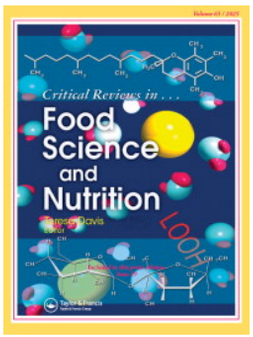

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REVIEW ARTICLE

Self-assembling of flavonoids and food-approved coformers: an emerging strategy for food preservation and controlled release of eco-friendly preservatives

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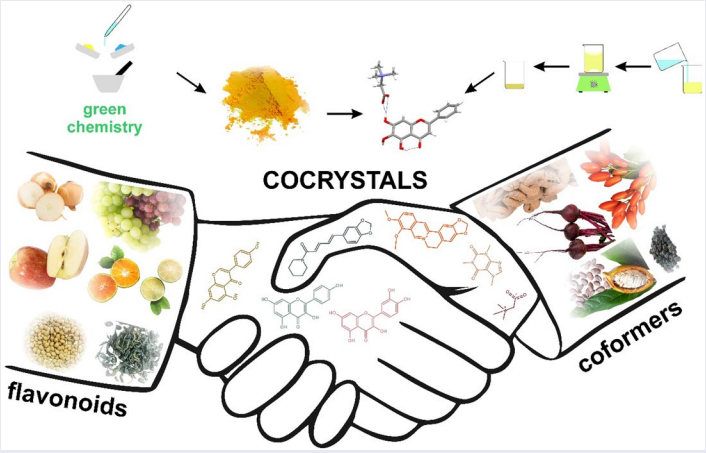
ABSTRACT

This review aims to provide a broad but detailed overview on cocrystal formulation involving flavonoids and food-grade coformers and its impact on modulating the physicochemical and biological properties of the parent flavonoid. We will briefly describe cocrystallization, the coformers, the main interactions, methods of production and characterization and the main physicochemical properties (stability, solubility, etc.) that are improved upon their formation. Some examples of flavonoid-based cocrystals, discussion on food preservation strategies based on cocrystals and potential applications are included. Flavonoids are natural compounds used as food ingredients and supplements, with anti-cancer, anti-inflammatory, and antioxidant properties. They are increasingly used in functional foods to improve human health and well-being, but their drawbacks, related to their poor water solubility and limited availability, restricts applications. An effective strategy to improve their functionalities is based on their transformation into molecular complexes (cocrystals) stabilized by non-covalent interactions, which impart new physicochemical properties to the cocrystal components. The combined properties of flavonoid-based cocrystals open up potential applications in food, biological, pharmaceutical, and medical formulations. Cocrystals, therefore, are opening many new doors in relevant industries showing scope for research and providing researchers and formulators with opportunities of making the difficult (or even the impossible), easier and achievable.

KEYWORDS

Antioxidants; cocrystals; flavonoids; food-grade coformers; solubility

GRAPHICAL ABSTRACT



Introduction

Cocrystallization is a supramolecular phenomenon of aggregation of two or more different chemical entities into a crystalline network through non-covalent interactions. Cocrystals have become very popular as potential new/alternative solid form of nutraceuticals, pharmaceuticals and other compounds which are relevant to health and food areas (Xu et al. 2023; Sakhiya and Borkhataria 2024; Sarangi et al. 2024; Wong et al. 2024; Li D et al. 2025; Pantwalawalkar et al. 2025). The term "cocrystal" is frequently used to describe crystalline materials composed of two or more

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neutral molecules present in the same crystal network. Thus, they can be described as highly oriented, three dimensional molecular assemblies in the solid state (Figure 1) whose structure is controlled by symmetry and intermolecular interactions that ultimately determine some of their physicochemical properties.

The intermolecular forces involved in cocrystal cohesion include hydrogen and halogen bonding, van der Waals, π-π, and electrostatic interactions. Hydrogen bonding is probably the most significant interaction in cocrystal design as many cocrystals are formed between molecules that behave as weak acids and/or bases. Hydrogen bonds not only serve to connect different molecules but also provide a degree of directionality and dimensionality to the three-dimensional structure of the solid. π-π interactions are observed in cocrystal systems with aromatic rings (e.g., flavonoids), maximizing interactions between electron-rich and electron-deficient regions of the aromatic ring quadrupoles and occur in either offset, face-to-face or edge-to-face geometry. Van der Waals interactions also play an important role in cocrystal engineering. Molecular crystals are typically characterized by minimal void space, as van der Waals forces are ubiquitous and help stabilize the structure through surface contact area (Sarangi et al. 2024).

The structural units that can be formed and/or assembled by intermolecular interactions are known as supramolecular synthons. Molecules are recognized *via* non-covalent interactions where some groups "recognize" others as complementary, and this molecular recognition can be used to define specific "coformers" for tuning the particular physicochemical properties of the prepared cocrystals. Overall, the spatial arrangement (balance) of these intermolecular interactions, combined with features of molecular recognition and geometrical conditions of crystal packing leads to the final cocrystal structure.

Cocrystals have the potential of preserving the integrity of the parent molecules until their final usage, minimizing their oxidation or photo-oxidation degradation and enhancing various properties such as solubility, wettability, flowability, stability, anticaking, permeability, bioavailability, hygroscopicity and hardness. They can even mask undesirable tastes (Luján-Torres et al. 2023). The final behavior of these unique supramolecular/non-covalent crystalline adducts is controlled by both the nature of the components involved

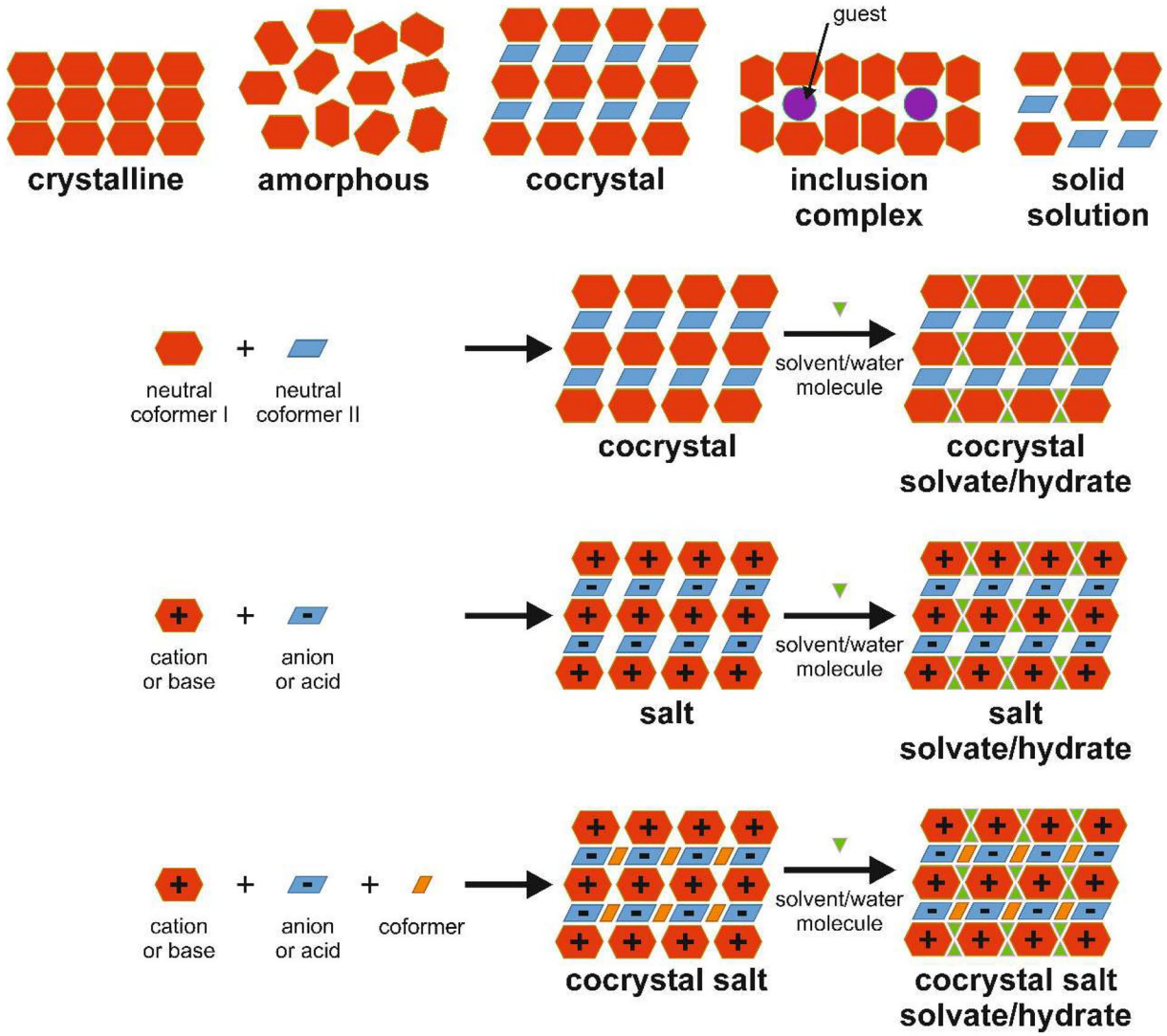

Figure 1. Schematic representation of the formation of different multicomponent crystals.

and the environmental conditions (temperature, solvent, pH, etc.).

A literature survey shows that most reported cocrystal investigations are related to, somehow, improving drug properties (Sakhiya and Borkhataria 2024; Sarangi et al. 2024; Wong et al. 2024; Pantwalawalkar et al. 2025). Still, the same principles as for pharmaceutical drugs may apply to food systems as restrictions in the use of flavonoids are primarily due to their undesirable physicochemical properties such as their low water solubility, preventing their regular use in food formulations. Research is ongoing and applications are currently expanding to food applications because of the enormous interest of the food industry in developing functional ingredients to prepare healthier and safer foods with longer shelf-lives to minimize food wasting, making such studies a particularly relevant and timely topic.

Bearing this in mind, the present review aims to provide a comprehensive overview of cocrystal formulations involving flavonoids and a range of coformers, including those of food-grade quality, with particular emphasis on their impact on modulating the physicochemical and biological properties of the parent flavonoids. For the purpose, we will introduce some specific features of flavonoids that make them important and valuables in the food and health areas. We will also add some discussion on the reasons why their current use in dietary foods is limited (bioavailability and food matrix effects) as well as some methods that eventually can help to overcome these limitations, introducing cocrystallization as a crucial aspect of molecular development for the improvement of solubility and bioavailability without compromising the original chemical structure of the coformers, which is retained as no covalent bonds are created or destroyed. We will also discuss how coformers can be chosen, on the most common synthesis methods, and characterization of cocrystals. Some discussion on the improvement of relevant physicochemical properties of flavonoids that can be achieved through cocrystallization, the potential applications of flavonoids and future research directions is also included.

