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Foodomics approaches: new insights in phenolic compounds analysis

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Abstract:	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. 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. 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
Response to Reviewers:	Manuscript ID: FOODRES-D-24-09608R1 Manuscript title: Foodomics approaches: new insights in phenolic compounds analysis 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. Please find below our corresponding answers. 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

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

Manuscript title: Foodomics approaches: new insights in phenolic compounds analysis

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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.

Foodomics approaches: new insights in phenolic compounds analysis

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Abstract

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.

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.

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.

Keywords

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

1. Introduction

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

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

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

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

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

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

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

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

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

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

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

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

biomarkers. A very good example is the use of LC-IM-Q-TOF-MS for the analysis of PC, which offers significant sensitivity and excellent peak capacity by using three dimensions of separation (Valdés et al., 2022). A critical aspect of foodomics lies in their capacity to generate large datasets, which, while offering profound insights, also introduce challenges in data management and analysis. The analysis of large datasets, generated by foodomics, are highly complex and with high dimensionality. To address this fact, advanced statistical approaches such as multivariate analysis, machine learning, and systems biology approaches are employed. For instance, principal component analysis (PCA) and cluster analysis are used to reduce dimensionality and cluster similar samples or variables, facilitating their visualization and the interpretation of patterns in the data (León et al., 2018). In addition, supervised machine learning techniques, such as support vector machines (SVM) and neural networks, are essential for classifying samples and predicting characteristics from complex data (León et al., 2018; Valdés et al., 2017). In systems biology, network models and predictive modelling help integrate multi-omics data and simulate the behaviour of biological systems, contributing to a deeper understanding of underlying biological pathways (Valdés et al., 2017). These approaches, combined with advanced computational tools, allow for the management and extraction of meaningful information from the large volumes of data generated by omics techniques.

In this review, we provide a comprehensive overview of the applications of omics technologies in PC biosynthesis, from gene expression to metabolite production. Moreover, the current limitations, challenges and insights related to this field are described.

2. Foodomics techniques

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

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

Following, a collection of studies focused on the investigation of PC biosynthesis using foodomics approaches is presented.

2.1. Transcriptomics

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

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

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

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

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

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

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

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

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

2.2. Micromics

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

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

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

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

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

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

2.3. Proteomics

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

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

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

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

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

2.4. Metabolomics

Metabolomics approaches allow us to identify and determine metabolites in multiple

biological samples, including foods (Klassen et al., 2017). This offers a comprehensive snapshot of metabolic activity, revealing key biochemical pathways and their regulation in response to various factors (Wishart, 2019). Two distinct metabolomics approaches can be applied: untargeted and targeted. Untargeted metabolomics analyzes all the measurable compounds in a sample, including unknown metabolites. On the other hand, targeted metabolomics is the analysis of defined groups of chemically characterized and biochemically annotated metabolites (Klassen et al., 2017). Analytical methods in metabolomics rely on mass spectrometry (MS) and nuclear magnetic resonance (NMR) to analyze small molecules (López-Yerena et al., 2021). In this sense, in general MS are coupled to chromatographic techniques including liquid chromatography (LC), gas chromatography (GC), or capillary electrophoresis (CE), in order to separate compounds (W. Li et al., 2019; Moco et al., 2007; Nagana Gowda & Djukovic, 2014). The application of metabolomics potentially adds significant value to crop and food science and meets future food demands (Shepherd et al., 2011). Furthermore, these analytical technologies have a significant impact on the quality and shelf life of food, raw materials, and postharvest processing as well (García-Cañas et al., 2012). These high-throughput analytic technologies permit measuring hundreds or even thousands of compounds at a time. Each of these techniques has its own advantages and disadvantages, but LC-MS may represent the preferred one when studying the PCs due to its sensitivity and breadth of coverage. Furthermore, integrating metabolomics with other omics approaches enhances our understanding of metabolic changes induced by dietary compounds, such as polyphenols, and their subsequent biological impacts Arapitsas et al., 2012). In the last few years, metabolomic-based technologies have become extremely popular in characterization of PCs (Piovesana et al., 2020) (Table 4). In one such study by Barros Santos *et al*. (Barros Santos et al., 2019), metabolomic techniques such as ultra-high-pressure liquid chromatography (UPLC) coupled to quadrupole-time of flight (QTOF) MS were used to characterize phenolic profile of 7 genotypes of immature and mature wheat, identifying 237 phenolics including isomers as free and bound forms, and revealing that phenolic profiles were different among genotypes and during the grain development. In fact, PCs progressively decreased along grain development from milky to mature. However, specifically the proportion bound to free phenolic gradually increased, reaching the maximum at physiological maturity. In a targeted metabolomic study, the comprehensive profiling of PCs in sour guava fruit was analyzed by HPLC-electrospray ionization (ESI)-triple quadrupole (QqQ) in multiple reaction monitoring (MRM) mode (Cuadrado-Silva et al., 2016). This fruit contained a total of 22 PCs in the form of hydroxybenzoic, phenylacetic, and hydroxycinnamic acid derivatives, reporting for the first time that sour guava contains (+)-catechin, (-)-epicatechin, and procyanidin B_1 and B_2. In a further study, Lyu *et al*. (Lyu et al., 2022) characterized the PCs profiles in mung bean sprouts under sucrose treatment by targeted metabolomics analysis a total of 106 PCs were detected, 21 of which had a positive correlation with antioxidant capacity. In a

