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Foodomics approaches: new insights in phenolic compounds analysis

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Abstract:	<p>Fruits, vegetables, and plant-based foods contain several bioactive substances such as phenolic compounds (PCs), that are plant secondary metabolites with attributed health properties. The study of the metabolic pathways of PCs, including those related with their synthesis, transport, accumulation, and degradation are essential to advance in this field of research. In this regard, omics tools such as foodomics are gaining relevance due to their versatility and their tremendous potential to generate significant advances in PC research.</p> <p>In this review, we present a comprehensive overview of the applications of omics technologies in PC analysis, including transcriptomics, micromics, proteomics and metabolomics, highlighting their role in metabolic pathways, current limitations, and emerging insights.</p> <p>Omics techniques as well as data analyses are continuously progressing, emerging new opportunities with the onset of artificial intelligence and machine learning. However, significant limitations and challenges still remain. The immense diversity of PC chemical structures and their variability across plant species, varieties, and the impact of agronomic factors complicate the analyses and limit the extrapolation of findings. Additionally, high data dimensionality, strong correlations among measured variables, and the general lack of standardization in the different omics techniques can impact in the results. Addressing these limitations requires integrating multi-omics approaches and developing standardized protocols to enhance comparability and interpretation in PC research. In summary, foodomics approaches arise as essential for the complete mapping of PC biosynthesis</p>
Response to Reviewers:	<p>Manuscript ID: FOODRES-D-24-09608R1</p> <p>Manuscript title: Foodomics approaches: new insights in phenolic compounds analysis</p> <p>We have revised the manuscript according to the reviewer and editor comments and addressed the points raised by them. We make an effort to improve the manuscript, and we hope that now the manuscript has the level required for publication in Food Research International.</p> <p>Please find below our corresponding answers.</p> <p>Reviewer #2: Approximately 30% of the review was either superficially addressed or not addressed at all (e.g. points 1,3, 5, and 12). Since this paper requires further review and I have already allocated significant amount of time to review this paper I</p>

recommend it for rejection.

We have revised again the points raised by the reviewer:

1. Abstract: Provide in the abstract specific limitations or challenges faced by foodomics in phenolic research.

We have rewritten the abstract including information of the specific limitations, challenges and insights.

In addition, we included more information in section "3. Current limitations and challenges" and section in section "4. Insights in phenolic compounds studies"

3. Tables: The Table 1 is informative but can be overwhelming with excessive details. Please provide a clear distinction between key findings and general data for that table. Maybe clear table summary should be provided as well.

We have revised further Table 1 and to present this clearly, we have divided the table in 4 different tables: 1 table for each omics technologies (Table 1. Transcriptomics studies, Table 2. Micromics studies, Table 3. Proteomics studies and Table 4. Metabolomics studies). In addition, we have rewritten most of the key findings and aims of the studies. We believe that now the Tables are clear and the key findings for each study are well described.

5. The authors mention multiple omics techniques (genomics, metabolomics, micromics, proteomics, transcriptomics) and then repeat them with minimal new information. This creates unnecessary redundancy without adding value to the reader. Please consolidate the discussion of omics techniques, focusing on their specific relevance to phenolic compound research rather than listing them multiple times without new insights.

We have included detailed information of the relevance of omics techniques to phenolic compound biosynthesis research at the beginning of section 2.

12. The authors state, "the studies carried out in one plant cannot be extrapolated to others" and mention environmental factors like temperature and irrigation. However, this section lacks detailed examples of how these variables have affected study outcomes and how future research could overcome these challenges. Please be more specific here, expand on these points with concrete examples (e.g., studies showing different results due to varying environmental conditions) and offer potential solutions (e.g., advancements in multi-omics integration or machine learning for better data interpretation) and identify current research gaps.

We have rewritten section "3. Current limitations and challenges" being more specific with concrete examples and identifying current research gaps. Moreover, we have incorporated potential solutions in section "4. Insights in phenolic compounds studies"

Editor-in-chief comments:

I agree with reviewer #2 and the manuscript needs further revision. The authors must take this seriously and revise the manuscript accordingly bringing it to a level required for publication in FRIN. Please, be aware that minor changes or rebuttal to address critical concerns will not bring this manuscript to the level required for publication in FRIN.

In addition to the above, the manuscript is completely out of the format of FRIN. For instance, the abstract MUST NOT be structured, citations MUST NOT be numbered, references MUST NOT be numbered and must be formatted according to the format required for FRIN. Tables and figures MUST NOT be embedded in the text.

I will give you the last chance to address all these points, otherwise I will reject the manuscript.

We thank the editor the opportunity to revise again the manuscript. We have now revised further the points raised by reviewer 2 and we believe that now the manuscript has the level required for publication in Food Research International.

The format now must fit with the required for Food Research International. We are really sorry for this mistake.

Yours sincerely,

Dr. Alvaro J Cruz,

September 11th, 2024

Chicago, IL U.S.

Dear members of the editorial board of Food Research International,

Please find enclosed review entitled “Foodomics approaches: new insights in phenolic compounds analysis” which we submit for your consideration to be published in Food Research International peer-reviewed scientific journal.

Phenolic compounds (PCs) are ubiquitous secondary metabolites synthesized by plants under stress conditions and with health effects described. Current studies are now targeting metabolic pathways of PCs to increase knowledge about their synthesis, transport, accumulation, and degradation. In this sense, using omics tools such as foodomics is gaining relevance in this field. Foodomics is a novel omics approach, including genomics, metabolomics, micromics, proteomics and transcriptomics, which can be applied to study PCs in plants. Therefore, in this review, a comprehensive overview of studies following omics approaches to analyze PCs is presented, showing their applications, current limitations, and new insights in the PCs analysis. We believe that this manuscript is proper for publication in the Food Research International because our review on foodomics approaches applied in phenolic compounds analysis is in line with journal aims, and knowledge of composition of these metabolites in foods and the way they are synthesized is relevant to nutrition and medicine. The use of omics technics in foodomics has given a boost to the understanding of the genes, proteins, metabolites and even microRNAs involved in their synthesis. Insights about the influence of external and internal factors have been described. New omics techniques are appearing such as epiomics and interactomics, as well as statistics and data analyses is continuously progressing such as system biology. These challenges the investigations in PCs biosynthesis to increase their understanding.

Neither the manuscript nor any parts of its content are currently under consideration or published in another journal. All the authors have read and approved the submission of the manuscript and we have no conflicts of interest to show.

Thank you for your consideration.

Yours sincerely,

Álvaro Cruz-Carrión, Ph.D.

Sr. Scientist – Analytical Sciences

Manuscript ID: FOODRES-D-24-09608R1

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Study of phenolic compounds synthesis is challenged by intrinsic samples variability.

These studies require high throughput methodologies and complex data analysis.

Foodomics provides a comprehensive overview of phenolic compounds biosynthesis.

1 **Foodomics approaches: new insights in phenolic compounds analysis**

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28 **Abstract**

29
30 Fruits, vegetables, and plant-based foods contain several bioactive substances such as
31 phenolic compounds (PCs), that are plant secondary metabolites with attributed health
32 properties. The study of the metabolic pathways of PCs, including those related with their
33 synthesis, transport, accumulation, and degradation are essential to advance in this field
34 of research. In this regard, omics tools such as foodomics are gaining relevance due to
35 their versatility and their tremendous potential to generate significant advances in PC
36 research.

37 In this review, we present a comprehensive overview of the applications of omics
38 technologies in PC analysis, including transcriptomics, micromics, proteomics and
39 metabolomics, highlighting their role in metabolic pathways, current limitations, and
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41 Omics techniques as well as data analyses are continuously progressing, emerging new
42 opportunities with the onset of artificial intelligence and machine learning. However,
43 significant limitations and challenges still remain. The immense diversity of PC chemical
44 structures and their variability across plant species, varieties, and the impact of agronomic
45 factors complicate the analyses and limit the extrapolation of findings. Additionally, high
46 data dimensionality, strong correlations among measured variables, and the general lack
47 of standardization in the different omics techniques can impact in the results. Addressing
48 these limitations requires integrating multi-omics approaches and developing
49 standardized protocols to enhance comparability and interpretation in PC research. In
50 summary, foodomics approaches arise as essential for the complete mapping of PC
51 biosynthesis.

52 53 **Keywords**

54 Genomics, metabolomics, micromics, multi-omics, omics, polyphenols, transcriptomics.

55 56 **1. Introduction**

57 Phenolic compounds (PCs), also known as (poly)phenols, are one of the most
58 heterogeneous groups among bioactive compounds, with more than 50,000 different
59 molecules identified. Despite its family of compounds with a wide variety of molecules,
60 structurally, they have in common, at least, a hydroxyl group linked to a benzene ring
61 (Ávila-Román et al., 2021; L. Zhang et al., 2021). These compounds can be divided into
62 two main groups: flavonoids and non-flavonoids, being the former the most distributed
63 among plants (L. Zhang et al., 2021). This classification is made by attending to the
64 number of phenolic rings they have, and the structural elements binding those rings. In
65 this sense, flavonoids are characterized to have two aromatic rings connected by a three-
66 carbon bridge (C6-C3-C6). These are further subclassified in flavanols (also known as
67 flavan-3-ols), flavonols, flavanones, flavones, isoflavones and anthocyanidins, according

68 to hydroxylation pattern, distribution of the rings, their index of hydrogen deficiency and/or
69 their no-hydroxylated functional groups (Figure 1)

70

71 [Insert Figure 1: Main chemical structures of phenolic compounds (PCs)]

72

73

74 Otherwise, non-flavonoids are those PCs that do not share the flavonoid main chemical
75 structure. These are composed of phenolic acids, phenolic alcohols, lignans and stilbenes
76 (Ávila-Román et al., 2021; W. Li & Beta, 2013; Yalcin & Çapar, 2017). Cocoa, beans, and
77 walnuts are examples of products with high phenolic concentration, ranging between
78 1,200 and 5,000 mg of total phenolics per 100 grams of fresh weight. According to PC
79 type, hesperidiums such as lemons and oranges are rich in flavanones, while in drupes
80 and berries, such as cherries, grapes, or blueberries, the most predominant are
81 anthocyanins (Arola-Arnal et al., 2019). Soybeans are rich in isoflavones, such as
82 genistein and daidzein, and herbs such as parsley and celery are rich in flavonols. In this
83 way, cocoa and tea are sources of (+)-catechin and (-)-epicatechin. Hydroxybenzoic acids
84 and their derivatives are found in certain red fruits, onions, and black radish. Finally,
85 derivatives of hydroxycinnamic acid, such as chlorogenic acid, are found in coffee, among
86 other plants (Manach et al., 2004; L. Zhang et al., 2021). Regarding tissue distribution,
87 PCs are distributed throughout the whole plant, including roots, leaves, and fruits. In
88 leaves and stems, they primarily accumulate in monomeric forms, whereas polymeric
89 forms are more abundant in fruits, the epidermis, and vacuoles (Ávila-Román et al.,
90 2021). Additionally, insoluble phenols are localized in the cell wall, while soluble phenols
91 are primarily stored in vacuoles (Naczki & Shahidi, 2004).

92 Once ingested PCs are recognized as xenobiotics. Due to their complex structure their
93 bioavailability is low, and only around 5-10% are absorbed in the small intestine, while
94 rest is absorbed by colonocytes after being metabolized by gut microbiota (D'Archivio et
95 al., 2007). Remarkably, although still in discussion, it is believed that bioactive forms are
96 products of PCs metabolism. In this regard, PCs have an important antioxidant activity,
97 enhancing potential of these compounds that can be used to improve human health
98 protecting against oxidative stress (Manach et al., 2004; Yalcin & Çapar, 2017). Therefore,
99 it is common to determine antioxidant activity in plants rich in PC by means of different
100 technics such as DPPH (2,2-difenil-1-picrilhidrazil) and oxygen radical absorbance
101 capacity (ORAC) or using advanced analytical techniques like HPLC coupled with
102 detectors for antioxidant activity (Ávila-Román et al., 2021). After that, together with PC
103 identification, correlation studies can be done in order to determine which polyphenols
104 are more responsible of its antioxidant activity (Suárez et al., 2009). In addition, PCs have
105 a wide range of bioactivities such as anti-inflammatory, anti-carcinogenic, or anti-
106 hypertensive. Those compounds play a key role in health promotion due to their ability to
107 mitigate oxidative stress and modulate inflammatory pathways, which contributes to their

108 protective effects against chronic diseases (Shahidi & Yeo, 2018). Additionally, these
109 compounds also have the capacity to modulate biochemical pathways related to energetic
110 and lipidic metabolism (L. Zhang et al., 2021).

111 Concerning their synthesis, PCs can be defined as plant secondary metabolites that are
112 produced under an abiotic stress such as drought, extreme temperature variations, or soil
113 salinity. The synthesis of PCs follows three different pathways: shikimate pathway,
114 phenylpropanoid pathway (PPP) and flavonoid pathway (Shahidi & Yeo, 2018; Suárez et
115 al., 2009) (Figure 2). In the shikimate pathway, phosphoenolpyruvate combines with
116 erythrose-4-phosphate to give shikimic acid, precursor of phenylalanine and
117 hydroxybenzoic acids (Cheynier et al., 2013; Deng & Lu, 2017; Zagoskina et al., 2023).
118 The action of different enzymes during all these processes is crucial; phenylalanine
119 ammonia-lyase (PAL) transforms phenylalanine in trans-cinnamic acid, which is first step
120 in the PPP Then, cinnamic acid hydroxylase (C4H) and coumarin CoA ligase (4CL)
121 transform trans-cinnamic acid into *p*-coumaroyl CoA, which is precursor of
122 hydroxycinnamic acids (Shen et al., 2022; Zagoskina et al., 2023). Then, chalcone
123 synthase (CHS), the key enzyme in flavonoid's biosynthesis, transforms *p*-coumaroyl CoA
124 into chalcone naringenin, the first product of flavonoid (Zagoskina et al., 2023).

125

126 [Insert Figure 2: Biosynthesis pathway of plant phenolic compounds (PCs)]

127

128

129 The action of chalcone isomerase (CHI) produces flavanone naringenin, which is the
130 precursor of isoflavones when the isoflavone synthase (IFS) acts, and flavones when the
131 flavone synthase (FNS). On the other hand, the enzyme flavanone 3-hydroxylase (FH3)
132 transforms flavanone naringenin into dihydroflavonol, precursor of flavonols. The last
133 product of the flavonoid pathway is formation of leucoanthocyanidin by action of
134 dihydroflavonol 4-reductase (DFR). This product is a precursor of anthocyanidins with
135 action of enzyme anthocyanidin synthase (ANS), and of proanthocyanidins. The enzyme
136 leucoanthocyanidin reductase (LAR) transforms leucoanthocyanidin into flavanols, and
137 enzyme anthocyanidin reductase (ANR) transforms anthocyanidins into flavanols
138 (Cheynier et al., 2013; Shen et al., 2022; Zagoskina et al., 2023). It is worth mentioning
139 biosynthesis of PCs also involves action of several transcription factors, such as MYBA
140 in grapevine, that controls anthocyanin synthesis and are responsible for skin coloration
141 in those berries (Matus et al., 2017; Yue et al., 2018).

142 The phenolic profile in plants depends on both internal factors, such as genetic and
143 external factors, including environmental conditions (L. Zhang et al., 2021). Therefore,
144 there can be differences in the phenolic profile not only between two different varieties of
145 the same cultivar, but also within the same variety depending on environmental
146 conditions. Moreover, postharvest treatments also have an important role in the total PCs
147 content since they can promote their synthesis or degradation (Ávila-Román et al., 2021;

148 Yalcin & Çapar, 2017; L. Zhang et al., 2021). In fact, abiotic stress in plants increases
149 production of reactive oxygen species (ROS), causing oxidative damage. This production
150 enhances activity of PAL, CHS, and other enzymes, which increase PCs accumulation to
151 protect the plant against oxidative stress (Kumar et al., 2023; Shen et al., 2022; Yue et
152 al., 2018). For example, a very common abiotic stress in plants is drought, which is
153 reported to increase accumulation of anthocyanins in *Arabidopsis*, generating a higher
154 stress tolerance (Nakabayashi et al., 2014). Another example is reported by Griesser *et*
155 *al.* (Griesser et al., 2015), where accumulation of several PCs, such as (-)-epicatechin or
156 (-)-epicatechin gallate in *Vitis vinifera* was increased after a prolonged period of drought.
157 The same results were obtained in grape berries after a period of drought, here a higher
158 accumulation of flavonoids, flavan-3-ols, and flavonols were found (Doshi et al., 2006).
159 Another stressing factor is ultraviolet radiation (UV), which damages protein structure,
160 leading to ROS generation, and, subsequently, to a higher PCs accumulation (Kumar et
161 al., 2023). In this regard, Goyal *et al.* (Goyal et al., 2014) analyzed the effect of UV in the
162 accumulation of PCs in mung bean sprouts and reported that higher phenolic
163 accumulation was found in plants treated with UV radiation compared to the control. The
164 treatment also increased their antioxidant activity. Jan *et al.* (Jan et al., 2022) reported
165 that the relative expression of FH3 was increased in wild and transgenic rice plants when
166 they were exposed to UV radiation. Soil salinity, a stress factor, also enhances phenolic
167 accumulation in plants (Kumar et al., 2023). Several studies were carried out in this
168 context. For example, Golkar *et al.* (Golkar & Taghizadeh, 2018) reported that the
169 concentration of total flavonoids and total PC increased in safflowers with high salinity
170 levels. Flavonoid biosynthesis in plants is regulated by several factors, transcription
171 factors being one of the most important. It has been seen that the overexpression of
172 transcriptional factor VvbHLH (*Vitis vinifera* basic Hoop-Loop-Hoop) induces the
173 biosynthesis of flavonoids, protecting the plant from salinity stress (F. Wang et al., 2016).
174 Other abiotic factors, such as temperature or the use of pesticides, can also stimulate the
175 phenolic biosynthesis in plants, to protect the plant against oxidative stress (Nakabayashi
176 et al., 2014).

