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REVIEW ARTICLE

Advances in extraction and purification of citrus flavonoids

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Abstract

Flavonoids are the representative active substances of citrus with various biological activities and high nutritional value. In order to evaluate and utilize citrus flavonoids, isolation and purification are necessary steps. This manuscript reviewed the research advances in the extraction and purification of citrus flavonoids. The structure classification, the plant and nutritional functions, and the biosynthesis of citrus flavonoids were summarized. The characteristics of citrus flavonoids and the selection of separation strategies were explained. The technical system of extraction and purification of citrus flavonoids was systematically described. Finally, outlook and research directions were proposed.

KEYWORDS
citrus, extraction strategy, flavonoids, purification methods

1 | INTRODUCTION OF FLAVONOIDS AND THE UNIQUENESS OF CITRUS FLAVONOIDS

1.1 | Structure and classification of flavonoids

Flavonoids exist widely in nature, usually refers to a series of phenolic compounds with phenyl-benzopyran (C6-C3-C6) as the skeleton. Broadly, according to the different connecting positions of aromatic ring (B ring) and benzopyran group (C ring), flavonoids can be classified as flavonoids (2-phenyl-benzopyran), isoflavonoids (3-phenyl-benzopyran), and neoflavonoids (4-phenyl-benzopyran) (Grotewold, 2006). In addition, chalcone and aurone also belong to flavonoids due to their similar C6-C3-C6 skeleton and are called minor flavonoids (Donnelly & Boland, 1995) (Figure 1). In a narrow sense, the flavonoid aromatic ring (B ring) is attached to the 2nd position of the benzopyran group (C ring). Flavonoids are generally divided into flavone, flavanone, flavonol, dihydroflavonol, flavan, flavanol, and anthocyanidin, depending on whether the C ring has a double bond at the 2nd and 3rd positions, and whether the 3rd position is connected to a hydroxyl group. Based on these basic structures, further modifications such as hydroxylation, methylation, prenylation, acylation, and glycosylation occur at different sites to form flavonoids with diverse structures and functions (Rauter et al., 2018). Some flavonoids also undergo polymerization to form macromolecules such as proanthocyanidins. And

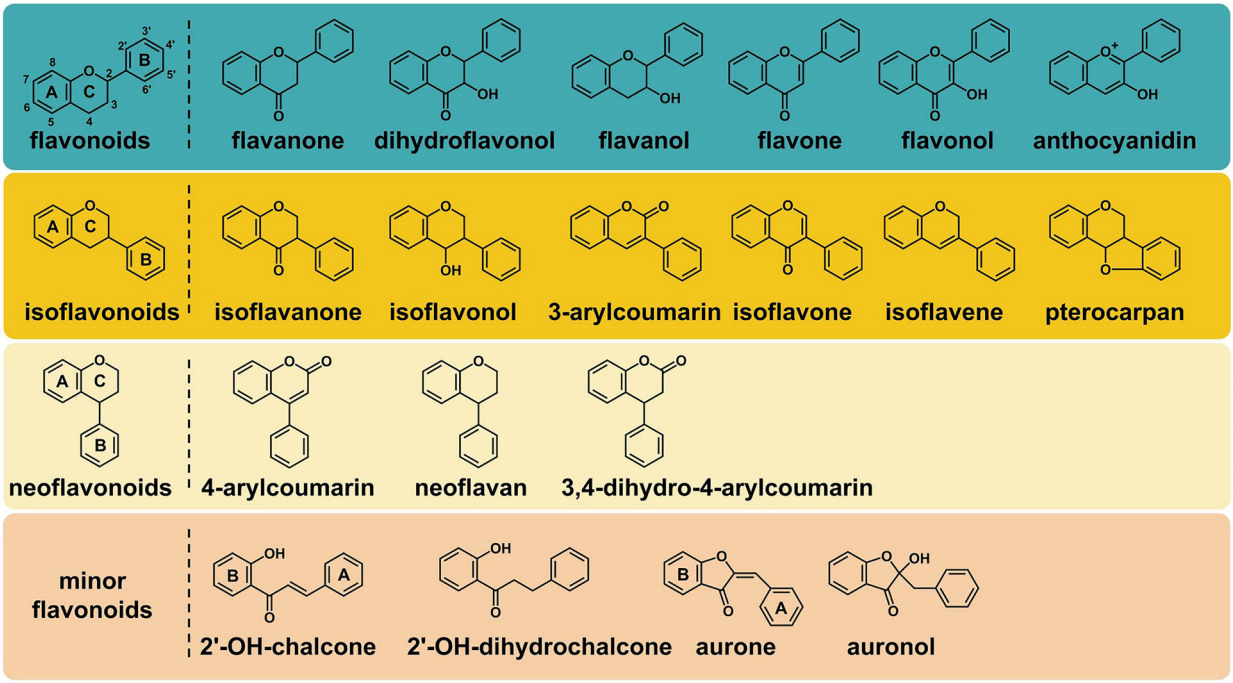


FIGURE 1 Flavonoids classification.

it is interesting to note that the different structures of flavonoids also contribute to the various interaction modes with other biological macromolecules (Guo et al., 2022).