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

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

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

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

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

3. Current limitations and challenges

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

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

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

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

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

4. Insights in phenolic compounds studies

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

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Abbreviations

4CL, 4-coumaroyl-CoA ligase
ANR, anthocyanidin reductase.
ANS, anthocyanidin synthase
AP2, APETALA2
C4H, cinnamic acid hydroxylase
CE, capillary electrophoresis
CHI, chalcone isomerase
CHS, chalcone synthase
DAD, diode array detector
DEPs, differentially expressed proteins
DFR, dyhydroflavonol 4-reductase
DPPH, 2,2-difenil-1-picrilhidrazil
ESI, electrospray ionization
FH3, flavanone 3-hydroxylase
FNS, flavone synthase
GC, gas chromatography
HPLC, high pressure liquid chromatography
IFS, isoflavone synthase
LAR, leucoanthocyanidin reductase
LC, liquid chromatography
LC-IM-Q-TOF-MS, liquid chromatography/ion mobility quadrupole time-of-flight mass spectrometry
LDOX, leucoanthocyanidin dioxygenase
miRNA, microRNA
mRNA, messenger RNA
MRM, multiple reaction monitoring
MS, mass spectrometry
MS^n, multistage mass spectrum
NMR, nuclear magnetic resonance
ORAC, oxygen radical absorbance capacity
PAL, phenylalanine ammonia-lyase
PAs, proanthocyanidins
PCA, principal component analysis
PCs, phenolic compounds
PP, polyphenols
PPP, phenylpropanoid pathway
PRL, pinoresinol-lariciresinol reductase
PTM, post-translational modifications
QqQ, triple quadrupole

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

Author contributions

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Consent to participate

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Consent to publication

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Tables

Table 1. Main studies focused on phenolic compounds (PC) biosynthesis using 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	Comparation 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)
***Prunus* 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)

Abbreviations: ANR, anthocyanidin reductase; CHS, chalcone synthase; LAR, leucoanthocyanidin reductase; LDOX, leucoanthocyanidin dioxygenase; PPP, phenylpropanoid pathway.

Table 2. Main studies focused on phenolic compounds (PC) biosynthesis using 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)

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

Table 3. Main studies focused on phenolic compounds (PC) biosynthesis using 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)

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

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 influences 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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Foodomics approaches: new insights in phenolic compounds analysis

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Abstract

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

~~Foodomics is a novel omics approach, including genomics, metabolomics, micromics, proteomics and transcriptomics, which can be applied to study PCs in plants. This multidisciplinary approach has advanced the understanding of the synthesis, regulation, and accumulation of PCs.~~ 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 ~~that continue to shape the field~~.

O~~New o~~mics techniques ~~are continuously emerging,~~ as well as ~~statistics and~~ data analyses are ~~also~~ continuously progressing, emerging new opportunities with the onset of artificial intelligence and machine learning. ~~with systems biology and advanced statistical methods, such as machine learning and multivariate analysis, enabling more accurate interpretation of omics data~~ However, significant limitations and challenges still remain. The immense diversity of PC chemical structures and their variability across plant species, varieties, and ~~environmental conditions~~the impact of agronomic factors complicate ~~data interpretation~~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 ~~that~~ can impact in the results~~lack of standardization in experimental procedures further limit reproducibility and cross-study comparisons~~. Addressing these limitations requires integrating multi-omics approaches ~~, leveraging machine learning for data processing,~~ and developing standardized protocols to enhance comparability and interpretation in PC research.~~The main challenges in studying PCs using omics techniques include the immense and diversity of PC chemical structures and their variability across different plant species, varieties, and environmental conditions. This variability limits the extrapolation of findings and requires extensive studies to fully understand not only biosynthesis pathways but also the internal and external impacts on such compounds.~~ In summary, foodomics approaches arise as essential for the complete mapping of PC biosynthesis.