177 Focusing on the study of PC biosynthesis, omics techniques have emerged as essential
178 tools due to their versatility. These are a set of disciplines that involve, genomics,
179 transcriptomics, micromics, proteomics and metabolomics, among others (Debnath et al.,
180 2011). In fact, when this set of techniques is applied to food it is called 'Foodomics' (Valdés
181 et al., 2017, 2022). This word was first described in 2009 as a discipline that studies the
182 Food and Nutrition domains through the application of omics technologies (Cifuentes,
183 2009). Foodomics has a number of advantages over traditional techniques: higher
184 sensitivity, greater specificity, and the possibility to analyse hundreds of compounds at
185 the same time, which allows a holistic view of the food matrix and its interaction with
186 biological systems (Cifuentes, 2012). For example, in the case of PC, foodomics has
187 already shown its power in elucidating complex metabolic pathways and discovering new

188 biomarkers. A very good example is the use of LC-IM-Q-TOF-MS for the analysis of PC,
189 which offers significant sensitivity and excellent peak capacity by using three dimensions
190 of separation (Valdés et al., 2022). A critical aspect of foodomics lies in their capacity to
191 generate large datasets, which, while offering profound insights, also introduce
192 challenges in data management and analysis. The analysis of large datasets, generated
193 by foodomics, are highly complex and with high dimensionality. To address this fact,
194 advanced statistical approaches such as multivariate analysis, machine learning, and
195 systems biology approaches are employed. For instance, principal component analysis
196 (PCA) and cluster analysis are used to reduce dimensionality and cluster similar samples
197 or variables, facilitating their visualization and the interpretation of patterns in the data
198 (León et al., 2018). In addition, supervised machine learning techniques, such as support
199 vector machines (SVM) and neural networks, are essential for classifying samples and
200 predicting characteristics from complex data (León et al., 2018; Valdés et al., 2017). In
201 systems biology, network models and predictive modelling help integrate multi-omics data
202 and simulate the behaviour of biological systems, contributing to a deeper understanding
203 of underlying biological pathways (Valdés et al., 2017). These approaches, combined with
204 advanced computational tools, allow for the management and extraction of meaningful
205 information from the large volumes of data generated by omics techniques.
206 In this review, we provide a comprehensive overview of the applications of omics
207 technologies in PC biosynthesis, from gene expression to metabolite production.
208 Moreover, the current limitations, challenges and insights related to this field are
209 described.

210

211 **2. Foodomics techniques**

212 Foodomics have become indispensable tools in the study of PCs biosynthesis. In this
213 sense, transcriptomics analyses are useful to identify key regulatory genes and
214 transcription factors that modulate the synthesis of PCs and provide insights of how
215 different agronomic factors or developmental stages influence the transcription of genes
216 related to PC production (Gutierrez et al., 2017). Recent advances in high-throughput and
217 single-cell RNA sequencing have further refined our understanding of these regulatory
218 networks, revealing novel gene candidates and signaling pathways implicated in phenolic
219 metabolism (Volná et al., 2024). For example, integrative transcriptomic studies in fruits
220 have correlated dynamic gene expression profiles with the accumulation of specific
221 phenolic metabolites, linking transcriptional activity with phenol production (K. Zhang et
222 al., 2023). On the other hand, proteomics analyses can detect changes in proteins
223 abundance, and their use is particularly useful for understanding post-translational
224 modifications (PTM) and protein-protein interactions that affect the metabolic pathways
225 involved in production of PCs. In this regard, advanced proteomic techniques have
226 demonstrated that PTM in enzymes influence the modulation of phenolic compound
227 biosynthetic pathways under environmental stress conditions (Lin et al., 2020). These

228 approaches have also uncovered protein complexes that regulate phenolic metabolism
229 under various conditions. Finally, metabolomics enables the comprehensive detection
230 and quantification of PCs in plants allowing the mapping of the entire metabolic network,
231 the identification of novel PCs, and providing an overall picture that ultimately contributes
232 to the understanding of their biosynthetic pathways. Metabolomics also helps in studying
233 the impact of genetic modifications or environmental changes on PCs composition.
234 Recent metabolomic studies employing both targeted and untargeted approaches have
235 revealed subtle metabolic changes during plant development and under stress, providing
236 high-resolution profiles that complement transcriptomic and proteomic data (D. Ma et al.,
237 2022). Furthermore, advancements in high-resolution mass spectrometry have facilitated
238 the discovery of previously uncharacterized PCs (Pérez-Ochoa et al., 2023). The
239 integration of these omics' techniques with multi-omics approaches provides a holistic
240 view of the complex regulatory networks of PCs biosynthesis. For instance, the integration
241 of proteomics and metabolomics can link enzymes to the production of specific phenolic
242 metabolites. Moreover, combining transcriptomic, proteomic, and metabolomic datasets
243 through advanced bioinformatics tools has enabled the construction of comprehensive
244 models of phenolic biosynthetic pathways, pinpointing key regulatory nodes and potential
245 targets for metabolic engineering (Xu et al., 2020; Yang et al., 2021).
246 Following, a collection of studies focused on the investigation of PC biosynthesis using
247 foodomics approaches is presented.

248

249 **2.1. Transcriptomics**

250 Modern transcriptomics tools can analyze the expression of multiple transcripts related to
251 PCs, not only in plants but also in animals and humans. This allows us to evaluate the
252 impact of consumption of phenolic-rich matrices, aiming to understand the correlation
253 between phenolics intake, transcriptome and healthy or unhealthy phenotypes (Van
254 Emon, 2016). For instance, Zhao *et al.* (Zhao et al., 2022) applied transcriptomic analysis
255 in different tea (*Camellia sinensis*) cultivars, identifying 212 unigenes encoding 13 key
256 enzymes in catechins biosynthesis and concluding that a higher expression of genes
257 linked to enzymes such as LAR and a ANR was strongly correlated to catechin content
258 (Table 1).

259 Furthermore, there are many studies on berry phenolics, such as the work by Gutierrez
260 *et al.* (Gutierrez et al., 2017), where they investigated blackberry (*Rubus* spp.) fruits and
261 leaves using transcriptomic analysis at different timepoints and combined them with
262 targeted metabolomic analysis. The expression pattern of flavonoid-related genes
263 suggested that, besides the higher activation of the flavonoid biosynthesis pathway is
264 reached during the fruit ripening stage, there is a translocation step of flavonols indicating
265 a flux of these metabolites from leaves to red fruits (not fully mature). Then, flavonols are
266 accumulated and transformed to anthocyanins when the fruit is fully mature (black). Both
267 studies underscore the importance of transcriptomics in elucidating the pathways involved

268 in the biosynthesis of phenolics, especially flavonoids. While Zhao et al. highlighted the
269 role of transcriptomic analysis in identifying gene expression patterns related to catechin
270 biosynthesis in tea plants, Gutierrez et al. expanded this approach by combining
271 transcriptomics with metabolomics, revealing dynamic changes in flavonoid metabolism
272 during fruit development in blackberries. A common challenge in both studies involves
273 correlating transcriptomic data with functional outcomes across different species due to
274 the diversity in gene expression and metabolic flux influenced by environmental and
275 genetic factors.

276 Moreover, Zhou *et al.* (Y. Zhou et al., 2022) recently published a similar study on sorghum
277 (*Sorghum bicolor*) seeds targeting the flavonoid regulatory networks concluding that
278 specific chalcone synthase genes were crucially implicated in flavonoid biosynthesis by
279 using integrated analysis of transcriptomics and metabolomics. Flavanones
280 (homoeriodictyol, naringin, prunin, naringenin, hesperidin, pinocembrin) were directly
281 involved in color regulation.

282 In addition, Yue *et al.* (Yue et al., 2018) compared the gene expression of red-fleshed
283 grape berries with other varieties and observed an upregulation of several genes involved
284 in the PPP such as *MybA1*, *MybA113*. As a matter of fact, different metabolic pathways
285 involved in polyphenol synthesis and catabolism were altered, as well as genes related
286 to the biosynthesis and transport of PCs. Another work studying grape berries identified
287 light exposure as a key factor and reported a light-responsive expression of genes
288 encoding transcription factors (bHLH, MYB, MADS-box, WRKY, NAC) as well as proteins
289 related to genetic information processing and epigenetic regulation. All this showed a
290 strong correlation with phenolics production and accumulation. Once again, *MybA1*, *LAR*
291 and *ANR* transcriptional changes were also involved and significant differences were
292 noticed in the transcriptome of bagged and non-bagged grapes, i.e., subjected to different
293 light regimes (R. Z. Sun et al., 2019). Besides berries, *Prunus* spp. (such as cherries,
294 plums, apricots, or peaches) have been also investigated and the expression of the CHS
295 gene encoding chalcone synthase was identified as crucial element in the flavonoid
296 pathway, whereas the regulation of LDOX gene expression (encoding leucoanthocyanidin
297 dioxygenase) seemed to be a key point for anthocyanin synthesis during *Prunus* fruits
298 development (García-Gómez et al., 2020).

299 These powerful studies led to a wider knowledge in the genomic architecture of other
300 species such as white spruce (*Picea glauca*) and other conifers, confirming the complexity
301 of flavonoid regulatory networks in these plants (Laoué et al., 2021).

302 Since PCs are frequently synthesized in response to stress, some external actions such
303 as wounding could promote the activation of the PPP and specific genes linked to
304 phenolics production. This hypothesis was confirmed in wounded carrots, where
305 transcriptomic analyses confirmed that metabolism of wounded or shredded carrots was
306 affected by this mechanical stress and genes associated to respiratory, sugar and energy
307 metabolism were modulated to produce phenolic antioxidants (Han et al., 2017).

308 Wounding also promoted the accumulation of phenolics in pitaya fruit by activating the
309 expression of genes related with phenolic biosynthesis (phenylpropanoid and flavonoid
310 pathways) but also signaling molecules such as ethylene, reactive oxygen species and
311 jasmonic acid and promoting genes linked to primary metabolism pathways (glycolysis,
312 pentose phosphate, shikimate pathways) (X. Li et al., 2021).

313

314 [Insert Table 1: Main studies focused on phenolic compounds (PC) biosynthesis using
315 transcriptomic techniques]

316

317 **2.2. Micromics**

318 Transcriptomics provides information for understanding gene expression on the
319 metabolic pathways of PC biosynthesis. However, to completely understand the results
320 of transcriptomics it is necessary to also consider data obtained from other omics
321 techniques. In this framework, micromics approaches offer a complementary level of
322 analysis at determining the levels of microRNAs (miRNAs) that in turn can regulate gene
323 expression. Specifically, miRNAs are single-stranded non-coding RNAs (18-22
324 nucleotides) that play a crucial role in post-transcriptional gene regulation through the
325 silencing of messenger RNA (mRNA) and translational repression, among other
326 mechanisms (Broughton et al., 2016; Friedman et al., 2009; Ha & Kim, 2014; Quévillon
327 Huberdeau & Simard, 2019; Vasudevan, 2012). The study of miRNAs is particularly
328 relevant, as not only it is necessary the understanding of the genes involved in PC
329 synthesis, but also to know the mechanisms by which their expression can be regulated.
330 Therefore, transcriptomics data only provides a small part of the whole picture in PC
331 synthesis that can be complemented by micromics.

332 Recent studies have focused on unraveling the regulatory role of miRNAs in polyphenol
333 biosynthesis, but their understanding is still limited. In this line, several works using
334 micromics have reported the regulatory role of miRNAs in flavonoid biosynthesis by
335 targeting the mRNAs encoding key enzymes (Marcela et al., 2019) or transcription factors
336 of the PPP (Šamec et al., 2021) (Table 2). In this regard, Biswas *et al.* (Biswas et al.,
337 2016) reported miRNAs involved in the polyphenol's biosynthesis in *Podophyllum*
338 *hexandrum* (Himalayan May apple). MiR5532 upregulates the 2-hydroxyisoflavanone
339 dehydratase gene, increasing the isoflavanone biosynthesis. miR1438 and miR1873
340 increase the expression of caffeoyl-CoA-O-methyltransferase and dihydroflavonol 4-
341 reductase C, respectively, both associated with flavonoid biosynthesis. Similarly,
342 miR828a and miR948a are also implicated in accelerating flavonoid biosynthesis in Clary
343 Sage (*S. sclarea*) plants through the regulation of the MYB12 lipoygenase enzyme
344 (Legrand et al., 2010). miR2919, miR1168.2, miR156b, and miR1858 have been reported
345 as miRNAs that promote the expression of the flavanone synthase gene and with it, the
346 synthesis of curcumin in *Curcuma long* (Singh & Sharma, 2017).

347 Regarding anthocyanins (Salehi et al., 2020), miR858 and miR156 are implicated in the

348 biosynthesis of proanthocyanidins (PAs). Concretely, miR858 has positive effects on
349 genes related to PAs production whereas negative effects have been associated with
350 miR156 (Luo et al., 2015). Singh *et al.* (Singh et al., 2016) studied the miRNAs involved
351 in the synthesis of PC in ginger following an *in silico* approach observed that miR5015
352 regulates the biosynthesis of gingerol by inhibiting PAL, the key enzyme of the PPP,
353 involved in gingerol biosynthesis. On the other hand, Wang *et al.* (S. Wang et al., 2020)
354 observed that the gene expression of PAL is inhibited by miR477 as a response to
355 pathogen infection (Legrand et al., 2010). Finally, it has been found that cytochromes
356 P450 involved in the PPP are also regulated by miRNAs. Concretely, these cytochromes
357 are regulated and targeted by miR413 in *Dimocarpus longan* (C. Zhang et al., 2022) and
358 targeted by miR5035, miR2275d, and lus-miR168b in *P. hexandrum* and *Linum*
359 *usitatissimum* (Barvkar et al., 2013; Biswas et al., 2016).

360 Regarding lignans and lignin, the lignans are synthesized by the shikimate pathway
361 through the action of PAL and pinoresinol-lariciresinol reductase (PRL) (Teponno et al.,
362 2016), whereas the biosynthesis of lignin involved two branches PRL and the monolignol
363 pathway (Park et al., 2017). Laccases are involved in the polymerization of monolignols,
364 being reported in their post-transcriptional regulation by miRNAs. In particular, soybean
365 laccases are potential targets of miR397a/b, miR408d, and miR5671a, whereas maize
366 laccase genes were potentially targeted by miR397a/b or miR528a/b. The expression of
367 both laccases genes has been related to the response to abiotic and biotic stress factors
368 (Liu et al., 2020). In addition, lus-miR397 and ptr-miR397a have shown an effect on the
369 expression of laccase genes of *L. usitatissimum* (C. Li et al., 2019) and *Arabidopsis*
370 *thaliana* (C. Y. Wang et al., 2014). With respect to lignans biosynthesis, the study of the
371 role of miRNAs in their biosynthesis is still in its initial stages. Lignans biosynthesis is
372 regulated positively by APETALA2 (AP2) (R. Ma et al., 2017), being AP2-domain-
373 containing transcription factors targets for lus-miR172e (Xie et al., 2021). Finally, it is
374 important to indicate that lignans and lignins share common enzymes and substrates in
375 their biosynthesis (Gupta et al., 2017), so some of the knowledge about the role of miRNA
376 in the lignins regulation might be implemented to understand the function of miRNAs in
377 the lignans biosynthesis.

378

379 [Insert Table 2: Main studies focused on phenolic compounds (PC) biosynthesis using
380 micromic techniques]

381

382

383 **2.3. Proteomics**

384 Proteomics is a powerful tool employed mainly for identifying biomarkers, especially those
385 related to human diseases. In this line, and due to the beneficial effects of polyphenols
386 on human health, most of the proteomic studies carried out with polyphenols have
387 focused on observing the effect of polyphenols on the human proteome, especially on

388 their health. Proteomics analyses are also widely used in plants and have contributed to
389 obtaining a more global and integrated vision of all the proteins involved in polyphenol
390 biosynthesis, through the detection and discovery of proteins involved in these metabolic
391 pathways. However, it is important to mention that unlike a genome, a proteome is
392 dynamic and in constant flux, making its knowledge more complicated and useful.
393 Therefore, the selection of the plant and more specifically the tissue to be evaluated is
394 crucial in a proteomic study, since in order to find and discover new proteins/enzymes
395 involved in the metabolism of polyphenols, the target pathway must be overrepresented
396 in the selected area.

397 The quantitative proteomics analysis of recombinant inbred lines of peanuts with different
398 concentrations of polyphenols (high and low) revealed that the overexpression of the PPP
399 resulted in increased polyphenols biosynthesis (Muralidharan et al., 2021). A comparative
400 proteomic study in germinated and Thai brown rice revealed differences in the expression
401 patterns of proteins after germination (Maksup et al., 2018). Among the Thai rice varieties
402 studied, the red rice Mali Daeng showed 2.6 and 2.2-fold higher of PCs content and
403 anthocyanin content, respectively, compared to the white rice Khao Dawk Mali.
404 Furthermore, germinated Mali Daeng contained higher anthocyanin content, consistent
405 with increased expression of several PCs biosynthesis-related proteins (Table 3).