Polyphenolic antioxidants: flavonoids

Polyphenols, including flavonoids, phenolic acids, and tannins are low-molecular-weight compounds and secondary metabolites of higher plants widely distributed in the plant kingdom (Costa et al. 2021; Bolat et al. 2024). Flavonoids constitute a large family of food-relevant compounds that include flavones, flavonols, flavanones, flavanols or catechins, anthocyanins and chalcones (Bolat et al. 2024; Williamson 2025). They are responsible for the color of flowers and fruits, attracting pollinators helping in seed and spore germination, protect plants from different biotic and abiotic stresses and act as unique UV filters, function as signal molecules, allelopathic compounds, phytoalexins, detoxifying agents and antimicrobial defensive compounds (Shen et al. 2022).

Most naturally occurring flavonoids have three hydroxyl groups (Figure 2): two of them are on the ring A at positions five and seven, while one is located on the ring B at position three. The unique chemical structures of different flavonoids, which have a pivotal role on their acid-base properties, solubilities and spatial configurations confer them the ability to bind selectively to specific targets, thereby causing diverse biological activities that underscore their incomparable advantages in modulating physiological processes (Williamson 2025). Their beneficial effects on nutrition and health are intricately linked to their structural characteristics as these compounds are highly sensitive to even minor alterations in molecular composition, which can severely affect their physicochemical and biological properties. Thus, understanding and improving the physicochemical properties of flavonoids is essential for the processing of foods containing flavonoid compounds and in the preparation of new food formulations.

Relevance of flavonoids to food and health

Since the discovery that polyphenols, and flavonoids in particular, play important biological roles in the activities of plants, animals and bacteria, researchers made increasing attempts to incorporate them in the human life style to get advantage of their health benefits (Farhan et al. 2023; Mir et al. 2024; Williamson 2025). An increasing body of evidence from epidemiological and randomized trials provides evidence supporting the protective effects of foods and dietary supplements rich in flavonoids against chronic diseases including diabetes, cancer, Alzheimer, Parkinson and coronary heart attack. Currently, several flavonoid-based commercial medications and clinical trial candidates are in various stages of clinical development (Rode et al. 2024).

Polyphenols, and particularly flavonoids, display a wide spectrum of biological activities including the inactivation of carcinogens, inhibition of cell proliferation and antidiabetic. Their beneficial effects in the fight of a variety of diseases and against viral infections are promising and are currently being explored (Mir et al. 2024; Cai et al. 2025). Flavonoids inhibit the formation of cytochromes protecting against cellular damage. It has also been reported that flavonoids stimulate apoptosis in some cancer lines (gastric colon, breast, lung, etc.) while sparing normal ones. For example, kaempferol and genistein have been shown to present antiproliferative and apoptosis-inducing activities in several cancer cell lines, such as breast cancer (Seo et al. 2024) and human cervical cancer cells (Janakiramulu and Mamidala 2025) but the molecular mechanisms by which flavonoids induce apoptosis have not been elucidated so far (Farhan et al. 2023; Mir et al. 2024).

Most probably, the best investigated and known effect of flavonoids (and of other polyphenols) is their antioxidant activity, protecting the human body against harmful reactive oxygen species (ROS), Figure 3 (Costa et al. 2021; Losada-Barreiro and Sezgin-Bayindir 2022). The antioxidant properties of flavonoids are largely determined by their structure and number and position of the functional hydroxyl groups, which can scavenge free radicals and/or by chelating metal ions. Flavonoids also enhance antioxidant defenses by protecting endogenous antioxidant systems regenerating

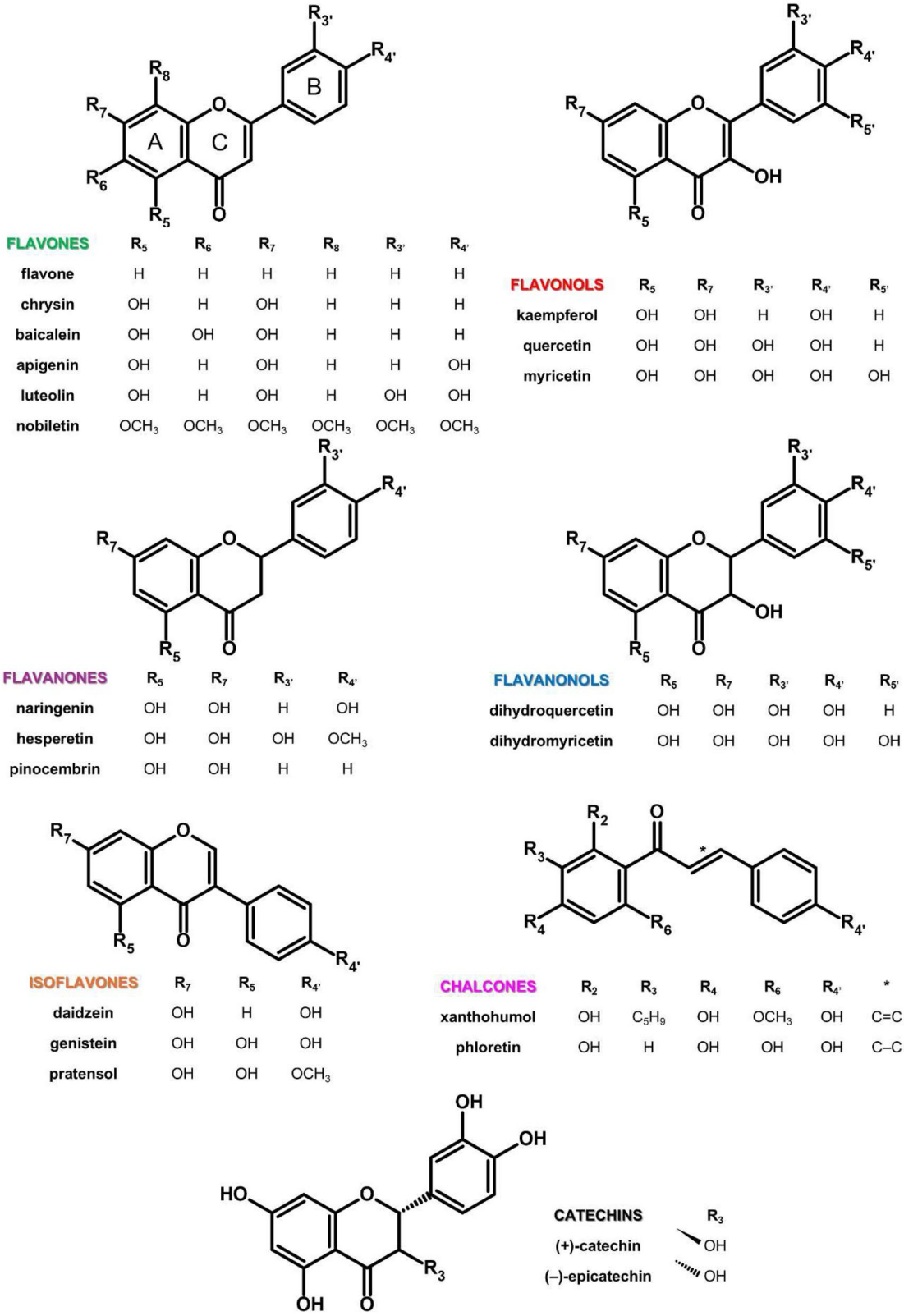

Figure 2. Chemical structures of common flavonoids.

them (Losada-Barreiro and Sezgin-Bayindir 2022). Additionally, the antioxidant effects of flavonoids may be linked to the activation of antioxidant enzymes possessing radical scavenging abilities such as glutathione peroxidase, catalase, and heme oxygenase-1.

It appears, thus, that flavonoids have noticeable positive effects on human and animal health and their use in disease therapy and chemoprevention is being explored (Losada-Barreiro and Sezgin-Bayindir 2022; Mir et al. 2024; Cai et al. 2025; Williamson 2025).

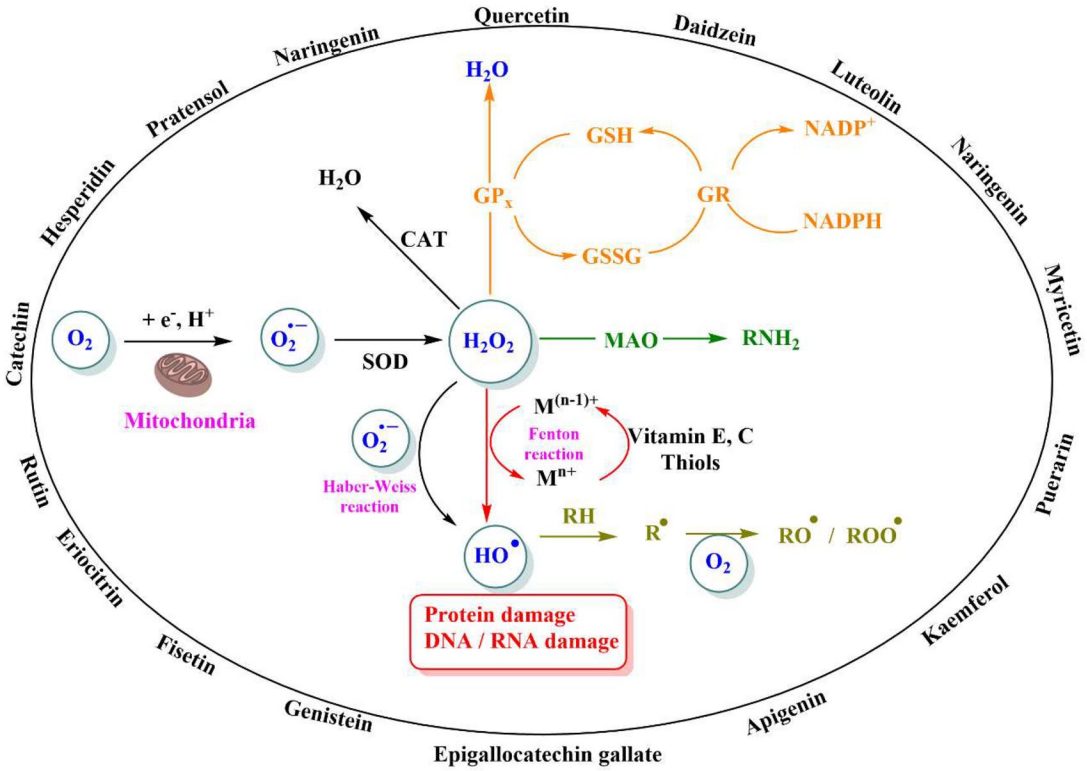

Figure 3. Different mechanisms of generation and loss of ROS and some flavonoids that have potent antioxidant activity. Their mechanisms of antioxidant action include direct scavenging of ROS, chelating metals, inhibiting enzymes (e.g., NADPH oxidases) and regenerating other antioxidants (e.g., tocopherols). The figure illustrates the formation of superoxide (O_2^-) from molecular oxygen. Its generation is mediated either by cytochrome c peroxidase or by xanthine oxidase in mitochondria, or by the NADPH oxidase complex. GR: glutathione reductase, GP_x: Glutathione peroxidase, GSSG: glutathione disulfide or oxidized glutathione, GSH: reduced glutathione, CAT: catalase, MAO: monoamine oxidase, SOD: superoxide dismutase, and RH: lipid. Figure adapted from (Sezgin-Bayindir et al. 2023).