Keywords

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

1. Introduction

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

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

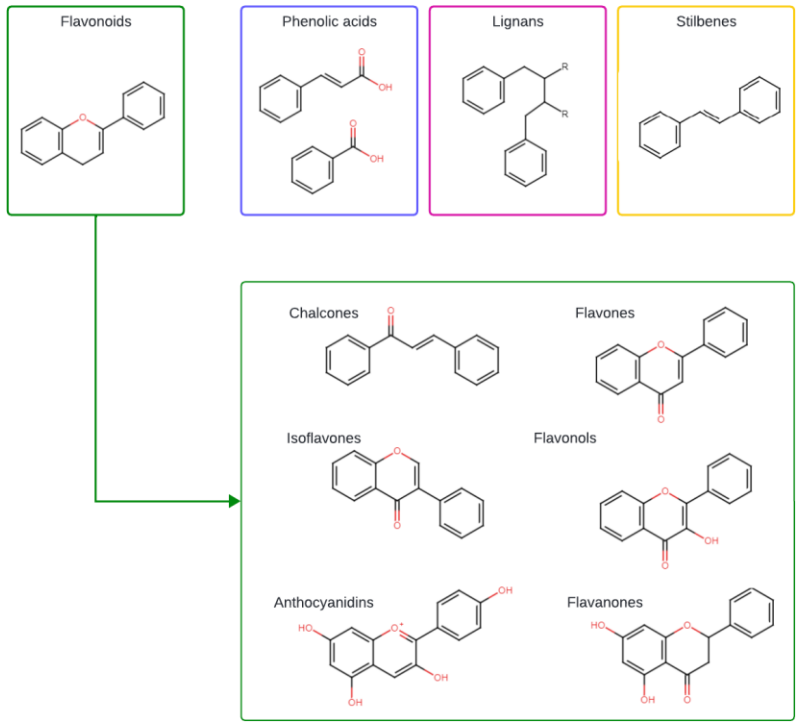


Figure 1. Main chemical structures of phenolic compounds (PCs). This figure illustrates the structural diversity of flavonoids, phenolic acids, lignans, and stilbenes, highlighting specific flavonoid subgroups, such as chalcones, isoflavones, anthocyanidins, flavones, flavonols, and flavanones.

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,

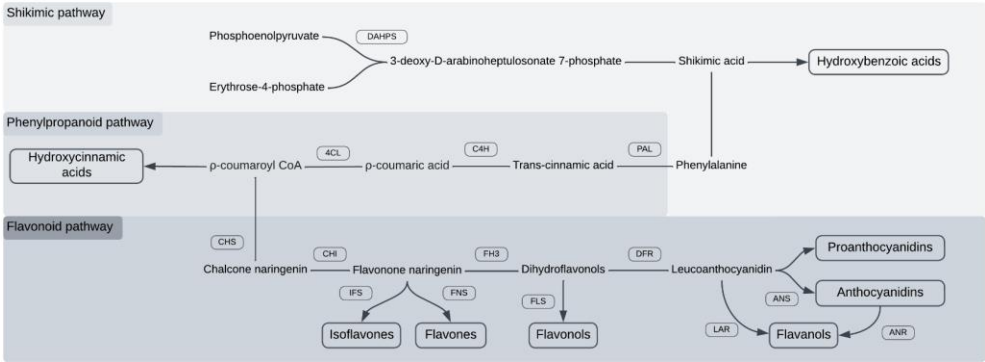
derivatives of hydroxycinnamic acid, such as chlorogenic acid, are found in coffee, among other plants (Manach et al., 2004; L. Zhang et al., 2021). Regarding tissue distribution, PCs are distributed throughout the whole plant, including roots, leaves, and fruits. In leaves and stems, they primarily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

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

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

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

al., 2023).



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

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

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

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

factors, such as MYBA in grapevine, that controls anthocyanin synthesis and are responsible for skin coloration in those berries (Matus et al., 2017; Yue et al., 2018).

