 here]

336

337 A very interesting field where Foodomics contributes significantly to food authenticity is the monitoring of the correct
338 labelling, composition, substantial equivalence and quality of GM foods, using advanced omic technologies, as has
339 been recommended by the EFSA[1]. These advanced analytical tools should enable the specific determination and
340 quantification of the genetically modified organism (GMO) content in food for screening and labeling compliance
341 but also allow a comprehensive compositional determination to evaluate potential adverse effects. The great
342 majority of screening methods are based on PCR and NGS targeted approaches that simultaneously amplify and
343 detect DNA sequences found in as many different GMOs as possible. On the other hand, several studies have
344 developed MS-based untargeted proteomics and metabolomics advanced analytical methodologies to detect
345 unintended effects produced in GM crops as a result of the genetic modification as well as to characterize their
346 molecular composition[67]. This type of analysis is gaining relevance with the development of the so-called second-
347 generation of GM organisms which incorporate novel traits intended for consumer benefit, such as the golden rice,
348 which has been modified to express a vitamin A precursor, and has met the regulatory requirements of target
349 countries such as Philippines or Bangladesh[68].

350 With a growing consumer demand in food quality, there is a clear need for the development of novel analytical
351 methods that meet these high standards. Therefore, omics technologies have also been used for the
352 characterization of food quality, as has been reviewed[39,47,69]. Genomics, transcriptomics, proteomics and
353 metabolomics have been especially employed in the evaluation of the molecular composition related to food
354 consistency, organoleptic properties, and their changes during processing and storage.

355 Next generation sequencing together with genome wide association analysis (GWAS) has been used in genomics
356 to understand the relationship between the genes that control the levels of major biochemical pathways in different
357 crops and the traits that define their quality or improve their yield [70,71]. Also, the sequencing of major crops and
358 their different varieties enables plant breeders to study genetic diversity and perform directed crop improvement
359 that can adapt to variations in climate, processing conditions or improve food quality[72]. Transcriptome data obtained
360 with RNA-Seq together with bioinformatics analysis can also be very useful to elucidate regulatory networks that
361 are activated or repressed in food exposed to various storage and processing conditions, or to geographical, soil,
362 feeding or climate variations. As an example, a recent study used RNA-Seq to evaluate the effects of dietary
363 supplementation of eucalyptus leaf polyphenols extracts to meat taste and color in chicken. The study identified
364 ten genes that were significantly related to the increase in redness and myoglobin redox form content observed in
365 the chicken fed with the polyphenol supplement[73].

366 Proteomics and metabolomics are of special interest in food quality, as they represent the major molecular
367 response of the cell once the genome loses its active influence, such as in food processing, pasteurization,
368 fermentation or cooking conditions. Also, they are the compounds that mainly provide the flavor and color in food.
369 Therefore, correlations between the proteome and metabolome profiles or their interactions with quality traits
370 enable the tailoring of organoleptic and technological properties of food[69]. Due to the complex and wide diversity
371 in physico-chemical properties of flavor components, there is not a single method that can identify and quantify all
372 of them at the same time. Therefore, different MS-based approaches coupled with separation techniques such as
373 2-DE gel electrophoresis for proteomics or GC, LC and CE for metabolomics have been widely used in this field.
374 Bottom-up approaches in proteomics have been used for the evaluation of protein changes during heat treatment
375 processing[74]. For example, 2-DE with in-gel peptide digestion coupled to MALDI-TOF MS peptide mass
376 fingerprinting was used to characterize protein modifications in cooked and raw pork meat, finding differences in
377 the heat-induced myosin breakdown and the oxidation of methionine. Also, the effect of post-translational
378 modifications in functional and structural properties of the proteome in stored and processed milk has been studied
379 using both LC and 2-DE coupled to high resolution MS. A metabolomics example is the evaluation of the effects of
380 ageing using two-dimensional hydrophilic interaction liquid chromatography (HILIC) and reverse phase (RP)-LC
381 coupled to Q/TOF MS to compare the profile of anthocyanines and their related pigments in young and aged red

382 wines[58]. Targeted and untargeted NMR metabolomics has also been widely used for the evaluation of food
383 composition, processing and physico-chemical properties as has been reviewed by Trimigno et al.[39].

384 Omics integration also provides clear advantages in the determination of molecular mechanisms related to
385 variations in food quality during processing, storage, cooking, etc. A combined proteomics and metabolomics
386 approach evaluated the tenderness of Piedmontese meat at different times after slaughter. The use of nano LC-
387 MS/MS for proteomics together with Q/TOF metabolomics showed a progressive decline in myofibrillar integrity,
388 impaired energy metabolism and accumulation of markers of nitrogen metabolism and glutamate, a marker of the
389 umami taste, throughout the ageing process[75]. Finally, integrated omics approaches may play an important role in
390 the analysis of the mechanisms of additive production performed by synthetically engineered bacteria consortiums.
391 An example of this application is the integrated use of proteomics and metabolomics for the characterization of the
392 one-step fermentation production of a precursor of vitamin C produced by the synthetic consortium of three
393 bacteria[76].

394

395 **X.5 Foodomics and Food Bioactivity**

396 One of the final goals of Foodomics is to understand the bioactivity of food and food ingredients in our body at the
397 molecular level[77]. This topic has been reviewed a few years ago[8], but due to its growing interest, here we
398 summarize and present the latest developments, advances, and applications of Foodomics in this field (Table X.2).
399 To achieve this great goal, the holistic omics approach is needed and therefore the integration of the information
400 obtained at the gene, protein and metabolite level is essential. However, and as it can be observed in Table X.2,
401 most of the studies performed in this field have used single omics approaches, and half of these works had the aim
402 of characterizing or identifying potential beneficial compounds in food matrixes.

403 [Insert Table X.2 here]

404

405 Only a few works have addressed the integration of multi-omics approaches for the study of the effects of dietary
406 components in human health. One of such studies was focused on the evaluation of the anti-inflammatory effect of
407 a combination of resveratrol, green tea extract, alpha-tocopherol, vitamin C, ω-3 polyunsaturated fatty acids, and
408 tomato extract in overweight men[78]. The metabolomics and proteomics studies were performed on plasma samples
409 while transcriptomics were performed on peripheral blood mononuclear cells (PBMC) and adipose tissue. The
410 results obtained indicated that the mixture of those ingredients induced several subtle changes indicative of
411 modulated inflammation of adipose tissue, improved endothelial function, affected oxidative stress, and increased
412 liver fatty acid oxidation. Other studies have been focused on the metabolic changes on plasma and the gene

413 expression changes in PBMC after diet supplementation with n-3 polyunsaturated fatty acid and fish gelatin on
414 humans[79]; or to evaluate the influence of *Hibiscus sabdariffa* polyphenols on humans[80]. The results of the last study
415 suggested that the ingested polyphenols play a regulatory role in metabolic health and in the maintenance of blood
416 pressure, protecting from metabolic and cardiovascular diseases. Apart from human studies, *in vivo* and *in vitro*
417 models have also been used. For instance, the effects of kiwifruit extracts on the colonic gene and protein
418 expression levels were evaluated on IL-10 deficient mice[81]; and the dietary signature of parsley interactions were
419 studied on a dextran sodium sulphate-induced colitic murine model[82]. Due to the down-regulation of inflammatory
420 cytokines and the up-regulation of fatty-acid synthesis genes, the results of the last study suggest parsley as a
421 healthy food against inflammatory bowel diseases. In the case of *in vitro* models, they have mainly been used to
422 evaluate the health benefits of dietary polyphenols. In a series of studies, different metabolomics platforms (RP-
423 LC-ESI-Q/TOF MS, HILIC-LC-ESI-Q/TOF MS and CE-ESI-TOF MS), in combination with gene expression
424 microarrays and complemented with advance proteomic techniques (2-DE together with MALDI-TOF/TOF MS)
425 were applied to investigate the effects of rosemary polyphenols against colon cancer or leukemia cells[83-86]. The
426 data integration of the different omic approaches suggested that rosemary polyphenols possess antioxidant activity
427 and induce apoptosis and cell cycle arrest, which could be related with the activation of the *Nrf2* transcription factor
428 and the unfolded protein response.