The antioxidant efficiency of flavonoids depends on their chemical stability in the different food matrices, their position and number of hydroxyl groups in their chemical structures, Figure 2, as well as on their effective concentration at the reaction site (Bravo-Díaz 2022; Costa et al. 2022). Flavones and catechins are among the most powerful antioxidants and, in general, the mechanisms of antioxidant action comprise one or more of the following processes: (1) direct scavenging of reactive oxygen species (ROS, e.g., peroxyl radicals), (2) the activation of antioxidant enzymes (inhibiting, for example, the enzymatic action of enzymes that produce free radicals (nitric-oxide synthase, xanthine oxidase, etc., regulating of the production of antioxidant defenses (Chandimali et al. 2025) and (3) chelating transition metal ions (Cu(II), Fe(III), etc.) involved in redox processes decreasing their effective concentration (Chen S et al. 2023).

Beyond the protection of cellular walls and blood vessels, flavonoids help to reduce blood cholesterol levels and cardiovascular disease risk factors. For example, quercetin has been shown to be an effective cardioprotective agent in rats (Espírito-Santo et al. 2023).

A variety of flavonoid-rich extracts have been investigated for their antimicrobial activity in the fight against harmful microorganisms including *Escherichia coli*, *Salmonella*, and *Listeria*. Luteolin, diosmetin, baicalein, naringin, fisetin are all examples of flavonoids that have been employed in the fight against microbes (Wu et al. 2024). The rapid advancement in omics technology and current understanding of the antimicrobial mechanisms of flavonoids lays a basis for their application in the food industry (Shamsudin et al. 2022; Wu et al. 2024). Moreover, recent studies have developed strategies to overcome the solubility and stability of flavonoids by incorporating them into edible films and coatings, encapsulation with nanocarriers and in intelligent packaging (Wu et al. 2024).

Flavonoids are also exploited as light preservatives. Proteins and peptides, carbohydrates, and lipids can be exposed to the harmful effects of light (depending on the transmission properties of the packaging material) initiating harmful reactions such as lipid oxidation (Schaich 2022; Chandimali et al. 2025). Flavonoids can help to protect food and beverages against light even when present in parts per million (Lingwan et al. 2023). Their mechanisms of action include (1) direct absorption of photons, acting as filters protecting sensitive food components; (2) deactivating excited states of sensitizers like chlorophyll and riboflavin; (3) quenching of singlet oxygen and scavenging of radicals formed as reaction intermediates in photosensitization reactions. The feasibility of these protective strategies is currently supported by solid kinetic data allowing for calculations of threshold levels of flavonoids to prevent beer and dairy products from premature quality loss. As flavonoids are safe, relatively cheap (they can often be extracted from food processing wastes), abundant in nature, exempt from food additives certification, they are most likely competitive with synthetic preservatives (Lingwan et al. 2023).

Unfortunately, the human body cannot produce most of the polyphenols, and so they can only be bioavailable if they are present in the consumed food or beverage or otherwise introduced in the form of various food/pharmaceutical preparations through the production of new food formulations with dietary and health benefits (Shen et al. 2022). So, in spite of their broad benefits and wide distribution of flavonoids, they have poor bioavailability, affecting their nutritional value. Food processing has an important effect on polyphenol content sometimes reducing it to almost zero. For instance, it has been reported that ultra-processed foods contain lower amounts of polyphenols and individuals whose daily food intake is mostly based on such foods have poorer health prospects than people who eats fresh fruits and vegetables (Grinshpan et al. 2024; Maki et al. 2024; Williamson 2025). Nowadays, it is advised the abundant consumption of dietary sources of flavonoids such as fruits and vegetables, herbs, legumes, nuts, and spices every day (Molina-Montes et al. 2020; Ergas et al. 2023). On the other hand, the polyphenol content of foods is quite variable, as many studies focused on measuring the polyphenol content of fruits and vegetables indicate that its content is highly inconsistent and frequently depends on the growing conditions, season and soil (Shen et al. 2022). Differences in flavonoid contents between plant species are usually moderate but require the intake of large amounts of them, and so new food formulations containing flavonoids are to be developed.

A brief survey on the fate of flavonoids in the human body: gut microbiome and metabolic parameters

When dietary flavonoid-rich products are ingested, most of the flavonoids pass through large to small intestine, reaching the colon and metabolized into phenolic acids by the colonic microflora. Thus, once ingested, flavonoids can alter the gut microbiota not only through antimicrobial actions but also becoming nutrients for some particular bacterial species (Baky et al. 2022). For example, enzymatic conversion to glycosidic flavonoids improved substantially their absorption compared to the parent flavonoid. Blocking the free hydroxyl groups by, for instance, capping them with methyl groups resulted in a significant improvement on their metabolic stability. The metabolic stability of flavones *in vitro* increased notably after inactivating the –OH groups, and therefore improving their bioavailability (Baky et al. 2022).

Borneol/methanol eutectic mixtures have been employed as intestinal adsorption enhancers of, for instance, daidzein, improving not only its adsorption but also its permeability (Berga et al. 2023). Some nano-delivery systems were also designed to improve its oral bioavailability and intestinal adsorption (Yuan et al. 2024). Complexation of flavonoids with cyclodextrins were also successfully employed to improve their bioavailability (Chen F et al. 2025).

Current understanding of microbial conversion of flavonoids has improved significantly and a quite comprehensive list of flavonoid conversion reactions with bacterial species present in the human gut microbiota and there is now a growing interest in the microbial contribution to intestinal flavonoid levels, in particular about conversion of flavonoids into active compounds that benefit the human beings (Baky et al. 2022).

Main limitations in the use of flavonoids in dietary foods: flavonoid bioavailability and effects of food matrix

The main limitations of the use of flavonoids in food and other areas are strongly associated to their chemical and biophysical properties, such as their low solubility in water, chemical stability, bioavailability, and their pharmacokinetics properties which significantly constrains their use in food and pharmaceutical preparations (Liga et al. 2023; Yuan et al. 2024; Williamson 2025). These properties are of paramount interest as no compound can be effective if, for whatever reason, it does not reach its site of action at sufficient concentration to act on a target.

Researchers are continuously trying to improve these properties by finding proper solubilization and delivery systems to attain the required concentrations at the action site. Encapsulation increases the solubility and bioaccessibility of poorly soluble polyphenols and other drugs. In this sense, cocrystallization may play a central role as it has become an attractive technique for tailoring the physicochemical properties of flavonoids and, in general, those of active pharmaceutical ingredients.

The problem of bioavailability of flavonoids is still far from being resolved (Williamson 2025) and three major areas of research have been developed: (a) studies on bioavailability, metabolic paths in humans and quantitative studies of absorption and excretion, (b) studies on the action of gut microbiota on polyphenols metabolism and (c) strategies to improve bioavailability including encapsulation employing various cyclodextrins and nanocarriers.

The gut microbiota plays an extremely important role in polyphenol bioavailability and is responsible for most of the observed variations in the metabolism of individuals (both the intra- and inter-individual metabolism). Even though much progress has be done in understanding the metabolic pathways and in obtaining quantitative estimations of absorption and excretion of many polyphenols, a detailed description of the metabolic pathways of common dietary polyphenols is out of the scope of this review and the interested reader is referred to specialized reviews on the topic (Aoi et al. 2021; Mishra et al. 2024; Mao et al. 2025).

Unfortunately, and in spite of the reported beneficial effects of flavonoids (Chen S et al. 2023; Williamson 2025), recent cohort studies (Framingham Offspring Cohort) (Shishtar et al. 2020) suggest that that there is no significant correlation between flavonoid intake and cardiovascular disease (CVD) incidence after multivariable adjustment. This lack of correlation suggests that the relationships between flavonoid intake and CVD risk requires further investigation as such a diversity in responsiveness to flavonoids intake may relate to a number of factors as, for example, the

chemical structure in terms of molecular weight, glycosylation degree and esterification play a pivotal role in flavonoid absorption. In addition, the presence of flavonoids in important dietary sources (vegetables, fruits, seeds, wine, tea, etc.) may greatly change as a function of the crop variety, type of processing, climate, seasonality, plant species, processing and storage (Baky et al. 2022). The microbiome is likely to be critical and it plays a key role in flavonoids metabolism and may alter the composition and function of the gut microbiome. On the contrary, the microbiota may enhance the metabolism of flavonoids, but this bidirectional relationship is not fully understood and needs more work (Baky et al. 2022). Molecular interactions between flavonoids and various constituents of the food matrix can affect their absorption. *In vivo* and *in vitro* studies have shown that, in general, the presence of proteins, dietary fiber and minerals may have undesired effects on the bioavailability of flavonoids. On the contrary, lipids, digestible carbohydrates, vitamins, carotenoids and other flavonoids improve flavonoid bioavailability.