The phenolic profile in plants depends on both internal factors, such as genetic and external factors, including environmental conditions (L. Zhang et al., 2021). Therefore, there can be differences in the phenolic profile not only between two different varieties of the same cultivar, but also within the same variety depending on environmental conditions. Moreover, postharvest treatments also have an important role in the total PCs content since they can promote their synthesis or degradation (Ávila-Román et al., 2021; Yalcin & Çapar, 2017; L. Zhang et al., 2021). In fact, abiotic stress in plants increases production of reactive oxygen species (ROS), causing oxidative damage. This production enhances activity of PAL, CHS, and other enzymes, which increase PCs accumulation to protect the plant against oxidative stress (Kumar et al., 2023; Shen et al., 2022; Yue et al., 2018). For example, a very common abiotic stress in plants is drought, which is reported to increase accumulation of anthocyanins in *Arabidopsis*, generating a higher stress tolerance (Nakabayashi et al., 2014). Another example is reported by Griesser *et al*. (Griesser et al., 2015), where accumulation of several PCs, such as (-)-epicatechin or (-)-epicatechin gallate in *Vitis vinifera* was increased after a prolonged period of drought. The same results were obtained in grape berries after a period of drought, here a higher accumulation of flavonoids, flavan-3-ols, and flavonols were found (Doshi et al., 2006). Another stressing factor is ultraviolet radiation (UV), which damages protein structure, leading to ROS generation, and, subsequently, to a higher PCs accumulation (Kumar et al., 2023). In this regard, Goyal *et al*. (Goyal et al., 2014) analyzed the effect of UV in the accumulation of PCs in mung bean sprouts and reported that higher phenolic accumulation was found in plants treated with UV radiation compared to the control. The treatment also increased their antioxidant activity. Jan *et al*. (Jan et al., 2022) reported that the relative expression of FH3 was increased in wild and transgenic rice plants when they were exposed to UV radiation. Soil salinity, a stress factor, also enhances phenolic accumulation in plants (Kumar et al., 2023). Several studies were carried out in this context. For example, Golkar *et al*. (Golkar & Taghizadeh, 2018) reported that the concentration of total flavonoids and total PC increased in safflowers with high salinity levels. Flavonoid biosynthesis in plants is regulated by several factors, transcription factors being one of the most important. It has been seen that the overexpression of transcriptional factor VvbHLH (*Vitis vinifera* basic Hoop-Loop-Hoop) induces the biosynthesis of flavonoids, protecting the plant from salinity stress (F. Wang et al., 2016). Other abiotic factors, such as temperature or the use of pesticides, can also stimulate the phenolic biosynthesis in plants, to protect the plant against oxidative stress (Nakabayashi et al., 2014). ~~As previously mentioned, the phenolic profile in plants is highly different as it depends on several factors.~~

~~Therefore~~Focusing on the study of PC biosynthesis, omics techniques have emerged as essential tools ~~to study PCs in depth~~due to their versatility. ~~–~~These are a set of disciplines

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

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

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

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

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

2. Foodomics techniques

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

metabolites. Moreover, combining transcriptomic, proteomic, and metabolomic datasets through advanced bioinformatics tools has enabled the construction of comprehensive models of phenolic biosynthetic pathways, pinpointing key regulatory nodes and potential targets for metabolic engineering (Xu et al., 2020; Yang et al., 2021).

~~As previously mentioned, several omics tools are used in foodomics, including genomics, transcriptomics, proteomics, and metabolomics, providing molecular information on gene, transcript, protein, and metabolite expression levels, and integrating this information from a systems biology perspective .~~

Following, a collection of studies focused on the investigation of PC biosynthesis using foodomics approaches is presented.

2.1. ~~Genomics and T~~transcriptomics

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

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

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

genetic factors.