1.2 | Characteristics of citrus flavonoids

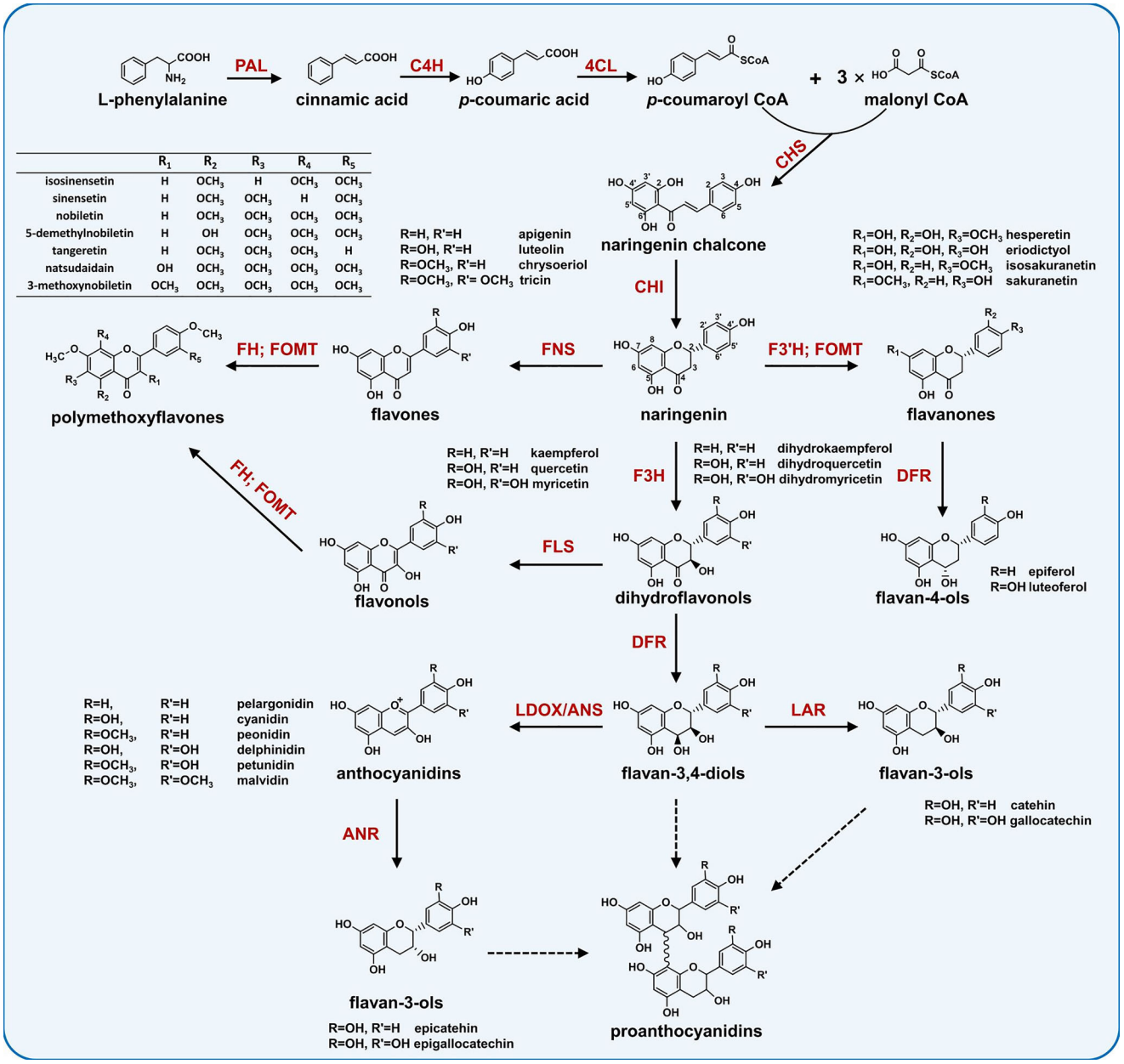
Taxonomically, citrus refers to a class of plants belonging to the genus *Citrus* of the family Rutaceae. When used as food, citrus generally also include the fruits of *Poncitrus*, *Fortunella*, *Eremcitrus*, *Clymenia*, and *Microcitrus*, collectively known as the citrus subfamily (Wu et al., 2018). Citrus is one of the fruits with the largest yield and consumption in the world and has high industrial and commercial application value. Because it is rich in bioactive substances such as flavonoids, it is also used as a traditional medicine and a homologous product of medicine and food.

Citrus contains a variety of flavonoids, of which flavanones and flavones are the most abundant, in addition to flavonols, dihydroflavonols, and anthocyanins. Isoflavones only exist in very small amounts in individual varieties (Wang et al., 2022). In citrus, flavanones mainly exist in the form of 7-*O*-glycosides, while flavones can undergo *O*/*C*-glycosidic modification at multiple sites or form polymethoxyflavones (PMFs) via multiple methoxy modification (Wang et al., 2017). Flavonols and dihydroflavonols also exist as polyglycosides (Zhao et al., 2020). The main monosaccharide glycosides that modify flavonoids in citrus are glucoside and rhamnoside, and the disaccharide glycosides are neohesperidoside and rutinoside (Abad-Garcia et al., 2012b). There are differences in the major glycoside types in different species of citrus (Nogata et al., 2006). In general, free anthocyanins under natural conditions are rare, and they are often formed with one or more glucose, rhamnose, galactose, xylose, arabinose through glycosidic bonds. In addition to glycosylation, anthocyanins can also undergo acylation modifications, which is further modification of anthocyanins (Wang et al., 2022).

The flavanone aglycones in citrus mainly include eriocityol, naringenin, hesperetin, homoeriodictyol, and isosakuranetin (Wang et al., 2021a). Flavone aglycones mainly include apigenin, luteolin, acacetin, chrysoeriol, tricin, and diosmetin (Durand-Hulak et al., 2015). In addition, some PMFs are specifically accumulated in citrus, mainly including sinensetin, isosinensetin, nobiletin, tangeretin, 5-demethylnobiletin, and so on (Li et al., 2009). The flavonols in citrus are mainly quercetin, kaempferol, and limocitrin, as well as a very small amount of dihydroflavonols such as taxifolin, aromadedrin and dihydroisorhamnetin (Wang et al., 2022).

