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Plants as a source of dietary bioactives: Flavonoids and basis for their health benefits

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ABSTRACT

Flavonoids are a group of bioactive compounds widely distributed in edible plants. They have gained special attention given strong scientific evidence supporting their health promoting actions. This review summarizes current knowledge on the biosynthetic pathways of flavonoids in plants, the regulation of those pathways, and the conservation of flavonoids in plant road to becoming a food. Additionally, the main dietary sources of flavonoid, evidence from population and clinical studies, and possible mechanisms involved in the beneficial effects of flavonoids on human health are also discussed.

1. Introduction

Through dietary consumption, animals have been exposed to plant chemicals that they use both as nutrients and as ancillary health promoters. The consequences of this exposure have received increased interest in the last decades fueled by veganism and vegetarianism and by the positive health effects associated with plant-based diets.

Molecules present in plants can be involved in a panoply of chemical reactions that can affect animal physiology. Thus, once ingested, these molecules can affect human biology and physiology. This is the basis for defining bioactives as molecules able to produce beneficial biological changes beyond those mediated by essential nutrients (Fraga and Oteiza, 2023). Within bioactives, flavonoids are a group of plant chemicals that have received extensive research interest, given their proposed human health benefits in conditions of altered physiology and disease (Fraga et al., 2019).

In this paper, we will summarize current knowledge on how plants synthesize flavonoids, how that production can be regulated, and how flavonoids can be better conserved when become a food component. Subsequently, we will discuss the associations between flavonoid consumption and human health, concluding on how optimizing flavonoids consumption from plant-based foods can be related to the promotion of optimal living conditions.

2. Flavonoids in plants

2.1. A brief overview of the synthesis of flavonoids

From a chemical point of view, (poly)phenolic compounds, e.g. phenolic acids, flavonoids, stilbenes, tannins, lignans and lignins are derived from phenylalanine (and in some plants from tyrosine), and are synthesized through the called shikimate pathway (Liu et al., 2021; Landolino et al., 2010). The elementary biosynthetic reactions are conserved over a range of plants, to give basic skeletons that can be modified by specific reactions to produce a great variety of compounds (Schijlen et al., 2004). Thus, plants may generate different classes of (poly)phenolic compounds, having a common building block in their carbon skeleton, the phenylpropanoid unit (phenyl ring and a C3 side chain) (Vogt, 2010). As depicted in Fig. 1, flavonoids derive from a precursor molecule, i.e. chalcone, produced by the condensation of *p*-coumaroyl-coenzyme A (coming from the phenyl propanoid pathway) and three molecules of malonyl-coenzyme A (derived from carbohydrate metabolism). This condensation is catalyzed by the enzyme chalcone synthase (Liu et al., 2021; Schijlen et al., 2004; Vogt, 2010; Dixon and Steele, 1999; Dixon and Paiva, 1995). Different types of flavonoids are then synthesized based on modifications in the central ring (C ring), generating subgroups of compounds with different chemical structures

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such as flavanones, flavones, isoflavones, flavanols, flavonols, and anthocyanins (Schijlen et al., 2004). In Text Box 1, are depicted edible plants carrying compounds belonging to each of these subgroups (Nijveldt et al., 2001; Shen et al., 2022).

In terms of individual flavonoids, more than 6000 different structures have been reported to occur in plants (Harborne and Williams, 2000; Panche et al., 2016; Dias et al., 2021). Some flavonoids are common for most plants; however, others are more limited to different lineages, e.g. isoflavones in legumes, 3-deoxyanthocyanins in sorghum and maize, and stilbenes (a non-flavonoid polyphenols) in grapes, peanuts and pines (Winkel-Shirley, 2001). It can be considered that each plant species has its own fingerprint of flavonoid composition. Within a particular plant species, the amount and distribution of flavonoids present in different cultivars are not only genetically defined, but are also dependent on environmental factors. Interestingly, certain compounds that are constitutively produced in one species can be induced by stress conditions in other species (Dixon and Paiva, 1995). In this regard, soybean cotyledons exposed to UV-C radiation (190–280 nm) accumulates the colored flavonoid apigeninidin in areas of the epidermis directly exposed to radiation (Boveris et al., 2001), although this compound is not usually present in soy.