Enhancement of bioavailability would be, therefore, of utmost importance in order to exert health effects, *in vivo*. These restrictions in their bioavailability can be overcome by improving the intestinal absorption *via* changing the site of absorption from large intestine to small intestine, improving metabolic stability, using absorption enhancers and developing novel delivery systems (Chen S et al. 2023). Figure 4 shows some of the most common drug delivery systems. In particular, emulsions, nanoemulsions, and cyclodextrins have been widely employed to increase the bioavailability of drugs of interest but in recent years, cocrystallization has emerged as a promising tool to deliver flavonoids, providing a unique opportunity of improving their physicochemical properties and overcoming some of their limitations, opening new opportunities to employ them as Active Food Ingredients (AFIs) (Liga et al. 2023).

Cocrystallization is a very attractive option to modulate the physicochemical properties of chemicals of interest without modifying their chemical structure (i.e., without changing covalent interactions) and thus cocrystals are usually designed to tackle the poor dissolution behavior and low bioavailability of potential poorly water-soluble candidates. The mechanisms by which cocrystals improve solubility are related to changes in lattice and solvation energies due to the presence of suitable coformers. These coformers are generally considered inactive partners necessary to slightly modify the properties (e.g., pK_a) of the polyphenol altering its dissolution and solubility properties, but they can also be bioactive molecules with beneficial effects on health or on

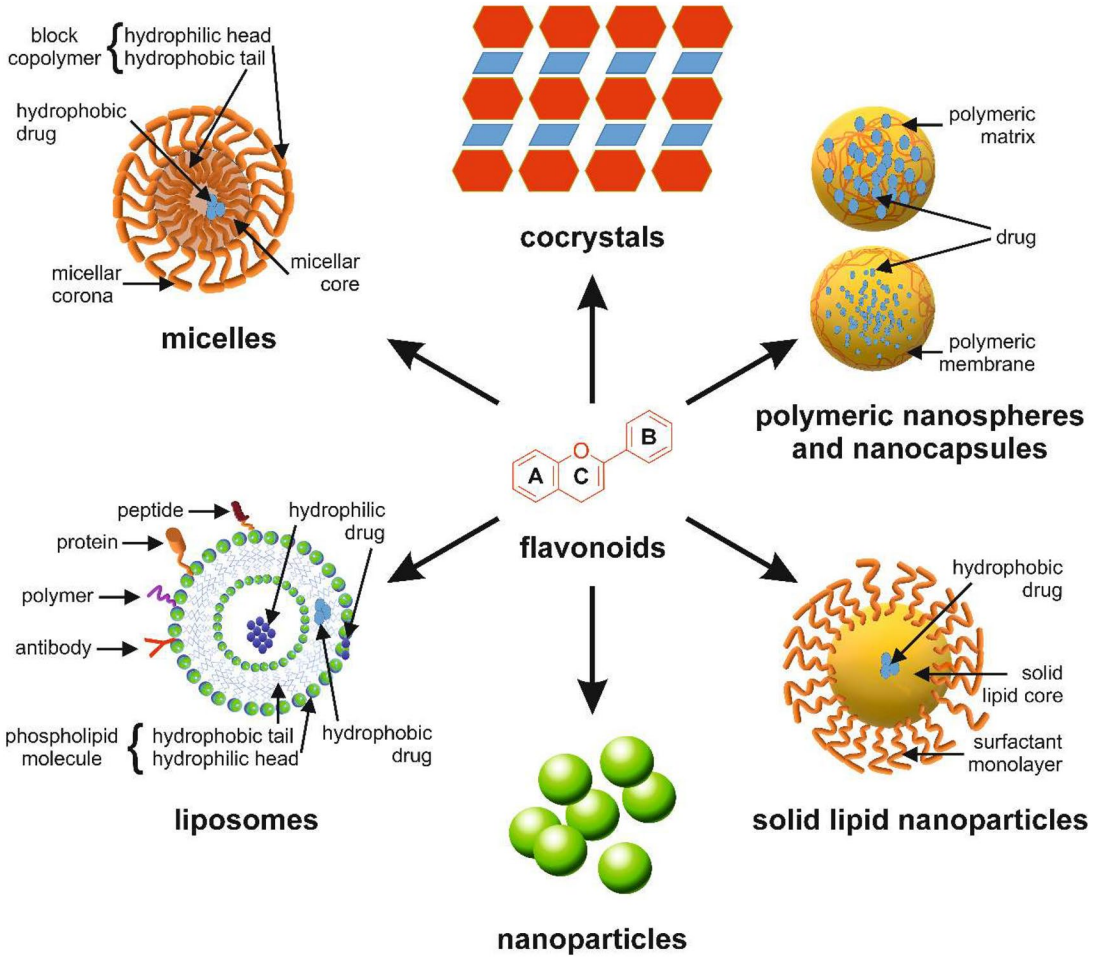

Figure 4. Schematic representation of different drug delivery systems. Among them, cocrystallization is emerging as a practical and useful method employed to modify the properties of flavonoids by altering their crystal structure.

biological activity. For example, some flavonoids can be employed as coformers of pharmaceutical compounds.

Cocrystals not only have the ability of increasing the solubility of the bioactive component (flavonoid, drug) but also to improve their dissolution, overcoming some of the problems of low and erratic drug bioavailability. During cocrystal development, researchers focus on finding correlations between cocrystal properties (stability, solubility, dissolution rate, etc.) and the expected environmental conditions that are presumed to occur during the formulations, storage, processing, and dissolution steps. Relevant to these relationships are the molecular mechanisms by which cocrystals dissolve. These mechanisms are usually described in terms of the various reaction equilibria that are involved and their quantitative description leading to solubility equations that can quantify the intercorrelation between solution conditions and cocrystal properties. Key thermodynamic parameters that are commonly used as stability indicators include transition temperature (polymorphs), critical water activity (hydrates), acidity, i.e., pH (salts and cocrystals), critical relative humidity (hydrates/anhydrous forms) and eutectic points (cocrystals). These stability indicators usually define regions of both thermodynamic stability and instability, which are central to material development and their use as delivery systems. A thorough discussion of these indicators and their implications is out of the scope of this review, the interested reader can find further information on the underlying mechanisms elsewhere (Xu et al. 2023; Panzade et al. 2024). However, we will come back to the topic and add more detailed discussion about some of these features in Section "Improvement of solubility and other relevant physicochemical properties of flavonoids".

Methods to improve bioavailability and bioaccessibility

Increasing the bioavailability and bioaccessibility of polyphenols has been a challenging task during the last years for the food community. Strategies usually consider the mechanisms of adsorption and the rate-determining steps in attempting to overcome them. The most successful delivery methods, Figure 4, are designed to improve the stability and solubility of the polyphenols and to facilitate the transfer of them across the mucus layers to the enterocyte. This mucus layer not only acts as an important barrier preventing damage to the underlying cells but also limits polyphenol adsorption (Williamson 2025).

A widely employed way to improve the bioavailability of polyphenols considers the use of suitable delivery systems so that the polyphenol of interest can easily reach the target places. Among these systems, encapsulation with cyclodextrins, nanoparticles and emulsions, and more recently, cocrystals, have been widely employed.

Accommodation of polyphenols in nanostructures, either solid (nanoparticles) or fluid (nanoemulsions), Figure 4, has also been widely employed to improve the bioavailability of polyphenols and other drugs both *in vivo* and *in vitro* (Abdi Syahputra et al. 2024; Morsy et al. 2025). Nanoencapsulated flavonoids improve their therapeutic effects by lowering oxidative stress and improving lipid profiles in cardiovascular diseases. Polymer-based nanosystems are best suited for controlled quercetin release, whereas inorganic nanoparticles provide stable characteristics. Consequently, nanoformulations can enhance the effects of quercetin, particularly in diabetes and diabetic nephropathy conditions. These findings suggest the possibility of using flavonoids prepared through nanotechnology to address metabolic syndromes and related issues (Abdi Syahputra et al. 2024).

Compared with other delivery systems, Figure 4, cocrystals offer some advantages but also have some limitations. On the positive side, the possibility of improving physicochemical properties closely related to the solubility, dissolution and availability of compounds of interests made cocrystals popular owing to their ability to fine tune physicochemical properties of pharmaceuticals/nutraceuticals without changing their chemical integrity, thus opening new ways for the improvement of physicochemical properties of molecules of interest expanding the opportunities to harness their beneficial effects. In fact, cocrystals have been recognized as the "rising star in drug delivery applications" (Panzade et al. 2024). Cocrystallization of polyphenols has been a trending topic in recent years because proper selection of suitable coformers not only improves the physicochemical properties but also their therapeutic efficiency reducing side effects, and their potential as delivery systems will be addressed in Section "Cocrystallization: a tool to delivery poorly soluble compounds". A large variety of coformers are available in currently marketed cocrystal-based products, including the carboxylic acid-based ones (fumaric, oxalic, succinic, etc.). A brief summary of the required properties of the coformers and some tips on their selection are provided in Section "Coformer screening applied to flavonoid-based cocrystals".

Cocrystallization: a tool to delivery poorly soluble compounds

During the last decades, cocrystals have become very popular as a potential new/alternate solid form of nutraceuticals, pharmaceuticals and other compounds relevant to different industrial areas (Sakhiya and Borkhataria 2024; Sarangi et al. 2024; Wong et al. 2024; Li D et al. 2025; Pantwalawalkar et al. 2025). From the food and pharmaceutical point of view, the cocrystal ingredients include an active compound (polyphenol or drug) and a "coformer" whose physicochemical properties are improved compared to those of the parent compounds (Figure 5).

Coformers play a major role in the development of flavonoid-based cocrystals, as they strongly influence the physical properties and stabilization of these systems. For successful cocrystal preparation, it is therefore essential to identify potential binding sites, while also considering health and safety aspects when necessary. Coformer selection can be carried out by employing different approaches including experimentation, "*in silico*" methods, knowledge-based methods (hydrogen-bonding rules, pK_a-based models, Hansen

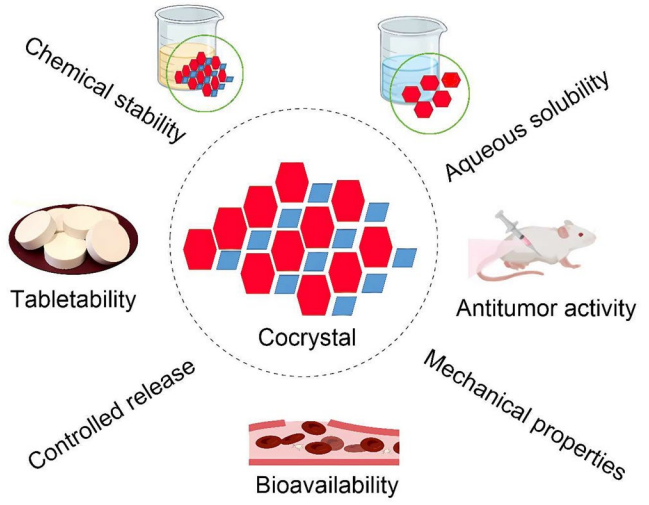

Figure 5. Some of the properties of flavonoid-based cocrystals that can be boosted compared to those of the parent compounds.

solubility parameters, and most importantly, the Cambridge Structural Database (CSD) (Groom et al. 2016; Wathoni et al. 2022; Singh et al. 2023). An useful and practical tool is the evaluation of the frequency of interactions between two specific functional groups by analyzing the main intermolecular interactions of reported flavonoid-based cocrystals based solely on well-characterized, solid-state structures reported in the CSD database. The frequency of a particular interaction is calculated as a ratio between the number of entries over the number of deposited structures containing the two functional groups (phenol and organic function). Based on these statistics, it is possible to discern which molecules represent potential coformers for flavonoid-based cocrystals.