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

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

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

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

[Insert Table 1: Main studies focused on phenolic compounds (PC) biosynthesis using

transcriptomic techniques]

2.2. Micromics

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

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

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

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

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

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

2.3. Proteomics

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

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

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

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

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

2.4. Metabolomics

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

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

This fruit contained a total of 22 PCs in the form of hydroxybenzoic, phenylacetic, and hydroxycinnamic acid derivatives, reporting for the first time that sour guava contains (+)-catechin, (-)-epicatechin, and procyanidin B_1 and B_2. In a further study, Lyu *et al*. (Lyu et al., 2022) characterized the PCs profiles in mung bean sprouts under sucrose treatment by targeted metabolomics analysis a total of 106 PCs were detected, 21 of which had a positive correlation with antioxidant capacity. In a recent study by Zhang *et al*. (M. Q. Zhang et al., 2023), a metabolomic approach was used to evaluate the phenolic composition in berry juice and pomace. A total of 568 PCs were identified in berry pomace samples by UPLC-MS/MS, including 238 flavonoids and 131 phenolic acids, suggesting that this fruit can be a valuable source of PCs of which the major components are

anthocyanins and phenolic acids.

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

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

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

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

~~Table 1. Main studies focused on phenolic compounds (PC) biosynthesis using foodomics approaches.~~

~~e~~	~~Aim of the study~~	~~Foodomics techniques~~	~~ResultsKey findings~~	~~Reference~~
~~ant *(Camelia sinensis)*~~	~~Catechins biosynthesis pathways~~	~~Transcriptomics~~	~~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~~	~~Transcriptomics~~ ~~Metabolomics~~	~~8 genes involved in flavonoid biosynthesis, playing a central role in color changeChalcone synthase genes were crucial for flavonoid biosynthesis~~	~~[34]~~
~~berry (Rubus sp. var. Loch Ness)~~	~~StudyComparation of flavonoid regulatory networks PC synthesis in leaves and fruits~~	~~Transcriptomics~~ ~~Metabolomics~~	~~Total PC in leaves were three-fold higher than in fruit; flavonols were six-fold higher, and anthocyanins was higher in fruits~~	~~[33]~~
~~rapes~~	~~Comparation of gene expression profile, PC, and antioxidant capacity of different red grapes~~	~~Transcriptomics~~	~~10 metabolic pathways related to PC synthesis differed compared to Cabernet Sauvignon~~	~~[16]~~
~~net Sauvignon grapes~~	~~Influence of cluster bagging on ripening, PC accumulation, and biosynthetic pathway~~	~~Transcriptomics~~	~~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 Nectarines Prunes Japanese plums Apricots Sweet cherry fruits Sour cherry fruits	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]
s		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 (*Hylocereus undatus*)		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 (*Curcuma longa*)		Identification of miRNAs involved in PC synthesis	Micromics	miR2919, miR1168, miR156b and miR1858, promote the expression of flavanone synthase gene and the synthesis of curcumin	[49]

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

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

		Blueberry (*Vaccinium* spp.) Mulberry (*Morus australis*) Black chokeberry (*Aronia melanocarpa*)	(pomace)		flavonoids and 131 phenolic acids	
barley (*Hordeum vulgare* ssp. *neum*)			Study the PC formation and the influence of environmental conditions	Metabolomics	Agmatine coumaroyl transferase was seen as the enzyme responsible for phenolic amide formation, and its activity is influenced by environmental circumstances	[84]
oes fruits (*solanum lycopersicum* cv. is)			Study the differences in PC content depending on the location	Metabolomics	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	Metabolomics	Concentrations of phenolic acids, including chlorogenic, caffeic, ferulic and p-coumaric are higher in traditional tomatoes cultivated in and open field	[86]
(*Vitis vinifera*)			Study the influence of water stress on the biosynthesis of different PC in skins	Metabolomics	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~~	~~Metabolomics~~	~~The concentration of (-)-epicatechin decreased after roasting, while (+)-epicatechin increased.~~	~~[89]~~

~~4CL, 4-coumaroyl-CoA ligase; AP2/ERF, APETAL2/ethylene response factor; CHS, chalcone synthase; DFR, dyhydroflavonol 4-reductase; LDOX, leucoanthocyanidin dioxygenase; miRNA, microRNA; PAL, phenylalanine ammonia-lyase; UDP, uridine diphosphate.~~