2.2. Flavonoid functions in plants

Flavonoids as well as other (poly)phenolic compounds, are defined as plant secondary metabolites, i.e. are not essential for growth, development, or reproduction although they participate in these processes. Flavonoids are molecules involved in an array of processes based on the interactions of plants with the environment (Forkmann and Martens, 2001; Hernández et al., 2009; Taylor and Grotewold, 2005). By expressing phenotypic characteristics, i.e. color, fragrance, and flavor, flavonoids provide benefits for plants through their participation in: i)

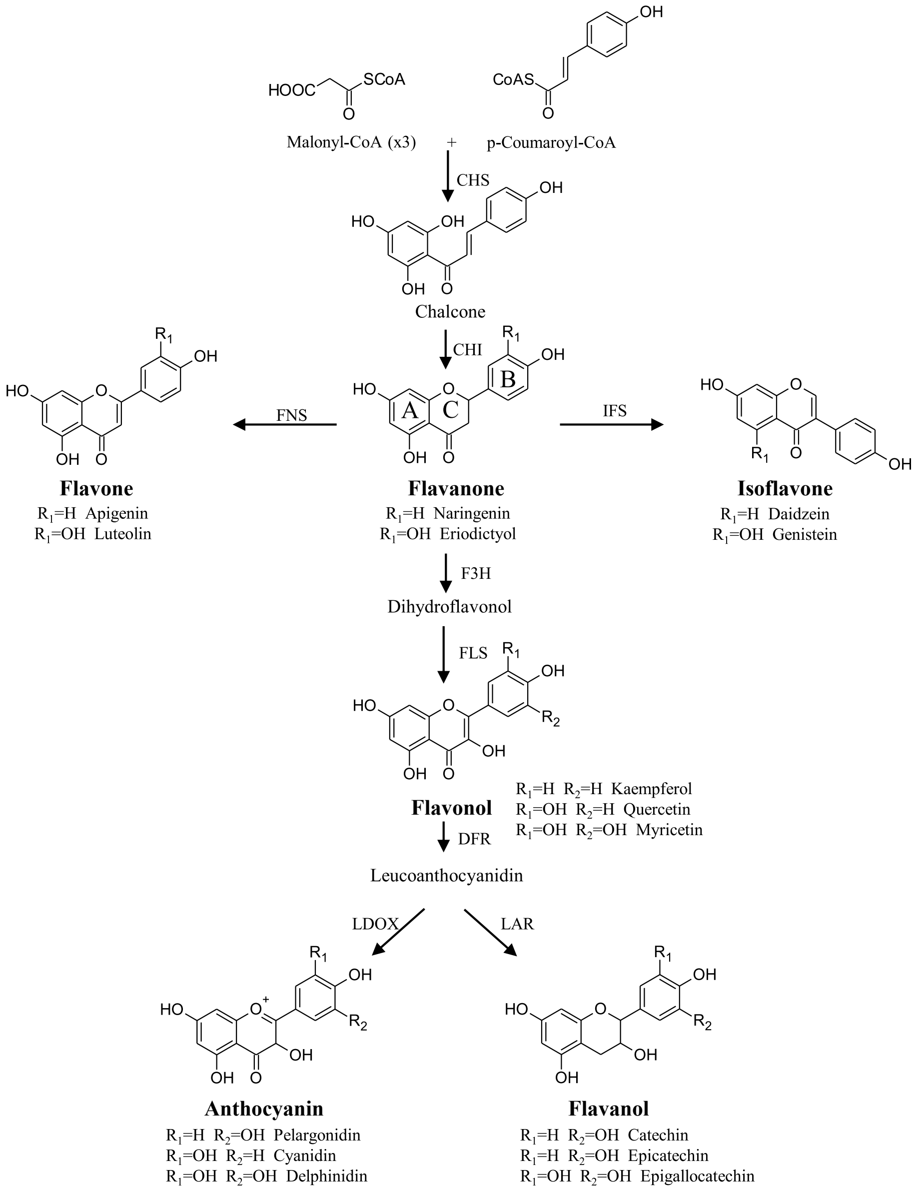

Fig. 1. Flavonoid biosynthetic pathway. A, B and C in flavanone structure name rings common to all flavonoids. This biosynthetic pathway is regulated by the enzymes chalcone synthase (CHS), chalcone isomerase (CHI), flavone synthase (FNS), isoflavone synthase (IFS), flavanone-3-hydroxylase (F3H), flavonol synthase (FLS), dihydroflavonol-4-reductase (DFR), leucoanthocyanidin dioxygenase (LDOX), and leucoanthocyanidin reductase (LAR). Catechin and epicatechin have chiral centers on C2 and C3 generating four diasteroisomers: (−)-catechin and (+)-catechin (*trans* configuration), and (−)-epicatechin and (+)-epicatechin (*cis* configuration).

Text Box 1
Edible plant sources of flavonoids

Flavonoid sub group	Edible plants
Flavones	Apples, berries (raspberries, blackberries, etc), broccoli, celery, grapes, lettuce, olives, onions, parsley, carrots, peppers, chamomile
Flavanones	Citrus (grapefruit, orange, limes, lemon)
Isoflavones	Soybean, chickpea
Flavonols	Onions, asparagus, cocoa, broccoli, leeks, kale, olives, berries
Anthocyanins	Berries (cherries, raspberries, strawberries, elderberries, etc), grapes, purple cabbage, tomato, eggplant
Flavanols	Cocoa, tea, apricots, apples, peaches, pecan nuts, plums, cherries

growth and development, by regulating cellular processes such as cell division, maintenance of membrane integrity, gene transcription, cell signaling, and auxin transport; ii) defense from pathogens, e.g. phytoalexins against bacteria, antifeedants for insects and herbivores, and protection from light (screen for UV-B) and other abiotic stresses; iii) reproduction and fertility, attracting insect pollinators and fruit dispersers affecting pollen germination; iv) plant–microbe interaction; and v) competition with other plants (allelopathy) (Taiz and Zeiger, 2010; Kumar et al., 2018; Zhuang et al., 2023).