1.3 | Biosynthesis of citrus flavonoids

The synthesis of flavonoids is a conservative secondary metabolic pathway in plants, which belongs to the pathway of propane metabolism. As shown in Figure 2, L-phenylalanine from the shikimate pathway is catalyzed by phenylalanine ammonia-lyase (PAL) to form trans-cinnamic acid. Trans-cinnamic acid forms synthetic p-coumaroyl-CoA under the sequential catalysis of cinnamic acid 4-hydroxylase and 4-coumarate: coenzyme A ligase (Zhao et al., 2021). This process not only separates the lignin metabolic pathway from the flavonoid metabolic pathway, but is also a key process connecting the shikimate pathway and the phenylpropane metabolic pathway (Tohge et al., 2013). Chalcone synthase catalyzes the polymerization of 1 molecule of p-coumaroyl-CoA and 3 molecules of malonyl-CoA to form naringenin chalcone,



	R_1	R_2	R_3	R_4	R_5
isosinensetin	H	OCH_3	H	OCH_3	OCH_3
sinensetin	H	OCH_3	OCH_3	H	OCH_3
nobiletin	H	OCH_3	OCH_3	OCH_3	OCH_3
5-demethylnobiletin	H	OH	OCH_3	OCH_3	OCH_3
tangeretin	H	OCH_3	OCH_3	OCH_3	H
natsudaidain	OH	OCH_3	OCH_3	OCH_3	OCH_3
3-methoxynobiletin	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3

FIGURE 2 Flavonoids metabolism pathway.

which is the most important precursor in flavonoid metabolism (Austin & Noel, 2003). Then chalcone is isomerized by chalcone isomerase to form the flavanone naringenin (Yonekura-Sakakibara et al., 2019).

Flavanones are important precursors for the synthesis of other flavonoids, which are catalyzed by flavone synthase, flavanone 3-hydroxylase, flavonol synthase, and isoflavone synthase to downstream metabolic branches such as flavones, dihydroflavonols, flavonols, and isoflavones (Wang et al., 2022). Dihydroflavonols and flavanones can be catalyzed by dihydroflavonol-4-reductase to form flavan-3,4-diols or flavan-4-ols, the former also known as leucoanthocyanidins. Flavan-4-ols can undergo condensation to form phlobaphenes. The leucoanthocyanidins can be directly condensed to form macromolecular polymer proanthocyanidins, also known as condensed tannins, or they can form flavan-3-ols under the action of leucoanthocyanidin reductase, and form proanthocyanidins after multistep reactions (Yonekura-Sakakibara et al., 2019). In addition, leucoanthocyanidins can finally enter the anthocyanidin metabolic branch through the catalysis of anthocyanidin synthase or leucoanthocyanidin dioxygenase. Anthocyanidin reductase can re-reduce anthocyanins to flavanols and re-enter flavonoid metabolism (Winkel-Shirley, 2001).

The formation of apigenin from naringenin is catalyzed by flavonoids hydroxylase and is formed at different sites in the flavone nucleus through the catalytic action of *O*-methyltransferases, glycosyltransferases, acyltransferases, prenyltransferases, and so on. Finally, PMFs and flavone glycosides are formed, which makes the types and

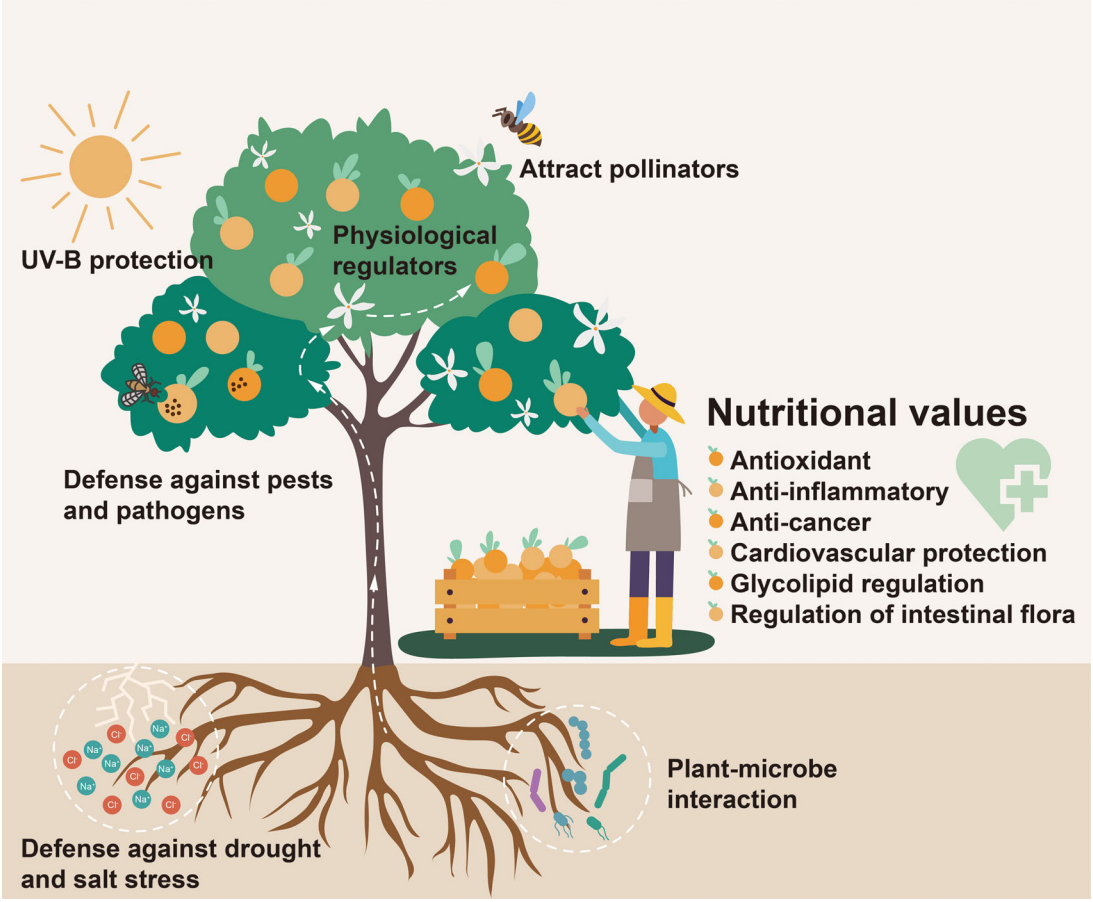


FIGURE 3 Plant and nutritional functions of flavonoids.

functions of flavonoids more abundant and diverse (Wang et al., 2022, Zhao et al., 2021).