3. ~~44.~~ Current limitations and challenges

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

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

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

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

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

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

4. ~~5~~5. ~~.~~ Insights in phenolic compounds studies

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

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

Abbreviations

4CL, 4-coumaroyl-CoA ligase
ANR, anthocyanidin reductase.
ANS, anthocyanidin synthase
AP2, APETALA2
C4H, cinnamic acid hydroxylase
CE, capillary electrophoresis
CHI, chalcone isomerase
CHS, chalcone synthase
DAD, diode array detector
~~DAHPS, 3-deoxy-D-arabinoheptulosonate-7-phosphate synthase~~
DEPs, differentially expressed proteins
DFR, dyhydroflavonol 4-reductase
DPPH, 2,2-difenil-1-picrilhidrazil
ESI, electrospray ionization
FH3, flavanone 3-hydroxylase
~~FLS, flavonol synthase~~
FNS, flavone synthase
GC, gas chromatography
HPLC, high pressure liquid chromatography
IFS, isoflavone synthase
LAR, leucoanthocyanidin reductase
LC, liquid chromatography
LC-IM-Q-TOF-MS, liquid chromatography/ion mobility quadrupole time-of-flight mass spectrometry
LDOX, leucoanthocyanidin dioxygenase
miRNA, microRNA
mRNA, messenger RNA
MRM, multiple reaction monitoring
MS, mass spectrometry
MS^n, multistage mass spectrum
NMR, nuclear magnetic resonance
ORAC, oxygen radical absorbance capacity
PAL, phenylalanine ammonia-lyase
PAs, proanthocyanidins
PCA, principal component analysis
PCs, phenolic compounds
PP, polyphenols
PPP, phenylpropanoid pathway
PRL, pinoresinol-lariciresinol reductase

PTM, post-translational modifications
QqQ, triple quadrupole
QTOF, quadrupole-time of flight
ROS, reactive oxygen species
SVM, support vector machines
UDP, uridine diphosphate
UPLC, ultra-high-pressure liquid chromatography
UHPLC-ESI-QqQ, ultra-high-pressure liquid chromatography electrospray ionization triple quadrupole
UV-C, ultraviolet C
~~VvbHLH, Vitis vinifera basic Hoop-Loop-Hoop~~

Author contributions

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Tables

Table 1. Main studies focused on phenolic compounds (PC) biosynthesis using 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	Comparation 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)
***Prunus* 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)

Abbreviations: ANR, anthocyanidin reductase; CHS, chalcone synthase; LAR, leucoanthocyanidin reductase; LDOX, leucoanthocyanidin dioxygenase; PPP, phenylpropanoid pathway.

Table 2. Main studies focused on phenolic compounds (PC) biosynthesis using 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)

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

Table 3. Main studies focused on phenolic compounds (PC) biosynthesis using 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)

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

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 influences 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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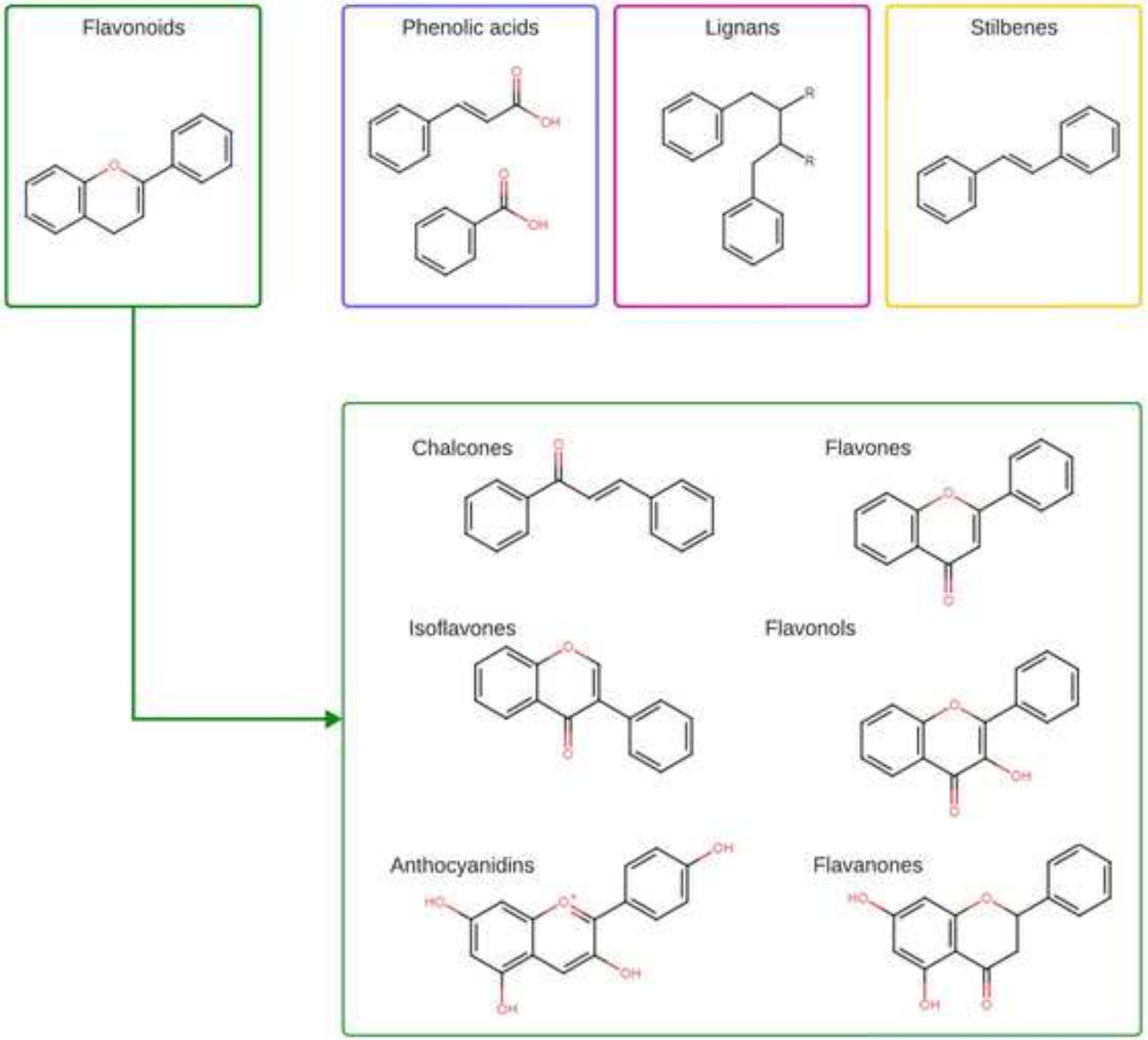
Figure