In addition, flavonoid functions may vary in different structures of the plant and may have changed during evolution. It has been proposed that flavonoids start functioning as internal physiological regulators or chemical messengers, beyond their properties of filtering UV and other undesirable radiation. Thus, the plant-environment interactions have been a crucial factor in the evolution of the synthesis of flavonoids among different plant species, affecting amount, localization, and their specific function (Stafford, 1991).

In summary, flavonoids have functions in the biochemistry, and ecophysiology of plants having a role in growth and development, and in the response to challenging stress conditions and plant survival.

3. Optimizing flavonoid content in plants and plant-based foods

Edible plants have been the subject of studies aimed at optimizing healthy food components, including flavonoids. Such optimization can be obtained by maneuvering crop conditions, applying postharvest procedures, and/or genetically modifying flavonoid content.

3.1. Regulating flavonoid content in plants: preharvest conditions

Growth conditions during plant development influence components that affect its composition and quality (Kishor et al., 2023). Nutrient and water availability, sun radiation, weather conditions during growth and at the time of cropping may determine the content of secondary metabolites in foods (Kishor et al., 2023; Ubi, 2004; Rodrigues et al., 2010; Pérez-Gregorio et al., 2011). For example, flavonoid composition in grapes depends on the variety, but also on the developing stage of the berries. Thus, by selecting the grape harvest time it is possible to obtain fruits with different flavonoid profiles (Crupi et al., 2013). Regarding growth conditions, Rodrigues et al. (2011) evaluated the interannual variation of flavonoid content in two Portuguese landrace varieties of onion, and concluded that despite the quantitative differences between varieties, the levels of flavonols were higher in dry and hot seasons. In addition, the red onion variety accumulated lower amounts of anthocyanins during the years of lowest global radiation. Global climate change seems to generate fluctuating temperatures, low water availability, and suboptimal nutritional conditions that can affect plant growth and development, and compromise flavonoid content. Despite this, some moderate stress conditions can stimulate secondary metabolism and lead to higher flavonoid accumulation.