429 The anti-proliferative effect of bioactive extracts from two food by-products (*Physalis peruviana* L. calyx and
430 *Passiflora mollissima* seeds) was evaluated against colon cancer cells, and the molecular changes at the
431 transcriptome and metabolome levels were studied[87,88]. In the case of *Physalis peruviana* calyx extracts,
432 significantly altered genes and metabolites were involved in the inactivation of the tRNA charging signalling
433 pathway, the carnitine shuttle and β-oxidation of fatty acids, and the pyrimidine ribonucleotide interconversion,
434 which are key biochemical processes to sustain cell function (Figure X.4)[87]; whereas *Passiflora mollissima* seeds
435 extracts altered the expression of genes and metabolites involved in the polyamine and the glutathione
436 metabolism[88].

437 [Insert Figure X.4 here]

438

439 Apart from multi-omics, individual transcriptomics approaches have been used to evaluate the effects of bioactive
440 compound from foods in different disorders. In humans, the effects of virgin olive oil consumption on PBMC gene
441 expression were explored in order to ascertain the molecular mechanisms underlying its beneficial action in the
442 prevention of atherosclerosis[90]; and the use of PBMC has been reviewed in the study of n-3 fatty acids
443 supplementation[91]. In addition, white blood cells (WBC) gene expression from healthy adults was also investigated
444 after vitamin D3 supplementation diets, suggesting to the authors that vitamin D deficiency is not only related with

445 the skeletal health[92]. Moreover, different *in vitro* cell cultured lines have been submitted to transcriptomics studies
446 after the treatment with natural compounds. For instance, LNCaP human prostate cancer cells were studied after
447 the treatment with genistein[93]; HT-29 human colon cancer cells to investigate the effects of epigallocatechin-3
448 gallate and rosemary polyphenols[94,95], and Caco-2 human colon adenocarcinoma cells were tested against
449 selenium[96], or to study the effect of *in vitro* digested yellow and white onion extracts[97]. This last study was
450 complemented with *in vivo* studies using rat intestine slices and pig small intestinal segments. Also using a rat
451 model, the cerebral cortex transcriptome was studied after caloric restriction and α-lipoic acid-supplementation diet,
452 demonstrating the overexpression of neuroprotective genes after the treatment[98]. Cell cultures from mice have also
453 been used to clarify the similarities and differences between two vitamin D metabolites on the global gene
454 expression changes[99]; or to characterize the potential genotoxic properties of quercetin in the small intestine and
455 liver of mice[100].

456 As well as transcriptomic, proteomics approaches have been mainly used to study the effects of bioactive foods
457 on different models. For example, a small cohort of healthy male volunteers was selected to investigate the
458 alterations in the steady-state levels of PBMC proteins after the daily supplementation of 0.4 g of flaxseed/kg body
459 weight[102]. By using 2-DE coupled to MALDI-TOF MS, the authors identified 16 proteins affected, some of them
460 atherosclerosis-relevant. On the other hand, more studies have been performed using *in vivo* models such as mice
461 or rats. Using mice xenografted with HT-29 human cancer cells, the molecular mechanisms behind the effects of
462 rosemary polyphenols in decreasing the tumor growth were evaluated by dimethyl labeling (DML) and nanoLC-
463 ESI-LTQ/Orbitrap MS[103]; and the effects of cell wall polysaccharides, soy and meat proteins, and Korean red
464 ginseng have been evaluated in rat heart, liver, and spleen and thymus tissues, respectively[104-106]. In this last study
465 more than 2000 proteins were identified in the different tissues using isobaric tags for relative and absolute
466 quantitation (iTRAQ) labeling and nanoLC-ESI-Q/Orbitrap MS, and the molecular signatures and functionality
467 analyses suggested to the authors that Korean red ginseng stimulate the immune responses[106]. Finally, several
468 studies have used *in vitro* cell culture models, being colorectal cancer cells the most used. For instance, the
469 bioactivity of rosemary polyphenols and liensinine (a constituent of *Nelumbo nucifera Gaertn*) have been evaluated
470 in HT-29 colon cancer cells[107-109]. In this last study, the use of the advanced Orbitrap Fusion Lumos MS allowed
471 the identification of more than 3300 proteins, and the bioinformatics analyses and complementary experiments
472 suggested the JNK-mitochondrial dysfunction to play a critical role in the anticancer effects of liensinine[109].
473 Moreover, the human breast adenocarcinoma cell model MCF7 was selected to study the anti-proliferative activity
474 of tiger milk mushroom (*Lignosus rhinocerotis*) sclerotium[110], and the human hepatoma cell model HepG2 was
475 used to investigate the anti-tumor mechanisms of mistletoe (*Viscum coloratum (Kom.) Nakai*) polysaccharides[111].
476 Furthermore, a novel proteomics approach was chosen to study the possible protein targets of curcumol from
477 *Curcuma zedoary* in CNE-2 and 5-8f nasopharyngeal carcinoma cells[112]. Using cellular thermal shift assay,

478 molecular docking, cell-based assay and SDS-PAGE coupled to MALDI-TOF/TOF MS proteomics, the authors
479 identified nucleolin protein as a target of curcumol, suggesting that the anti-cancer effects of curcumol are
480 mediated, at least in part, by the loss of nuceolin functions.

481 In contrast to transcriptomics and proteomics, peptidomics approaches (the analysis of the low-molecular weight
482 subset of the proteome, including peptides and small proteins with molecular weights ranging from 0.5 to 15 kDa)
483 have been mainly used to identify peptides with possible health beneficial effects (bioactive peptides). In dietary
484 proteins, bioactive peptides are encrypted as a part of a protein that remains inactive as long as it is confined within
485 the protein, and later on they are released by *in vitro* or *in vivo* proteolysis. The study of bioactive peptides usually
486 requires the development and application of advanced separation methods coupled to a MS and bioinformatics
487 tools for the prediction, identification, and characterization of their sequence[200]. In addition, these technologies are
488 often complemented with different bioassays to evaluate their bioactive activities (bioavailability assays to test the
489 resistance of peptides to gastric digestion; anti-oxidant, hypo-cholesterolemic, anti-hyperglycemic or anti-
490 hypertensive *in vitro* or *in vivo* assays; or *in silico* predictions). One of the most studied sources of bioactive peptides
491 are milk and dairy products[201], but other sources have been also explored[115-118,202,2013]. And in the last years, food
492 by-products have also gained important interest. For instance, hemp flour and hemp protein isolate have been
493 characterized by 2-DE-LC-ESI-Q-Orbitrap MS[119], and tilapia skin collagen hydrolysates have been investigated in
494 alleviating liver and kidney injuries in aging mice[120]. Moreover, coffee silverskin protein hydrolysates from coffee
495 beans submitted to different degrees of roasting process have shown antioxidant and hypo-cholesterolemic
496 activities[121]; and prunus seeds protein hydrolysates have shown ACE-inhibitory capacity, *in vitro* cytotoxicity and
497 *in vivo* antihypertensive activity in rats[122]. In this last study, RP and HILIC LC-ESI-Q/TOF MS enabled the
498 identification of 33 peptides, and among them, the oral administration of IYSPH peptide to rats significantly
499 decreased the systolic blood pressure of the animals.

500 In the case of metabolomics approaches, several studies have used a metabolic profiling approach (focused on
501 the study of a group of related metabolites, such as polyphenols, flavonoids or carotenoids) or a metabolic
502 fingerprinting (for the characterization and comparison of phenotypes between two or more conditions after different
503 diets, as a consequence of a treatment with bioactive compounds, or because of environmental alterations). Due
504 to this heterogeneity, metabolomics studies can be grouped in two main categories: those focused on the
505 evaluation of the metabolomics effects of specific bioactive compounds from food[204], or those focused on the
506 identification and characterization of potential bioactive compounds [205].

507 In humans, the metabolomics impact of bioactive compounds or diets have been mainly evaluated in urine, plasma
508 or feces samples, and by using diverse technologies. For instance, urine has been analyzed using ^{1}H NMR to
509 observe the different metabolic responses after intake of red wine polyphenol[126], or cholorogenic acids from
510 coffee[127]. And LC-ESI-Q/TOF MS have been used to study the changes due to a 28-days daily consumption of a

511 dried *Curcuma longa* L. extract[128], or to evaluate the effects of long-term cocoa consumption[129]. The authors of this
512 last study identified three metabolites altered (tyrosine sulfate, butyrylcarnitine and methylglutarylcarnitine) after
513 cocoa ingestion, but because the absorption, metabolism, and excretion of cocoa metabolites depend on the food
514 matrix, the dose, age, gender and overall health status, more clinical studies are needed to fully understand their
515 possible beneficial effects[206]. ^{1}H NMR was also selected to investigate the effects of docosahexaenoic acid
516 supplementation on the plasma metabolome of human volunteers at risk of metabolic syndrome[130]; and the
517 combination of different separation techniques coupled to MS (LC-ESI-LTQ MS and GC-MS) was applied to
518 investigate the freeze-dried black raspberries-mediated urine and plasma metabolite changes in human colorectal
519 cancer patients[131].