Importance of flavonoid cocrystals for the food industry

Food cocrystals contain one active food ingredient (e.g., flavonoid, polyphenol, essential oil) and a second component which is food acceptable (e.g., sucrose, lactose, caffeine, theophylline, theobromine, nicotinamide, isonicotinamide, etc.) (Chezanoglou and Goula 2021; Dias et al. 2021; Luján-Torres et al. 2023). Nicotinamide, isonicotinamide, and picolinic acid, which are components that form vitamin B3 complexes, are the most used coformers. These components participate in important human biochemical reactions, and are precursors of nucleotide coenzymes, which play crucial roles in a wide variety of metabolic pathways including electron transport chain (Dias et al. 2021). Methylxanthines (Venkatesan et al. 2023) are also widely employed as coformers in the polyphenol cocrystal production, as they are naturally occurring alkaloids with therapeutic potential against neurodegenerative diseases, and in some instances favoring liposis, a key effect on weight loss and obesity control.

An important advantage of food cocrystals grounds on their potential for preserving the integrity of the parent molecules until their final usage, minimizing their oxidation or photo-oxidation degradation and enhancing various properties such as solubility, wettability, flowability, stability, anticaking, permeability, bioavailability, hygroscopicity and hardness. They can even mask undesirable tastes (Luján-Torres et al. 2023). The final behavior of these unique supramolecular/non-covalent crystalline adducts is controlled by both the nature of the components involved and the environmental conditions (temperature, solvent, pH etc.). A literature survey shows that most reported cocrystal investigations are related to, somehow, improving drug properties (Figure 5) (Sakhiya and Borkhataria 2024; Sarangi et al. 2024; Wong et al. 2024; Pantwalawalkar et al. 2025). The research interests are, however, currently expanding to food applications because of the enormous interest of the food industry in developing functional ingredients to prepare healthier and safer foods with longer shelf-lives to minimize food wasting, making of such studies a particular relevant trendy topic. Still, the food industry has to face the restriction in the use of flavonoids because of some of their undesirable physicochemical properties such as their low water solubility, which prevents their regular use in foods.

Coformer screening applied to flavonoid-based cocrystals

As expected, coformers play a major role in the development of flavonoid-based cocrystals as they strongly affect their physical properties (solubility, stability, and bioavailability) and their physical stabilization, which finally results in an improvement of their performance compared to that of the raw material (Chettri et al. 2024). Although there may be a large number of potential coformers, only those which are harmless should be used for food purposes. Identification of potential binding sites is necessary to succeed in the preparation of cocrystals alongside health safety aspects. Ideal coformers are those included in the "Substances Added to Food" (Substances Added to Food (formerly EAFUS) | FDA) and the GRAS ("Generally Recognized As Safe" database) (GRAS Substances (SCOGS) Database | FDA) databases and the Regulation EC N° 1333/2008 of the European parliament and of the council of 16 December 2008 on food additives (Food and Feed Information Portal Database | FIP, accessed 2025-01-09).

Coformer selection can be carried out in different ways including experimentation, by employing "*in silico*" methods, by employing a variety of knowledge-based methods, e.g., hydrogen-bonding rules, pK_a-based models, Cambridge Structural Database (CSD) screening, supramolecular synthon compatibility, lattice energy calculations, Hansen solubility parameters, thermal analysis and saturation temperature measurements, and virtual cocrystal screening (Wathoni et al. 2022; Singh et al. 2023).

A practical and useful tool to choose appropriate coformers exploits the analysis of the feasibility of hydrogen bonding between the flavonoid and the coformer through the evaluation of the frequencies of particular interactions between two specific functional groups by employing, for instance, the CSD (Abourahma 2024). Since flavonoids contain hydroxyl groups in their structure, hydrogen-bond interactions are expected to play a relevant role. The frequency of a particular hydrogen bond embodies the ratio

between the number of entries and the number of deposited structures containing both functional groups (flavonoid and coformer). On the basis of these statistics, we can discern which molecules represent potential coformers for new flavonoid-based cocrystals. This tool can also be employed in the search of structural units within supermolecules that can be generated through intermolecular interactions (synthons) (Dias et al. 2021).

On view of the chemical structure of flavonoids, Figure 2, these compounds have numerous possibilities for non-covalent interactions and should be considered highly labile synthons, exhibiting structural polymorphism. Hydroxyl and carbonyl groups can participate in both intra- and intermolecular interactions, serving as donors and acceptors in hydrogen bonding and the molecular interactions between -OH groups and H-bond donating groups (such as carboxyl, carbonyl, amide, and pyridyl) have been reported as the main synthon for the formation of polyphenol-based cocrystals (Dias et al. 2021).

Although these intermolecular interactions should be determinant in seeking potential coformers, we approached the search of optimal coformers by analyzing the main intermolecular interactions of reported flavonoid-based cocrystals based solely on well-characterized, solid-state, structures reported in the CSD according to the following criteria: (1) structural precision, (2) property predictability, and (3) utility in the material design.

On searching the CSD database (Groom et al. 2016) (accessed August 2025), we found that, in the past 7 years, the number of reports providing well-defined solid state structures (>140) is representative enough to permit a thorough analysis and the extraction of some important conclusions (Table S1). The analysis of the main intermolecular interactions was carried out by employing the ConQuest and Mercury computer programs, which search and upload structural data of the well-defined structures in the CSD database, providing the nature and frequency of any interaction between two specific functional groups. Such an analysis reveals that the -OH and carbonyl groups the in flavonoid–coformer/solvent systems have an uneven distribution of intermolecular interactions with coformer molecules. The main functional groups involved are 7OH, 3′OH and 4′OH, located at the periphery of flavonoid rings A and B, Figure 2. The same analysis revealed that the coformer molecules interact through groups that may function either as hydrogen bond acceptors or donors, Figure 6. Their chemical structures contain functional groups such as amines, amides, carbonyls, carboxyls, pyridyl and heterocyclic rings containing nitrogen or sulfur atoms, among others.

The analysis of the reported structures in CSD also revealed that there are also some other, much less important, non-covalent interactions between flavonoid-flavonoid, flavonoid-coformer, and coformer-coformer. Moreover, in some cocrystals, solvent molecules water, ethanol, propan-2-ol, t-butanol, ethyl acetate, dichloromethane, tetrahydrofuran, methanol, acetone, and acetonitrile form hydrogen bonds with the flavonoid and/or the coformer, or fill the channels within the spatial structure of the crystals (Makadia et al. 2023; Sun J et al. 2023), being incorporated into the crystal network forming solvated cocrystals (Figure 1).

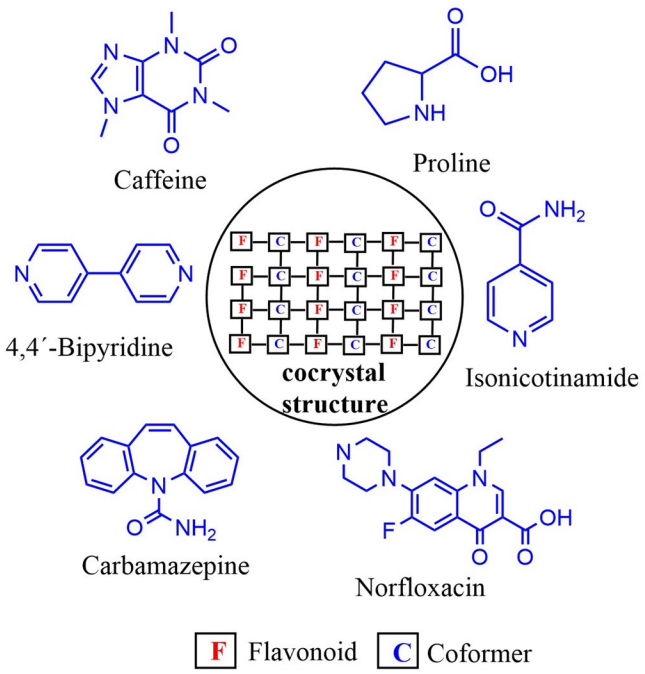

Figure 6. Selected coformers leading to the formation of flavonoid cocrystals. Coformers can have functional groups acting both as H-bond acceptors and as H-bond acceptors/donors.

Methods of preparation of flavonoid-based cocrystals

A variety of methods are employed to both prepare them and to fully characterize cocrystals. Ideally, the synthesis of flavonoid-based (and, in general, of any other polyphenol) cocrystals should target the preparation of cocrystal powders and their single crystals. However, selecting the most suitable cocrystallization method remains, in a large extent, empirical and unfortunately, in most cases, is based on the expertise of the researcher and trial-and-error experiments. The currently employed techniques for the preparation of reported flavonoid-based cocrystals can be broadly classified into two main categories: solid-based and solvent-based methods (Maciołek et al. 2023; Sun et al. 2023b; Zhang J et al. 2024).

Some of the main advantages and drawbacks of the techniques and methods employed are summarized in Table 1.

Solid-state methods are effective and environmentally friendly as they need no solvent to facilitate cocrystal formation through direct contact between components (or only few amounts of it to facilitate non-covalent interactions between cocrystal components) but require the input of high amounts of energy. They combine coupling mechanical and chemical phenomena on molecular scale. The method is effective in the preparation of cocrystals, which are produced by mechanical energy absorption producing fractures and stress on the starting materials, so that they increase their surface area making the number of surface molecules capable of interpenetration to increase considerably, facilitating molecular contacts.