3.2. Regulating flavonoid content in plants: postharvest strategies

An important global concern is that a high percentage of the harvested fruits and vegetables are lost or change their quality before reaching consumers (Buet et al., 2021; Habibi et al., 2024). Thus, modifying postharvest handling, storage technology, and other postharvest conditions will contribute to improve the quality of fresh plant products, including their flavonoid content.

In terms of flavonoids, it is important to maintain, or even increase their content in the fruit or vegetable from harvest to consumption. For example, within this period controlled (mild) stress conditions may be used as tools for fresh produce, during food processing, and in dietary supplement industry to enhance flavonoid content (Cisneros-Zevallos, 2003). The effects of UV treatments on flavonoid content were studied in different fruits such as mango (González-Aguilar et al., 2007), tomato (Liu et al., 2011), and table grape (Crupi et al., 2013). It can be concluded that UV radiation increases the content of both total flavonoids and of particular type of flavonoids, maintaining the shelf life of the fruits for market commercialization. These overall effects were observed despite the particular condition to which each fruit was exposed, e.g. the dose of UV, and optimal time and storage conditions. Thus, UV radiation is a promising residue-free physical method that can help sustain or improve fruit health benefits (Zhang and Jiang, 2019).

Temperature is another important factor during postharvest management, being low temperatures usually employed for storage. Regarding flavonoids, plants respond differently to storage temperatures. Experiments in onions showed that storage (7 months) at ambient temperature enhanced flavanols content, being better than low temperature conditions. However, the content of other flavonoids like anthocyanins, are significantly reduced after storage in both temperature conditions (Rodrigues et al., 2010). Total flavonoid content in sour cherry, strawberry and raspberry stored at 25 °C were higher when compared to storage at 4 °C; but the opposite was observed for cherries and red currants (Piljac-Žegarac and Šamec, 2011). Thus, an adequate balance between the quality for shelf-life preservation (low temperature) and the maintenance or increase of flavonoids content, should be considered.

In addition to postharvest storage, processing (e.g. cutting and washing) and packaging technologies may influence the exposure to light, oxygen, and water condensation, thus defining flavonoid levels (Pérez-Gregorio et al., 2011).

The promising advances in multi-omics approaches including genomics, transcriptomics, proteomics, and metabolomics, will provide new insights into the molecular networks and regulatory processes affecting postharvest physiology, which would be useful for developing strategies to maintain or enhance fruit and vegetable flavonoid content (Habibi et al., 2024). As an example, Huang et al. (2024) investigated the molecular basis of anthocyanin biosynthesis in cashew apples employing integrative analyses with metabolomics and transcriptomics. This helped to identify the expression levels of anthocyanin biosynthetic genes, and potential transcription factors implicated.

3.3. Regulating flavonoid content in plants: metabolic genetic engineering

Edible crop plants that are important components of human diet frequently lack or have low levels of some desired flavonoids. To improve the amount of flavonoids, the genetic manipulation of the metabolic pathways involved in flavonoid synthesis seems promising. Improvement of crop varieties to enhance yield, disease resistance, and quality traits has been made by conventional breeding (through selective hybridization), by mutational breeding (using physical, chemical and biological mutagenesis), and by transgenic techniques (Ikwebe and Onuche, 2022; Zhou et al., 2020).