406 In a further study by Wu *et al.* (Wu et al., 2018), dynamic changes in proteomes of
407 postharvest tea leaves during withering stages were investigated. A total of 863 unique
408 differentially expressed proteins (DEPs) were identified by isobaric tags for relative and
409 absolute quantitation, showing dynamic changes in tea plant characteristics. The findings
410 revealed that the biosynthesis of tea polyphenols is restricted during withering. In this
411 context, tea leaves fermented by *Aspergillus niger*, *Aspergillus tamaris* and *Aspergillus*
412 *fumigatus* have been analyzed by proteomic methods. Here, changes to the flavonoids
413 were detected. Also, glycoside hydrolase, glycosyltransferases, tannases, laccases,
414 vanillyl-alcohol oxidases and benzoquinone reductase were identified and hypothesized
415 to be involved in hydrolysis, oxidation, polymerization, and degradation of PCs (Y. Ma et
416 al., 2021). In a subsequent study, Zhou *et al.* (D. Zhou et al., 2020) researched the
417 metabolism of PCs in ultraviolet C treated peaches during storage, showing that most
418 DEPs were largely matched to carbohydrates and PCs. In addition, proteomic analysis
419 revealed that UV-C irradiation modulates the phenolic synthesis by up-regulating
420 expressions of PAL, 4CL, CHS, DFR and UDP-glucose: flavonoid glucosyltransferase.

421
422 [Insert Table 3: Main studies focused on phenolic compounds (PC) biosynthesis using
423 proteomic techniques]

424

425

426 **2.4. Metabolomics**

427 Metabolomics approaches allow us to identify and determine metabolites in multiple

428 biological samples, including foods (Klassen et al., 2017). This offers a comprehensive
429 snapshot of metabolic activity, revealing key biochemical pathways and their regulation
430 in response to various factors (Wishart, 2019). Two distinct metabolomics approaches
431 can be applied: untargeted and targeted. Untargeted metabolomics analyzes all the
432 measurable compounds in a sample, including unknown metabolites. On the other hand,
433 targeted metabolomics is the analysis of defined groups of chemically characterized and
434 biochemically annotated metabolites (Klassen et al., 2017). Analytical methods in
435 metabolomics rely on mass spectrometry (MS) and nuclear magnetic resonance (NMR)
436 to analyze small molecules (López-Yerena et al., 2021). In this sense, in general MS are
437 coupled to chromatographic techniques including liquid chromatography (LC), gas
438 chromatography (GC), or capillary electrophoresis (CE), in order to separate compounds
439 (W. Li et al., 2019; Moco et al., 2007; Nagana Gowda & Djukovic, 2014). The application
440 of metabolomics potentially adds significant value to crop and food science and meets
441 future food demands (Shepherd et al., 2011). Furthermore, these analytical technologies
442 have a significant impact on the quality and shelf life of food, raw materials, and
443 postharvest processing as well (García-Cañas et al., 2012). These high-throughput
444 analytic technologies permit measuring hundreds or even thousands of compounds at a
445 time. Each of these techniques has its own advantages and disadvantages, but LC-MS
446 may represent the preferred one when studying the PCs due to its sensitivity and breadth
447 of coverage. Furthermore, integrating metabolomics with other omics approaches
448 enhances our understanding of metabolic changes induced by dietary compounds, such
449 as polyphenols, and their subsequent biological impacts Arapitsas et al., 2012). In the last
450 few years, metabolomic-based technologies have become extremely popular in
451 characterization of PCs (Piovesana et al., 2020) (Table 4). In one such study by Barros
452 Santos *et al.* (Barros Santos et al., 2019), metabolomic techniques such as ultra-high-
453 pressure liquid chromatography (UPLC) coupled to quadrupole-time of flight (QTOF) MS
454 were used to characterize phenolic profile of 7 genotypes of immature and mature wheat,
455 identifying 237 phenolics including isomers as free and bound forms, and revealing that
456 phenolic profiles were different among genotypes and during the grain development. In
457 fact, PCs progressively decreased along grain development from milky to mature.
458 However, specifically the proportion bound to free phenolic gradually increased, reaching
459 the maximum at physiological maturity. In a targeted metabolomic study, the
460 comprehensive profiling of PCs in sour guava fruit was analyzed by HPLC-electrospray
461 ionization (ESI)-triple quadrupole (QqQ) in multiple reaction monitoring (MRM) mode
462 (Cuadrado-Silva et al., 2016). This fruit contained a total of 22 PCs in the form of
463 hydroxybenzoic, phenylacetic, and hydroxycinnamic acid derivatives, reporting for the
464 first time that sour guava contains (+)-catechin, (-)-epicatechin, and procyanidin B₁ and
465 B₂. In a further study, Lyu *et al.* (Lyu et al., 2022) characterized the PCs profiles in mung
466 bean sprouts under sucrose treatment by targeted metabolomics analysis a total of 106
467 PCs were detected, 21 of which had a positive correlation with antioxidant capacity. In a

468 recent study by Zhang *et al.* (M. Q. Zhang *et al.*, 2023), a metabolomic approach was
469 used to evaluate the phenolic composition in berry juice and pomace. A total of 568 PCs
470 were identified in berry pomace samples by UPLC-MS/MS, including 238 flavonoids and
471 131 phenolic acids, suggesting that this fruit can be a valuable source of PCs of which
472 the major components are anthocyanins and phenolic acids.

473 Metabolomic-based approaches offer a powerful analytical platform for obtaining more
474 detailed and comprehensive information about food composition than traditional food
475 component analysis, including phenolic biosynthesis. These techniques have proven
476 essential for identifying biomarkers of dietary intake, which are crucial for assessing the
477 bioavailability and physiological effects of food-derived bioactive compounds (Johnson *et al.*,
478 2016). Indeed, metabolomics is a potent tool for clarifying the differences of plants
479 cultivated under different geographical origins, shading treatments, and processed using
480 different techniques. In this sense, field-based metabolomics provides new insights for
481 genotype discrimination and phenolic metabolism structuring (Shepherd *et al.*, 2011). In
482 this context, experiments to identify genetic regions responsible for phenolic acid
483 synthesis have been carried out. A metabolomics-based approach coupled with genome-
484 wide association studies identified agmatine coumaroyl transferase as the enzyme
485 responsible for phenolic amide formation in barley and its activity was strongly influenced
486 by environmental cues like day length and temperature (Wiegmann *et al.*, 2019). In a
487 subsequent study, Cruz-Carrión *et al.* (Cruz-Carrión *et al.*, 2022) used UPLC-MSⁿ
488 analyses to obtain a detailed phenolic profile of tomatoes from two locations in Spain,
489 detecting 57 PCs and showing different phenolic composition between tomatoes due to
490 the geographical origins of cultivation. In this framework, quantification of PC by HPLC
491 coupled to a diode array detector (DAD) confirmed that the concentrations of phenolic
492 acids, including chlorogenic, caffeic, ferulic, and *p*-coumaric acids, were higher in Spanish
493 traditional tomatoes grown in open fields compared to those cultivated in greenhouses
494 (Asensio *et al.*, 2019). In this line, the study of Vaičiulyte and Ložiene (Vaičiulyte &
495 Ložiene, 2015), who monitored effects of meteorological factors on phenolics of *Thymus*
496 *pulegioides* L. cultured in the same locality using GC-MS, demonstrated that the
497 meteorological factors differently influence the accumulation of carvacrol. This phenolic
498 showed the most stable quantitative composition of essential oil due to significant effects
499 of both temperature and photosynthetically active solar radiation. In a subsequent 96 PCs
500 were quantified by UHPLC-QqQ-MS on the skins of mature grape berries from a core-
501 collection of 279 *Vitis vinifera* cultivars grown with or without watering. Metabolomics
502 analysis demonstrated an influence of water stress on the biosynthesis of different PCs
503 and cultivar differences in metabolic response to drought (Pinasseau *et al.*, 2017).

504 As above mentioned, metabolomics-based approaches provide evidence on plants
505 phenolic profile changes during processing methods. For example, in the study of Zhou
506 *et al.* (J. Zhou *et al.*, 2019), chemical changes of large-leaf yellow tea during processing
507 were analyzed by LC-MS. Untargeted and targeted metabolomics analyses revealed that

508 epicatechin and free amino acids significantly decreased in tea samples after roasting,
509 while epimerized catechin intensely increased. Similarly, the analysis of PCs profile
510 changes with different drying processing methods were evaluated in daylily using UPLC
511 with multistage fragmentation techniques, showing that quercetin 3-O-rutinoside and 5-
512 O-caffeoylquinic acids were higher in freeze-dried and steam-dried samples (J. Sun et
513 al., 2018).

514

515 [Insert Table 4: Main studies focused on phenolic compounds (PC) biosynthesis using
516 metabolomic techniques]

517

518

519

520 **3. Current limitations and challenges**

521 Several omics techniques such as genomics, transcriptomics, proteomics, and targeted
522 and untargeted metabolomics analyses are used in foodomics to provide molecular
523 information on gene, transcript, protein, and metabolite levels involved in the biosynthesis
524 pathway of PCs. By use of this technique there is considerable information regarding the
525 biosynthesis pathway of PCs and the enzymes involved in. In addition, relevant data on
526 how the synthesis of metabolites is affected by external and internal data have been
527 obtained. However, there are a high number of limitations in the use of Foodomics to
528 evaluate the PCs synthesis and content in plants. The most important ones are the
529 following: i) High diversity of structures. The world of PCs is wide and thousands of
530 different chemical structures are already characterized with different mixtures of these
531 compounds present in plants. In addition, PCs can have a different degree of
532 glycosylation and polymerization, resulting in multiple isomeric forms (Zagoskina et al.,
533 2023). Actually, each variety of the same plant can have different composition of PCs. For
534 example, Man et al (Man et al., 2022) have analysed the PC composition of pomegranate
535 peel from different cultivars showing that each cultivar has a different PC profile.
536 Multivariate analysis performed by PCA showed a clear separation of the samples
537 depending of the type of cultivar (65.7 % of variability reached by the two components).
538 Regarding proteomics analysis, it is important to consider the impact of post-translational
539 modifications (PTM), which play a crucial role in biological processes. In eukaryotic
540 organisms, most proteins undergo PTMs (i.e., phosphorylation, sulfation, oxidation,
541 ubiquitination, acetylation, methylation, lipidation, or glycosylation). These modifications,
542 along with alternative RNA splicing, greatly enhance the complexity of the proteome
543 relative to the transcriptome. Similar to the transcriptome, the proteome is highly dynamic
544 and varies based on tissue type, microenvironment, and life cycle stage. External and
545 internal signals, including growth factors, hormones, metabolites, and cell-to-cell
546 interactions, can regulate gene expression, leading to a broad spectrum of mRNA and

547 protein levels—ranging from complete silence to millions of copies and protein molecules
548 per cell. As a result, proteomes and their modifications undergo significant changes during
549 processes such as cell differentiation, activation, trafficking, and malignant
550 transformation, thus increasing the diversity of structures and the complexity of the
551 analysis. ii) Impact of agronomic factors. A wide variety of agronomic factors such as
552 temperature, sun exposure and irrigation can impact the PCs synthesis. In fact, the same
553 variety of plant subjected to different external conditions can show different PCs
554 composition. This variability has been demonstrated in numerous studies. For example,
555 research on *Lavandula viridis* and *Thymus lotocephalus* exposed to different
556 temperatures showed that phenolic compounds and antioxidant activity increased with
557 rising temperatures in micropropagated plants (Mansinhos et al., 2022). Similarly, studies
558 on tomatoes have shown that controlled water deficit can increase the concentration of
559 anthocyanins and other phenolic compounds (Jin et al., 2022). Another example of this
560 variability is found in lettuce, where a reduction in nitrogen supply prior to harvest
561 significantly altered the composition of phenolic compounds, enhancing the cellular
562 antioxidant potential without affecting plant biomass (W. Zhou et al., 2018). Likewise, an
563 analysis of the roots of *Eryngium montanum* under different annual growth conditions
564 demonstrated that environmental factors significantly impact the accumulation of phenolic
565 compounds and their antioxidant activity (Pérez-Ochoa et al., 2023). In another study, Li
566 et al. (X. Li et al., 2015) observed that temperature, latitude and longitude have a clear
567 impact on PC profile in pomegranate juices of different cultivars cultivated in different
568 regions. Therefore, a high number of studies is needed to have a clear understanding of
569 the biosynthesis pathway of PCs and how this is affected by internal and external factors
570 of the plants.

571 iii) High dimensionality of the data. Another important limitation in omics-based studies is
572 the high dimensionality of the data, which poses challenges in interpretation and study.
573 This complexity is further intensified by the high degree of correlation among measured
574 variables, including metabolites and proteins. This leads to overfitting in models and
575 difficulties in validating results in independent datasets. To address these challenges,
576 multi-omics integration approaches, such as combining transcriptomic and metabolomic
577 analyses, have been successfully applied to identify candidate genes involved in phenolic
578 biosynthesis. For example, a study in *Cyclocarya paliurus* used a combined metabolomic
579 and transcriptomic approach to elucidate key pathways regulating the synthesis of
580 phenolic acids, demonstrate the potential of integrating different omics sciences to
581 improve the interpretation of the data (Lin et al., 2020).

582 iv) Standardization. There is a general lack of standardization in the different omics
583 techniques that can have an impact in the observed results. In this regard, in metabolomic
584 studies, the wide variety of PCs, degrees and glycosylation and polymerization results in
585 a need of standard compounds to precisely quantify all PCs composition. Hence, still
586 nowadays there is a lack for commercial standards of these compounds and researchers

587 tend to tentatively quantify the compounds referred to a selected group of commercial
588 standards (Iglesias-Carres et al., 2019), or express the results as relative abundance
589 (García-Villalba et al., 2015). Otherwise, the lack of standardization in experimental
590 procedures further complicates the comparison of studies across different plants and
591 experimental conditions (Saccenti et al., 2011, 2018). Developing standardized protocols
592 for omics studies will be crucial to improving reproducibility and comparability across
593 different research. In this regard, studies like those on *Lactuca sativa*, which employed a
594 genotype-dependent metabolomic approach to assess functional profile changes under
595 varying nutrient conditions, highlight the importance of standardized methodologies to
596 achieve robust and transferable findings (W. Zhou et al., 2019).

597

598 **4. Insights in phenolic compounds studies**

599 PCs are secondary metabolites produced by plants under stress conditions and with
600 several health effects described. Thus, the knowledge of the composition of these
601 metabolites in foods and the way they are synthesized is relevant to nutrition and
602 medicine. The use of omics techniques in foodomics has given a boost to the
603 understanding of the genes, proteins, metabolites and even microRNAs involved in their
604 synthesis. In addition, some insights regarding the influence of external and internal
605 factors have been described. Interestingly, new omics techniques are emerging such as
606 epimomics (i.e., epigenomics, epitranscriptomics and epiproteomics) and interactomics (i.e.,
607 complexes between DNA, RNA, proteins and metabolites), as well as statistics and data
608 analyses are continuously progressing such as system biology (Dai & Shen, 2022). In
609 addition, another significant challenge is the vast diversity of PC chemical structures and
610 their variability across different plant species, varieties, and environmental conditions.
611 These challenges the investigations in PCs biosynthesis to increase their understanding.
612 Machine learning has emerged as a powerful tool in the study of polyphenol biosynthesis,
613 offering insights into the complex biochemical pathways and regulatory mechanisms
614 involved. Therefore, advances in artificial intelligence are now being leveraged to process
615 large omics datasets. Specifically, these tools are being used to predict biosynthesis
616 pathways (García-Pérez et al., 2021). In the study of García-Pérez, they combined
617 previous data from untargeted metabolomics with machine learning to obtain the
618 phytochemical characterization of unexplored species from *Bryophyllum* subgenus
619 (García-Pérez et al., 2021). In another study, in strawberry cultivar classification studies,
620 support vector machines and extreme learning algorithms were used to study phenolic
621 profiles with high accuracy (Bao et al., 2018). On the other hand, machine learning has
622 been used integrated with multi-omics data from *Arabidopsis* to predict genes encoding
623 enzymes involved in biosynthesis of plant PCs (Bai et al., 2024). Therefore, it is clear that
624 matching learning and artificial intelligence will play a key role in PCs biosynthesis
625 studies.

626

627
628
629

630 **Abbreviations**

- 631 4CL, 4-coumaroyl-CoA ligase
632 ANR, anthocyanidin reductase.
633 ANS, anthocyanidin synthase
634 AP2, APETALA2
635 C4H, cinnamic acid hydroxylase
636 CE, capillary electrophoresis
637 CHI, chalcone isomerase
638 CHS, chalcone synthase
639 DAD, diode array detector
640 DEPs, differentially expressed proteins
641 DFR, dihydroflavonol 4-reductase
642 DPPH, 2,2-difenil-1-picrilhidrazil
643 ESI, electrospray ionization
644 FH3, flavanone 3-hydroxylase
645 FNS, flavone synthase
646 GC, gas chromatography
647 HPLC, high pressure liquid chromatography
648 IFS, isoflavone synthase
649 LAR, leucoanthocyanidin reductase
650 LC, liquid chromatography
651 LC-IM-Q-TOF-MS, liquid chromatography/ion mobility quadrupole time-of-flight mass
652 spectrometry
653 LDOX, leucoanthocyanidin dioxygenase
654 miRNA, microRNA
655 mRNA, messenger RNA
656 MRM, multiple reaction monitoring
657 MS, mass spectrometry
658 MSⁿ, multistage mass spectrum
659 NMR, nuclear magnetic resonance
660 ORAC, oxygen radical absorbance capacity
661 PAL, phenylalanine ammonia-lyase
662 PAs, proanthocyanidins
663 PCA, principal component analysis
664 PCs, phenolic compounds
665 PP, polyphenols
666 PPP, phenylpropanoid pathway
667 PRL, pinoresinol-lariciresinol reductase
668 PTM, post-translational modifications
669 QqQ, triple quadrupole

670 QTOF, quadrupole-time of flight
671 ROS, reactive oxygen species
672 SVM, support vector machines
673 UDP, uridine diphosphate
674 UPLC, ultra-high-pressure liquid chromatography
675 UHPLC-ESI-QqQ, ultra-high-pressure liquid chromatography electrospray ionization
676 triple quadrupole
677 UV-C, ultraviolet C

678

679 **Author contributions**

680 SG-R, AC-C, DM, AG-R, MS, and AA-A prepared the original draft. SG-R, AC-C, MS, and
681 AA-A reviewed and edited the manuscript. “All authors contributed to manuscript revision,
682 read and approved the submitted version”.