Table 1. Main methods of cocrystallization and some of their advantages and limitations.

Cocrystallization methods	Operational principle	Advantages	Drawbacks	Example
Solid-state methods				
Neat grinding	Cocrystallization by particle size reduction	Cheap, simple, solvent-free, minimum solvate-hydrate formation, convenient for screening assays, ecological	Incomplete cocrystallization, time consuming, large fractions of amorphous materials, low control over the process, high mechanical energy can cause undesirable heating of the material	(Souza et al. 2022)
Liquid-assisted grinding	Cocrystallization assisted by small amounts of solvents	Easy and efficient process, green-solvents can be used, low amounts of solvent required, suitable for screening assays, addition of liquid may allow better control on the kinetics, the solvent acts as a catalyst for the cocrystal formation reaction	Time consuming, risk of solvate formation, solvent disposal and solvent separation issues, solubility problems, finding the right amount and type of liquid is usually a trial and error process	(Dias et al. 2021; Wang L et al. 2022; Chettri et al. 2024)
Hot melt extrusion	Cocrystallization involving melting and extrusion of starting materials	Solvent-free, short operational times, low waste, scalable, minimize solvate-hydrate formation, high cocrystal conversion degree	Thermal degradation of labile molecules	
Solvent-based methods				
Slow evaporation	Cocrystallization triggered by oversaturation after solvent evaporation	Simple process, relatively cheap equipment, high efficiency, high purity of cocrystals, slow rates of evaporation allows formation of well-shaped and large crystals for structural studies, the process is easy to monitor visually	Material loss due to residual solubility, difficult to scale-up, time-consuming, time dependent on the solvent used, not ideal for fast processes or industrial production, dependence on experimental conditions, temperature and humidity may affect rates of evaporation, risk of polymorph formation	(Makadia et al. 2023; Zhang J et al. 2024; Li D et al. 2025)
Isothermal slurry conversion	Cocrystallization from suspension /slurry of starting materials in a particular liquid solvent	Efficient for poorly soluble components, ideal for systems where one or both components have low solubility as the liquid medium helps mediate interactions without requiring dissolution, relatively simple but high efficiency process, requires cheap equipment, compared to solution-based methods this technique uses minimal amounts of solvent, reducing costs and environmental impact, the isothermal condition ensures consistent results and prevents thermal degradation of temperature-sensitive materials	Selection of an appropriate solvent or slurry medium is critical, limitations in the solubility of materials, difficult to scale-up, the process can be slow requiring times ranging hours or days to reach completion as it relies on equilibrium conditions, post-processing required, may be time consuming because the final product often needs filtration, drying or washing steps	(Sun et al. 2023a)
Supercritical fluid techniques	Cocrystallization by solution-mediated phase transformation or expansion of a supercritical solution of the starting materials, can be induced by CO_2 as antisolvent in a solute-solution mixture	Versatile, minimizes solvates and hydrates, low waste of materials, scalable, environmental friendly process, supercritical CO_2 is nontoxic, non-flammable, and recyclable, making it a sustainable alternative to conventional solvents, solubility and diffusion properties of supercritical fluids can be finely tuned by adjusting pressure and temperature, enabling precise control over cocrystal formation	High operating pressure, initial investment in equipment for supercritical fluids processing is high, limiting its accessibility for smaller labs or pilot studies, limitations in the nature of the solvents that can be employed and the solubility of materials in CO_2, the interplay between temperature, pressure, and solubility requires careful optimization for each system, which can be time-consuming, optimization process may be complex	(Dias et al. 2023)

Solution-based methods are much more widely employed than solid-based methods to prepare flavonoid-based cocrystals, and are reasonable alternatives to solid-state methods as the contact between the target molecule and the coformer is facilitated through thermal motion of the molecules and the degree of saturation of the solutions. Solvents are usually selected on the basis of the differential solubility of the starting material (e.g., flavonoid and coformer): if they are too different, the method is not effective because, as expected, solvent plays a crucial role affecting various cocrystal properties including their shape, solvate tendency and their polymorphism, cocrystal purity. Solvent-based techniques commonly employed include the (slow) evaporation of the solvent from the solution, addition of anti-solvents, melt crystallization, sublimation, cocrystallization from a suspension.

Other methods exploit extrusion and pressing techniques, mechanochemical methods with a solvent drop or liquid-assisted, polymer-assisted milling, ultrasound-stimulated crystallization, acoustic resonance, microfluidic crystallization, electrospray technology and the use of supercritical fluids.

Common analytical techniques employed to characterize cocrystals

A full characterization of flavonoid cocrystals is necessarily connected with investigating their physicochemical properties (e.g., specific surface area determination, solubility, selectivity, saturation studies), preparation of ternary phase diagram, stability studies, food, biological and health activities (toxicity, antioxidant, antibacterial, antihemolytic, hepatotoxicity, cytotoxicity test, antitumor, etc.).

A literature survey allowed us to conclude that researchers use two broad approaches to investigate cocrystals. For one side, researchers investigate the result of the synthetic process (cocrystal screening) and, if the crystals are formed, then further characterization of the newly formed cocrystals is required (Wong et al. 2024).

Cocrystal screening techniques can be divided in two broad groups, those employed to investigate their structural characteristics and those employed to investigate their properties.

Structural techniques include diffraction methods (e.g., single crystal X-ray diffraction (SCXRD) (Makadia et al. 2023; Zhang J et al. 2024), powder X-ray diffraction (PXRD) (Dias et al. 2023; Zhou et al. 2023)), while those employed to study cocrystal properties include thermal analysis (e.g., differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) (Meng et al. 2023; Zhang J et al. 2024)), spectroscopic methods (e.g., Fourier-transform infrared (FTIR) (Zhang J et al. 2024), Raman spectroscopy (FT-Raman) (Dias et al. 2022, 2023; Maciołek et al. 2023; Ouyang et al. 2024b), solid-state nuclear magnetic resonance (ssNMR) (Pang et al. 2021)), and a number of other methods (e.g., microscopy, biological activity) (Dias et al. 2021).

When a positive verification of the formation of cocrystals is achieved, further characterization is required and a combination of the following methods is commonly used: (1) variable-temperature powder X-ray diffraction (VT-PXRD) (Fiore et al. 2024), (2) spectroscopic methods such as ^{1}H-NMR (Zhang M et al. 2023; Fiore et al. 2024) and ^{13}C-NMR in solution (Liu L et al. 2022), LC-MS (Wang L et al. 2022), solid UV-Vis (Li Z et al. 2022), XPS (Maciołek et al. 2023), (3) microscopic methods such as polarizing microscopy, hot-stage microscopy and light microscopy (Bolus et al. 2020; Liu L et al. 2023; Ouyang et al. 2024a, 2024b), optical microscopy (Maciołek et al. 2023), SEM and TEM (Figure 7) (Dias et al. 2022; Zeng et al. 2024).

Full characterization of the flavonoids cocrystals is connected with investigation their physicochemical properties (mostly related to solubility, dissolution rates, hygroscopicity and tabletability) (Wang Z et al. 2024; Pantwalawalkar et al. 2025) and biological properties (pK_a, antioxidant activity, antihemolytic activity, anti-inflammatory evaluation, antibacterial properties, hepatotoxicity study, cytotoxicity test, antitumor activities, toxicity test) (Dias et al. 2021; Lu et al. 2023; Zeng et al. 2024). It should be underline also that, very frequently, computational studies are an important complementary tool in the empirical process and methods of preparing cocrystals (Zhou et al. 2023).

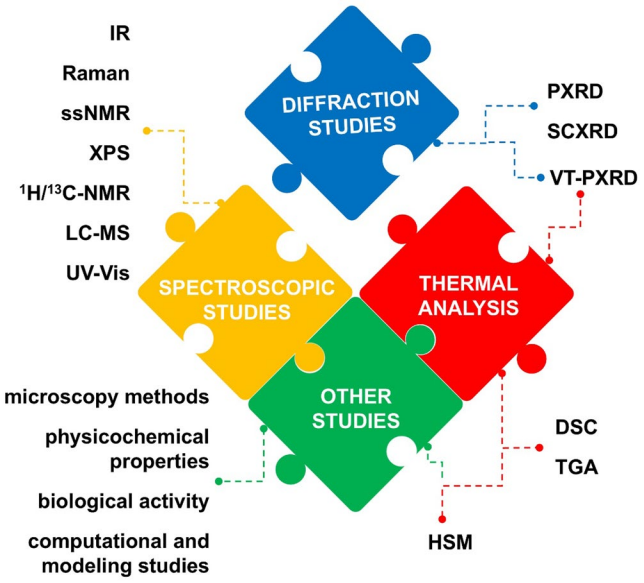

Figure 7. Common methods for studying cocrystals.

Food preservation strategies based on cocrystals

Consumers' concerns about the use of natural components in food products made the food industry and researchers to explore different strategies in the formulation, manufacturing and storage procedures of food products. Moreover, current concerns about food loss and waste and in the preparation of healthier and safer foods make that the development of food preservation technologies to be critical, having an enormous interest to both consumers and the food industry. Particularly, active ingredients (e.g., flavonoids) extracted from natural sources are increasingly being employed as eco-friendly preservatives and in the search of functional foods. However, in many cases, the active ingredients cannot be employed as they are extracted but need to be employed with different formulations or materials to modulate, as desired, their physicochemical properties. These properties, including solubility, dissolution rate and tabletability, can be enhanced by forming self-assembly cocrystals comprising flavonoids (or other polyphenols of interest) and suitable coformers (Table S1).

Polyphenol-based cocrystals have recently come to light as an interesting, effective and practical approach for dealing with the chemical instability of food components, for example, the spontaneous oxidation of lipids (peroxidation reactions) (Li Y et al. 2024). The chemical degradation of food ingredients frequently occurs during production and storage, making it difficult to develop stable and healthy food products. Bianchi et al. (2021) developed a novel cocrystal-based food packaging with antimicrobial and antioxidant properties by means of cocrystallization of microbiologically active

compounds present in essential oils to minimize food waste, and to increase the shelf-life of food as resulting of improving the package type.

The suitability of flavonoids to be employed as functional ingredient for food products to preserve them and to gain health benefits depends on their absorption, transport and bioavailability (Abdi Syahputra et al. 2024; Williamson 2025). Regardless of the specificity of each flavonoid, their absorption depends on their ability to be solubilized in the gastrointestinal fluids, and quantification of the flavonoid content in each liquid sample (water, aqueous buffers or other bio-relevant fluids) provides the concentration-time curves from where dissolution profiles can be inferred when needed.