The use of genetic engineering of secondary metabolic pathways in plants may decrease or increase the quantity of certain required compound(s) by regulating the levels of mRNA or the gene expression of enzymes involved in synthetic pathways. Also changing the expression of transcription factors controlling multiple genes may be an alternative, but it requires thorough knowledge of pathways' regulation. In some cases, synthetic pathways not present in the host plant may be included through the introduction of foreign genes (Verpoorte and Memelink, 2002). These approaches have been assessed and reviewed by several authors (Schijlen et al., 2004; Forkmann and Martens, 2001; Verpoorte and Memelink, 2002). In this sense, the biosynthesis of flavonols in tomatoes was upregulated through the introduction in tomato plants of a Petunia gene encoding for the chalcone isomerase enzyme (Muir et al., 2001). Thus, these transgenic tomato lines showed increased levels of flavonols in the fruit.

Nowadays, new molecular genetic techniques such as CRISPR/Cas9 genome editing tools are more promising than transgenic approaches with random insertions, producing defined mutants and avoiding random phenotypes (Ikwebe and Onuche, 2022; Zhou et al., 2020; Xu et al., 2020). Tu et al. (2022) employed CRISPR/Cas9 technology in combination with transcriptome and metabolome analysis to evaluate the effects of knocking out a gene (VvbZIP36) in grapevine (*Vitis vinifera*), which acts as a negative regulator of anthocyanin biosynthesis and an activator of flavonol and lignan biosynthesis. Single allele mutations lead to anthocyanins accumulation in leaves but inhibited the synthesis of stilbenes (α-viniferin), lignans, and some flavonols. CRISPR/Cas9 technology has also been applied in tartary buckwheat (*Fagopyrum tataricum*) a crop rich in rutin and other flavonoids. Targeted mutagenesis of a transcriptional repressor of the flavonoid biosynthetic pathway increased the content of some flavonoids, e.g. kaempferol-3-*O*-β-D-glucoside, methylquercetin-*O*-hexose, rutin, proanthocyanidins, catechin, epicatechin-3-*O*-glucoside, and catechin-3-*O*-glucoside, in mutant lines (Wen et al., 2022). In tomato plants, gene editing (through the insertion of a strong promoter upstream of a gene controlling anthocyanin biosynthesis) enhanced the accumulation of anthocyanins producing purple tomato fruits (Čermák et al., 2015).

Overall, advances into the regulation of flavonoid biosynthetic pathways by gene editing will be useful in the development of new breeding programs. However, unpredicted results may occur, considering the multiple pathways and branches involved in those pathways (Verpoorte and Memelink, 2002). In addition, in some cases, ecological consequences may arise, if particular flavonoids involved in multiple plant-microorganism signals (both, beneficial and pathogenic microorganisms) are affected, as it has been proposed for isoflavones, i.e. genistein and daidzein in soybean (Dixon and Steele, 1999).

When planning such flavonoid enrichment strategies, organoleptic characteristics should be carefully preserved to accomplish consumer demands. For example, phenolic compounds like flavonoids and tannins are responsible for bitterness and astringency of many foods. Then, in the case of increasing these compounds to improve their health benefits, it should be taken into consideration potential changes in their palatability (Drewnoski and Gomez-Carneros, 2000).

An interesting example in which health and proper plant characteristics coincide, was the development of apples that never browns employing interfering RNA to reduce enzymatic flavonoid degradation catalyzed by polyphenol oxidases. These apples resist browning after being cut, preserving their flavor and nutritional and bioactive value (Stowe and Dhingra, 2020).

4. Flavonoid consumption and health promotion

Extensive research has been devoted in the last decades to study the associations between flavonoid consumption and health. Most studies focused on the consequences of exposing *in vitro* systems and animals to flavonoids, e.g. pure compounds and their metabolites, extracts, infusion and decoctions, enriched foods, beverages. The overall results demonstrate positive health effects associated with flavonoid consumption/presence and support the consideration of flavonoids as bioactives. Within this consideration, it is important to mention that many of the studies could be of limited physiological value given limitations in the experimental design used, e.g. flavonoid dose/concentration used, route of administration.

In terms of potential toxicity, considering that flavonoids are usually consumed by humans, their intake as part of 'normal' diets do not present toxic effects. In addition, when flavonoids (cocoa flavanols) were consumed by healthy men and women at higher levels, i.e. up to 2000 mg/d for 12 weeks, no toxic effects were observed (Ottaviani et al., 2015). Further studies on different compounds are necessary to establish non-toxic consumption levels.