1.4 | Plant and nutritional functions of flavonoids

As a secondary metabolite, flavonoid is an important metabolite in the interaction between plants and the environment. There are three main hypotheses about its biological function in plants (Figure 3). One is that during the evolution of plants from the aquatic environment to the terrestrial environment, the emergence of flavonoids could help plants resist the stresses of ultraviolet radiation, pathogenic bacteria, low temperature, drought, and metal salt ions in the external environment (Davies et al., 2018, Orhan et al., 2010, Petrussa et al., 2013). The second is that flavonoids are involved in plant development as physiological regulators or chemical signaling molecules (Brunetti et al., 2018, Buer & Muday, 2004, Hernandez & Munne-Bosch, 2012). The third is that flavonoids could help plants signal with other organisms and attract pollinators (Hassan & Mathesius, 2012, Shirley, 1996).

Flavonoids have a broad-spectrum light absorption ability due to their structure, and have a maximum absorption value in the UV-B band range (280–320 nm), which can reduce the flux of short-wave ultraviolet rays into cells to a certain extent (Shirley, 1996). More importantly, flavonoids can also inhibit the oxidative damage caused by short-wave ultraviolet rays to plants by scavenging oxidant reactions such as active oxygen free radicals (Agati et al., 2012, Agati & Tattini, 2010). This free radical scavenging ability also provides support for its broad ability to respond to adversity stress. Drought, low temperature, salt, and other stresses can lead to the production of reactive oxygen species in cells, and these factors can also induce the synthesis of flavonoids. Multiple functions allow flavonoids to protect delicate plant tissues. Flavonoids can also act as regulators of plant hormone signaling such as auxin and abscisic acid, affecting the growth and differentiation of plant cells, such as root growth, seed organ density, and pollen germination (Davies et al., 2018).

The anthocyanins in flavonoids are one of the main color-forming substances in plants. They show different colors through changes in pH, chelation of metal ions, and modification of molecular structure, giving plants flowers and fruits colors (Sigurdson et al., 2016, Wrolstad, 2004). These complex and diverse colors could guide insects to spread pollen (Rudall, 2020, Weiss, 1991) or attract animals to pick ripe fruit and spread seeds (Willson and Whelan, 1990). Therefore, flavonoids such as anthocyanins are also important factors affecting plant reproduction.

Flavonoids also play an important role in plant–microbe interactions. Studies have shown that flavonoids have a bidirectional effect

in the interaction with microorganisms, which can not only act as a defense factor against harmful fungi on plants (Snyder & Nicholson, 1990, Tomasbarberan et al., 1988), but also serve as signaling molecules to attract bacteria into plant cells. For example, kaempferol glycosides and quercetin glycosides have been shown to aid in gene transformation of *Agrobacterium tumefaciens* (Zerback et al., 1989). Isoflavones secreted by soybean roots can induce rhizobia bacteria to enter soybean roots and knots (Bais et al., 2006).

Flavonoids, also known as vitamin P, have important nutritional value and are an indispensable part of maintaining human health. Studies have shown that flavonoids have health utility values such as glycolipid regulation, anti-inflammatory, cardiovascular protection, anticancer, and regulation of intestinal flora (Wang et al., 2021a, Wang et al., 2022, Zhao et al., 2020). Our study also found that citrus flavonoids could induce cellular antioxidant activity by inhibiting the ubiquitination of Nrf2 (Wang et al., 2021b). PMFs in citrus could reverse LPS-induced circadian rhythm disturbance in mouse liver by inhibiting Nlrp3 inflammasome formation (Wang et al., 2021c). The biological activities of flavonoids are closely related to their molecular structures. *O*-methylation modification could improve the lipophilicity of flavonoids, protect free phenolic hydroxyl groups, and increase metabolic stability, thereby greatly improving bioavailability (Li et al., 2009, Walle, 2007). Biological experiments and bio-assay model also showed that *O*-methylation enhanced its biological activity to a certain extent (Tsuchiya, 2010).

2 | STRATEGIES OF CITRUS EXTRACTION AND PURIFICATION

2.1 | Strategies guided by purpose and cost

Flavonoid isolation strategy selection is purpose guided. For example, in the process of industrial waste recovery, it was necessary to control the economic cost and carry out large-volume and high-efficiency separation and purification of a certain component with high economic value (Raman et al., 2004). While in the detailed analysis of flavonoids, multiple monomers could be separated at the same time. In this situation, the volume and recovery rate of the separated products were not the key parameters. It was necessary to optimize the experimental system and obtain as many different components of the sample as possible (Uckoo et al., 2015).

According to the number of flavonoids obtained in a separation process, the separation strategy can be divided into a single-substance strategy and a multisubstance strategy. Single-substance strategies can optimize the system more efficiently, and it is not necessary to repeat the system optimization due to the adsorption degree, polarity, partition coefficient, and other issues of different substances, but this method will lose other substances with economic value and is only suitable for specific scenarios (Mauro et al., 2000) . For instance, Danijela et al. explored the method of separating hesperidin from orange peel by the use of calcium(II) and changes in the pH and established a new eco-friendly water-based extraction process with a purity of 98% (Stanisic et al., 2020). In multisubstance strategies, multiple components or monomers can be obtained in a single separation process, and the utilization of active components in raw materials can be completed with maximum efficiency by exploring the experimental system. For example, Wang et al. (2019b) established an efficient method for separation of PMFs from Ougan (*Citrus reticulata* cv. *Suavissima*) by ultrasonic-assisted extraction, solid-phase extraction (SPE), and high-speed countercurrent chromatography (HSCCC) separation, and successfully isolated nobiletin, hesperidin, and 5-demethylnobiletin. However, there are problems such as cumbersome optimization of the experimental system, difficulty in complete separation of relatively similar substances, and long separation time (Chu et al., 2012).