Improvement of solubility and other relevant physicochemical properties of flavonoids

The solubility of flavonoids in food (and in pharmaceutical) systems is of major importance as flavonoids must be first dissolved before reaching the human body and being absorbed (Yuan et al. 2024; Williamson 2025). Ideally, food flavonoid-based cocrystals should be made, in addition of the hydrophobic flavonoid, of hydrophilic coformer molecules because coformer aqueous solubility is correlated with cocrystal solubility (Yuan et al. 2024). When present in food formulations, cocrystals may be incorporated into aqueous solutions of varying pH, and most likely will be close to solubilizing agents such as endogenous surfactants, lipids, etc. Hence, their solubilization degree will change depending on the exact food formulation as a consequence of the various existing equilibria as illustrated in Figure 8.

Different mathematical relationships describing the cocrystal solubilization in terms of the various equilibrium constants (cocrystal dissociation, coformer ionization), and colloidal (micellar, microemulsion, emulsion) solubilization

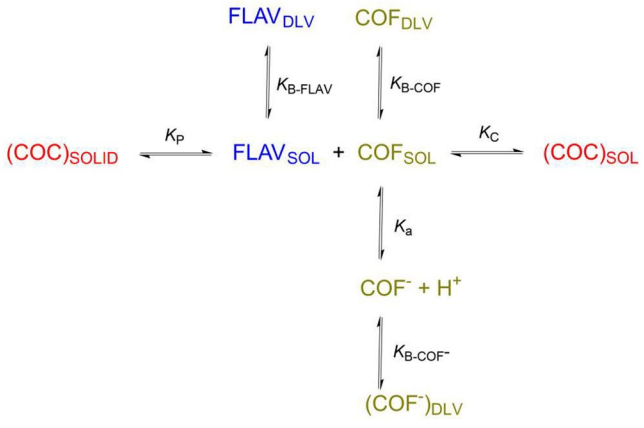

Figure 8. The fate of the molecular constituents of cocrystals in solution controls their solubility. The scheme illustrates various interactions of a cocrystal COC composed of a non-ionizable flavonoid FLAV and an ionizable coformer COF and the equilibria involved when in solution (SOL) and in the presence of a deliver (DLV) system (e.g., micelle, emulsion, cyclodextrin, etc.) K_P stands for the cocrystal product solubility, K_B-FLAV is the binding constant of the flavonoid to the delivery system, K_B-COF and K_B-COF$^-$ are the binding constant of the coformer and of the ionized coformer, respectively, to the delivery system, and K_a is the ionization constant of the coformer.

have been derived for different cocrystal-coformer stoichiometries, and they constitute the basis for the more practical relationships between cocrystal solubility advantage and cocrystal solubilization in presence of solubilizing agents (Yuan et al. 2024). Enhanced solubilities were also reported for baicalein-caffeine and baicalein-isonicotinamide cocrystals (Xu et al. 2023). Results are, thus, promising and provide a strong scientific basis for exploring new potential applications of flavonoid-based cocrystal formulations. Table 2 displays some relevant examples flavonoid-based cocrystals (acting either as bioactives or coformers) and some of the main improvements achieved in the physicochemical properties compared to those of the parent compounds. All examples of improvements for cocrystals with a well-defined structure, for which such studies were performed, are presented in Table S1.

Cocrystallization also improves the rates of dissolution of the parent compounds, reducing the required doses, cost and chances of toxicity, playing therefore crucial role in gastrointestinal absorption. Some attention has been given to flavonoid-based (and, in general, polyphenol-based) cocrystals produced by safe coformers for food applications, presenting (at least *in vitro*) significant ability to dissolution modulation (Dias et al. 2021). The effects of cocrystallization on increasing dissolution and apparent solubility of polyphenols have been associated to the "spring and parachute" effect comprising to complementary steps: (i) generation of a metastable supersaturated state and (ii) preservation of this supersaturated state for a long period (Dias et al. 2021).

Flavonoids have also been employed as coformers to improve pharmacokinetic, physicochemical and mechanical properties of active pharmaceutical ingredients. For example, the naringenin cocrystal of carbamazepine exhibited much higher thermal stability and hydration resistivity compared pure carbamazepine (Lee et al. 2023). The urea groups of carbamazepine form hydrogen bonds with resorcinol groups of naringenin leading to cocrystals of 1:1 stoichiometric ratio. Kaempferol, myricetin and quercetin formed cocrystals with praziquantel (drug employed in parasitic worm infections) and results showed that the melting points of these cocrystals increase with the number of phenolic groups on the backbone of flavonoid, respectively (Lee et al. 2023). Ethionamide is an excellent anti-tuberculosis active compound but its fearful hepatotoxicity limits its clinical applicability. J.-Y. Li et al. (2022) showed its liver toxicity was almost removed by the formation of a cocrystal with chrysin. Chrysin is a flavonoid compound with a significant antioxidant activity but its bioavailability is limited by its extremely poor solubility. However, the pharmaceutical properties of chrysin improved significantly after cocrystallization by increasing its aqueous solubility and, at the same time, removing, in practice, the hepatotoxicity of ethionamide.

The mechanical properties of flavonoid-based cocrystals (e.g., tabletability, hygroscopicity, etc.) may play an important role in their manufacturing of solid dosage form and in the design of functional foods with the desired properties. Several reports of the preparation of flavonoid-based cocrystals have been published, and the results suggest a promising

Table 2. Representative examples of flavonoid-based cocrystals showing some of the main improvements detected in the physicochemical properties of the flavonoid or of the coformer.

Flavonoid	Coformer	Improvements	Reference
Baicalein	4,4′-bipyridine	The solubility of the cocrystal is ~40 times higher than that of pure baicalein.	(Liu L-X et al. 2021)
Baicalein	Pyrazinamide	• The rate of dissolution increased 12-fold *via* cocrystallization with pyrazinamide. • Pyrazinamide's liver toxicity was almost eliminated in rats.	(Hao et al. 2023)
Phloretin	Isoniazid	• Cocrystal solubility increased ~11-fold at pH 1.2 and ~23-fold at pH 6.8. • *In vitro* antioxidant and anti-cancer activity enhanced.	(Lu et al. 2023)
Quercetin	Pentoxifylline Betaine Theophylline L-proline	• All cocrystals demonstrated enhanced dissolution rates of quercetin. • In Sprague–Dawley rats, plasma concentrations of quercetin increased 7–64 fold, indicating a significant improvement in oral bioavailability compared to quercetin anhydrate.	(Haskins et al. 2023)
Daidzein	Piperazine	• Daidzein's solubility increased 3.9–60.8 at pH 1.2, 4.5, 6.8, 7.0. • Significant increases in permeability (4.8×), and bioavailability (3.2×) versus the parent drug.	(Wang Z et al. 2024)
Daidzein	4,4′-vinylenedipyridine 4,4′-ethylenedipyridine	• The solubilities of the cocrystals were enhanced 1.2–30.4 fold compared to daidzein (pH = 6.8, phosphate buffer).	(Hou et al. 2025)
Myricetin Genistein (S)-Hesperetin Pratensol	4,4′-ethylenebispyridine	• Dissolution tests in 0.5% micellar (Tween 80) solution increased solubility of flavonoid. cocrystals with respect to that of their physical mixtures. • Anti-tumor studies showed enhanced inhibition of HCT-8 and Caco-2 cells by all four cocrystals, with myricetin and genistein cocrystals being most effective.	(Zhang Y et al. 2022)
Genistein	Tetramethylpyrazine (Ligustrazine)	• Cocrystal showed a markedly lower sublimation tendency than ligustrazine. • The *in vitro* release rate and bioavailability in rats significantly increased compared to genistein.	(Li X et al. 2021)
Hesperetin	Piperine	• Solubility and plasma concentration of the cocrystal increased significantly in comparison with those of pure hesperetin. • Formation of cocrystal reduced the difference of the dissolution rates between hesperetin and piperazine. • Bioavailability of hesperetin cocrystals were 6-times higher than that of parent compound.	(Liu Y et al. 2022)

Naringenin	Norfloxacin	• Enhancement of Norfloxacin's antibacterial activity against:
		  • one Gram-positive bacterium (*Staphylococcus aureus*),
		  • three Gram-negative bacteria (*Escherichia coli*, *Dysentery bacillus*, and *Pseudomonas aeruginosa*),
		  • and one fungus (*Candida albicans*).
		• Improvement of naringenin's solubility.
		• Reduction of Norfloxacin's hygroscopicity.
		• Strengthening of naringenin's anticancer activity against MDA-MB-231 human breast cancer cells.
			(Zeng et al. 2024)

Nobiletin	Gallic acid	Cocrystallization led to a slight enhancement in the dissolution of nobiletin.	(Tokunaga et al. 2023)
Naringenin	Betaine	• Enhancement of both the solubility and dissolution rate of naringenin, which may contribute to improved oral bioavailability. • Synergistic effect of naringenin and betaine • Increased permeation through the blood brain barrier. • The cocrystal may be beneficial for targeting naringenin to the brain after oral administration.	(Oliveira et al. 2024)

strategy for improving palatability and even enhance their health benefits (antitumor, anticancer, etc.) activity, reducing dose-related problems of the parent compounds. Pang et al. (2021) prepared cocrystals of L-carnitine with myricetin with improved tabletability (i.e., tablet-forming ability), concluding that the cocrystal was more suitable for manufacturing solid dosage forms than the parent compounds. They also showed that the prepared cocrystal had a much lower hygroscopicity (~16 fold). Zhou et al. (2023) reported the preparation of a novel palbociclib-kaempferol cocrystal with improved tabletability and with synergistic antitumor activity. Wang J et al. (2021) reported on the preparation of hesperetin and temozolomide cocrystal, which exhibited superior tabletability in comparison with the parent compounds. Cocrystals show advantages in terms of hygroscopic stability compared to that of pure kaempferol, suggesting that the hygroscopic stability of kaempferol can indeed be enhanced *via* cocrystals (Xu et al. 2023; Zhou et al. 2023).