683

684 **Conflicts of interest**

685 The authors declare that they have no conflicts of interest.

686

687 **Ethical approval**

688 Not applicable.

689

690 **Consent to participate**

691 Not applicable.

692

693 **Consent to publication**

694 Not applicable.

695

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707

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1143

1144 **Tables**1145 **Table 1. Main studies focused on phenolic compounds (PC) biosynthesis using**
1146 **transcriptomic techniques.**

Sample	Aim of the study	Key findings	Reference
Tea plant	Catechins biosynthesis pathways	Expression of genes of the enzymes LAR and ANR positively correlated with catechin content	(Zhao et al., 2022)
Blackberry	Study of flavonoid synthesis during ripening	Flavonols translocate from leaves to fruits and then transforms into anthocyanins with ripening.	(Gutierrez et al., 2017)
Sweet sorghum	Flavonoid biosynthesis pathways	Chalcone synthase genes were crucial for flavonoid biosynthesis	(Y. Zhou et al., 2022)
Red grapes	Comparison of gene expression profile, PC, and antioxidant capacity of different red grapes	An upregulation of genes in the PPP is observed in Cabernet Sauvignon.	(Yue et al., 2018)
Cabernet Sauvignon grapes	Influence of agronomic procedures (cluster bagging) on ripening and PC accumulation	Transcriptomic changes were observed based on bagging conditions, mainly influenced by light.	(R. Z. Sun et al., 2019)
<i>Prunus</i> species	Identification of molecular bases of PC synthesis during ripening	CHS and LDOX gene were crucial for flavonoid and anthocyanin synthesis, respectively	(García-Gómez et al., 2020)
Carrots	Evaluate the impact of wounding on primary and secondary metabolism	Genes related to respiratory, sugar and energy metabolism were modulated to produce PC in wounding carrots	(Han et al., 2017)

Pitaya fruit	Evaluate the molecular mechanisms underlying the wound PC synthesis	Genes related to PC biosynthesis (PP and flavonoid pathways) were activated by wounding	(X. Li et al., 2021)
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1147 Abbreviations: ANR, anthocyanidin reductase; CHS, chalcone synthase; LAR,
1148 leucoanthocyanidin reductase; LDOX, leucoanthocyanidin dioxygenase; PPP,
1149 phenylpropanoid pathway.

1150

1151 **Table 2. Main studies focused on phenolic compounds (PC) biosynthesis using**
 1152 **micromic techniques**

Sample	Aim of the study	Key findings	Reference
Curcuma	Identification of miRNAs involved in PC synthesis	miR2919, miR1168, miR156b and miR1858 promote the expression of flavanone synthase gene and the synthesis of curcumin	(Singh & Sharma, 2017)
Tea plant	Study of the miRNAs involved in PAL regulation after pathogen infection	The gene expression of PAL is inhibited by miR477	(S. Wang et al., 2020)
Ginger	miRNAs involved in ginger metabolites biosynthesis	miR5015 was observed to regulate the biosynthesis of gingerol by PAL	(Singh et al., 2016)

1153 Abbreviations: miRNA, microRNA; PAL, phenylalanine ammonia-lyase

1154

1155 **Table 3. Main studies focused on phenolic compounds (PC) biosynthesis using**
 1156 **proteomic techniques**

Sample	Aim of the study	Key findings	Reference
Rice	Compare the proteome related to PC in germinated and Thai brown rice	Germinated rice contained higher anthocyanin content, consistent with increased expression of several PCs biosynthesis-related proteins	(Maksup et al., 2018)
Tea plant	Evaluation of dynamic changes in the proteome of postharvest tea leaves during withering	The biosynthesis of tea PC is restricted during withering	(Wu et al., 2018)
Tea plant	Study of the impact of fermentation by different microorganisms on the proteome and metabolome	Glycoside hydrolase, glycosyltransferases, tannases, laccases, vanillyl-alcohol oxidases and benzoquinone reductase were correlated to be involved in hydrolysis, oxidation, polymerization, and degradation of PCs	(Y. Ma et al., 2021)
Peach	Study the impact of UV-C irradiation on PC biosynthesis	UV-C irradiation modulates the PC synthesis by up-regulating expressions of PAL, 4CL, CHS, DFR and UDP-glucose: flavonoid glucosyltransferase	(D. Zhou et al., 2020)

1157 Abbreviations: 4CL, 4-coumaroyl-CoA ligase; CHS, chalcone synthase; DFR,
 1158 dyhydroflavonol 4-reductase; PAL, phenylalanine ammonia-lyase; UDP, uridine
 1159 diphosphate.

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Table 4. Main studies focused on phenolic compounds (PC) biosynthesis using metabolomic techniques

Sample	Aim of the study	Key findings	Reference
Sour Guava fruit	Study the PCs profile	22 PC were determined, including hydroxybenzoic, phenylacetic, and hydroxycinnamic acid derivatives, (+)-catechin, (-)-epicatechin, and procyanidin B1 and B2	(Cuadrado-Silva et al., 2016)
Berry	Determine the PC profile in juices and pomace	568 PCs were identified, including 238 flavonoids and 131 phenolic acids	(M. Q. Zhang et al., 2023)
Wild barley	Identify genetic regions responsible for phenolic acid synthesis (metabolomics coupled with genomics)	Agmatine coumaroyl transferase was found to be the key enzyme in phenolic amide formation	(Wiegmann et al., 2019)
Tomatoes	Study the differences in PC content depending on the location	PCs profile was influenced by the geographical origins of cultivation	(Cruz-Carrión et al., 2022)
Tomatoes	Study the differences in PC depending on the growing conditions	Phenolic acid concentrations were higher in tomatoes grown in open fields compared to greenhouse cultivars	(Asensio et al., 2019)
Grape	Study changes in response to drought on the PCs biosynthesis in skins of a wide variety of grape cultivars	Water stress influences the biosynthesis of different PCs classes	(Pinasseau et al., 2017)
Yellow tea	Study the PC changes of large-	After roasting, the concentration of epicatechin	(J. Zhou et al., 2019)

	leaf yellow tea during processing	decreased, while epimerized catechin increased	
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1 **Foodomics approaches: new insights in phenolic compounds analysis**

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28 **Abstract**

29
30 Fruits, vegetables, and plant-based foods contain several bioactive substances such as
31 phenolic compounds (PCs), that are plant secondary metabolites with attributed health
32 properties. ~~Current studies are now targeting. The study of the~~ metabolic pathways of PCs,
33 ~~including to increase the knowledge those related with their about their~~ synthesis,
34 transport, accumulation, and degradation ~~are essential to advance in this field of~~
35 ~~research.~~ In this regard, ~~using~~ omics tools such as foodomics ~~is~~ ~~are~~ gaining relevance ~~in~~
36 ~~this field~~ ~~due to their versatility and their tremendous potential to generate significant~~
37 ~~advances in PC research.~~

38 ~~Foodomics is a novel omics approach, including genomics, metabolomics, micromics,~~
39 ~~proteomics and transcriptomics, which can be applied to study PCs in plants. This~~
40 ~~multidisciplinary approach has advanced the understanding of the synthesis, regulation,~~
41 ~~and accumulation of PCs.~~ In this review, we present a comprehensive overview of the
42 applications of omics technologies in PC analysis, ~~including transcriptomics, micromics,~~
43 ~~proteomics and metabolomics,~~ highlighting their role in metabolic pathways, current
44 limitations, and emerging insights ~~that continue to shape the field.~~

45 ~~Now~~ omics techniques ~~are continuously emerging,~~ as well as ~~statistics and~~ data
46 analyses are ~~also continuously~~ progressing, ~~emerging new opportunities with the onset~~
47 ~~of artificial intelligence and machine learning, with systems biology and advanced~~
48 ~~statistical methods, such as machine learning and multivariate analysis, enabling more~~
49 ~~accurate interpretation of omics data.~~ ~~However, significant limitations and challenges still~~
50 ~~remain. The immense diversity of PC chemical structures and their variability across plant~~
51 ~~species, varieties, and environmental conditions~~ the impact of agronomic factors
52 ~~complicate data interpretation~~ the analyses and limit the extrapolation of findings.
53 ~~Additionally, high data dimensionality, strong correlations among measured variables, and~~
54 ~~the general lack of standardization in the different omics techniques~~ ~~that~~ can impact in
55 ~~the results~~ ~~lack of standardization in experimental procedures~~ further limit reproducibility
56 ~~and cross study comparisons. Addressing these limitations requires integrating multi-~~
57 ~~omics approaches, leveraging machine learning for data processing, and developing~~
58 ~~standardized protocols to enhance comparability and interpretation in PC research.~~ The
59 main challenges in studying PCs using omics techniques include the immense and
60 diversity of PC chemical structures and their variability across different plant species,
61 varieties, and environmental conditions. This variability limits the extrapolation of findings
62 and requires extensive studies to fully understand not only biosynthesis pathways but
63 also the internal and external impacts on such compounds. ~~In summary, foodomics~~
64 ~~approaches arise as essential for the complete mapping of PC biosynthesis.~~

65
66 **Keywords**

67 Genomics, metabolomics, micromics, multi-omics, omics, polyphenols, transcriptomics.

68
69 **1. Introduction**
70 Phenolic compounds (PCs), also known as (poly)phenols, are one of the most
71 heterogeneous groups among bioactive compounds, with more than 50,000 different
72 molecules identified. Despite its family of compounds with a wide variety of molecules,
73 structurally, they have in common, at least, a hydroxyl group linked to a benzene ring
74 (Ávila-Román et al., 2021; L. Zhang et al., 2021). These compounds can be divided into
75 two main groups: flavonoids and non-flavonoids, being the former the most distributed
76 among plants (L. Zhang et al., 2021). This classification is made by attending to the
77 number of phenolic rings they have, and the structural elements binding those rings. In
78 this sense, flavonoids are characterized to have two aromatic rings connected by a three-
79 carbon bridge (C6-C3-C6). These are further subclassified in flavanols (also known as
80 flavan-3-ols), flavonols, flavanones, flavones, isoflavones and anthocyanidins, according
81 to hydroxylation pattern, distribution of the rings, their index of hydrogen deficiency and/or
82 their no-hydroxylated functional groups (Figure 1)

83
84 [\[Insert Figure 1: Main chemical structures of phenolic compounds \(PCs\)\]](#)

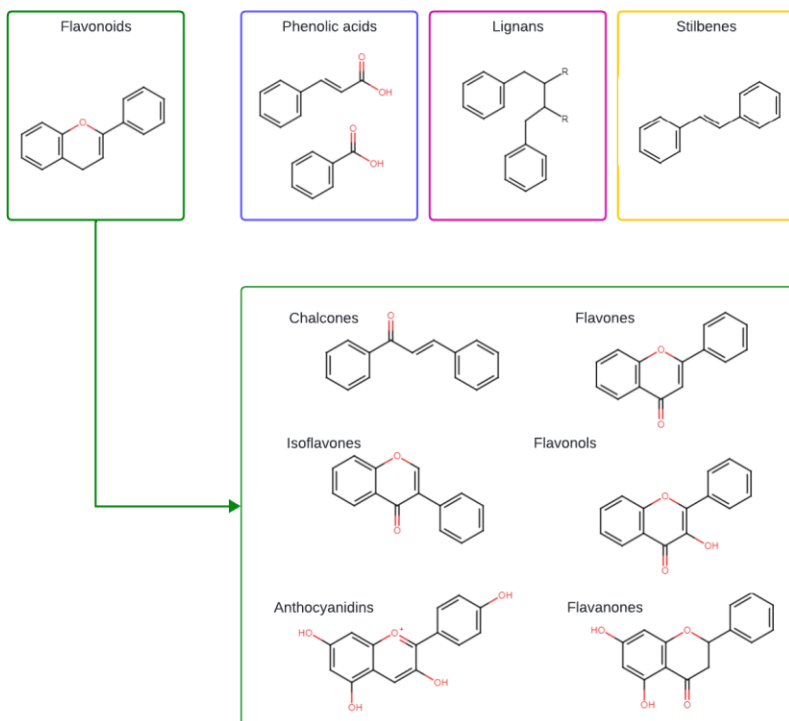


Figure 1. Main chemical structures of phenolic compounds (PCs). This figure illustrates the structural diversity of flavonoids, phenolic acids, lignans, and stilbenes, highlighting specific flavonoid subgroups, such as chalcones, isoflavones, anthocyanidins, flavones, flavonols, and flavanones.

Otherwise, non-flavonoids are those PCs that do not share the flavonoid main chemical structure. These are composed of phenolic acids, phenolic alcohols, lignans and stilbenes (Ávila-Román et al., 2021; W. Li & Beta, 2013; Yalcin & Çapar, 2017). Cocoa, beans, and walnuts are examples of products with high phenolic concentration, ranging between 1,200 and 5,000 mg of total phenolics per 100 grams of fresh weight. According to PC type, hesperidiums such as lemons and oranges are rich in flavanones, while in drupes and berries, such as cherries, grapes, or blueberries, the most predominant are anthocyanins (Arola-Arnal et al., 2019). Soybeans are rich in isoflavones, such as genistein and daidzein, and herbs such as parsley and celery are rich in flavonols. In this way, cocoa and tea are sources of (+)-catechin and (-)-epicatechin. Hydroxybenzoic acids and their derivatives are found in certain red fruits, onions, and black radish. Finally,

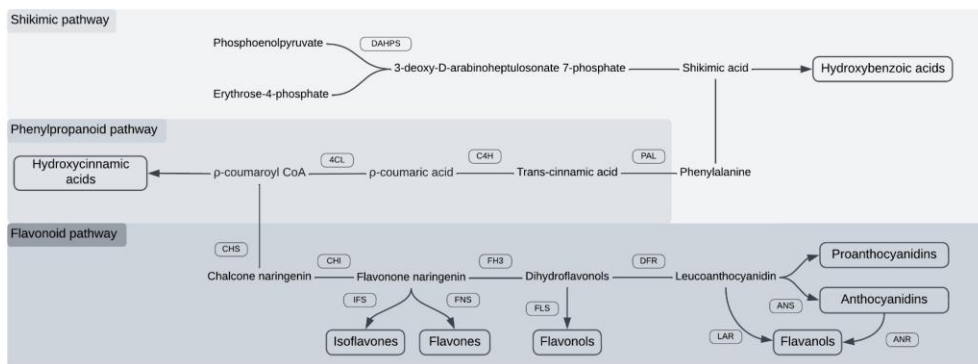
102 derivatives of hydroxycinnamic acid, such as chlorogenic acid, are found in coffee, among
103 other plants (Manach et al., 2004; L. Zhang et al., 2021). Regarding tissue distribution,
104 PCs are distributed throughout the whole plant, including roots, leaves, and fruits. In
105 leaves and stems, they primarily accumulate in monomeric forms, whereas polymeric
106 forms are more abundant in fruits, the epidermis, and vacuoles (Ávila-Román et al.,
107 2021). Additionally, insoluble phenols are localized in the cell wall, while soluble phenols
108 are primarily stored in vacuoles (Naczka & Shahidi, 2004).

109 Once ingested PCs are recognized as xenobiotics. Due to their complex structure their
110 bioavailability is low, and only around 5-10% are absorbed in the small intestine, while
111 rest is absorbed by colonocytes after being metabolized by gut microbiota (D'Archivio et
112 al., 2007). Remarkably, although still in discussion, it is believed that bioactive forms are
113 products of PCs metabolism. In this regard, PCs have an important antioxidant activity,
114 enhancing potential of these compounds that can be used to improve human health
115 protecting against oxidative stress (Manach et al., 2004; Yalcin & Çapar, 2017). Therefore,
116 it is common to determine antioxidant activity in plants rich in PC by means of different
117 techniques such as DPPH (2,2-difenil-1-picrilhidrazil) and oxygen radical absorbance
118 capacity (ORAC) or using advanced analytical techniques like HPLC coupled with
119 detectors for antioxidant activity (Ávila-Román et al., 2021). After that, together with PC
120 identification, correlation studies can be done in order to determine which polyphenols
121 are more responsible of its antioxidant activity (Suárez et al., 2009). In addition, PCs have
122 a wide range of bioactivities such as anti-inflammatory, anti-carcinogenic, or anti-
123 hypertensive. Those compounds play a key role in health promotion due to their ability to
124 mitigate oxidative stress and modulate inflammatory pathways, which contributes to their
125 protective effects against chronic diseases (Shahidi & Yeo, 2018). Additionally, these
126 compounds also have the capacity to modulate biochemical pathways related to energetic
127 and lipidic metabolism (L. Zhang et al., 2021).