520 The combination of metabolomics and lipidomics platforms based on LC-ESI-LTQ/Orbitrap MS were chosen to
521 characterize *Angelica keiskei* extracts and to evaluate their beneficial effects on human plasma[132]. The results
522 obtained suggest to the authors that five components of *Angelica keiskei* are responsible of the reduction of bile
523 acids and fatty acids levels after the ingestion. Regarding feces samples, and even though different metabolomics
524 methods have been developed[133], scarce studies have been performed. One of such studies was focused on the
525 evaluation of the effects of a 4-week moderate wine consumption in healthy volunteers by using LC-ESI-Q/TOF
526 MS[134]. The authors found 37 biomarkers of wine consumption which may reflect changes in microbiota functionality.
527 Other than humans, metabolomics in fluids from rats mimicking different diseases have been used to investigate
528 the biochemical changes and therapeutic effects of shenfu decoction in chronic heart failure [135], crude and
529 processed "Baizhu Shaoyao San" on ulcerative colitis[136], green tea polyphenols in ovariectomized rats[137], or mango
530 peel and pulp in diabetes[138]. Taking the last study as an example, 26 and 29 significantly altered metabolites were
531 potentially annotated in serum and liver, suggesting that mango-supplemented diet exerts significant antioxidant
532 effects due to the phenolic compounds, like mangiferin. Moreover, most of the studies aiming to investigate the
533 beneficial effects of food compounds in gastrointestinal diseases have been performed using *in vitro* models. For
534 instance, the Caco-2 human colon adenocarcinoma model have been used to evaluate the effect of olive pomace
535 on the cell metabolome using ^{1}H NMR [139,140], or to investigate the *in vitro* gastrointestinal protective effects of bee
536 pollen against inflammatory bowel disease using LC-ESI-Q/TOF MS[141]. The results of this last study show that bee
537 pollen has great therapeutic potential in induced colitis by the alteration of key metabolites involved in the
538 glycerophospholipid metabolism.

539 Among the studies focused on the identification and characterization of bioactive compound in foods, plants are
540 the most widely studied, and those studies can be grouped according to the metabolomics platforms used. NMR
541 have been used to characterize the bioactive compounds of black raspberry [147], different date varieties and
542 curcuma species[148,149], or different plants[150-152]. And the combination of NMR and LC with different MS analyzers
543 has shown to enhance the coverage of compounds identified in argan fruits[153], goji berries[154] or *Clinacanthus*

544 *nutans* leaves[155]. But despite the benefits of combining both orthogonal platforms, MS is the most used
545 methodology in metabolomics. It has been used standalone to carry out the metabolic profiling of blueberry
546 leaves[156], but a separation technique upfront the MS is often desired. CE has demonstrated to be a very useful
547 analytical tool in food science[207], but only a few studies have coupled it to MS for the identification of bioactive
548 metabolites[157,158]. On the other hand, the use of GC-MS is more widespread, and it has been used to identify and
549 characterize possible bioactive compounds in extracts from mint seeds[159], nettle leaves[160], ginseng roots[161],
550 pistachio resin[162,163], or *Nigella sativa* seeds[164]. But on top of these technologies, the gold standard method of
551 choice is LC-MS. As it can be observed in Table X.2, more than 30 studies have been published on this topic over
552 the last 10 years, and more than half in the last 2 years[165,194]. The starting material is very heterogeneous (fruits,
553 roots, rhizomes, seeds, stems, flowers or leaves), as well as the MS analyzers used (Q, IT, TOF, Orbitrap, or a
554 combination of them: QqQ, QTOF, Q-Orbitrap or IT-Orbitrap). In addition, in several of these studies LC-MS has
555 been complemented with GC-MS to provide a wider picture of the bioactive compounds. For instance, several
556 multi-analytical platform has been presented for obtaining and characterize bioactive compounds with anti-
557 proliferative activity in cancer cells from different food by-products (goldenberry calyx[188], banana passion fruit seeds
558 extracts[189], or sugar mango seed kernels[190]); or from different species of algae[191,192]. Apart from plants, another
559 interesting group of foods submitted to metabolomics analyses are beverages such as wine[195], or infusions from
560 tea leaves or other plants[196-199].

561

562 **X.6 Challenges and Future Trends**

563 One of the main challenges in Foodomics is related to the great complexity intrinsic to food matrices, and the huge
564 dynamic range of concentrations of food components. The development of novel food analysis methods must face
565 this heterogeneity and avoid the analytical interferences from these matrices in order to improve reproducibility and
566 facilitate biological interpretation of the results[1]. For example, the use of PCR-based methodologies for food safety
567 or authenticity is sometimes limited due to food compounds that inhibit polymerase reaction[32]. Routine food testing
568 reference methods mostly rely on traditional microbiological analysis techniques. These methods are usually very
569 time-consuming and expensive, as for example they need to use bacterial culture-based techniques. However,
570 omics approaches are still underused in food safety mainly due to expensive instrumentation and the high level of
571 experience and technical skills needed for method development as well as for software management and statistical
572 data analysis[58,66]. Moreover, molecular engineering of microorganisms through clustered regularly interspaced
573 short palindromic repeats (CRISPR)-Cas9 and other genome editing methods together with synthetic biology
574 applications pose a great potential to modify microbial communities in food, improving processes such as
575 fermentation or generating enhanced probiotic strains. The use of advanced analytical omics technologies must

576 go hand in hand with these technologies in order to evaluate possible unintended effects, ensuring food safety,
577 traceability and preventing fraud[208].

578 Furthermore, the integration of the different omics approaches is still a challenge because of the lack of adequate
579 bioinformatics tools and our limited understanding of the biological and chemical process taking place inside any
580 biological system, what makes especially demanding the study about the effect of food components on health
581 [58,209,210]. In addition, to understand the impact of diet on health as a whole it is necessary to consider many
582 parameters, just to mention a few: the broad nature of food molecules, the microbiota, the inter-individual variability,
583 the food dynamic processing starting from the ingestion, and followed by the digestion in the gastrointestinal tract,
584 the intestinal transference to the circulation, the transformation by the liver, the usage by every organ, and the final
585 excretion in urine and feces[211,212.]

586 The achievement of all these goals also requires the collaborative work within the scientific community to compare
587 and share data. Therefore, more harmonized and standardized sampling methods, improvements in computational
588 techniques and biological databases (e.g., with functional annotations), and further developments in the analytical
589 technologies used on each specific omics field are essential.

590 In the transcriptomics field, the RNA-seq technology is becoming more affordable and has been applied to the
591 characterization of transcriptomes of different foods, and its wider application in the study of the effects of bioactive
592 food compounds is expected. In the proteomics field, the combination of more sensitive, faster and higher resolution
593 MS instruments coupled to liquid separations and fractionation techniques will increase the coverage of proteomes,
594 subproteomes and peptidomes. However, there are still some limitations when the time-aspect is considered, which
595 is essential to understand the metabolic and physiological changes occurring during molecular and cellular
596 processes[213]. The same technological advances have already improved the peptidomics field[200], but even though
597 bioactive peptides have shown multiple health beneficial activities, the proper exploration of their mechanisms of
598 action and their bioavailability after their intake need more clinical trials[214,215]. In the case of metabolomics, great
599 advances in extraction, separation and detection techniques have been performed (such as the introduction of ion
600 mobility analysis), but the main limitations are still the identification and accurate quantification of metabolites.
601 Again, to face these challenges it is required a global scientific effort to create or contribute to the creation of
602 standardized and freely available MS and MS/MS spectral databases for the identification of unknown compounds,
603 the development of biostatistical methods, as well as the improvement and application of quantum chemistry and
604 computational methods for elucidating or predicting the structures of novel metabolites[216-218]

605 Overcoming the abovementioned limitations will allow scientists to gain a more comprehensive foodomic insight
606 about the relation between food and health, while reinforcing the control of food safety, quality and traceability.

607

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FIGURE AND TABLE CAPTIONS

Figure X.1. Graphical representation of the Foodomics integrative framework, including the main omics approaches involved and research areas of application in Food science and Nutrition.