Cost is an important reference for selecting separation and purification methods, including economic cost, time cost, environmental cost, technical difficulty cost, and so on. By effectively combining a variety of separation and purification techniques and optimizing process conditions, the above costs can be comprehensively controlled, and an environment-friendly separation and purification with short time, high efficiency, and high purity can be completed. At the same time, cost control also needs to consider material selection, yield, product price, labor and other factors.

2.2 | Raw materials for separation and purification of citrus flavonoids

In the separation and purification of flavonoids, the selection of raw materials is crucial. The distribution of flavonoids in citrus is cultivar specific, tissue specific, and developmental stage specific. Flavanones and flavones are the most abundant flavonoids in citrus and are present in almost all citrus varieties and tissues (Khan et al., 2014, Ledesma-Escobar & de Castro, 2014, Nogata et al., 2006, Wang et al., 2022). While for flavonols and dihydroflavonols are mainly accumulated in citrons and lemons, with small amounts detected in some mandarins or grapefruit fruits (Abad-Garcia et al., 2012b, Nogata et al., 2006). Anthocyanins are only accumulated varieties with obvious red color like blood orange or purple pomelo and can also be synthesized in the tender leaves and shoots of some germplasms such as lemon (Brunetti et al., 2018, Huang et al., 2018, Lee, 2002). In addition to differences in cultivar distribution, previous research also found that flavonoids varied greatly in different parts of plants and had dynamic changes during the development stage (Liu et al., 2020, Zhao et al., 2021).

2.2.1 | Flavones

At present, more than 120 flavones have been detected in citrus (Table 1), among which the most common substituents are hydroxyl (—OH), methoxyl (—OCH_3), and glycosides. Glycosides include -glucoside, -rutinoside, -neohesperidoside, -rhamnoside, and so on (Durand-Hulak et al., 2015). The differences in the number and position of the three substituents resulted in the diversity of citrus flavones. As a unique class of flavones in citrus, PMFs are highly tissue specific

TABLE 1 Flavones detected in Citrus

Name	Chemical name	Molecular formula	Molecular weight (g/mol)	CAS	References
Flavone	Flavone	$C_{15}H_{10}O_2$	222.24	525-82-6	(Moulehi et al., 2012)
Chrysin	5,7-Dihydroxyflavone	$C_{15}H_{10}O_4$	254.24	480-40-0	(Wang et al., 2016)
Apigenin	5,7,4′-Trihydroxyflavone	$C_{15}H_{10}O_5$	270.24	520-36-5	(Doostdar et al., 1995)
Acacetin	5,7-Dihydroxy-4′-methoxyflavone	$C_{16}H_{12}O_5$	284.26	480-44-4	(Chuang et al., 2007)
Scutellarein	5,6,7,4′-Tetrahydroxyflavone	$C_{15}H_{10}O_6$	286.24	529-53-3	(Ooghe & Detavernier, 1997)
Luteolin	5,7,3′,4′-Tetrahydroxyflavone	$C_{15}H_{10}O_6$	286.24	491-70-3	(Doostdar et al., 1995)
Isoscutellarein	5,7,8,4′-Tetrahydroxyflavone	$C_{15}H_{10}O_6$	286.24	41440-05-5	(Oufedjikh et al., 1998)
5-Hydroxy-7,4′-dimethoxyflavone	5-Hydroxy-7,4′-dimethoxyflavone	$C_{17}H_{14}O_5$	298.30	5128-44-9	(Zhao et al., 2018)
Hydroxygenkwanin	5,3′,4′-Trihydroxy-7-methoxyflavone	$C_{16}H_{12}O_6$	300.26	20243-59-8	(Wang et al., 2020)
Diosmetin	5,7,3′-Trihydroxy-4′-methoxyflavone	$C_{16}H_{12}O_6$	300.26	520-34-3	(Miyake et al., 1997)
Chrysoeriol	5,7,4′-Trihydroxy-3′-methoxyflavone	$C_{16}H_{12}O_6$	300.26	491-71-4	(Gattuso et al., 2007)
Tricetin	5,7,3′,4′,5′-Pentahydroxyflavone	$C_{15}H_{10}O_7$	302.23	520-31-0	(Wang et al., 2020)
3′,4′,5′-Trimethoxyflavone	3′,4′,5′-Trimethoxyflavone	$C_{18}H_{16}O_6$	312.32	67858-30-4	(Yu et al., 2020)
5,7,4′-Trimethoxyflavone	5,7,4′-Trimethoxyflavone	$C_{18}H_{16}O_5$	312.32	5631-70-9	(Yu et al. 2020)
Pilloin	5,3′-Dihydroxy-7,4′-dimethoxyflavone	$C_{17}H_{14}O_6$	314.29	32174-62-2	(Zheng et al., 2019)
Velutin	5,4′-Dihydroxy-7,3′-dimethoxyflavone	$C_{17}H_{14}O_6$	314.29	25739-41-7	(Wang et al., 2020)
5,4′-Dihydroxy-7,8-dimethoxyflavone	5,4′-Dihydroxy-7,8-dimethoxyflavone	$C_{17}H_{14}O_6$	314.29	6608-33-9	(Luo et al., 2019)
Pedalitin	5,6,3′,4′-Tetrahydroxy-7-methoxyflavone	$C_{16}H_{12}O_7$	316.26	22384-63-0	(Wang et al., 2020)
4′-Hydroxy-5,6,7-trimethoxyflavone	4′-Hydroxy-5,6,7-trimethoxyflavone	$C_{18}H_{16}O_6$	328.32	6938-18-7	(Zhao et al., 2018)
Salvigenin	5-Hydroxy-6,7,4′-trimethoxyflavone	$C_{18}H_{16}O_6$	328.32	19103-54-9	(Li et al., 2006b)
5-Hydroxy-7,3′,4′-trimethoxyflavone	5-Hydroxy-7,3′,4′-trimethoxyflavone	$C_{18}H_{16}O_6$	328.32	29080-58-8	(Xing et al., 2017)
5-Hydroxy-7,8,2′-trimetehoxyflavone	5-Hydroxy-7,8,2′-trimetehoxyflavone	$C_{18}H_{16}O_6$	328.32	1165-40-8	(Luo et al., 2019)
7-Hydroxy-5,3′,4′-trimethoxyflavone	7-Hydroxy-5,3′,4′-trimethoxyflavone	$C_{18}H_{16}O_6$	328.32	10544-05-5	(Luo et al. 2019)
8-Hydroxy-5,7,4′-trimethoxyflavone	8-Hydroxy-5,7,4′-trimethoxyflavone	$C_{18}H_{16}O_6$	328.32	21919-71-1	(Zhao et al., 2018)
Tricin	5,7,4′-Trihydroxy-3′,5′-dimethoxyflavone	$C_{17}H_{14}O_7$	330.29	520-32-1	(Wang et al., 2016)
Demethoxysudachitin	5,7,4′-Trihydroxy-6,8-dimethoxyflavone	$C_{17}H_{14}O_7$	330.29	4323-80-2	(Luo et al., 2019)
Tetramethylkaempferol	3,5,7,4′-Tetramethoxyflavone	$C_{19}H_{18}O_6$	342.34	16692-52-7	(Ke et al., 2017)
Tetramethylscutellarein	5,6,7,4′-Tetramethoxyflavone	$C_{19}H_{18}O_6$	342.34	1168-42-9	(Chen et al., 1997)
Tetramethoxyluteolin	5,7,3′,4′-Tetramethoxyflavone	$C_{19}H_{18}O_6$	342.34	855-97-0	(Ke et al., 2017)
6-Demethoxytangeretin	5,7,8,4′-Tetramethoxyflavone	$C_{19}H_{18}O_6$	342.34	6601-66-7	(Chen et al., 1997)
6,7,3′,4′-Tetramethoxyflavone	6,7,3′,4′-Tetramethoxyflavone	$C_{19}H_{18}O_6$	342.34	76622-27-0	(Yu et al., 2020)
7,8,3′,4′-Tetramethoxyflavone	7,8,3′,4′-Tetramethoxyflavone	$C_{19}H_{18}O_6$	342.34	65548-55-2	(Senevirathne et al., 2009)
Xanthomicrol	5,4′-Dihydroxy-6,7,8-trimethoxyflavone	$C_{18}H_{16}O_7$	344.32	16545-23-6	(Luo et al., 2019)