As indicated in the previous sections, flavonoids are omnipresent in plants, which makes the recommendation of increasing fruit and vegetable consumption coherent with an elevated flavonoid consumption. Clearly, fruits and vegetables with high flavonoid content, or which content has been increased and/or well preserved, would favor the health promoting actions.

4.1. Human consumption of flavonoids

The main sources of flavonoids include plants and parts of plants that are usually consumed as part of human diets. Consumption of such plants includes raw and cooked fruits and vegetables, e.g. apples, berries, grapes, beverages like tea, red wine, and cocoa, and other plant processed products (Text Box 1). Interestingly, tea (*Camellia sinensis* infusion), grape wine (especially red wine), and cocoa beverages have been historically used not only as drinks but also as medicines (Samanta, 2020; Haseeb et al., 2019; Dillinger et al., 2000).

4.2. Population and clinical studies

In terms of population studies, many flavonoid-rich foods have been associated with better health and reduced risk of cancer and cardiovascular disease (Yang et al., 2023; Mazidi et al., 2020; Grosso et al., 2017; Chung et al., 2020; Menezes et al., 2017; Parmenter et al., 2022, 2023; Micek et al., 2021). A recent major clinical study, i.e. the COSMOS trial, relates the long-term (>4 years) administration of a cocoa extract (containing 500 mg of flavanols per day) to reductions of cardiovascular disease (Sesso et al., 2022) and in improvements in cognition (Brickman et al., 2023) in older women and men (>60 years old). In addition, several other studies have shown that the consumption of flavonoid-rich foods provide health benefits. For example, showing associations between anthocyanin consumption and reduction of inflammation (Cremonini et al., 2022), green tea polyphenols and decreased diabetic nephropathy (Borges et al., 2016), and flavanols and improved vascular function (Gröne et al., 2020; Dower et al., 2016; Mastroiacovo et al.,

Table 1
Examples of flavonoids interacting with specific proteins: receptors, enzymes and transcription factors, and types of studies.

Flavonoid	Protein	Type of study	Reference
Epigallocatechin-3-gallate	67 kDa Laminin B receptor	In vitro	Tachibana et al. (2004)
Epigallocatechin-3-gallate	Pancreatic lipase	In silico	Bello et al. (2017)
Genistin	Estrogen receptor β	In vitro	Tang et al. (2024)
Baicalin	Human angiotensin-converting enzyme II	In vitro	Lin et al. (2024)
Isorhamnetin	Cytochrome P450 enzymes (CYP1A1 and CYP1B1)	In silico	Odoemelam et al. (2022)
Kaempferol	Nuclear receptor 4A1	In vitro/in vivo	Shrestha et al. (2021)
B1 and B2 dimeric procyanidins	RelA and p50 DNA consensus sequence	In silico/*in vitro*	Mackenzie et al. (2009)

2015; Sansone et al., 2015; Desideri et al., 2012; Grassi et al., 2012; Almoosawi et al., 2010; Balzer et al., 2008; Heiss et al., 2005; Fraga et al., 2005).

4.3. Mechanisms: how to relate flavonoid consumption to health promoting effects

Flavonoid actions in animals differ substantially from those described in plants. In most cases, biological actions in animals/humans are not expected to cure diseases, but could act delaying the onset, attenuating the progression, and/or reducing comorbidities of non-communicable chronic diseases.

A relevant aspect to advance in the understanding of the mechanisms of flavonoid actions, is the understanding of their ADME (absorption, distribution, metabolism, and excretion). It has been proposed that ADME processes are subject to inter-person variability, which would have a major relevance in conditioning their effects on human health (Favari et al., 2024).