Figure X.2. Main gene groups involved in the response of foodborne pathogens to environmental conditions of the food production chain, as reviewed by Lamas et al.[50]*, with permission from Elsevier.*

928 *Figure X.3. Challenges and MS-based proteomics approaches in food authenticity, as reviewed by Ortea et al.[21].*

929 *This Figure is under open creative commons licence (CC-BY).*

930 *Figure X.4. Representative pathways integrating transcriptomics and metabolomics results corresponding to (A)*
931 *t-RNA charging, (B) Glutathione Redox Reactions I, (C) Carnitine shuttle and fatty acid β-oxidation and (D)*
932 *Pyrimidine ribonucleotides interconversion. Rhombus-shape nodes represent the expression of genes and*
933 *rectangular nodes represent metabolites. Down- and up-regulated components are shown on a green or red*
934 *background, respectively. Reprinted from Ref. [12-Ballesteros-Vivas et al., 2019] with permission from Elsevier.*

935 *Table X.1. Representative review articles about the main Foodomics applications discussed in this chapter: i)*
936 *food safety ii) food quality and traceability, iii) food bioactivity and health research*

937 *Table X.2. Representative applications of Foodomics in Nutrition and Health Research*

938

939 **ABBREVIATIONS**

940 CE, capillary electrophoresis;
941 CRISPR, clustered regularly interspaced short palindromic repeats;
942 DART, direct analysis in real time;
943 DEGs, differentially expressed genes;
944 DESI, desorption electrospray ionization;
945 DML, dimethyl labeling;
946 EFSA, European Food Safety Agency;
947 ESI, electrospray ionization;
948 FT-ICR, fourier transform ion cyclotron resonance;
949 GC, gas chromatography;
950 GM, genetically modified;
951 GMO, genetically modified organism;
952 GWAS, genome-wide association study;
953 HILIC, hydrophilic interaction liquid chromatography;
954 HPLC, high performance liquid chromatography;
955 HRMS, high resolution mass spectrometry;
956 IT, ion trap;
957 iTRAQ, isobaric tags for relative and absolute quantitation;
958 LC, liquid chromatography;

959 lncRNA, long non-coding RNA;

960 MALDI, matrix-assisted laser desorption ionization;

961 miRNA, microRNA;

962 mRNA, messenger RNA;

963 MS, mass spectrometry;

964 MS/MS, tandem mass spectrometry;

965 NGS, Next Generation Sequencing;

966 NMR, nuclear magnetic resonance;

967 PBMC, peripheral blood mononuclear cells;

968 PCR, polymerase chain reaction;

969 PTM, post-translational modification;

970 Q, cuadrupole;

971 QqQ, triple quadrupole;

972 qRT-PCR, quantitative real-time PCR;

973 Q-TOF, quadrupole-time of flight;

974 RNA-seq, whole transcriptomic sequencing;

975 RP, reverse phase;

976 SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis;

977 TMT, tandem mass tags;

978 UPLC, ultra-performance liquid chromatography;

979 WBC, white blood cells

980

981 Table X.1

Foodomics research topic	Year	Reference
Miscellaneous		
2D-LC approaches in Foodomics	2019	[27]
The future of analytical chemistry in foodomics	2018	[28]
Omics Technology: Foodomics	2018	[4]
Sample preparation in foodomic analyses	2018	[29]
Analytical chemistry methods in Foodomics	2016	[30]
Foodomics: exploring safety, quality and bioactivity of foods	2015	[7]
Food Safety		
Nanoscale separations based on LC and CE for food safety	2019	[31]
Foodomics and food safety	2017	[32]
Foodomics to investigate the mycobolome	2017	[33]
Foodomics of foodborne pathogens and their toxins	2016	[34]
Foodomics for investigations of food toxins	2015	[35]
Food Quality and Traceability		
Omics in fermented foods and beverages	2020	[36]
DNA-Based Methods for Main Food-Authentication	2019	[37]
Antioxidant phytochemicals in fresh produce	2018	[38]
Foodomics for quality control of food processing	2017	[12]
Foodomics to differentiate organic and conventional foods	2016	[13]
Definition of food quality by NMR-based Foodomics	2015	[39]
Food Bioactivity & Health		
Nutrimetabolomics	2018	[9, 10]
Foodomics for human health	2018	[40]
Food science, bioengineering, and medical innovation	2018	[14]
Foodomics evaluation of bioactive compounds in foods	2017	[8]
Green Foodomics and bioactive compounds	2017	[41]
Foodomics imaging by MS and NMR	2016	[42]
Foodomics in microbiological investigations	2015	[43]
Omics in Nutraceuticals and Functional Foods	2015	[11]

982

983 Table X. 2.

Food matrix/Food compound	Aim	Analyzed sample	Approach	Analytical technique/s	Ref.
Resveratrol, green tea extract, alpha-tocopherol, vitamin C, n-3 (omega-3) polyunsaturated fatty acids, and tomato extract	Evaluate the anti-inflammatory effect of a dietary mix in overweight men	Human plasma and urine, human PBMC and human adipose tissue	Transcriptomics, proteomics and metabolomics	NuGO Affymetrix Human Genechip; microsphere-based immuno-multiplexing assays; GC-MS, LC-ESI-IT/FT MS, LC-ESI-IT/Orbitrap MS	78
n-3 polyunsaturated fatty acids	Investigate gene expression changes after n n-3 polyunsaturated fatty acid and n-3 polyunsaturated fatty acid plus fish gelatin supplementation	Human plasma and human PBMC	Transcriptomics and metabolomics	Human-6 v3 Expression BeadChips; LC-ESI MS	79
Hibiscus sabdariffa extract	Assess the influence of Hibiscus sabdariffa polyphenols on the overall metabolic host response	Human plasma and human PBMC	Transcriptomics and metabolomics	Affymetrix GeneChip® HG-U133; LC-ESI-IT MS, GC-MS	80
Kiwifruit extracts	Study the effects of kiwifruit extracts on colonic gene and protein expression levels in IL-10 deficient mice	Mice colon tissue	Transcriptomics and proteomics	Agilent Whole Mouse Genome Microarray 4 × 44K; 2-DE and LC-ESI-IT MS	81
Petroselinum crispum	Identify the dietary signature of parsley interactions and to uncover potential novel mechanisms in a induced colitic murine model	Mice colon and liver tissues	Transcriptomics, proteomics and metabolomics	Affymetrix Mouse Genome 2.0 Array; iTRAQ and nanoLC–MS/MS; CE-ESI-TOF MS, CE-ESI-QqQ MS	82
Rosemary polyphenols	Study the health benefits of rosemary polyphenols against colon cancer cells	HT-29 human colon cancer cells	Transcriptomics, proteomics and metabolomics	Affymetrix Human Gene 1.1 ST microarrays; 2-DE and MALDI-TOF/TOF MS; LC-ESI-Q/TOF MS, CE-ESI-TOF MS	83
Rosemary polyphenols	Study the antiproliferative effect of dietary polyphenols from rosemary on two human leukemia lines	K562 human leukemia cells	Transcriptomics and metabolomics	Affymetrix Human Gene 1.0 ST; CE-TOF MS, LC-Q/TOF MS	84
Carnosic acid and carnosol	Investigate the cellular and molecular changes operating in HT-29 cells in response to CA treatments	HT-29 human colon cancer cells	Transcriptomics and metabolomics	Affymetrix Human Gene 1.0 ST; LC-ESI-Q/TOF MS, CE-MS	85
Rosemary polyphenols and carnosic acid	Study the relations between the observed metabolic changes and the transcriptional responses in colon cancer cells after carnosic acid and rosemary polyphenols	HT-29 human colon cancer cells	Transcriptomics and metabolomics	Affymetrix Human Gene 1.0 ST and 2.0 ST; GC-MS	86
Physalis peruviana L.	Test the anti-proliferative activity of a goldenberry calyx extract against cancer and normal colon cells and to investigate the molecular changes	HT-29 human colon cancer cells	Transcriptomics and metabolomics	Agilent SurePrint G3 Human GE 8x60k, LC-ESI-Q/TOF MS	87