(Continues)

TABLE 1 (Continued)

Name	Chemical name	Molecular formula	Molecular weight (g/mol)	CAS	References
3′,4′,5′-Trimethoxytricetin	5,7-Dihydroxy-3′,4′,5′-trimethoxyflavone	$C_{18}H_{16}O_7$	344.32	18103-42-9	(Wang et al., 2020)
4′-Hydroxy-5,6,7,8-tetramethoxyflavone	4′-Hydroxy-5,6,7,8-tetramethoxyflavone	$C_{19}H_{18}O_7$	358.34	36950-98-8	(Zheng et al., 2019)
5-Hydroxy-3,6,7,8-tetramethoxyflavone	5-Hydroxy-3,6,7,8-tetramethoxyflavone	$C_{19}H_{18}O_7$	358.34	15249-62-4	(Xing et al., 2017)
Retusin	5-Hydroxy-3,7,3′,4′-tetramethoxyflavone	$C_{19}H_{18}O_7$	358.34	1245-15-4	(Li et al., 2006b)
5-Demethylsinensetin	5-Hydroxy-6,7,3′,4′-tetramethoxyflavone	$C_{19}H_{18}O_7$	358.34	21763-80-4	(Hijaz et al., 2016)
Gardenin B	5-Hydroxy-6,7,8,4′-tetramethoxyflavone	$C_{19}H_{18}O_7$	358.34	2798-20-1	(Li et al., 2006b)
5-Hydroxy-7,8,3′,4′-tetramethoxyflavone	5-Hydroxy-7,8,3′,4′-tetramethoxyflavone	$C_{19}H_{18}O_7$	358.34	13003-74-2	(Ribeiro et al., 2008)
7-Demethyltangeretin	7-Hydroxy-5,6,8,4′-tetramethoxyflavone	$C_{19}H_{18}O_7$	358.34	73213-66-8	(Xing et al., 2017)
4′-Hydroxy-5,6,7,3′-tetramethoxyflavone	4′-Hydroxy-5,6,7,3′-tetramethoxyflavone	$C_{19}H_{18}O_7$	358.35	51145-80-3	(Zhao et al., 2018)
Sudachitin	5,7,4′-Trihydroxy-6,8,3′-trimethoxyflavone	$C_{18}H_{16}O_8$	360.32	4281-28-1	(Tsutsumi et al., 2014)
3,5,6,7,4′-Pentamethoxyflavone	3,5,6,7,4′-Pentamethoxyflavone	$C_{20}H_{20}O_7$	372.37	4472-73-5	(Bellete et al., 2018)
Pentamethoxyquercetin	3,5,7,3′,4′-Pentamethoxyflavone	$C_{20}H_{20}O_7$	372.37	1247-97-8	(Uckoo et al., 2015)
Auranetin	3,6,7,8,4′-Pentamethoxyflavone	$C_{20}H_{20}O_7$	372.37	522-16-7	(He et al., 1997)
Sinensetin	5,6,7,3′,4′-Pentamethoxyflavone	$C_{20}H_{22}O_7$	372.37	2306-27-6	(Iwase et al., 2001)
Tangeretin	5,6,7,8,4′-Pentamethoxyflavone	$C_{20}H_{20}O_7$	372.37	81-53-8	(Iwase et al. 2001)
5,7,2′,3′,4′-Pentamethoxyflavone	5,7,2′,3′,4′-Pentamethoxyflavone	$C_{20}H_{20}O_7$	372.37	89121-55-1	(Luo et al., 2019)
5,7,3′,4′,5′-Pentamethoxyflavone	5,7,3′,4′,5′-Pentamethoxyflavone	$C_{20}H_{20}O_7$	372.37	53350-26-8	(Wang et al., 2017)
Isosinensetin	5,7,8,3′,4′-Pentamethoxyflavone	$C_{20}H_{22}O_7$	372.37	17290-70-9	(Chen et al., 1997)
Casticin	5,3′-Dihydroxy-3,6,7,4′-tetramethoxyflavone	$C_{19}H_{18}O_8$	374.34	479-91-4	(Venturini et al., 2014)
Ternatin	5,4′-Dihydroxy-3,7,8,3′-tetramethoxyflavone	$C_{19}H_{18}O_8$	374.34	571-71-1	(Wang et al., 2017)
5,4′-Dihydroxy-6,7,8,3′-tetramethoxyflavone	5,4′-Dihydroxy-6,7,8,3′-tetramethoxyflavone	$C_{19}H_{18}O_8$	374.34	29202-00-4	(Hamdan et al., 2011)
Hymenoxin	5,7-Dihydroxy-6,8,3′,4′-tetramethoxyflavone	$C_{19}H_{18}O_8$	374.34	56003-01-1	(Chen and Montanari, 1998)
Arteanoflavone	5,7-Dihydroxy-6,3′,4′,5′-tetramethoxyflavone	$C_{19}H_{18}O_8$	374.35	68710-17-8	(Yu et al., 2020)
3′-Demethylnobiletin	3′-Hydroxy-5,6,7,8,4′-pentamethoxyflavone	$C_{20}H_{20}O_8$	388.37	112448-39-2	(Zhao et al., 2018)
5-Hydroxyauranetin	5-Hydroxy-3,6,7,8,4′-pentamethoxyflavone	$C_{20}H_{20}O_8$	388.37	50439-46-8	(Luo et al., 2019)
5-Hydroxy-3,7,8,3′,4′-pentamethoxyflavone	5-Hydroxy-3,7,8,3′,4′-pentamethoxyflavone	$C_{20}H_{20}O_8$	388.37	14965-12-9	(Li et al., 2006b)
Umuhengerin	5-Hydroxy-6,7,3′,4′,5′-pentamethoxyflavone	$C_{20}H_{20}O_8$	388.37	29215-55-2	(Xing et al., 2017)
5-Demethylnobiletin	5-Hydroxy-6,7,8,3′,4′-pentamethoxyflavone	$C_{20}H_{20}O_8$	388.37	2174-59-6	(Chen et al., 1997)
6-Demethylnobiletin	6-Hydroxy-5,7,8,3′,4′-pentamethoxyflavone	$C_{20}H_{20}O_8$	388.37	\	(Hamdan et al., 2011)