Figure

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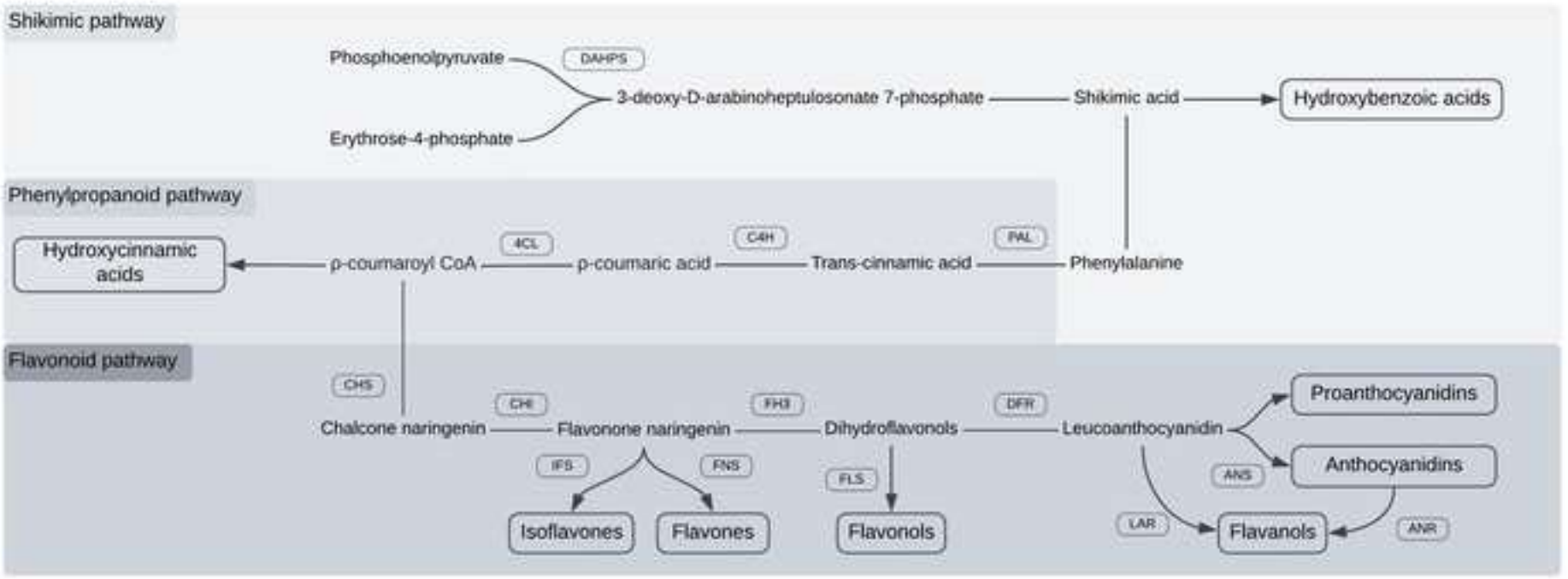
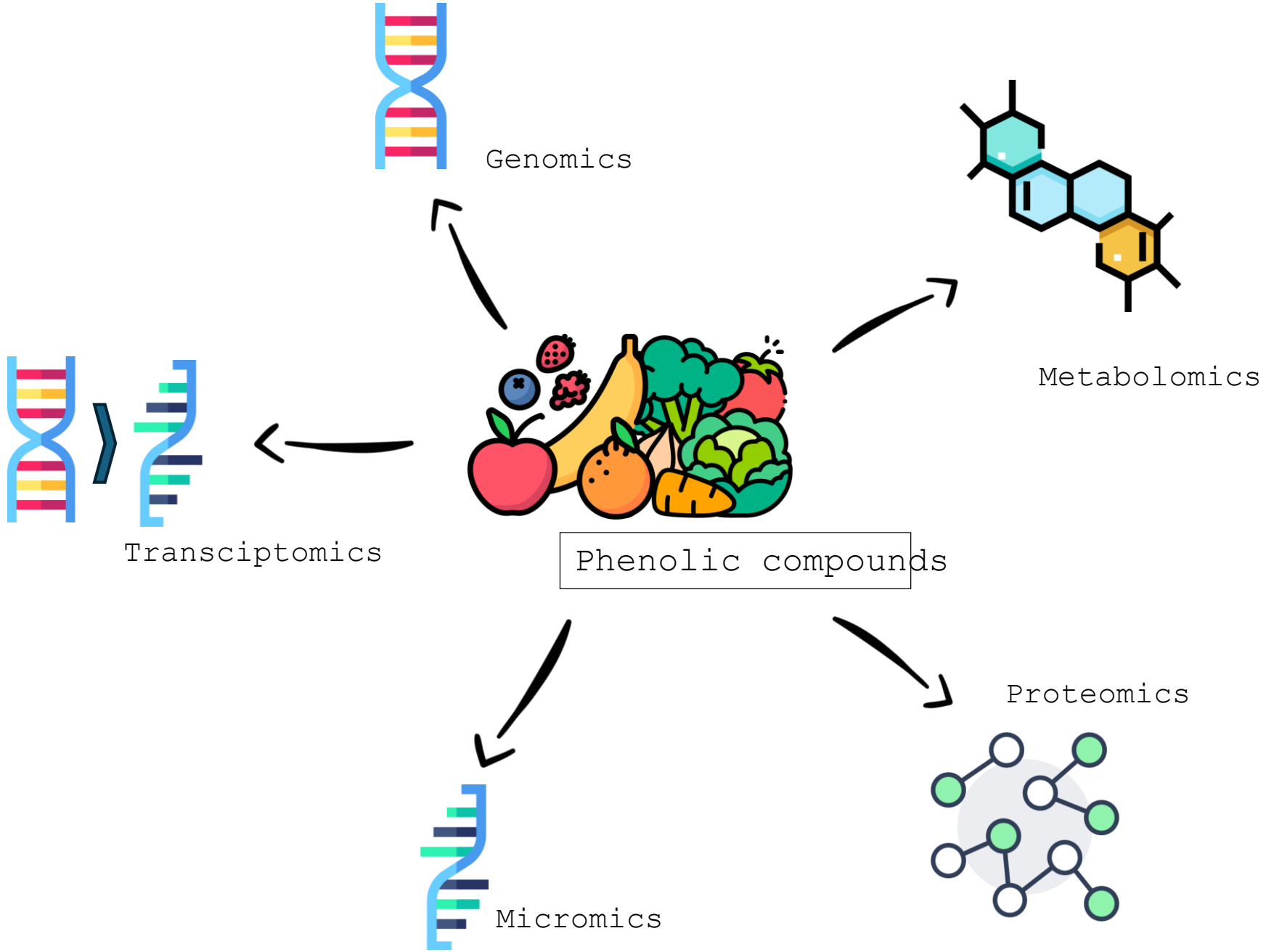


Graphical Abstract



Conflict of Interest

The authors have declared no conflict of interest

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