128 Concerning their synthesis, PCs can be defined as plant secondary metabolites that are
129 produced under an abiotic stress such as drought, extreme temperature variations, or soil
130 salinity. The synthesis of PCs follows three different pathways: shikimate pathway,
131 phenylpropanoid pathway (PPP) and flavonoid pathway (Shahidi & Yeo, 2018; Suárez et
132 al., 2009) (Figure 2). In the shikimate pathway, phosphoenolpyruvate combines with
133 erythrose-4-phosphate to give shikimic acid, precursor of phenylalanine and
134 hydroxybenzoic acids (Cheyrier et al., 2013; Deng & Lu, 2017; Zagorskina et al., 2023).
135 The action of different enzymes during all these processes is crucial; phenylalanine
136 ammonia-lyase (PAL) transforms phenylalanine in trans-cinnamic acid, which is first step
137 in the PPP. Then, cinnamic acid hydroxylase (C4H) and coumarin CoA ligase (4CL)
138 transform trans-cinnamic acid into *p*-coumaroyl CoA, which is precursor of
139 hydroxycinnamic acids (Shen et al., 2022; Zagorskina et al., 2023).

140 Then, chalcone synthase (CHS), the key enzyme in flavonoid's biosynthesis, transforms
141 *p*-coumaroyl CoA into chalcone naringenin, the first product of flavonoid (Zagorskina et

142 al., 2023).



143

144 [\[Insert Figure 2: Biosynthesis pathway of plant phenolic compounds \(PCs\)\]](#)

145

146 **Figure 2. Biosynthesis pathway of plant phenolic compounds (PCs).**

147 **Figure 2. Biosynthesis pathway of plant phenolic compounds (PCs).** This figure
148 illustrates the sequential metabolic steps leading from primary precursors through
149 hydroxycinnamic acids, finishing in the formation of diverse flavonoid subclasses such as
150 isoflavones, flavones, flavonols, anthocyanidins, and proanthocyanidins. Abbreviations:
151 DAHPS: 3-deoxy-D-arabinoheptulose 7-phosphate synthase; PAL: phenylalanine
152 ammonia-lyase; C4H: cinnamate 4-hydroxylase; 4CL: 4-coumaroyl CoA ligase; CHS:
153 chalcone synthase; CHI: chalcone isomerase; FH3: flavanone 3-hydroxylase; DFR:
154 dihydroflavonol 4-reductase; IFS: isoflavone synthase; FNS: flavone synthase; FLS:
155 flavonol synthase; LAR: leucoanthocyanidin reductase; ANS: anthocyanidin synthase;
156 ANR: anthocyanidin reductase.

157

158 The action of chalcone isomerase (CHI) produces flavanone naringenin, which is the
159 precursor of isoflavones when the isoflavone synthase (IFS) acts, and flavones when the
160 flavone synthase (FNS). On the other hand, the enzyme flavanone 3-hydroxylase (FH3)
161 transforms flavanone naringenin into dihydroflavonol, precursor of flavonols. The last
162 product of the flavonoid pathway is formation of leucoanthocyanidin by action of
163 dihydroflavonol 4-reductase (DFR). This product is a precursor of anthocyanidins with
164 action of enzyme anthocyanidin synthase (ANS), and of proanthocyanidins. The enzyme
165 leucoanthocyanidin reductase (LAR) transforms leucoanthocyanidin into flavanols, and
166 enzyme anthocyanidin reductase (ANR) transforms anthocyanidins into flavanols
167 (Cheynier et al., 2013; Shen et al., 2022; Zagorskina et al., 2023).

168 It is worth mentioning biosynthesis of PCs also involves action of several transcription

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169 factors, such as MYBA in grapevine, that controls anthocyanin synthesis and are
170 responsible for skin coloration in those berries (Matus et al., 2017; Yue et al., 2018).
171 The phenolic profile in plants depends on both internal factors, such as genetic and
172 external factors, including environmental conditions (L. Zhang et al., 2021). Therefore,
173 there can be differences in the phenolic profile not only between two different varieties of
174 the same cultivar, but also within the same variety depending on environmental
175 conditions. Moreover, postharvest treatments also have an important role in the total PCs
176 content since they can promote their synthesis or degradation (Ávila-Román et al., 2021;
177 Yalcin & Çapar, 2017; L. Zhang et al., 2021). In fact, abiotic stress in plants increases
178 production of reactive oxygen species (ROS), causing oxidative damage. This production
179 enhances activity of PAL, CHS, and other enzymes, which increase PCs accumulation to
180 protect the plant against oxidative stress (Kumar et al., 2023; Shen et al., 2022; Yue et
181 al., 2018). For example, a very common abiotic stress in plants is drought, which is
182 reported to increase accumulation of anthocyanins in *Arabidopsis*, generating a higher
183 stress tolerance (Nakabayashi et al., 2014). Another example is reported by Griesser *et*
184 *al.* (Griesser et al., 2015), where accumulation of several PCs, such as (-)-epicatechin or
185 (-)-epicatechin gallate in *Vitis vinifera* was increased after a prolonged period of drought.
186 The same results were obtained in grape berries after a period of drought, here a higher
187 accumulation of flavonoids, flavan-3-ols, and flavonols were found (Doshi et al., 2006).
188 Another stressing factor is ultraviolet radiation (UV), which damages protein structure,
189 leading to ROS generation, and, subsequently, to a higher PCs accumulation (Kumar et
190 al., 2023). In this regard, Goyal *et al.* (Goyal et al., 2014) analyzed the effect of UV in the
191 accumulation of PCs in mung bean sprouts and reported that higher phenolic
192 accumulation was found in plants treated with UV radiation compared to the control. The
193 treatment also increased their antioxidant activity. Jan *et al.* (Jan et al., 2022) reported
194 that the relative expression of FH3 was increased in wild and transgenic rice plants when
195 they were exposed to UV radiation. Soil salinity, a stress factor, also enhances phenolic
196 accumulation in plants (Kumar et al., 2023). Several studies were carried out in this
197 context. For example, Golkar *et al.* (Golkar & Taghizadeh, 2018) reported that the
198 concentration of total flavonoids and total PC increased in safflowers with high salinity
199 levels. Flavonoid biosynthesis in plants is regulated by several factors, transcription
200 factors being one of the most important. It has been seen that the overexpression of
201 transcriptional factor VvbHLH (*Vitis vinifera* basic Hoop-Loop-Hoop) induces the
202 biosynthesis of flavonoids, protecting the plant from salinity stress (F. Wang et al., 2016).
203 Other abiotic factors, such as temperature or the use of pesticides, can also stimulate the
204 phenolic biosynthesis in plants, to protect the plant against oxidative stress (Nakabayashi
205 et al., 2014). ~~As previously mentioned, the phenolic profile in plants is highly different as
206 it depends on several factors.~~
207 ~~Therefore~~ Focusing on the study of PC biosynthesis, omics techniques have emerged as
208 essential tools ~~to study PCs in depth~~ due to their versatility. –These are a set of disciplines

209 that involve ~~metabolomics, proteomics, genomics~~ transcriptomics, ~~genomics and~~
210 micromics, ~~proteomics and metabolomics~~, among others (Debnath et al., 2011). In fact,
211 when this set of techniques is applied to food it is called 'Foodomics' (Valdés et al., 2017,
212 2022). This word was first described in 2009 as a discipline that studies the Food and
213 Nutrition domains through the application of omics technologies (Cifuentes, 2009).

214 Foodomics has a number of advantages over traditional techniques: higher sensitivity,
215 greater specificity, and the possibility to analyse hundreds of compounds at the same
216 time, which allows a holistic view of the food matrix and its interaction with biological
217 systems (Cifuentes, 2012). For example, in the case of polyphenols PC, foodomics has
218 already shown its power in elucidating complex metabolic pathways and discovering new
219 biomarkers. A very good example is the use of LC-IM-Q-TOF-MS LC-IM-Q-TOF-MS for
220 the analysis of phenolic compounds PC in herbal liqueurs, which offers significant
221 sensitivity and excellent peak capacity by using three dimensions of separation (Valdés
222 et al., 2022). A critical aspect of ~~these foodomics techniques~~ lies in their capacity to
223 generate large datasets, which, while offering profound insights, also introduce
224 challenges in data management and analysis.

225 The analysis of large datasets, generated by ~~techniques such as genomics,~~
226 ~~metabolomics, and proteomics~~ foodomics, ~~presents significant challenges due to their~~
227 ~~highly~~ complex~~ity~~ and ~~with~~ high dimensionality. To address ~~these~~ ~~challenges~~ ~~fact~~,
228 advanced statistical approaches such as multivariate analysis, machine learning, and
229 systems biology ~~approaches~~ are employed. ~~For instance, p~~Principal component analysis
230 (PCA) and cluster analysis are used to reduce dimensionality and ~~group-cluster~~ similar
231 samples or variables, facilitating their visualization and ~~the~~ interpretation of patterns in the
232 data (León et al., 2018). In addition, supervised machine learning techniques, such as
233 support vector machines (SVM) and neural networks, are essential for classifying
234 samples and predicting characteristics from complex data (León et al., 2018; Valdés et
235 al., 2017). In systems biology, network models and predictive modelling help integrate
236 multi-omics data and simulate the behaviour of biological systems, contributing to a
237 deeper understanding of underlying biological pathways (Valdés et al., 2017). These
238 approaches, combined with advanced computational tools, allow for the management and
239 extraction of meaningful information from the large volumes of data generated by omics
240 techniques.

241 ~~Foodomics plays a significant role in the study of polyphenols because it provides a~~
242 ~~comprehensive and multi-disciplinary approach surpassing the conventional methods.~~
243 ~~This emerging science combines state of the art omics technologies, such as~~
244 ~~transcriptomics, proteomics, and metabolomics, together with biostatistics and~~
245 ~~bioinformatics, to investigate complex biological systems and the behaviour of bioactive~~
246 ~~food components . Foodomics has a number of advantages over traditional techniques:~~
247 ~~higher sensitivity, greater specificity, and the possibility to analyse hundreds of~~
248 ~~compounds at the same time, which allows a holistic view of the food matrix and its~~

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249 ~~interaction with biological systems. For example, in the case of polyphenols, foodomics~~
250 ~~has already shown its power in elucidating complex metabolic pathways and discovering~~
251 ~~new biomarkers. A very good example is the use of LC-IM-Q-TOF-MS for the analysis of~~
252 ~~phenolic compounds in herbal liqueurs, which offers significant sensitivity and excellent~~
253 ~~peak capacity by using three dimensions of separation. Therefore, in this review, we aim~~
254 ~~to provide a comprehensive overview of the applications of omics technologies in PC~~
255 ~~biosynthesis, from gene expression to metabolite production. Moreover, the current~~
256 ~~limitations, [challenges and insights](#) related to this field are described.~~

257 **2. Foodomics techniques**

259 [Foodomics have become indispensable tools in the study of PCs biosynthesis. In this](#)
260 [sense, transcriptomics analyses are useful to identify key regulatory genes and](#)
261 [transcription factors that modulate the synthesis of PCs and provide insights of how](#)
262 [different agronomic factors or developmental stages influence the transcription of genes](#)
263 [related to PC production \(Gutierrez et al., 2017\). Recent advances in high-throughput and](#)
264 [single-cell RNA sequencing have further refined our understanding of these regulatory](#)
265 [networks, revealing novel gene candidates and signaling pathways implicated in phenolic](#)
266 [metabolism \(Volná et al., 2024\). For example, integrative transcriptomic studies in fruits](#)
267 [have correlated dynamic gene expression profiles with the accumulation of specific](#)
268 [phenolic metabolites, linking transcriptional activity with phenol production \(K. Zhang et](#)
269 [al., 2023\). On the other hand, proteomics analyses can detect changes in proteins](#)
270 [abundance, and their use is particularly useful for understanding post-translational](#)
271 [modifications \(PTM\) and protein-protein interactions that affect the metabolic pathways](#)
272 [involved in production of PCs. In this regard, advanced proteomic techniques have](#)
273 [demonstrated that PTM in enzymes influence the modulation of phenolic compound](#)
274 [biosynthetic pathways under environmental stress conditions \(Lin et al., 2020\). These](#)
275 [approaches have also uncovered protein complexes that regulate phenolic metabolism](#)
276 [under various conditions. Finally, metabolomics enables the comprehensive detection](#)
277 [and quantification of PCs in plants allowing the mapping of the entire metabolic network,](#)
278 [the identification of novel PCs, and providing an overall picture that ultimately contributes](#)
279 [to the understanding of their biosynthetic pathways. Metabolomics also helps in studying](#)
280 [the impact of genetic modifications or environmental changes on PCs composition.](#)
281 [Recent metabolomic studies employing both targeted and untargeted approaches have](#)
282 [revealed subtle metabolic changes during plant development and under stress, providing](#)
283 [high-resolution profiles that complement transcriptomic and proteomic data \(D. Ma et al.,](#)
284 [2022\). Furthermore, advancements in high-resolution mass spectrometry have facilitated](#)
285 [the discovery of previously uncharacterized PCs \(Pérez-Ochoa et al., 2023\). The](#)
286 [integration of these omics' techniques with multi-omics approaches provides a holistic](#)
287 [view of the complex regulatory networks of PCs biosynthesis. For instance, the integration](#)
288 [of proteomics and metabolomics can link enzymes to the production of specific phenolic](#)

289 [metabolites. Moreover, combining transcriptomic, proteomic, and metabolomic datasets](#)
290 [through advanced bioinformatics tools has enabled the construction of comprehensive](#)
291 [models of phenolic biosynthetic pathways, pinpointing key regulatory nodes and potential](#)
292 [targets for metabolic engineering \(Xu et al., 2020; Yang et al., 2021\).](#)
293 ~~As previously mentioned, several omics tools are used in foodomics, including genomics,~~
294 ~~transcriptomics, proteomics, and metabolomics, providing molecular information on gene,~~
295 ~~transcript, protein, and metabolite expression levels, and integrating this information from~~
296 ~~a systems biology perspective.~~
297 [Following, a collection of studies focused on the investigation of PC biosynthesis using](#)
298 [foodomics approaches is presented.](#)

300 **2.1. Genomics and Transcriptomics**

301 ~~The 'omics revolution' has placed genomics studies as a key tool to elucidate the factors~~
302 ~~that can modulate the biosynthesis of PCs, complementing the information revealed by~~
303 ~~genetic approaches focused on individual genes.~~

304 ~~Moreover, m~~Modern transcriptomics [tools](#) can analyze the expression of multiple
305 transcripts related to PCs, not only in plants but also in animals and humans. This allows
306 us to evaluate the impact of consumption of phenolic-rich matrices, aiming to understand
307 the correlation between phenolics intake, transcriptome and healthy or unhealthy
308 phenotypes (Van Emon, 2016). For instance, Zhao *et al.* (Zhao et al., 2022) applied
309 transcriptomic analysis in different tea (*Camellia sinensis*) cultivars, identifying 212
310 unigenes encoding 13 key enzymes in catechins biosynthesis and concluding that a
311 higher expression of genes linked to enzymes such as LAR and a ANR was strongly
312 correlated to catechin content (Table 1).

313 Furthermore, there are many studies on berry phenolics, such as the work by Gutierrez
314 *et al.* (Gutierrez et al., 2017), where they investigated blackberry (*Rubus* spp.) fruits and
315 leaves using transcriptomic analysis at different timepoints and combined them with
316 targeted metabolomic analysis. The expression pattern of flavonoid-related genes
317 suggested that, besides the higher activation of the flavonoid biosynthesis pathway is
318 reached during the fruit ripening stage, there is a translocation step of flavonols indicating
319 a flux of these metabolites from leaves to red fruits (not fully mature). Then, flavonols are
320 accumulated and transformed to anthocyanins when the fruit is fully mature (black). Both
321 studies underscore the importance of transcriptomics in elucidating the pathways involved
322 in the biosynthesis of phenolics, especially flavonoids. While Zhao et al. highlighted the
323 role of transcriptomic analysis in identifying gene expression patterns related to catechin
324 biosynthesis in tea plants, Gutierrez et al. expanded this approach by combining
325 transcriptomics with metabolomics, revealing dynamic changes in flavonoid metabolism
326 during fruit development in blackberries. A common challenge in both studies involves
327 correlating transcriptomic data with functional outcomes across different species due to
328 the diversity in gene expression and metabolic flux influenced by environmental and

329 genetic factors.

330 Moreover, Zhou *et al.* (Y. Zhou et al., 2022) recently published a similar study on sorghum
331 (*Sorghum bicolor*) seeds targeting the flavonoid regulatory networks concluding that
332 specific chalcone synthase genes were crucially implicated in flavonoid biosynthesis by
333 using integrated analysis of transcriptomics and metabolomics. Flavanones
334 (homoeriodictyol, naringin, prunin, naringenin, hesperidin, pinocembrin) were directly
335 involved in color regulation.

336 In addition, Yue *et al.* (Yue et al., 2018) compared the gene expression of red-fleshed
337 grape berries with other varieties and observed an upregulation of several genes involved
338 in the PPP such as *MybA1*, *MybA113*. As a matter of fact, different metabolic pathways
339 involved in polyphenol synthesis and catabolism were altered, as well as genes related
340 to the biosynthesis and transport of PCs. Another work studying grape berries identified
341 light exposure as a key factor and reported a light-responsive expression of genes
342 encoding transcription factors (bHLH, MYB, MADS-box, WRKY, NAC) as well as proteins
343 related to genetic information processing and epigenetic regulation. All this showed a
344 strong correlation with phenolics production and accumulation. Once again, *MybA1*, *LAR*
345 and *ANR* transcriptional changes were also involved and significant differences were
346 noticed in the transcriptome of bagged and non-bagged grapes, i.e., subjected to different
347 light regimes (R. Z. Sun et al., 2019). Besides berries, *Prunus* spp. (such as cherries,
348 plums, apricots, or peaches) have been also investigated and the expression of the CHS
349 gene encoding chalcone synthase was identified as crucial element in the flavonoid
350 pathway, whereas the regulation of LDOX gene expression (encoding leucoanthocyanidin
351 dioxygenase) seemed to be a key point for anthocyanin synthesis during *Prunus* fruits
352 development (García-Gómez et al., 2020).