(Continues)

TABLE 1 (Continued)

Name	Chemical name	Molecular formula	Molecular weight (g/mol)	CAS	References
7-Hydroxy-3,5,6,3′,4′-pentamethoxyflavone	7-Hydroxy-3,5,6,3′,4′-pentamethoxyflavone	$C_{20}H_{20}O_8$	388.37	57393-68-7	(Chen et al., 1997)
7-Demethylnobiletin	7-Hydroxy-5,6,8,3′,4′-pentamethoxyflavone	$C_{20}H_{20}O_8$	388.37	149402-88-0	(Zheng et al., 2019)
4′-Hydroxy-3,5,6,7,3′-pentamethoxyflavone	4′-Hydroxy-3,5,6,7,3′-pentamethoxyflavone	$C_{20}H_{20}O_8$	388.38	910-43-0	(Zhao et al., 2018)
Hexamethylquercetagetin	3,5,6,7,3′,4′-Hexamethoxyflavone	$C_{21}H_{22}O_8$	402.39	1251-84-9	(Abad-Garcia et al., 2007)
Gossypetin hexamethyl ether	3,5,7,8,3′,4′-Hexamethoxyflavone	$C_{21}H_{22}O_8$	402.40	7741-47-1	(Uckoo et al., 2015)
5,6,7,3′,4′,5′-Hexamethoxyflavone	5,6,7,3′,4′,5′-Hexamethoxyflavone	$C_{21}H_{22}O_8$	402.40	29043-07-0	(Xing et al., 2017)
Nobiletin	5,6,7,8,3′,4′-Hexamethoxyflavone	$C_{21}H_{22}O_8$	402.40	478-01-3	(Mak et al., 1996)
Bannamurpanisin	5,7,8,3′,4′,5′-Hexamethoxyflavone	$C_{21}H_{22}O_8$	402.40	80324-51-2	(Xing et al., 2017)
3-Methoxytangeretin	3,5,6,7,8,4′-Hexamethoxyflavone	$C_{21}H_{22}O_8$	402.40	34170-18-8	(Sugiyama et al., 1993)
5,4′-Dihydroxy-3,6,7,8,3′-pentamethoxyflavone	5,4′-Dihydroxy-3,6,7,8,3′-pentamethoxyflavone	$C_{20}H_{20}O_9$	404.37	50439-47-9	(Luo et al., 2019)
5-Hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone	5-Hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone	$C_{21}H_{22}O_9$	418.39	1176-88-1	(Li et al., 2006b)
Gardenin A	5-Hydroxy-6,7,8,3′,4′,5′-hexamethoxyflavone	$C_{21}H_{22}O_9$	418.39	21187-73-5	(Xing et al., 2017)
7-Hydroxy-3,5,6,8,3′,4′-hexamethoxyflavone	7-Hydroxy-3,5,6,8,3′,4′-hexamethoxyflavone	$C_{21}H_{22}O_9$	418.39	\	(Chen et al., 1997)
8-Hydroxy-5,6,7,3′,4′,5′-hexamethoxyflavone	8-Hydroxy-5,6,7,3′,4′,5′-hexamethoxyflavone	$C_{21}H_{22}O_9$	418.39	135010-80-9	(Xing et al., 2017)
8-Hydroxy-3,5,6,7,3′,4′-hexamethoxyflavone	8-Hydroxy-3,5,6,7,3′,4′-hexamethoxyflavone	$C_{21}H_{22}O_9$	418.40	1000415-56-4	(Johann et al., 2007)
Apigenin-5-*O*-glucoside	5,7,4′-Trihydroxyflavone-5-*O*-glucoside	$C_{21}H_{20}O_{10}$	432.38	28757-27-9	(Wang et al., 2020)
Isovitexin	5,7,4′-Trihydroxyflavone-6-*C*-glucoside	$C_{21}H_{20}O_{10}$	432.38	38953-85-4	(Abad-Garcia et al., 2012a)
Cosmosiin	5,7,4′-Trihydroxyflavone-7-*O*-glucoside	$C_{21}H_{20}O_{10}$	432.38	578-74-5	(Wang et al., 2020)
Vitexin	5,7,4′-Trihydroxyflavone-8-*C*-glucoside	$C_{21}H_{20}O_{10}$	432.38	3681-93-4	(Gardana et al., 2008)
3-Methoxynobiletin	3,5,6,7,8,3′,4′-Heptamethoxyflavone	$C_{22}H_{24}O_9$	432.42	1178-24-1	(Zhao et al., 2017b)
5,6,7,8,3′,4′,5′-Heptamethoxyflavone	5,6,7,8,3′,4′,5′-Heptamethoxyflavone	$C_{22}H_{24}O_9$	432.42	6965-36-2	(Nakanishi et al., 2019)
Baicalin	5,6,7-Trihydroxyflavone-7-*O*-glucuronide	$C_{21}H_{18}O_{11}$	446.36	21967-41-9	(Wang et al., 2020)
Luteolin-4′-*O*-glucoside	5,7,3′,4′-Tetrahydroxyflavone-4′-*O*-glucoside	$C_{21}H_{20}O_{11}$	448.38	6920-38-3	(Durand-Hulak et al., 2015)
Cynaroside	5,7,3′,4′-Tetrahydroxyflavone-7-*O*-glucoside	$C_{21}H_{20}O_{11}$	448.38	5373-11-5	(Durand-Hulak et al. 2015)
Orientin	5,7,3′,4′-Tetrahydroxyflavone-8-c-glucoside	$C_{21}H_{20}O_{11}$	448.38	28608-75-5	(Abad-Garcia et al., 2012a)
Isoorientin	5,7,3′,4′-Tetrahydroxyflavone-6-*C*-glucoside	$C_{21}H_{20}O_{11}$	448.38	4261-42-1	(Zheng et al., 2019)
Swertiajaponin	5,3′,4′-Trihydroxy-7-methoxyflavone-6-*C*-glucoside	$C_{22}H_{22}O_{11}$	462.40	6980-25-2	(Zhao et al., 2018)
Diosmetin-7-*O*-glucoside	5,7,3′-Trihydroxy-4′-methoxyflavone-7-*O*-glucoside	$C_{22}H_{22}O_{11}$	462.40	20126-59-4	(Zhao et al., 2017a)