Passiflora mollissima	Evaluate the molecular changes induced at transcript and metabolite expression levels on HT-29 human colon cancer cells	HT-29 human colon cancer cells	Transcriptomics and metabolomics	Agilent SurePrint G3 Human GE 8x60k, LC-ESI-Q/TOF MS	88
Selenium	Elucidate whether expression of factors crucial for colorectal homoeostasis is affected by physiologic differences in Se status	Rectal biopsies	Transcriptomics and proteomics	Whole-genome Human HT-12 v3; 2-DE and MALDI-TOF/TOF MS	89
Virgin olive oil	Identify the PBMC genes that respond to virgin olive oil consumption in order to ascertain the molecular mechanisms underlying its beneficial action in the prevention of atherosclerosis	Human PBMC	Transcriptomics	Applied Biosystems Human Genome Survey Microarray V2.0	90
n3 fattly acids	Study the effect of n3 fatty acids in peripheral blood mononuclear cells	Human PBMC	Transcriptomics	Affymetrix and Illumina	91
Vitamin D3 metabolites	Determine the effect of vitamin D status and subsequent vitamin D supplementation on broad gene expression in healthy adults	Human WBC	Transcriptomics	Affymetrix Human Gene Array 1.0 ST	92
Genistein	Evaluate the effects of low concentrations of genistein on micro-array expression patterns in human androgen-responsive LNCaP prostate cancer cells	LNCaP human prostate cancer cells	Transcriptomics	Human Genome U133A Array	93
Epigallocatechin-3 gallate	Examine the effect of EGCG on spheroid formation of HT-29 colon cancer cells	HT-29 human colon cancer cells	Transcriptomics	Human Genome U95Av2 GeneChip	94
Rosemary polyphenols	Investigate the effect of rosemary extracts enriched in polyphenols in two colon cancer cell lines	HT-29 and SW480 human colon cancer cells	Transcriptomics	Affymetrix Human Gene 1.0 ST	95
Selenium	Study the effect of Se in Caco-2 human colon adenocarcinoma cells	Caco-2 human colon adenocarcinoma cells	Transcriptomics	V2 Agilent miRNA microarray, Illumina HumanRef-8 V3 Expression BeadChips array	96
Onion extracts	Study the effect of *in vitro* digested yellow and white onion extracts in different intestine models	Caco-2 human colon adenocarcinoma cells; rat intestine slices; Pig small intestinal segments	Transcriptomics	Affymetrix Human Gene 1.1 ST, Affymetrix Rat 1.1 ST, 8 × 60K Agilent pig arrays G2519F	97
Caloric restriction or α-Lipoic-acid supplementation	Study the transcriptomes of the cerebral cortex of rats subjected to caloric restriction and a-lipoic acid-supplemented rats	Rat cerebral cortex	Transcriptomics	SOLiD platform from Thermofisher	98
Vitamin D3 metabolites	Clarify the similarities and differences between different vitamin D3 metabolites on the global gene expression	P29SN Prostate stromal cells and Cyp27b1 knockout mouse primary skin fibroblasts	Transcriptomics	GeneChip® Human Genome U133 Plus 2.0 Arrays, GeneChip® Mouse Genome 430 2.0 Arrays	99

Quercetin	Characterize the potential genotoxic properties of quercetin in the small intestine and liver of mice	Mice small intestine and liver	Transcriptomics	Agilent 8 × 60K G4852A mice microarray	100
Rooster combs extract rich in hyaluronic acid	Explore the peripheral blood gene expression as a source of biomarkers of joint health improvement related to glycosaminoglycan intake	Human PBMC	Transcriptomics	Agilent 4 × 44 K G4845A human microarray	101
Flaxseed	Identify alterations in the steady-state levels of proteins in PBMC of healthy males ingesting daily flaxsee	Human PBMC	Proteomics	2-D PAGE and MALDI-TOF MS	102
Rosemary polyphenols	Study the effects of rosemary extract on xenograft tumor growth	Mice xenograft tumor	Proteomics	DML and nanoLC-ESI-IT/Orbitrap MS	103
Cell wall polysaccharides from various food components	Investigate if cell wall polysaccharides from various food components can protect against myocardial injury	Rat heart	Proteomics	TMT and 2D-nanoLC-ESI-Orbitrap MS	104
Soy and meat proteins	Study the proteomic response of rat liver to isolated soy and different meat proteins	Rat liver	Proteomics	iTRAQ and nanoLC-ESI-Orbitrap MS	105
Panax ginseng Meyer	Identify the molecular signatures and functionality of Korean red ginseng during the course of understanding its underlying mechanisms	Rat spleen and thymus tissues	Proteomics	iTRAQ and nanoLC-ESI-Q/Orbitrap MS	106
Rosemary polyphenols	Identify changes in amplitude and kinetics of proteins altered by a rosemary extract enriched in polyphenols	HT-29 human colon cancer cells	Proteomics	DML and nanoLC-ESI-IT/Orbitrap MS	107
Carnosic acid and carnosol	Investigate global protein changes in HT-29 colon cancer cells in response to individual rosemary diterpenes	HT-29 human colon cancer cells	Proteomics	DML and nanoLC-ESI-IT/Orbitrap MS	108
Liensinine (*Nelumbo nucifera Gaertn*)	Examine the anticancer bioactivity of liensinine in colorectal cancer and investigate the action mechanisms involved	HT-29 and DLD-1 human colorectal ancer cells and mice xenograft tumor	Proteomics	LC-ESI-Orbitrap Fusion MS	109
Lignosus rhinocerotis sclerotium	Elucidate the proteome of L. rhinocerotis sclerotium and to further isolate and identify the cytotoxic components bearing anticancer potential	MCF7 human breast adenocarcinoma cells	Proteomics	SDS-PAGE and nano-LC-ESI-Q/TOF MS	110
Viscum coloratum (Kom.) Nakai	Study the anti-tumor mechanisms of mistletoe polysaccharides	HepG2 human hepatoma cells	Proteomics	iTRAQ and 2D-LC-ESI-Q/TOF MS	111
Curcuma zedoary	Reveal the possible protein targets of curcumol in nasopharyngeal carcinoma cells	CNE-2 and 5-8f human nasopharyngeal cancer cells	Proteomics	SDS-PAGE and MALDI-TOF/TOF MS	112
7-O-pentyl quercetin	Synthesize quercetin derivatives and to test for their cytostatic/cytotoxic action on tumoral and non-tumoral cell lines	Jurkat human T lymphocytes	Proteomics	Reverse Phase Protein Arrays	113

Cod and Chicken protein hydrolysates	Investigate the effect of digested and undigested hydrolysates on intracellular oxidation, cellular metabolic energy and proteome changes in yeast	Saccharomyces cerevisiae	Proteomics	2-DE and MALDI-TOF MS	114
Nutraceuticals	Identify antihypertensive peptides in nutraceuticals	Nutraceuticals	Peptidomics	CE-MS	115
Crassostrea angulata	Predict the potential bioactivities of Portuguese oyster proteins through in silico analyses and confirmed by *in vitro* tests	Oyster meat	Peptidomics	SDS-PAGE and nanoLC-ESI-Orbitrap MS	116
Cooked beef, pork, chicken and turkey meat	Investigate the potential contribution of bioactive peptides to the biological activities related to the consumption of pork, beef, chicken and turkey meat	Cooked beef, pork, chicken and turkey meat hydrolysates	Peptidomics	nanoLC-ESI-Q/TOF MS	117
Bresaola Valtellina	Assess the effects of maturation time and simulated gastrointestinal digestion on the molecular and peptide profiles of Bresaola Valtellina	Bresaola Valtellina meat hydrolysates	Peptidomics	2-DE and MALDI-TOF MS, ^{1}H NMR	118
Cannabis sativa L.	Set up an efficient and scalable method for production of hemp flour and hemp protein isolates and for their proteomic characterization	Hemp seed meal protein hydrolysates	Peptidomics	2-DE-LC-ESI-Q/Orbitrap MS	119
Tilapia	Investigate the role of a tilapia skin collagen polypeptide in alleviating liver and kidney injuries	Tilapia skin collagen hydrolysates	Peptidomics	LC-ESI-Q/Orbitrap MS	120
Coffee silverskin	Study the peptide composition of protein hydrolysates of coffee silverskin and their antioxidant and hypocholesterolemic activities	Coffee silverskin protein hydrolysates	Peptidomics	LC-ESI-Q/TOF MS	121
Prunus seed	Study peptides from peach seeds hydrolysates and evaluate their ACE-inhibitory capacity, *in vitro* cytotoxicity and *in vivo* antihypertensive activity	Peach seed hydrolysates	Peptidomics	LC-ESI-Q/TOF MS	122
Deer antler velvet	Track the fate of protein of antler velvet by protein digestomics	Deer antler velvet extract	Peptidomics	LC-IT/Orbitrap MS	123
Prunus armeniaca L.	In silico predict 10 and 14 peptides and to suggest a variety of bioactivities	Apricot kernels hydrolysates	Peptidomics	Peptide ligand libraries, SDS-PAGE and nanoLC-ESI-IT MS	124
Pomegranate peel	Separate proteins and polyphenols, and to reveal the true contribution of polyphenols, proteins, and peptides to different bioactivities	Pomegranate peel hydrolysates	Peptidomics	LC-ESI-Q/TOF MS	125
Wine	Classify a specific population into phenotypic groups according to their biochemical characteristics, and to observe the different metabolic responses after red wine polyphenol intake	Human urine	Metabolomics	^{1}H NMR	126
Coffee	Determine if cholorogenic acids from coffee impact the human urine metabolome and to identify the changes on the metabolome after both acute and sustained consumptions	Human urine	Metabolomics	^{1}H NMR	127