353 These powerful studies led to a wider knowledge in the genomic architecture of other
354 species such as white spruce (*Picea glauca*) and other conifers, confirming the complexity
355 of flavonoid regulatory networks in these plants (Laoué et al., 2021).

356 Since PCs are frequently synthesized in response to stress, some external actions such
357 as wounding could promote the activation of the PPP and specific genes linked to
358 phenolics production. This hypothesis was confirmed in wounded carrots, where
359 transcriptomic analyses confirmed that metabolism of wounded or shredded carrots was
360 affected by this mechanical stress and genes associated to respiratory, sugar and energy
361 metabolism were modulated to produce phenolic antioxidants (Han et al., 2017).
362 Wounding also promoted the accumulation of phenolics in pitaya fruit by activating the
363 expression of genes related with phenolic biosynthesis (phenylpropanoid and flavonoid
364 pathways) but also signaling molecules such as ethylene, reactive oxygen species and
365 jasmonic acid and promoting genes linked to primary metabolism pathways (glycolysis,
366 pentose phosphate, shikimate pathways) (X. Li et al., 2021).

367 [Insert Table 1: Main studies focused on phenolic compounds \(PC\) biosynthesis using](#)
368

369 [transcriptomic techniques\]](#)

371 2.2. Micromics

372 Transcriptomics provides information for understanding gene expression on the
373 metabolic pathways of PC biosynthesis. However, to completely understand the results
374 of transcriptomics it is necessary to also consider data obtained from other omics
375 techniques. In this framework, micromics approaches offer a complementary level of
376 analysis at determining the levels of microRNAs (miRNAs) that in turn can regulate gene
377 expression. Specifically, miRNAs are single-stranded non-coding RNAs (18-22
378 nucleotides) that play a crucial role in post-transcriptional gene regulation through the
379 silencing of messenger RNA (mRNA) and translational repression, among other
380 mechanisms (Broughton et al., 2016; Friedman et al., 2009; Ha & Kim, 2014; Quévillon
381 Huberdeau & Simard, 2019; Vasudevan, 2012). The study of miRNAs is particularly
382 relevant, as not only it is necessary the understanding of the genes involved in PC
383 synthesis, but also to know the mechanisms by which their expression can be regulated.
384 Therefore, transcriptomics data only provides a small part of the whole picture in PC
385 synthesis that can be complemented by micromics.

386 Recent studies have focused on unraveling the regulatory role of miRNAs in polyphenol
387 biosynthesis, but their understanding is still limited. In this line, several works using
388 micromics have reported the regulatory role of miRNAs in flavonoid biosynthesis by
389 targeting the mRNAs encoding key enzymes (Marcela et al., 2019) or transcription factors
390 of the PPP (Šamec et al., 2021) (Table 2). In this regard, Biswas *et al.* (Biswas et al.,
391 2016) reported miRNAs involved in the polyphenol's biosynthesis in *Podophyllum*
392 *hexandrum* (Himalayan May apple). MiR5532 upregulates the 2-hydroxyisoflavanone
393 dehydratase gene, increasing the isoflavanoid biosynthesis. miR1438 and miR1873
394 increase the expression of caffeoyl-CoA-O-methyltransferase and dihydroflavonol 4-
395 reductase C, respectively, both associated with flavonoid biosynthesis. Similarly,
396 miR828a and miR948a are also implicated in accelerating flavonoid biosynthesis in Clary
397 Sage (*S. sclarea*) plants through the regulation of the MYB12 lipxygenase enzyme
398 (Legrand et al., 2010). miR2919, miR1168.2, miR156b, and miR1858 have been reported
399 as miRNAs that promote the expression of the flavanone synthase gene and with it, the
400 synthesis of curcumin in *Curcuma long* (Singh & Sharma, 2017).

401 Regarding anthocyanins (Salehi et al., 2020), miR858 and miR156 are implicated in the
402 biosynthesis of proanthocyanidins (PAs). Concretely, miR858 has positive effects on
403 genes related to PAs production whereas negative effects have been associated with
404 miR156 (Luo et al., 2015). Singh *et al.* (Singh et al., 2016) studied the miRNAs involved
405 in the synthesis of PC in ginger following an *in silico* approach observed that miR5015
406 regulates the biosynthesis of gingerol by inhibiting PAL, the key enzyme of the PPP,
407 involved in gingerol biosynthesis. On the other hand, Wang *et al.* (S. Wang et al., 2020)
408 observed that the gene expression of PAL is inhibited by miR477 as a response to

409 pathogen infection (Legrand et al., 2010). Finally, it has been found that cytochromes
410 P450 involved in the PPP are also regulated by miRNAs. Concretely, these cytochromes
411 are regulated and targeted by miR413 in *Dimocarpus longan* (C. Zhang et al., 2022) and
412 targeted by miR5035, miR2275d, and lus-miR168b in *P. hexandrum* and *Linum*
413 *usitatissimum* (Barvkar et al., 2013; Biswas et al., 2016).

414 Regarding lignans and lignin, the lignans are synthesized by the shikimate pathway
415 through the action of PAL and pinoresinol-lariciresinol reductase (PRL) (Teponno et al.,
416 2016), whereas the biosynthesis of lignin involved two branches PRL and the monolignol
417 pathway (Park et al., 2017). Laccases are involved in the polymerization of monolignols,
418 being reported in their post-transcriptional regulation by miRNAs. In particular, soybean
419 laccases are potential targets of miR397a/b, miR408d, and miR5671a, whereas maize
420 laccase genes were potentially targeted by miR397a/b or miR528a/b. The expression of
421 both laccases genes has been related to the response to abiotic and biotic stress factors
422 (Liu et al., 2020). In addition, lus-miR397 and ptr-miR397a have shown an effect on the
423 expression of laccase genes of *L. usitatissimum* (C. Li et al., 2019) and *Arabidopsis*
424 *thaliana* (C. Y. Wang et al., 2014). With respect to lignans biosynthesis, the study of the
425 role of miRNAs in their biosynthesis is still in its initial stages. Lignans biosynthesis is
426 regulated positively by APETALA2 (AP2) (R. Ma et al., 2017), being AP2-domain-
427 containing transcription factors targets for lus-miR172e (Xie et al., 2021). Finally, it is
428 important to indicate that lignans and lignins share common enzymes and substrates in
429 their biosynthesis (Gupta et al., 2017), so some of the knowledge about the role of miRNA
430 in the lignins regulation might be implemented to understand the function of miRNAs in
431 the lignans biosynthesis.

432
433 [\[Insert Table 2: Main studies focused on phenolic compounds \(PC\) biosynthesis using](#)
434 [micromic techniques\]](#)

435
436

437 **2.3. Proteomics**

438 Proteomics is a powerful tool employed mainly for identifying biomarkers, especially those
439 related to human diseases. In this line, and due to the beneficial effects of polyphenols
440 on human health, most of the proteomic studies carried out with polyphenols have
441 focused on observing the effect of polyphenols on the human proteome, especially on
442 their health. Proteomics analyses are also widely used in plants and have contributed to
443 obtaining a more global and integrated vision of all the proteins involved in polyphenol
444 biosynthesis, through the detection and discovery of proteins involved in these metabolic
445 pathways. However, it is important to mention that unlike a genome, a proteome is
446 dynamic and in constant flux, making its knowledge more complicated and useful.
447 Therefore, the selection of the plant and more specifically the tissue to be evaluated is
448 crucial in a proteomic study, since in order to find and discover new proteins/enzymes

449 involved in the metabolism of polyphenols, the target pathway must be overrepresented
450 in the selected area.

451 The quantitative proteomics analysis of recombinant inbred lines of peanuts with different
452 concentrations of polyphenols (high and low) revealed that the overexpression of the PPP
453 resulted in increased polyphenols biosynthesis (Muralidharan et al., 2021). A comparative
454 proteomic study in germinated and Thai brown rice revealed differences in the expression
455 patterns of proteins after germination (Maksup et al., 2018). Among the Thai rice varieties
456 studied, the red rice Mali Daeng showed 2.6 and 2.2-fold higher of PCs content and
457 anthocyanin content, respectively, compared to the white rice Khao Dawk Mali.
458 Furthermore, germinated Mali Daeng contained higher anthocyanin content, consistent
459 with increased expression of several PCs biosynthesis-related proteins ([Table 3](#)).

460
461
462 In a further study by Wu *et al.* (Wu et al., 2018), dynamic changes in proteomes of
463 postharvest tea leaves during withering stages were investigated. A total of 863 unique
464 differentially expressed proteins (DEPs) were identified by isobaric tags for relative and
465 absolute quantitation, showing dynamic changes in tea plant characteristics. The findings
466 revealed that the biosynthesis of tea polyphenols is restricted during withering. In this
467 context, tea leaves fermented by *Aspergillus niger*, *Aspergillus tamarii* and *Aspergillus*
468 *fumigatus* have been analyzed by proteomic methods. Here, changes to the flavonoids
469 were detected. Also, glycoside hydrolase, glycosyltransferases, tannases, laccases,
470 vanillyl-alcohol oxidases and benzoquinone reductase were identified and hypothesized
471 to be involved in hydrolysis, oxidation, polymerization, and degradation of PCs (Y. Ma et
472 al., 2021). In a subsequent study, Zhou *et al.* (D. Zhou et al., 2020) researched the
473 metabolism of PCs in ultraviolet C treated peaches during storage, showing that most
474 DEPs were largely matched to carbohydrates and PCs. In addition, proteomic analysis
475 revealed that UV-C irradiation modulates the phenolic synthesis by up-regulating
476 expressions of PAL, 4CL, CHS, DFR and UDP-glucose: flavonoid glucosyltransferase.

477
478 [\[Insert Table 3: Main studies focused on phenolic compounds \(PC\) biosynthesis using](#)
479 [proteomic techniques\]](#)

480

481

482 **2.4. Metabolomics**

483 Metabolomics approaches allow us to identify and determine metabolites in multiple
484 biological samples, including foods (Klassen et al., 2017). This offers a comprehensive
485 snapshot of metabolic activity, revealing key biochemical pathways and their regulation
486 in response to various factors (Wishart, 2019). Two distinct metabolomics approaches
487 can be applied: untargeted and targeted. Untargeted metabolomics analyzes all the
488 measurable compounds in a sample, including unknown metabolites. On the other hand,

489 targeted metabolomics is the analysis of defined groups of chemically characterized and
490 biochemically annotated metabolites (Klassen et al., 2017). Analytical methods in
491 metabolomics rely on mass spectrometry (MS) and nuclear magnetic resonance (NMR)
492 to analyze small molecules (López-Yerena et al., 2021). In this sense, in general MS are
493 coupled to chromatographic techniques including liquid chromatography (LC), gas
494 chromatography (GC), or capillary electrophoresis (CE), in order to separate compounds
495 (W. Li et al., 2019; Moco et al., 2007; Nagana Gowda & Djukovic, 2014). The application
496 of metabolomics potentially adds significant value to crop and food science and meets
497 future food demands (Shepherd et al., 2011). Furthermore, these analytical technologies
498 have a significant impact on the quality and shelf life of food, raw materials, and
499 postharvest processing as well (García-Cañas et al., 2012). These high-throughput
500 analytic technologies permit measuring hundreds or even thousands of compounds at a
501 time. Each of these techniques has its own advantages and disadvantages, but LC-MS
502 may represent the preferred one when studying the PCs due to its sensitivity and breadth
503 of coverage. Furthermore, integrating metabolomics with other omics approaches
504 enhances our understanding of metabolic changes induced by dietary compounds, such
505 as polyphenols, and their subsequent biological impacts Arapitsas et al., 2012). In the last
506 few years, metabolomic-based technologies have become extremely popular in
507 characterization of PCs (Piovesana et al., 2020) (Table 4). In one such study by Barros
508 Santos *et al.* (Barros Santos et al., 2019), metabolomic techniques such as ultra-high-
509 pressure liquid chromatography (UPLC) coupled to quadrupole-time of flight (QTOF) MS
510 were used to characterize phenolic profile of 7 genotypes of immature and mature wheat,
511 identifying 237 phenolics including isomers as free and bound forms, and revealing that
512 phenolic profiles were different among genotypes and during the grain development. In
513 fact, PCs progressively decreased along grain development from milky to mature.
514 However, specifically the proportion bound to free phenolic gradually increased, reaching
515 the maximum at physiological maturity. In a targeted metabolomic study, the
516 comprehensive profiling of PCs in sour guava fruit was analyzed by HPLC-electrospray
517 ionization (ESI)-triple quadrupole (QqQ) in multiple reaction monitoring (MRM) mode
518 (Cuadrado-Silva et al., 2016).

519 This fruit contained a total of 22 PCs in the form of hydroxybenzoic, phenylacetic, and
520 hydroxycinnamic acid derivatives, reporting for the first time that sour guava contains (+)-
521 catechin, (-)-epicatechin, and procyanidin B₁ and B₂. In a further study, Lyu *et al.* (Lyu et
522 al., 2022) characterized the PCs profiles in mung bean sprouts under sucrose treatment
523 by targeted metabolomics analysis a total of 106 PCs were detected, 21 of which had a
524 positive correlation with antioxidant capacity. In a recent study by Zhang *et al.* (M. Q.
525 Zhang et al., 2023), a metabolomic approach was used to evaluate the phenolic
526 composition in berry juice and pomace. A total of 568 PCs were identified in berry pomace
527 samples by UPLC-MS/MS, including 238 flavonoids and 131 phenolic acids, suggesting
528 that this fruit can be a valuable source of PCs of which the major components are

529 anthocyanins and phenolic acids.

530 Metabolomic-based approaches offer a powerful analytical platform for obtaining more
531 detailed and comprehensive information about food composition than traditional food
532 component analysis, including phenolic biosynthesis. These techniques have proven
533 essential for identifying biomarkers of dietary intake, which are crucial for assessing the
534 bioavailability and physiological effects of food-derived bioactive compounds (Johnson et
535 al., 2016). Indeed, metabolomics is a potent tool for clarifying the differences of plants
536 cultivated under different geographical origins, shading treatments, and processed using
537 different techniques. In this sense, field-based metabolomics provides new insights for
538 genotype discrimination and phenolic metabolism structuring (Shepherd et al., 2011). In
539 this context, experiments to identify genetic regions responsible for phenolic acid
540 synthesis have been carried out. A metabolomics-based approach coupled with genome-
541 wide association studies identified agmatine coumaroyl transferase as the enzyme
542 responsible for phenolic amide formation in barley and its activity was strongly influenced
543 by environmental cues like day length and temperature (Wiegmann et al., 2019). In a
544 subsequent study, Cruz-Carrión *et al.* (Cruz-Carrión et al., 2022) used UPLC-MSⁿ
545 analyses to obtain a detailed phenolic profile of tomatoes from two locations in Spain,
546 detecting 57 PCs and showing different phenolic composition between tomatoes due to
547 the geographical origins of cultivation. In this framework, quantification of PC by HPLC
548 coupled to a diode array detector (DAD) confirmed that the concentrations of phenolic
549 acids, including chlorogenic, caffeic, ferulic, and *p*-coumaric acids, were higher in Spanish
550 traditional tomatoes grown in open fields compared to those cultivated in greenhouses
551 (Asensio et al., 2019). In this line, the study of Vaičiulyte and Ložiene (Vaičiulyte &
552 Ložiene, 2015), who monitored effects of meteorological factors on phenolics of *Thymus*
553 *pulegioides* L. cultured in the same locality using GC-MS, demonstrated that the
554 meteorological factors differently influence the accumulation of carvacrol. This phenolic
555 showed the most stable quantitative composition of essential oil due to significant effects
556 of both temperature and photosynthetically active solar radiation. In a subsequent 96 PCs
557 were quantified by UHPLC-QqQ-MS on the skins of mature grape berries from a core-
558 collection of 279 *Vitis vinifera* cultivars grown with or without watering. Metabolomics
559 analysis demonstrated an influence of water stress on the biosynthesis of different PCs
560 and cultivar differences in metabolic response to drought (Pinasseau et al., 2017).

561 As above mentioned, metabolomics-based approaches provide evidence on plants
562 phenolic profile changes during processing methods. For example, in the study of Zhou
563 *et al.* (J. Zhou et al., 2019), chemical changes of large-leaf yellow tea during processing
564 were analyzed by LC-MS. Untargeted and targeted metabolomics analyses revealed that
565 epicatechin and free amino acids significantly decreased in tea samples after roasting,
566 while epimerized catechin intensely increased. Similarly, the analysis of PCs profile
567 changes with different drying processing methods were evaluated in daylily using UPLC
568 with multistage fragmentation techniques, showing that quercetin 3-O-rutinoside and 5-

569 O-caffeoylquinic acids were higher in freeze-dried and steam-dried samples (J. Sun et
 570 al., 2018).

571
 572 [Insert Table 4: Main studies focused on phenolic compounds (PC) biosynthesis using
 573 metabolomic techniques]

574
 575
 576 Table 1. Main studies focused on phenolic compounds (PC) biosynthesis using foodomics
 577 approaches.