In general, flavonoids are poorly absorbed in the gastrointestinal tract. In the small intestine, some flavonoids are metabolized by phase II enzymes, whereas in the colon, most flavonoids are extensively degraded by the microbiota (Ottaviani et al., 2016; Di Pede et al., 2023). Metabolites produced by the microbiota can be absorbed into enterocytes and, after a potential further metabolism by intestinal phase II enzymes, they can reach the circulation. Thus, the flavonoids in the chemical form provided by the edible plants (parent compounds) will be present in high concentration only in the upper gastrointestinal tract, while other tissues will be mostly exposed to a variety of metabolites (Oteiza et al., 2021). Experimental evidence indicates that in humans, after consumption of high amounts of a specific flavonoid (e.g. 60 mg of the flavanol (−)-epicatechin), low concentration of metabolites (e.g. 359 nM of (−)-epicatechin 3′-glucuronide, and 272 nM of 5-(4′ hydroxyphenyl)-γ−valerolactone-sulfate, among others chemical species) were largely detected in circulation (Ottaviani et al., 2016). These metabolites should be the chemical entities responsible for the primary interactions with biological targets. In the case of non-absorbable flavonoids, their action site would be restricted to the intestinal tract lumen, e.g. acting on gut epithelial cells, diminishing inflammation and protecting gut permeability barrier and/or interacting with the microbiota, changing its composition (Oteiza et al., 2023; Lan et al., 2023; Li et al., 2023) and potentially affecting different organs through the different gut-organ interactions (Wang et al., 2023).

In terms of mechanisms, flavonoids and their metabolites could act either through generic or specific actions. Generic actions are unspecific in nature and can be promoted by a group of flavonoids sharing chemical moieties, such as the phenolic groups. Examples of this category are the general interaction with cell membranes modifying physical properties, or with particular areas of the membranes, such as lipid rafts. In turn, those interactions can affect the activity of intracellular signaling pathways (Fraga et al., 2018). On the other hand, specific actions are mediated by reactions between an individual flavonoid or flavonoid metabolite and a particular enzyme or component of a signaling pathway (Table 1) (Tachibana et al., 2004; Bello et al., 2017; Tang et al., 2024; Lin et al., 2024; Odoemelam et al., 2022; Shrestha et al., 2021; Mackenzie et al., 2009).

As a result of those actions, a panoply of physiological mechanisms appears to be modified in experimental animals and/or cell cultures, being some of them of higher relevance for human health. For example, the flavanol (−)-epicatechin has been involved in the: i) protection of intestinal barrier integrity (Cremonini et al., 2018) ii) regulation of superoxide and nitric oxide metabolism in aorta (Litterio et al., 2012, 2015) and kidney (Prince et al., 2016); iii) modulation of insulin and NF-κB signaling pathways (Hid et al., 2022; Cremonini et al., 2019, 2020), and iv) stimulation of mitochondrial biogenesis (Moreno-Ulloa et al., 2018**).** Additionally, we and other researchers have provided evidence of the participation of flavonoids in the regulation of redox sensitive signaling, with consequent benefits for human health (Fraga et al., 2018).

5. Conclusions

Flavonoids regulate different physiological and molecular mechanisms in plants and in animals. Assuming the importance of flavonoids in animal physiology, it may be useful to optimize flavonoid presence in plants and in the plant-based foods to be consumed. Selecting flavonoid-rich foods, improving flavonoid content in plants using genetic engineering, preserving flavonoid content in foods, or using flavonoids as food supplements, are possibilities to improve human and animal health. However, when it comes to establish mechanisms that could allow define specific compounds, doses, timing of administration, and other variables, the multiple flavonoids participating in various physiological pathways generate a highly complex matrix. Today we are aware of some aspects of this matrix, however, the final understanding of the relevance of flavonoids for human health requires further research that include clinical interventions, characterization of metabolites reaching biological targets, and of the biochemical pathways affected by that interaction.

CRediT authorship contribution statement

Andrea Galatro: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Agustin Lucini Mas:** Writing – review & editing, Visualization. **Melisa Luquet:** Writing – review & editing, Visualization. **Cesar G. Fraga:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Monica Galleano:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Section Editor - Nutrients and Bioactives: CGF.

Editorial Board Member: MG. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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