Curcuma longa L. extract	Study the changes of 24-hours urinary composition on healthy volunteers due to daily consumption of a dried C. longa extract	Human urine	Metabolomics	LC-ESI-Q/TOF MS	128
Cocoa powder	Evaluate the effects of long-term cocoa consumption on urinary metabolome	Human urine	Metabolomics	LC-ESI-Q/TOF MS	129
Docosahexaenoic acid (DHA)	Investigate the effects of supplementation with DHA on the plasma metabolome of human volunteers at risk of metabolic syndrome	Human plasma	Metabolomics	^{1}H-NMR	130
Black raspberry	Investigate the freeze-dried black raspberries-mediated metabolite changes in human colorectal cancer patients	Human plasma and urine	Metabolomics	LC-ESI-IT MS, GC-MS	131
Angelica keiskei	Confirm the bioactive effects of Angelica keiskei on humans	Human plasma	Metabolomics	LC-ESI-IT/Orbitrap MS	132
	Develop and validate a GC-MS method for the metabotyping of human feces	Human feces	Metabolomics	GC-MS	133
Red wine	Find relevant markers in feces and evaluate the effects of a 4-week moderate wine consumption in healthy volunteers	Human feces	Metabolomics	LC-ESI-Q/TOF MS	134
Panax ginseng C.A. Meyer	Investigate the biochemical changes in chronic heart failure and therapeutic effects and mechanisms of Shenfu decoction	Rat urine	Metabolomics	GC-MS	135
Baizhu Shaoyao San	Find the underlying correlations between serum chemical profiles and curative effects of crude and processed Baizhu Shaoyao San on ulcerative colitis rats	Rat serum	Metabolomics	LC-ESI-Q/TOF MS	136
Green tea polyphenols	Evaluate the effects of polyphenols from green tea in ovariectomized rats	Rat serum and muscle tissue	Metabolomics	^{1}H NMR	137
Mango	Evaluate the metabolic changes in serum and liver of STZ-induced diabetic Wistar rats after prolonged intake of bioactive compounds from ‘Ataulfo’ mango peel and pulp	Rat serum and liver tissue	Metabolomics	LC-ESI-Q/TOF MS	138
Defatted olive pomace	Evaluate the effect of olive pomace on the cell metabolome and its anti-inflammatory potential	Caco-2 human colon adenocarcinoma cells	Metabolomics	^{1}H NMR	139
Olive oil by-product	Study the exploitation of olive pomace as functional ingredient in biscuits and bread	Caco-2 human colon adenocarcinoma cells	Metabolomics	^{1}H-NMR	140
Bee pollen	Reveal the *in vitro* gastrointestinal protective effects of bee pollen against inflammatory bowel diseases using molecular and metabolic methods	Caco-2 human colon adenocarcinoma cells	Metabolomics	LC-ESI-Q/TOF MS	141

Rosemary polyphenols	Develop CE–MS based methods for the evaluation or profiling of tentative bioactive compounds	HT-29 human colon cancer cells	Metabolomics	CE-MS	142
Artemisia dracunculus L. extract	Study the bioactive effect of Artemisia dracunculus L. extract against insulin resistance in rat skeletal muscle cells	Rat skeletal muscle cells	Metabolomics	LC-ESI-QqQ MS	143
Theobroma cacao and *Lippia citriodora*	Test the antioxidant and anti-inflammatory properties of food polyphenols found in cocoa and lemon verbena	PON-1 KO and tgMCP-1 mouse fibroblast cells	Metabolomics	GC-MS	144
Phyto-sesquiterpene lactone deoxyelephantopin and cisplatin	Investigate the bioefficacy of a phytoagent deoxyelephantopin in inhibiting B16 melanoma cell activity, its synergism with CP against metastatic melanoma, and its capability to attenuate CP side effects in animals	Mice kidney tissue	Metabolomics	LC-ESI-Q/TOF MS	145
Anthocyanins and xanthophylls	Unravel the possible effect on cardiometabolic parameters of the ingestion of anthocyanins, xanthophylls in postmenopausal women	Human serum	Metabolomics	LC-ESI-Q/TOF MS	146
Rubus occidentalis extracts	Develop a high-resolution 1H NMR-based multivariate statistical model for discerning the biological activity of black Raspberry constituents	Black Raspberry	Metabolomics	^{1}H NMR	147
Phoenix dactylifera L.	Evaluate the antioxidant activity of five different date varieties and to profile the bioactive metabolites present in the dates	Date fruits	Metabolomics	^{1}H NMR	148
Curcuma zedoaria, C. xanthorrhiza, C. aeruginosa and C. mangga	Explore the changes in the metabolic profile of four Curcuma species and to correlate these changes with bioactive effects	Curcuma rhizome	Metabolomics	^{1}H NMR	149
Tamarindus indica L.	Evaluate the protective mechanisms of polyphenols from Tamarindus indica against oxidative stress in HepG2 cells	Tamarindus indica seed extracts	Metabolomics	^{1}H NMR, LC-DAD	150
Uraria crinita (L.) Desv. ex DC	Elucidate the central role of the immunomodulatory isoflavone genistein present in uraria crinita root methanolic extract	Uraria crinita roots	Metabolomics	^{1}H NMR	151
Different plants	Assess the robustness of NMR-based metabolomics in discriminating classes of secondary compounds that are responsible for the observed antimalarial activity and the isolation of antiplasmodial compounds	Different plants	Metabolomics	^{1}H NMR	152
Argania spinosa	Provide a more complete profile of phenolic compounds including quantitation in argan fruits	Argan fruits	Metabolomics	^{1}H, ^{13}C and 15N NMR, LC-ESI-QqQ MS	153
Lycium barbarum	Report on the isolation and identification of the main phenolic compounds from goji berries	Goji berries	Metabolomics	^{1}H and ^{13}C NMR, DI-IT/Orbitrap MS	154

Clinacanthus nutans	Evaluate the relationship between the chemical composition of C. nutans and its anti-inflammatory properties	Clinacanthus nutans leaves	Metabolomics	^{1}H NMR, LC-DAD/ESI-QqQ MS	155
Blueberry	Study the metabolic profiling of leaves from 20 blueberry cultivars collected at 5 time points	Blueberry	Metabolomics	DI-EI-MS	156
Infant formulas	Identify and simultaneous quantify several ribonucleotide 5'-monophosphates in infant formula samples	Infant formulas	Metabolomics	CE-MS	157
Undaria pinnatifida	Develop and validate CE-MS method for separation of six harmala alkaloids	Algae	Metabolomics	CE-MS	158
Mentha viridis	Determine the phytochemical composition of methanolic extract of Mentha viridis	Mint seeds	Metabolomics	GC-MS	159
Urtica dioica	Analyze the chemical compounds of Urtica dioica leaves	Nettle leaves	Metabolomics	GC-MS, FT-IR	160
Panax ginseng C.A. Meyer	Investigate the aroma fingerprint characteristics of ginsengs of different ages	Ginseng roots	Metabolomics	GC-MS	161
Pistacia lentiscus	Compare the qualitative and quantitative composition of triterpenes in resin samples	Pistacia lentiscus resin	Metabolomics	GC-MS	162
Pistacia lentiscus	Evaluate the bioactivity and composition of terpenes and phenolic compounds in different culture conditions of Pistacia	Pistacia lentiscus resin	Metabolomics	GC-MS	163
Nigella sativa	Exploit the ASE-based extraction method for extracting the secondary volatiles from Nigella sativa obtained from two different countries	Nigella sativa seeds	Metabolomics	GC-MS, GC-FID	164
Lycopersicon esculentum Mill.	Identify the constituents of tomato samples	Tomato fruits	Metabolomics	LC-ESI-IT/Orbitrap MS and LC-ESI-QqQ MS	165
Sarcandra glabra	Identify bioactive constituents in Sarcandra glabra and its related four preparations	Sarcandra glabra	Metabolomics	LC-PDA/ESI-IT/Orbitrap MS	166
Natural extracts	Demonstrate that the combination of several analytical separation techniques could be used as a small and versatile platform for drug discovery	Natural extracts	Metabolomics	LC-ESI-IT MS and CE-LIF	167
Smilacis glabrae	Develop a rapid and simple LC-ESI-MS method for analyzing and discovering minor new constituents, and quantifying the active components in Smilacis glabrae	Smilacis glabrae rhizoma	Metabolomics	LC-ESI-IT/Orbitrap MS	168
Eryngium amethystinum and *E. planum*	Carry out a TLC-DPPH bioauthographic test of anti-radical compounds	Eryngium amethystinum and E. planum	Metabolomics	TLC/LC-ESI-TOF MS	169