		Aim of the study	Foodomics techniques	Results/Key findings	Reference
ant (<i>Camelia sinensis</i>)		Catechins biosynthesis pathways	<u>Transcriptomics</u>	Expression of genes of the enzymes LAR and ANR positively correlated with catechin content. t212 unigenes encoding 13 key enzymes in catechins biosynthesis	[32]
of sSweet sorghum		Flavonoid biosynthesis pathways in different seeds	<u>Transcriptomics</u> <u>Metabolomics</u>	8 genes involved in flavonoid biosynthesis, playing a central role in color change. Chalcone synthase genes were crucial for flavonoid biosynthesis	[34]
erry (<i>Rubus sp. var. Loch Ness</i>)		Study/Comparison of flavonoid regulatory networks PC synthesis in leaves and fruits	<u>Transcriptomics</u> <u>Metabolomics</u>	Total PC in leaves were three-fold higher than in fruit; flavonols were six-fold higher, and anthocyanins was higher in fruits	[33]
apes		Comparison of gene expression profile, PC, and antioxidant capacity of different red grapes	<u>Transcriptomics</u>	10 metabolic pathways related to PC synthesis differed compared to Cabernet Sauvignon	[16]
et Sauvignon grapes		Influence of cluster bagging on ripening, PC accumulation, and biosynthetic pathway	<u>Transcriptomics</u>	Cluster bagging influences the synthesis of flavan-3-ol and flavonol at different	[35]

				developmental stages	
				Anthocyanin derivatives and flavonol glycosides were identified as markers for bagged and non-bagged grapes	
s-species	Peaches	Identification of molecular bases of PC synthesis during ripening	Integrated metabolomics, genomics, transcriptomics, and epigenetics	CHS and LDOX gene were crucial for flavonoid and anthocyanin synthesis, respectively	[36]
	Nectarines				
	Prunes				
	Japanese plums				
	Apricots				
	Sour cherry fruits				
		Evaluate the impact of wounding on primary and secondary metabolism	Transcriptomics	Differentially expressed genes involved in the conversion of sugars to phenolics were extensively up regulated after wounding	[38]
fruit (<i>Hylocereus undatus</i>)	Evaluate the molecular mechanisms underlying the wound-PC synthesis	Transcriptomics	1 HuMYB, 3 HuBHLHs, 7 HuAP2-EREBPs putative transcription factors participating in the regulation of wound-induced PC biosynthesis	[39]	
ma (<i>Curcuma longa</i>)	Identification of miRNAs involved in PC synthesis	Micromics	miR2910, miR1168, miR156b and miR1858, promote the expression of flavanone synthase gene and the synthesis of curcumin	[49]	

ant (<i>Camelia sinensis</i>)	Study the expression patterns of miR477 and PAL, its target gene, after pathogen treatment	<u>Micromics</u>	A negative correlation between the expression of miR477 and PAL was found in when plants are infected by <i>Pseudopestalotiopsis</i>	[52]
r (<i>Zingiber officinale</i>)	miRNA and their targets in ginger by bioinformatics approach	<u>Micromics</u>	PAL have seen to be involved in the conversion of L-phenylalanine to ammonia <i>Trans</i> -cinnamic acid is a target of miR1873	[53]
se-indigolsatis-indigotica	Study the role of gene <i>li049</i> in regulation of lignan biosynthesis	<u>Micromics</u>	Ligan and lignin biosynthesis pathway is modulated positively by the APETAL2/ethylene response factor (AP2/ERF) family, and by the gene <i>li049</i>	[61]
hai cultivars)	Comparative analysis of proteome-derived bioactive compounds	<u>Proteomics</u>	Mali Daong rice showed higher concentration of PC and anthocyanins.	[65]
ant (<i>Camellia sinensis</i>)	Evaluation of dynamic changes in the proteome of postharvest tea leaves in four withering treatments	<u>Proteomics</u>	863 differentially expressed proteins were identified	[66]
ant (<i>Camellia sinensis</i>)	Study of the impact of fermentation of tea leaves under different microorganisms on PC	<u>Proteomics</u>	Identification of different enzymes involved in hydrolysis, oxidation, polymerization, and degradation of PC. Changes in flavonoids depending on the	[67]

				microorganism were detected	
			<u>Metabolomics</u>	Changes in flavonoids depending on the microorganism were detected. Identification of different enzymes involved in hydrolysis, oxidation, polymerization, and degradation of PC.	
fruit (<i>Prunus persica</i>)		Study of the metabolism of PC in ultraviolet C treated fruits during storage	<u>Transcriptomics</u> <u>Proteomics</u>	Ultraviolet C irradiation modulate the phenolic synthesis by up-regulating expressions of PAL, 4CL, CHS, DFR, and UDP-glucose flavonoid glucosyltransferase	[68]
Guava fruit (<i>Psidium friedrichsthalianum</i>)		Study the polyphenols profile with antioxidant activity in sour guava	<u>Targeted metabolomics</u>	22 PC were found in this fruit, including hydroxybenzoic, phenylacetic, and hydroxycinnamic acid derivatives, (+)-catechin, (-)-epicatechin, and procyanidin B1 and B2	[80]
	Red raspberry (<i>Rubus idaeus</i>) Blackberry (<i>Rubus ulmifolius</i>)	Compare the PC profile and their antioxidant capacity in berries juices and by-products	<u>Metabolomics</u>	568 different compounds were identified, including 238	[82]

	Blueberry (<i>Vaccinium</i> spp.) Mulberry (<i>Morus australis</i>) Black chokeberry (<i>Aronia melanocarpa</i>)	(pomace)		flavonoids and 134 phenolic acids	
barley (<i>Hordeum vulgare</i> ssp. <i>monneum</i>)		Study the PC formation and the influence of environmental conditions	<u>Metabolomics</u>	Agmatine coumaroyl transferase was seen as the enzyme responsible for phenolic amide formation, and its activity is influenced by environmental circumstances	[84]
oes fruits (<i>Solanum lycopersicum</i> cv. <i>is</i>)		Study the differences in PC content depending on the location	<u>Metabolomics</u>	57 polyphenol compounds, and differences between the phenolic profile were found in tomatoes from two different locations	[85]
oes		Study the differences in PC in tomatoes depending on the conditions they are growing	<u>Metabolomics</u>	Concentrations of phenolic acids, including chlorogenic, caffeic, ferulic and p-coumaric are higher in traditional tomatoes cultivated in and open field	[86]
(<i>Vitis vinifera</i>)		Study the influence of water stress on the biosynthesis of different PC in skins	<u>Metabolomics</u>	96 PC were identified, constituting different phenolic profiles, and demonstrating the influence of water stress in the biosynthesis of PC	[88]

tea		Study the PC changes of large leaf yellow tea during processing	<u>Metabolomics</u>	The concentration of (-)-epicatechin decreased after roasting, while (+)-epicatechin increased.	[89]
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578 4CL, 4-coumaroyl-CoA ligase; AP2/ERF, APETAL2/ethylene response factor; CHS,
579 chalcone synthase; DFR, dihydroflavonol 4-reductase; LDOX, leucoanthocyanidin
580 dioxygenase; miRNA, microRNA; PAL, phenylalanine ammonia-lyase; UDP, uridine
581 diphosphate.

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584

585 **3. ~~4.4~~ Current limitations and challenges**

586 Several omics techniques such as genomics, transcriptomics, proteomics, and targeted
587 and untargeted metabolomics analyses are used in foodomics to provide molecular
588 information on gene, transcript, protein, and metabolite levels involved in the biosynthesis
589 pathway of PCs. By use of this technique there is considerable information regarding the
590 biosynthesis pathway of PCs and the enzymes involved in. In addition, relevant data on
591 how the synthesis of metabolites is affected by external and internal data have been
592 obtained. However, there are a high number of limitations in the use of Foodomics to
593 evaluate the PCs synthesis and content in plants. The most important ones are the
594 following: i) High diversity of structures. †The world of PCs is wide and thousands of
595 different chemical structures are already characterized with different mixtures of these
596 compounds present in plants. In addition, PCs can have a different degree of
597 glycosylation and polymerization, resulting in multiple isomeric forms (Zagoskina et al.,
598 2023). Actually, each variety of the same plant can have different composition of PCs. For
599 example, Man et al (Man et al., 2022) have analysed the PC composition of pomegranate
600 peel from different cultivars showing that each cultivar has a different PC profile.
601 Multivariant analysis performed by PCA showed a clear separation of the samples
602 depending of the type of cultivar (65.7 % of variability reached by the two components).
603 Regarding proteomics analysis, it is important to consider the impact of post-translational
604 modifications (PTM), which play a crucial role in biological processes. In eukaryotic
605 organisms, most proteins undergo PTMs (i.e., phosphorylation, sulfation, oxidation,
606 ubiquitination, acetylation, methylation, lipidation, or glycosylation). These modifications,
607 along with alternative RNA splicing, greatly enhance the complexity of the proteome
608 relative to the transcriptome. Similar to the transcriptome, the proteome is highly dynamic
609 and varies based on tissue type, microenvironment, and life cycle stage. External and
610 internal signals, including growth factors, hormones, metabolites, and cell-to-cell
611 interactions, can regulate gene expression, leading to a broad spectrum of mRNA and
612 protein levels—ranging from complete silence to millions of copies and protein molecules
613 per cell. As a result, proteomes and their modifications undergo significant changes during
614 processes such as cell differentiation, activation, trafficking, and malignant
615 transformation, thus increasing the diversity of structures and the complexity of the
616 analysis. ii) Impact of agronomic factors. A wide variety of agronomic factors such as
617 temperature, sun exposure and irrigation can impact the PCs synthesis. In fact, Thus, the
618 studies carried out in one plant cannot be extrapolated to others, not only within different
619 varieties of the same plant but with the the same variety of plant subjected to different
620 external conditions (temperature, sun exposure, irrigation, among others) can show
621 different PCs composition. This variability has been demonstrated in numerous studies.
622 For example, research on *Lavandula viridis* and *Thymus lotocephalus* exposed to

623 different temperatures showed that phenolic compounds and antioxidant activity
624 increased with rising temperatures in micropropagated plants (Mansinhos et al., 2022).
625 Similarly, studies on tomatoes have shown that controlled water deficit can increase the
626 concentration of anthocyanins and other phenolic compounds (Jin et al., 2022). Another
627 example of this variability is found in lettuce, where a reduction in nitrogen supply prior to
628 harvest significantly altered the composition of phenolic compounds, enhancing the
629 cellular antioxidant potential without affecting plant biomass (W. Zhou et al., 2018).
630 Likewise, an analysis of the roots of *Eryngium montanum* under different annual growth
631 conditions demonstrated that environmental factors significantly impact the accumulation
632 of phenolic compounds and their antioxidant activity (Pérez-Ochoa et al., 2023). In
633 another study, Li et al. (X. Li et al., 2015) observed that temperature, latitude and longitude
634 have a clear impact on PC profile in pomegranate juices of different cultivars cultivated in
635 different regions.

636 Therefore, a ~~greater~~ high number of studies is needed to have a clear understanding of
637 the biosynthesis pathway of PCs and how this is affected by internal and external factors
638 of the plants.

639 ~~However,~~ iii) High dimensionality of the data. ~~Another significant~~ important limitation in
640 omics-based studies is the high dimensionality of the data, which poses challenges in
641 interpretation and study. This complexity is further intensified by the high degree of
642 correlation among measured variables, including metabolites and proteins. This leads to
643 overfitting in models and difficulties in validating results in independent datasets. To
644 address these challenges, multi-omics integration approaches, such as combining
645 transcriptomic and metabolomic analyses, have been successfully applied to identify
646 candidate genes involved in phenolic biosynthesis. For example, a study in *Cyclocarya*
647 *paliurus* used a combined metabolomic and transcriptomic approach to elucidate key
648 pathways regulating the synthesis of phenolic acids, demonstrate the potential of
649 integrating different omics sciences to improve the interpretation of the data (Lin et al.,
650 2020).

651 iv) Standardization. There is a general lack of standardization in the different omics
652 techniques that can have an impact in the observed results. In this regard, in metabolomic
653 studies, the wide variety of PCs, degrees and glycosylation and polymerization results in
654 a need of standard compounds to precisely quantify all PCs composition. Hence, still
655 nowadays there is a lack for commercial standards of these compounds and researchers
656 tend to tentatively quantify the compounds referred to a selected group of commercial
657 standards (Iglesias-Carres et al., 2019), or express the results as relative abundance
658 (García-Villalba et al., 2015). ~~Moreover,~~ Otherwise, the lack of standardization in
659 experimental procedures further complicates the comparison of studies across different
660 plants and experimental conditions (Saccenti et al., 2011, 2018). Developing standardized
661 protocols for omics studies will be crucial to improving reproducibility and comparability
662 across different research. In this regard, studies like those on *Lactuca sativa*, which

663 [employed a genotype-dependent metabolomic approach to assess functional profile](#)
664 [changes under varying nutrient conditions, highlight the importance of standardized](#)
665 [methodologies to achieve robust and transferable findings](#) (W. Zhou et al., 2019).
666

667 4. ~~55~~-Insights in phenolic compounds studies

668 PCs are secondary metabolites produced by plants under stress conditions and with
669 several health effects described. Thus, the knowledge of the composition of these
670 metabolites in foods and the way they are synthesized is relevant to nutrition and
671 medicine. The use of omics techniques in foodomics has given a boost to the
672 understanding of the genes, proteins, metabolites and even microRNAs involved in their
673 synthesis. In addition, some insights regarding the influence of external and internal
674 factors have been described. Interestingly, new omics techniques are emerging such as
675 epimomics (i.e., epigenomics, epitranscriptomis and epiproteomics) and interactomics (i.e.,
676 complexes between DNA, RNA, proteins and metabolites), as well as statistics and data
677 analyses are continuously progressing such as system biology (Dai & Shen, 2022). In
678 addition, another significant challenge is the vast diversity of PC chemical structures and
679 their variability across different plant species, varieties, and environmental conditions.
680 These challenges the investigations in PCs biosynthesis to increase their understanding.
681

682 [Machine learning has emerged as a powerful tool in the study of polyphenol biosynthesis,](#)
683 [offering insights into the complex biochemical pathways and regulatory mechanisms](#)
684 [involved. Therefore, advances in artificial intelligence are now being leveraged to process](#)
685 [large omics datasets. Specifically, these tools are being used to predict biosynthesis](#)
686 [pathways](#) (García-Pérez et al., 2021). [In the study of García-Pérez, they combined](#)
687 [previous data from untargeted metabolomics with machine learning to obtain the](#)
688 [phytochemical characterization of unexplored species from *Bryophyllum* subgenus](#)
689 [\(García-Pérez et al., 2021\). In another study, in strawberry cultivar classification studies,](#)
690 [support vector machines and extreme learning algorithms were used to study phenolic](#)
691 [profiles with high accuracy](#) (Bao et al., 2018). [On the other hand, machine learning has](#)
692 [been used integrated with multi-omics data from *Arabidopsis* to predict genes encoding](#)
693 [enzymes involved in biosynthesis of plant PCs](#) (Bai et al., 2024). [Therefore, it is clear that](#)
694 [matching learning and artificial intelligence will play a key role in PCs biosynthesis](#)
695 [studies.](#)
696
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698
699

700 **Abbreviations**

701 4CL, 4-coumaroyl-CoA ligase
702 ANR, anthocyanidin reductase.
703 ANS, anthocyanidin synthase
704 AP2, APETALA2
705 C4H, cinnamic acid hydroxylase
706 CE, capillary electrophoresis
707 CHI, chalcone isomerase
708 CHS, chalcone synthase
709 DAD, diode array detector
710 ~~DAHPS, 3-deoxy-D-arabinoheptulose 7-phosphate synthase~~
711 DEPs, differentially expressed proteins
712 DFR, dihydroflavonol 4-reductase
713 DPPH, 2,2-difenil-1-picrilhidrazil
714 ESI, electrospray ionization
715 FH3, flavanone 3-hydroxylase
716 ~~FLS, flavonol synthase~~
717 FNS, flavone synthase
718 GC, gas chromatography
719 HPLC, high pressure liquid chromatography
720 IFS, isoflavone synthase
721 LAR, leucoanthocyanidin reductase
722 LC, liquid chromatography
723 LC-IM-Q-TOF-MS, liquid chromatography/ion mobility quadrupole time-of-flight mass
724 spectrometry
725 LDOX, leucoanthocyanidin dioxygenase
726 miRNA, microRNA
727 mRNA, messenger RNA
728 MRM, multiple reaction monitoring
729 MS, mass spectrometry
730 MSⁿ, multistage mass spectrum
731 NMR, nuclear magnetic resonance
732 ORAC, oxygen radical absorbance capacity
733 PAL, phenylalanine ammonia-lyase
734 PAs, proanthocyanidins
735 PCA, principal component analysis
736 PCs, phenolic compounds
737 ~~PP, polyphenols~~
738 PPP, phenylpropanoid pathway
739 PRL, pinoresinol-lariciresinol reductase

740 [PTM, post-translational modifications](#)

741 QqQ, triple quadrupole

742 QTOF, quadrupole-time of flight

743 ROS, reactive oxygen species

744 SVM, support vector machines

745 UDP, uridine diphosphate

746 UPLC, ultra-high-pressure liquid chromatography

747 UHPLC-ESI-QqQ, ultra-high-pressure liquid chromatography electrospray ionization

748 triple quadrupole

749 [UV-C](#), ultraviolet [C](#)

750 ~~VvbHLH, Vitis vinifera basic Hoop-Loop Hoop~~

751

752 **Author contributions**

753 SG-R, AC-C, DM, AG-R, MS, and AA-A prepared the original draft. SG-R, AC-C, MS, and

754 AA-A reviewed and edited the manuscript. “All authors contributed to manuscript revision,

755 read and approved the submitted version”.