Cocrystallization of polyphenols has also been employed to modulate the photoluminescence properties of polyphenols, and to improve their *in vitro* antioxidant, antihemolytic and anti-inflammatory properties (Xu et al. 2023). *In vitro* and *in vivo* (animal) studies have demonstrated that flavonoids are thought to play important roles in human health because of their antioxidant and antimutagenic properties and their regular consumption may reduce the risk of cardiovascular disease and stroke. Most recent research focuses on the health aspects of flavonoids from food sources for humans and such research progress attempts to find new ways of incorporating these natural plant pigments into food formulations (Dias et al. 2021; Li Y et al. 2024). Their implementation is not an easy pathway because they are not, in general, water soluble and this fact causes problems regarding their bioavailability in the human body, though health benefits and some promising results have been reporting by using flavonoid cocrystals. Recently, Zhou et al. (2023) prepared a novel palbociclib-kaempferol cocrystal and results showed that its antitumor efficiency against OVCAR3 cell line was enhanced by ~4-fold in comparison with palbociclib. The formation of cocrystals of myricetin and genistein with 4,4′-ethylenebispyridine revealed an improved anti-tumor impact against HCT-8 and Caco-2 cancer cells (Zhang Y et al. 2022).

Oral bioavailability of cocrystals of quercetin with betaine, theophylline, proline and pentoxifylline showed a

significant enhancement (7–64 fold) compared with that of quercetin anhydrate (Haskins et al. 2023). This *in vivo* and *in vitro* enhancement in the bioavailability was rationalized (Haskins et al. 2023) in terms of dissolution-supersaturation-precipitation approach; the relative bioavailability, the relative C_{max} (the maximum plasma concentration) and melting points of these cocrystals were compared against those in the literature, showing that the prepared cocrystals quercetin-pentoxifylline and quercetin- betaine exhibited the highest values for these parameters.

Formation of cocrystals has also been shown as alternative strategy to sustain the drug release (Meng et al. 2023). The continued release dosage form shows important advantages in minimized dosing frequency, reducing side effects because of the steady-state blood level with less plasma changes and enhanced patient compliance. Olaparib is a pharmaceutical compound that is employed in the treatment of ovarian cancer selectively killing cancer cells without damaging normal cells. However, its toxic side effects limit its therapeutic application. Cocrystals of olaparib-kaempferol and olaparib-quercetin showed lower intrinsic dissolution rate and reduced solubility than the olaparib, contributing to its sustained release and extending half-life and reducing dose-limiting side effects (Duan et al. 2022).

Another important characteristic of cocrystals relates to the toxicity of the parent compounds. Unfortunately, reported studies were carried out under very different experimental conditions, making difficult to homogenize results and getting definitive conclusions, but all those studies point to the fact that the potential toxicity of the parent coformers decreases in different extents upon cocrystallization (Banerjee et al. 2022; Yan et al. 2023). For example, Ma et al. (2019) investigated the biological security of cocrystals formed with 4,4′-bipyridine (Figure 6) with apigenin (Figure 2), with concluding that, upon oral, subchronic treatment of several groups of mices, no significant changes in the biological measurements carried out, providing evidence in terms of the safety and pharmacological efficacy of the prepare cocrystals. Similar results were reported by Cao et al. (2023). Hao et al. (2023) prepared cocrystals of baicalein with pyrazinamide reporting that the prepared cocrystal almost removed the toxicity of pyrazinamide. Yin et al. (2021) reported that the cell toxicity of cocrystals formed with oxaliplatin and naringenin has higher safety that of the parent compound. All these reports, although in many cases are method- and dose-dependent, demonstrate the effectiveness of cocrystals in reducing drug toxicity, suggesting that cocrystallization could serve as a valuable reference for addressing challenges related to toxic drugs (Li Z et al. 2019; Yin et al. 2021; Duan et al. 2022; Sripadi et al. 2024). A larger number of examples regarding toxicity studies is provided in Table S1.

Most researchers have focused on the pharmaceutical properties of polyphenol-based cocrystals, and a number of excellent reviews on this topic are available (Berry and Steed 2017; Banerjee et al. 2022; Chavan et al. 2024; Panzade et al. 2024; Rode et al. 2024; Ammar et al. 2025; Roshni and Karthick 2025). However, little has been done in the field of food science and, to the best of our knowledge, there are currently no marketed flavonoid-based cocrystals. Nevertheless, considering the tunable aspects related to flavonoid (and polyphenol in general) cocrystallization, their potential application for food products and their implementation at the various food processes (canning, freezing, fresh storage, jellies and preserves, etc.) remains completely open and the way cocrystals are implemented will most likely depend on the particular product to be preserved or fortified (Wang et al. 2018; Barreca et al. 2021; Dias et al. 2021).

Cocrystallization processes are mostly operated in batch mode, which is considered simple and flexible in responding to market demands. However, the main drawbacks of batch processes are their susceptibility to batch-to-batch variations, increased human intervention, and higher production costs. Continuous cocrystallization is preferred, as it offers better control of the process, reduced production costs, and less human intervention offering interesting scale-up of the process. Hence, cocrystallization provides a scalable solution for the industrial production of cocrystals that can be added at to food products at different stages of their production (Pawar et al. 2021). Cocrystal properties such as purity, yield and crystal size can be effectively controlled by using a combination of the cocrystallization techniques mentioned in this review. Intensive research efforts are currently directed toward exploiting cocrystallization to enhance the solubility, stability, and bioavailability of flavonoids, as evidenced by the growing number of recent publications and patent applications in this field. In some cases, the challenges of employing cocrystals in foods are related to safety issues of the coformer employed as it needs to be food approved. Currently, flavonoid formulations are produced on a large scale and are available in several dosage forms such as capsules, tablets, gels, and creams. They are also employed as dietary supplements due to their recognized antioxidant properties.

Conclusions and perspective

In this review, we aimed to provide an overview of the importance of flavonoid-based (and, in a broader sense, polyphenol cocrystals) discussing the various methods of formation, coformer selection, characterization providing suitable examples reported in the literature. Cocrystals are continuously showing promising results in the modification of relevant physicochemical properties of natural molecules of interest and a large variety of methods for the preparation of cocrystals are available from the lab-scale to the industry-level. On view of the reported number of patents for cocrystals, one may expect that flavonoid-based cocrystals will become a more routine approach for food and pharmaceutical development. It may be important to highlight that many of the examples presented in the review are based on products obtained in the laboratory scale, and scaling-up their formation to the industrial-scale production remains a significant challenge for commercialization purposes as it is necessary to ensure safety, reproducibility and both physical and chemical stability. Other factors such as yields, morphology and even particle size, should also be

considered (Saha et al. 2023). A literature survey reveals that there are not many reports focused on scalability issues related to the food chemistry, but there are many of them in the context of pharmaceutical cocrystals. Thus, interested researchers can benefit from adapting methodologies that are effectively used by the pharmaceutical industry to adopt and implement them in food as some of the requirements for cocrystal formation (e.g., safety, purity, etc.) are similar in both the pharmaceutical and food industries. It should be emphasized that not all methods of preparation of cocrystals reported in the literature are suitable for scale-up. Consequently, the translation of laboratory-scale production of food cocrystals to the industrial-scale production remains a major hurdle for commercialization (Saha et al. 2023). Methods such as supercritical spray-assisted drying (Kumar Bandaru et al. 2021; Saha et al. 2023), hot-melt extrusion (HME) (Kumar Bandaru et al. 2021; Saha et al. 2023), mechanochemical milling (Kumar Bandaru et al. 2021; Gomollón-Bel 2022; Liu X and Li 2022; Reynes et al. 2023; Bodach et al. 2024) are methods that allow scale-up to kilogram quantities. Among these methods, the advantages of continuous manufacturing over batch processing should be highlighted as continuous manufacturing reduces material waste, energy consumption, and scaling up challenges, enabling full automatization and improved process control. On the basis of current literature reports, HME appears to be the most promising technique for scalable cocrystallization, offering some advantages over the others in terms of process parameters and compatibility with continuous manufacturing. However, it may not be suitable for thermolabile coformers (Kumar Bandaru et al. 2021).

Regarding the potential applications of flavonoid-based cocrystals in the food industry, though promising, they largely remain unexplored and more work is required. The possibility of modulating and/or tailoring physicochemical properties of flavonoid-based cocrystals opens a variety of opportunities for their application in food products, and in this review we also aimed to show a broad scope of the different approaches for evaluating the potential of cocrystallization as a way to control and enhance the physicochemical, pharmaceutical, medical and biological properties of flavonoids in the context of application in food systems. However, further research is required as, unfortunately, there is not (yet) any available standardized (universal) methodology to produce cocrystals and no standardized methodology to predict "*a priori*" their potential food/health benefits. Both aspects should stimulate further research for the development of new safer and beneficial food products.

Ideal coformers in flavonoids cocrystals should bear functional groups serving as hydrogen bond acceptors or donors, such as carboxyl, carbonyl, hydroxyl, amine, imide, or heterocyclic groups (nitrogen and oxygen-containing). The major synthesis methods were presented, revealing that the used technologies employed to produce flavonoid-based cocrystals are solvent-based, and the slurry, grinding and evaporation methods are widely employed. Another major challenge in cocrystal formulation and/or preparation is confirming the successful synthesis of the cocrystals as it requires the use of appropriate analytical methods with sufficient sensitivity and precision to preliminarily screen suitable coformer candidates for a given compound. Methods such as PXRD and SCXRD can be employed to confirm the synthesis of cocrystals, but unfortunately the equipment is complex and quite expensive, and so they may not be easily available to researchers, making necessary to develop less expensive methods to at least help to identify successful cocrystal synthesis.

Future research should not only focus on optimizing methodologies to produce food-relevant flavonoid cocrystals but also on the functional integration of these bioactive compounds into food systems and, given the potential health benefits of flavonoids, on their incorporation in new food products of food supplements. Finally, it may be worthy to remark that the variety of functional groups in the flavonoid molecular structures opens up a large array of possibilities for the generation of novel solid state cocrystals and hence expanding their potential applications opening doors to innovative applications to satisfy consumer demands for natural, health-enhancing ingredients, and their applications in, for example, controlling the production of reactive oxygen species (antioxidant activity) and in the fight against different diseases.

Authors contributions

Urszula Maciołek: conceptualization; investigation; formal analysis; writing-original draft; illustrations, visualization, project administration, writing–review and editing; funding acquisition, Małgorzata Kosińska-Pezda: writing-original draft, illustrations, review and editing, funding acquisition, Sonia Losada-Barreiro: visualization; writing–review and editing; funding acquisition, illustrations, Carlos Bravo-Díaz: conceptualization; writing–review and editing; supervision; project administration. All authors approve the final version of the manuscript and agree to be accountable for all aspects of the work.

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