Tunisian Punica granatum L.	Investigate the comprehensive phenolic fingerprints of flowers, peels and leaves of two Tunisian Punica granatum L. cultivars	Pomegranate	Metabolomics	LC-ESI-Q/TOF MS	170
Fucus vesiculosus	Investigate the seasonal variations in the metabolome of the Baltic Sea brown alga Fucus vesiculosus and its potential relation to the bioactivity profile	Algae	Metabolomics	LC-ESI-Q/TOF MS	171
Physalis peruviana	Explore the effect of organic and conventional growing conditions on the specific chemicals of Goldenberry	Goldenberry fruits	Metabolomics	LC-ESI-Q/TOF MS	172
Baccharis grisebachii	Study the gastroprotective, antioxidant, antibacterial and cytotoxicity effects on tumoral and non-tumoral human cell lines, and the full metabolome polyphenolic profile of the lyophilized decoction from Baccharis grisebachii	Baccharis grisebachii	Metabolomics	LC PDA/ESI-Q/Orbitrap MS	173
Mulinum crassifolium Phil. (*Apiaceae*)	Describe the isolation and structural elucidation of two new diterpenoids from M. crassifolium and to discuss their gastroprotective action	Mulinum crassifolium aerial parts	Metabolomics	LC-PDA/ESI-Q/Orbitrap MS	174
Carissa macrocarpa (Eckl.) A.DC	Characterize leaves, stems, and flowers of Carissa macrocarpa (Eckl.) A.DC and to correlate the phenolic content with bioactive properties	Leaves, Stems, and Flowers extracts	Metabolomics	LC-DAD/ESI-IT MS	175
Kalimeris indica (Linn.) Sch.	Determine the total phenolic content and anti-inflammatory effect by inhibition of nitric oxide and tumor necrosis factor-alpha (TNF-α) of different Kalimeris indica fractions	Kalimeris indica (whole plant including roots)	Metabolomics	LC-DAD/ESI-Q/TOF MS	176
Piper kadsura, Piper nigrum, Ophiopogon japonicas and Salvia miltiorrhiza	Develop a new strategy for the efficient discovery of herb-derived ligands towards a specific protein target site	Piper kadsura, Piper nigrum, Ophiopogon japonicas and Salvia miltiorrhiza herbs	Metabolomics	LC-ESI-TTOF MS	177
Blackberry	Investigate the modulation of polyphenols profile of blackberry purees by soluble dietary fibres during a simulated *in vitro* gastrointestinal digestion and large intestine fermentation process	Blackberry purees	Metabolomics	LC-ESI-Q/TOF MS	178
Fungi associated with marine algae	Investigate culture-dependent fungal communities associated with the Baltic seaweed Fucus vesiculosus	Fungui from algae	Metabolomics	LC-ESI-Q/TOF MS	179
Polygonum cuspidatum Sieb. et Zucc.	Identify and quantitatively describe the bioactive compounds in different polygonum cuspidatum tissues	Root, rhizome, leaf, flower, stem and seed	Metabolomics	LC-ESI-Q/TOF MS	180
Lactuca sativa	Assess the impact of different transformations on the primary and secondary metabolites of Lactuca sativa	Lettuce leaves	Metabolomics	LC-ESI-Q/TOF MS	181
Camellia	Determine the chemical composition of recognized tea bioactives	Camellia leaves	Metabolomics	LC-ESI-Q/TOF MS	182

Black garlic	Explore component changes in fermented black garlic and study the pharmacological and molecular regulation on zebrafish and HUVEC models	Fermented black garlic	Metabolomics	LC-ESI-Q/TOF MS	183
Syzygium species	Perform a metabolomics-based phytochemical screening of six Syzygium species and to characterize their *in vitro* cytotoxic and estrogenic activities	Syzygium leaf extracts	Metabolomics	LC-ESI-Q/TOF MS	184
Physalis peruviana L.	Present a multi-analytical platform for obtaining and characterize bioactive compounds in goldenberry calyx	Goldenberry calyx extracts	Metabolomics	LC-ESI-QTOF MS	185
Mangifera indica L.	Obtain a phenolic MSK extract with improved inhibitory effect on HT-29 colon cancer cells	Sugar mango seed kernel	Metabolomics	LC-ESI-Q/TOF MS	186
Moringa oleifera	Evaluate the impact of the extraction solvent on the comprehensive recovery of phenolics from M. oleifera leaves and to evaluate their enzymatic, antioxidant and antimicrobial activities	Moringa oleifera leaves	Metabolomics	LC-ESI-Q/TOF MS	187
Physalis peruviana L.	Present a multi-analytical platform for obtaining and characterize bioactive compounds in goldenberry calyx	Goldenberry calyx extracts	Metabolomics	LC-ESI-Q/TOF MS, GC-MS	188
Passiflora mollissima	Present an integrated analytical methodology including a sequential PLE for the fractionated extraction of phenolic and lipidic metabolites	Banana passion fruit seeds	Metabolomics	LC-ESI-Q/TOF MS, GC-MS	189
Mangifera indica L.	Develop an integrated valorization strategy to obtain mangiferin and other phenolic compounds from 'sugar mango seed kernels'	Sugar mango seed kernel	Metabolomics	LC-ESI-Q/TOF MS, GC-MS	190
Chondrus crispus	Characterize the fatty acid and polar lipid composition of the red seaweed Chondrus crispus	Chondrus crispus	Metabolomics	LC-ESI-IT MS, GC-MS	191
Codium tomentosum	To report the lipidomic characterization of Codium tomentosum	Algae	Metabolomics	LC-ESI-IT MS, GC-MS	192
Cinnamomum zeylanicum and *C. cassia*	Determine the anti-inflammatory activity of Cinnamomum zeylanicum and Cinnamomum cassia and elucidate their main phytochemical compounds	Cinnamon extracts	Metabolomics	LC-PDA/ESI-QqQ MS, GC-MS	193
Salicornia brachiata	Characterize the bioactive compounds of Salicornia brachiata grown under abiotic stress conditions	Salicornia shoot	Metabolomics	LC-ESI-TOF MS, GC-MS	194
Wine	Identify new natural sweet compounds	Wine	Metabolomics	^{1}H and ^{13}C NMR, DI-IT/Orbitrap MS	195
Pu-erh green tea	Identify and evaluate the quality of Yunnan Pu-erh green tea	Tea volatile compounds	Metabolomics	GC-MS	196
Matricaria chamomilla L.	Evaluate the enzymatic hydrolysis of an aqueous infusion of *Matricaria chamomilla* L., to perform the metabolic profile, and to evaluate the antioxidant activity and the inhibitory effect on digestive enzymes	Matricaria chamomilla infusion	Metabolomics	LC-ESI-Q/TOF MS	197

Huangqi Jianzhong Tang	Identify constituents contributing to the bioactivity of Huangqi Jianzhong Tang	Huangqi Jianzhong Tang decoction mixture	Metabolomics	LC-ESI-Q/TOF MS	198
Kombuchas from green and black teas	Investigate the phenolic profile of kombuchas produced from the fermentation of green tea or black tea, and to determine their antioxidant capacities, antibacterial and antiproliferative activities	Kombucha extract	Metabolomics	LC-ESI-Q/TOF MS	199