756

757 **Conflicts of interest**

758 The authors declare that they have no conflicts of interest.

759

760 **Ethical approval**

761 Not applicable.

762

763 **Consent to participate**

764 Not applicable.

765

766 **Consent to publication**

767 Not applicable.

768

769 **Availability of data and materials**

770 Not applicable.

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777

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Tables

Table 1. Main studies focused on phenolic compounds (PC) biosynthesis using transcriptomic techniques.

<u>Sample</u>	<u>Aim of the study</u>	<u>Key findings</u>	<u>Reference</u>
<u>Tea plant</u>	<u>Catechins biosynthesis pathways</u>	<u>Expression of genes of the enzymes LAR and ANR positively correlated with catechin content</u>	<u>(Zhao et al., 2022)</u>
<u>Blackberry</u>	<u>Study of flavonoid synthesis during ripening</u>	<u>Flavonols translocate from leaves to fruits and then transforms into anthocyanins with ripening.</u>	<u>(Gutierrez et al., 2017)</u>
<u>Sweet sorghum</u>	<u>Flavonoid biosynthesis pathways</u>	<u>Chalcone synthase genes were crucial for flavonoid biosynthesis</u>	<u>(Y. Zhou et al., 2022)</u>
<u>Red grapes</u>	<u>Comparison of gene expression profile, PC, and antioxidant capacity of different red grapes</u>	<u>An upregulation of genes in the PPP is observed in Cabernet Sauvignon.</u>	<u>(Yue et al., 2018)</u>
<u>Cabernet Sauvignon grapes</u>	<u>Influence of agronomic procedures (cluster bagging) on ripening and PC accumulation</u>	<u>Transcriptomic changes were observed based on bagging conditions, mainly influenced by light.</u>	<u>(R. Z. Sun et al., 2019)</u>
<u>Prunus species</u>	<u>Identification of molecular bases of PC synthesis during ripening</u>	<u>CHS and LDOX gene were crucial for flavonoid and anthocyanin synthesis, respectively</u>	<u>(García-Gómez et al., 2020)</u>
<u>Carrots</u>	<u>Evaluate the impact of wounding on primary and secondary metabolism</u>	<u>Genes related to respiratory, sugar and energy metabolism were modulated to produce PC in wounding carrots</u>	<u>(Han et al., 2017)</u>

<u>Pitaya fruit</u>	<u>Evaluate the molecular mechanisms underlying the wound PC synthesis</u>	<u>Genes related to PC biosynthesis (PP and flavonoid pathways) were activated by wounding</u>	<u>(X. Li et al., 2021)</u>
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1221 Abbreviations: ANR, anthocyanidin reductase; CHS, chalcone synthase; LAR,
1222 leucoanthocyanidin reductase; LDOX, leucoanthocyanidin dioxygenase; PPP,
1223 phenylpropanoid pathway.
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1226 **Table 2. Main studies focused on phenolic compounds (PC) biosynthesis using**1227 **micromic techniques**

<u>Sample</u>	<u>Aim of the study</u>	<u>Key findings</u>	<u>Reference</u>
<u>Curcuma</u>	<u>Identification of miRNAs involved in PC synthesis</u>	<u>miR2919, miR1168, miR156b and miR1858 promote the expression of flavanone synthase gene and the synthesis of curcumin</u>	<u>(Singh & Sharma, 2017)</u>
<u>Tea plant</u>	<u>Study of the miRNAs involved in PAL regulation after pathogen infection</u>	<u>The gene expression of PAL is inhibited by miR477</u>	<u>(S. Wang et al., 2020)</u>
<u>Ginger</u>	<u>miRNAs involved in ginger metabolites biosynthesis</u>	<u>miR5015 was observed to regulate the biosynthesis of gingerol by PAL</u>	<u>(Singh et al., 2016)</u>

1228 Abbreviations: miRNA, microRNA; PAL, phenylalanine ammonia-lyase

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1230 **Table 3. Main studies focused on phenolic compounds (PC) biosynthesis using**
 1231 **proteomic techniques**

<u>Sample</u>	<u>Aim of the study</u>	<u>Key findings</u>	<u>Reference</u>
Rice	Compare the proteome related to PC in germinated and Thai brown rice	Germinated rice contained higher anthocyanin content, consistent with increased expression of several PCs biosynthesis-related proteins	(Maksup et al., 2018)
Tea plant	Evaluation of dynamic changes in the proteome of postharvest tea leaves during withering	The biosynthesis of tea PC is restricted during withering	(Wu et al., 2018)
Tea plant	Study of the impact of fermentation by different microorganisms on the proteome and metabolome	Glycoside hydrolase, glycosyltransferases, tannases, laccases, vanillyl-alcohol oxidases and benzoquinone reductase were correlated to be involved in hydrolysis, oxidation, polymerization, and degradation of PCs	(Y. Ma et al., 2021)
Peach	Study the impact of UV-C irradiation on PC biosynthesis	UV-C irradiation modulates the PC synthesis by up-regulating expressions of PAL, 4CL, CHS, DFR and UDP-glucose: flavonoid glucosyltransferase	(D. Zhou et al., 2020)

1232 Abbreviations: 4CL, 4-coumaroyl-CoA ligase; CHS, chalcone synthase; DFR,
 1233 dyhydroflavonol 4-reductase; PAL, phenylalanine ammonia-lyase; UDP, uridine
 1234 diphosphate.

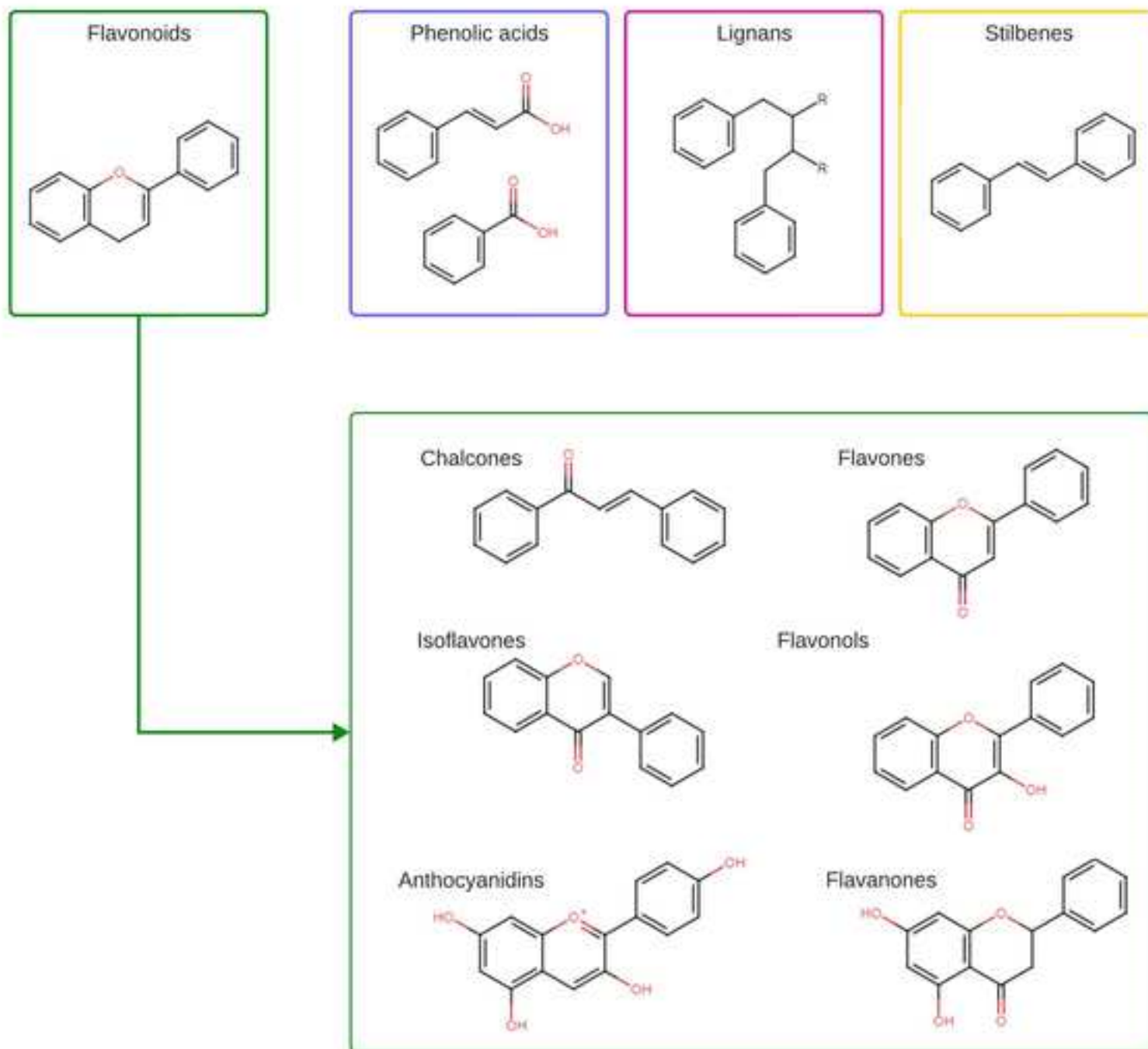
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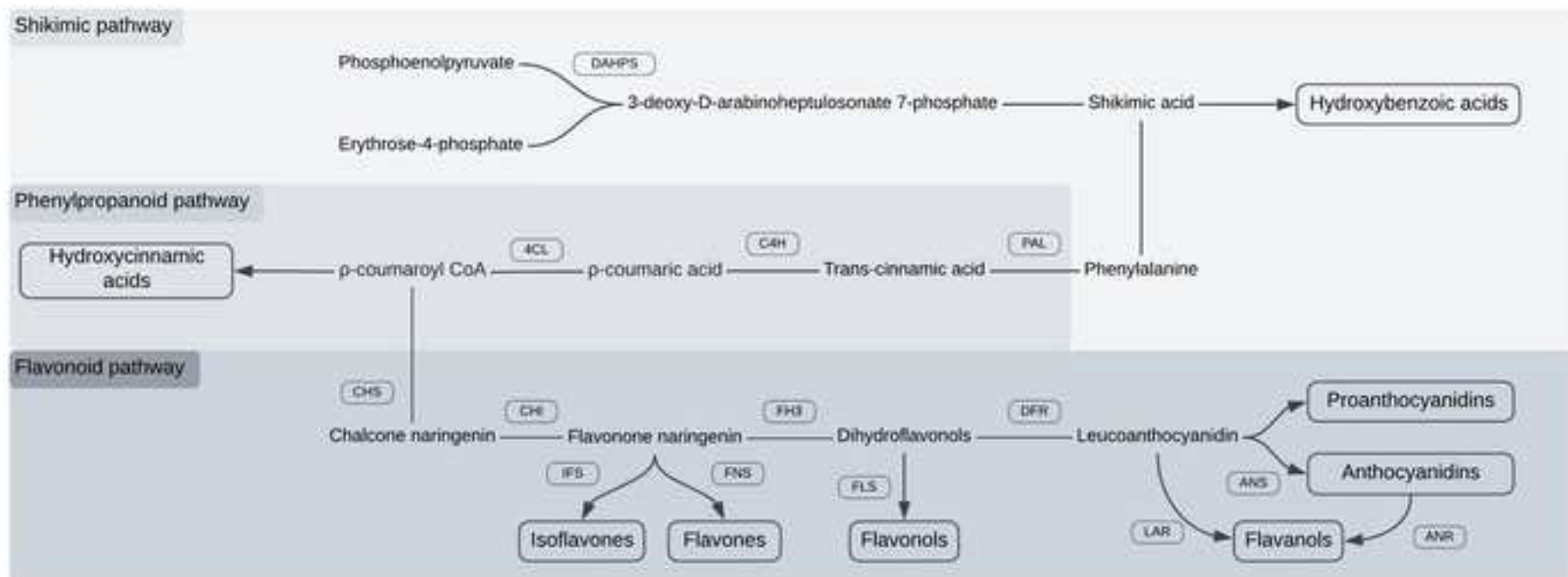
Table 4. Main studies focused on phenolic compounds (PC) biosynthesis using metabolomic techniques

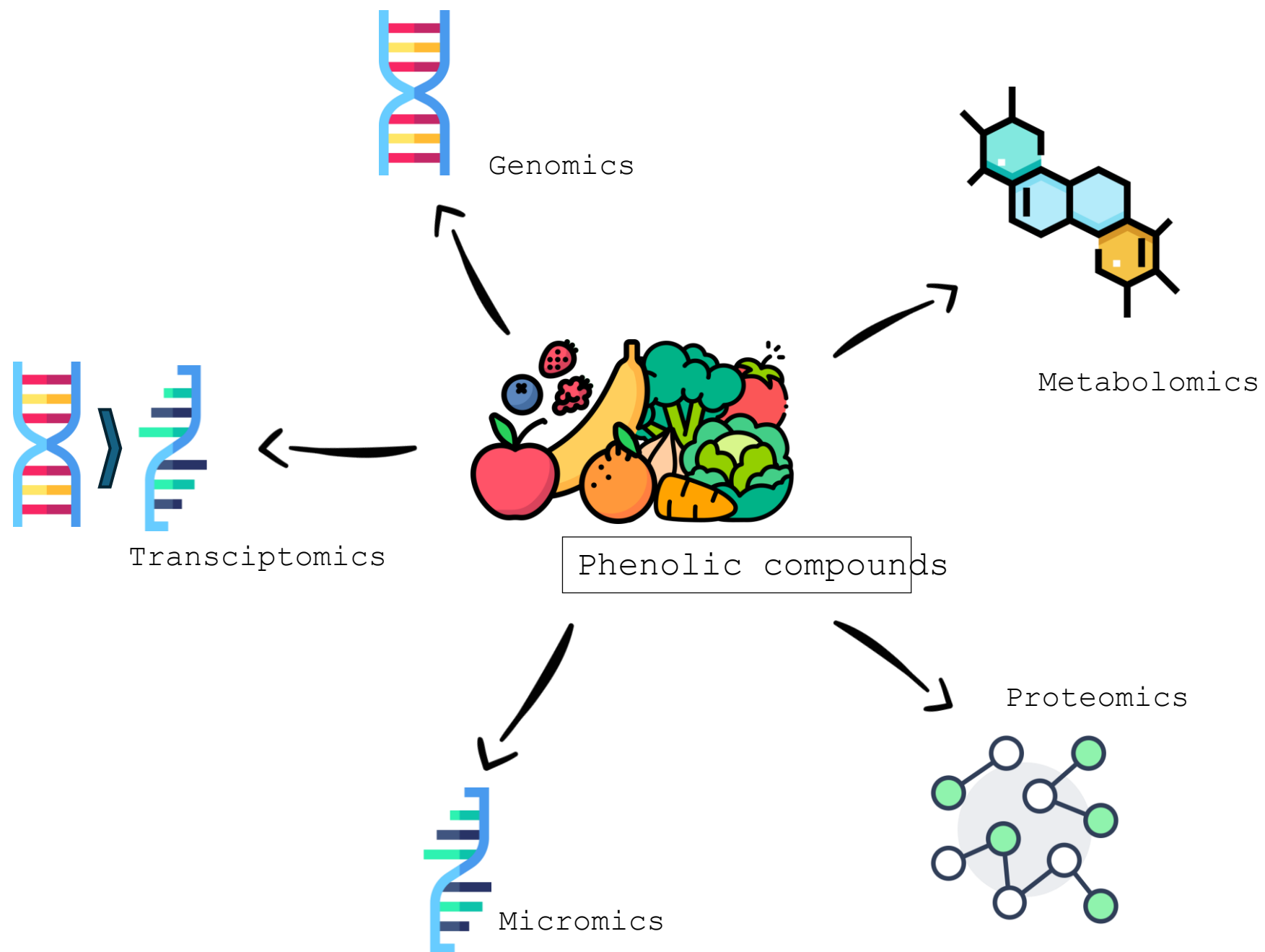
<u>Sample</u>	<u>Aim of the study</u>	<u>Key findings</u>	<u>Reference</u>
<u>Sour Guava fruit</u>	<u>Study the PCs profile</u>	<u>22 PC were determined, including hydroxybenzoic, phenylacetic, and hydroxycinnamic acid derivatives, (+)-catechin, (-)-epicatechin, and procyanidin B1 and B2</u>	(Cuadrado-Silva et al., 2016)
<u>Berry</u>	<u>Determine the PC profile in juices and pomace</u>	<u>568 PCs were identified, including 238 flavonoids and 131 phenolic acids</u>	(M. Q. Zhang et al., 2023)
<u>Wild barley</u>	<u>Identify genetic regions responsible for phenolic acid synthesis (metabolomics coupled with genomics)</u>	<u>Agmatine coumaroyl transferase was found to be the key enzyme in phenolic amide formation</u>	(Wiegmann et al., 2019)
<u>Tomatoes</u>	<u>Study the differences in PC content depending on the location</u>	<u>PCs profile was influenced by the geographical origins of cultivation</u>	(Cruz-Carrión et al., 2022)
<u>Tomatoes</u>	<u>Study the differences in PC depending on the growing conditions</u>	<u>Phenolic acid concentrations were higher in tomatoes grown in open fields compared to greenhouse cultivars</u>	(Asensio et al., 2019)
<u>Grape</u>	<u>Study changes in response to drought on the PCs biosynthesis in skins of a wide variety of grape cultivars</u>	<u>Water stress influences the biosynthesis of different PCs classes</u>	(Pinasseau et al., 2017)
<u>Yellow tea</u>	<u>Study the PC changes of large-</u>	<u>After roasting, the concentration of epicatechin</u>	(J. Zhou et al., 2019)

leaf yellow tea
during processing

decreased, while
epimerized catechin
increased







Conflict of Interest

The authors have declared no conflict of interest

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