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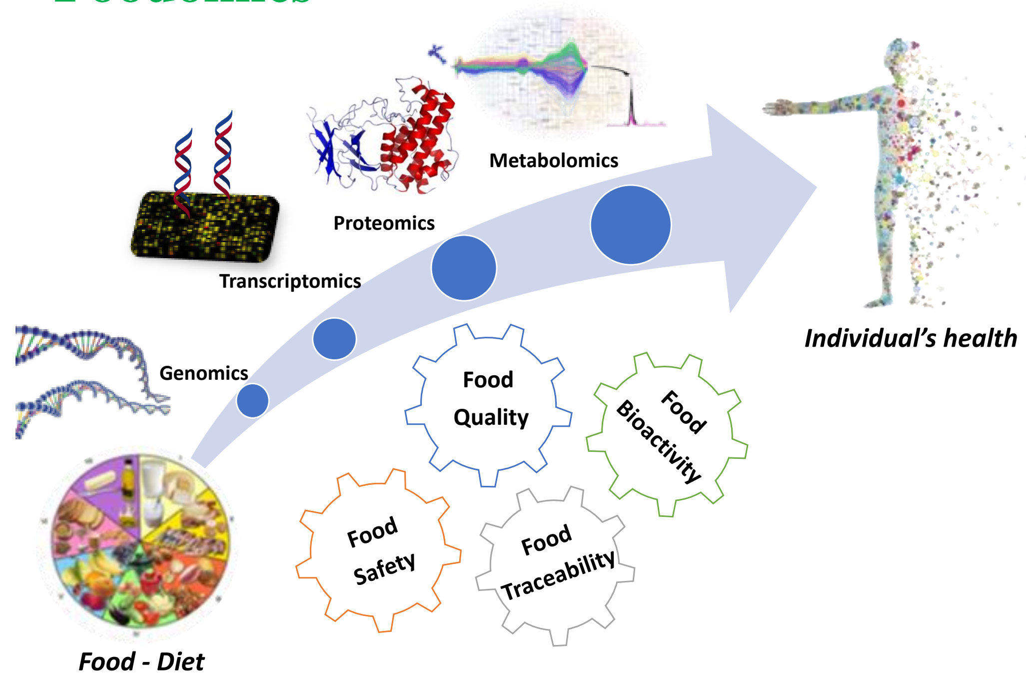

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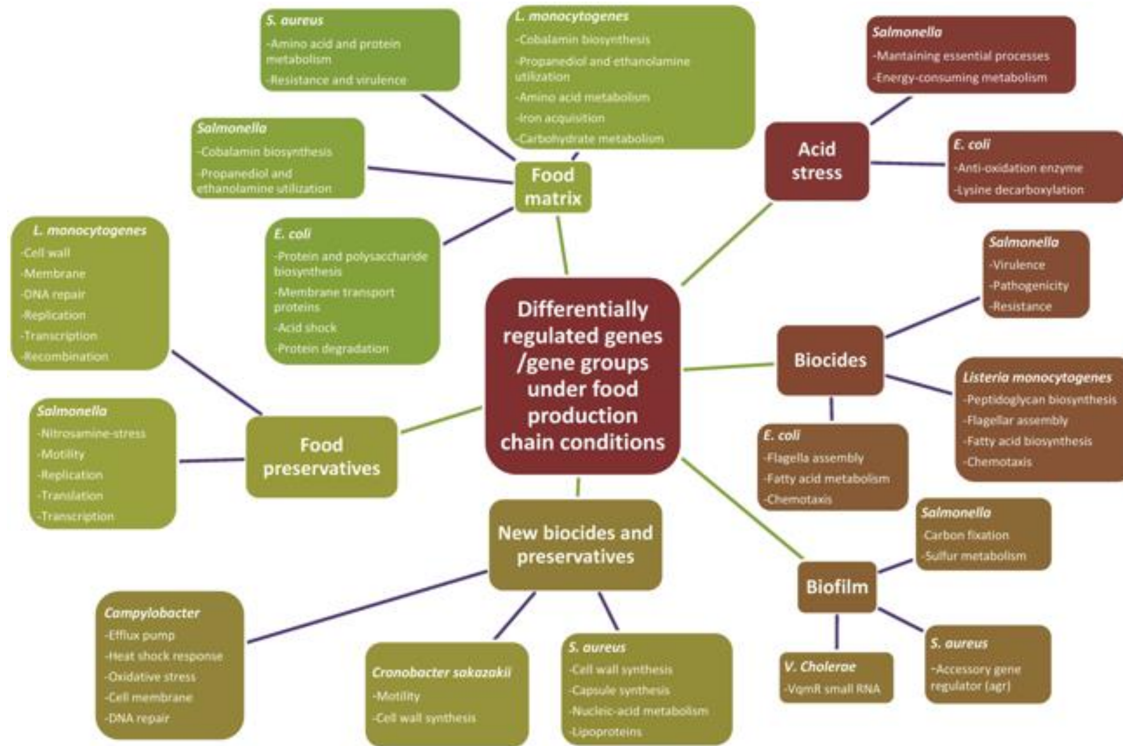

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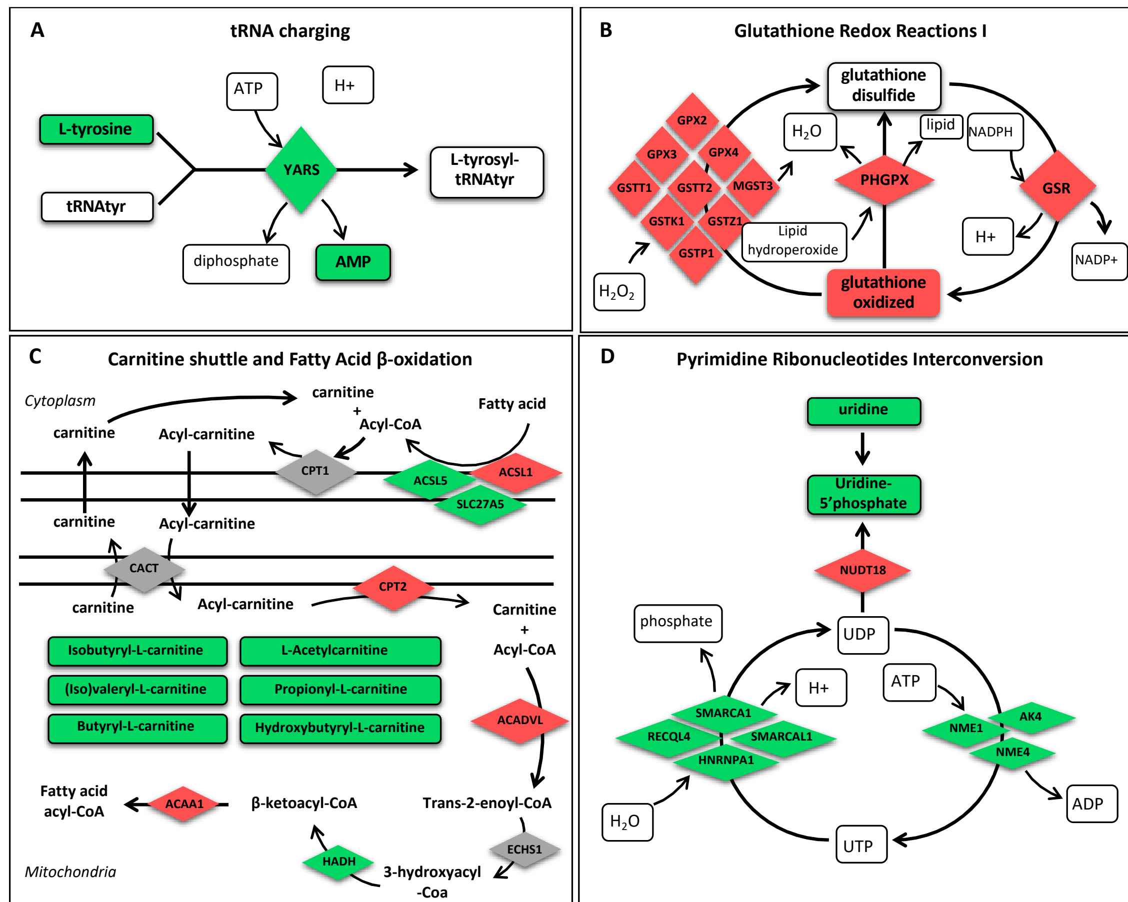

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998 Figure 4