(Continues)

TABLE 1 (Continued)

Name	Chemical name	Molecular formula	Molecular weight (g/mol)	CAS	References
Scoparin	5,7,4′-Trihydroxy-3′-methoxyflavone-8-*C*-glucoside	$C_{22}H_{22}O_{11}$	462.41	301-16-6	(Formisano et al., 2019)
Diosmetin-6-*C*-glucoside	5,7,3′-Trihydroxy-4′-methoxyflavone-6-*C*-glucoside	$C_{22}H_{22}O_{12}$	478.41	\	(Roowi and Crozier, 2011)
Diosmetin-8-*C*-glucoside	5,7,3′-Trihydroxy-4′-methoxyflavone-8-*C*-glucoside	$C_{22}H_{22}O_{12}$	478.41	\	(Gattuso et al., 2007)
Isopyrenin	5,7,4′-Trihydroxy-3′,5′-dimethoxyflavone-6-*C*-glucoside	$C_{23}H_{24}O_{12}$	492.43	61252-85-5	(Zhao et al., 2018)
5,7,3′,4′-Tetramethoxyflavone-6-*O*-glucoside	5,7,3′,4′-Tetramethoxyflavone-6-*O*-glucoside	$C_{25}H_{28}O_{12}$	520.49	\	(Zhao et al. 2018)
Amentoflavone	5,7,4′-Trihydroxyflavone (3′→8)−5,7,4′-trihydroxyflavone	$C_{30}H_{18}O_{10}$	538.47	1617-53-4	(Tounsi et al., 2011)
Isoschaftoside	5,7,4′-Trihydroxyflavone-6-*C*-arabinoside 8-*C*-glucoside	$C_{26}H_{28}O_{14}$	564.49	52012-29-0	(Wang et al., 2020)
Vicenin-3	5,7,4′-Trihydroxyflavone-6-*C*-glucoside-8-*C*-xyloside	$C_{26}H_{28}O_{14}$	564.49	51938-32-0	(Wang et al. 2020)
Apiin	5,7,4′-Trihydroxyflavone-7-*O*-apioglucoside	$C_{26}H_{28}O_{14}$	564.49	26544-34-3	(Sommella et al., 2017)
Rhoifolin	5,7,4′-Trihydroxyflavone-7-*O*-neohesperidoside	$C_{27}H_{30}O_{14}$	578.52	17306-46-6	(Wang et al., 2020)
Isorhoifolin	5,7,4′-Trihydroxyflavone-7-*O*-rutinoside	$C_{27}H_{30}O_{14}$	578.52	552-57-8	(Wang et al. 2020)
Vitexin-2′′-*O*-rhamnoside	5,7,4′-Trihydroxyflavone-8-*C*-glucoside-2′′-*O*-rhamnoside	$C_{27}H_{30}O_{14}$	578.52	64820-99-1	(Roowi and Crozier, 2011)
Linarin	5,7-Dihydroxy-4′-methoxyflavone-7-*O*-rutinoside	$C_{28}H_{32}O_{14}$	592.54	480-36-4	(Durand-Hulak et al., 2015)
Acacetin-6-*C*-neohesperidoside	5,7-Dihydroxy-4′-methoxyflavone-6-*C*-neohesperidoside	$C_{28}H_{32}O_{14}$	592.55	\	(Barreca et al., 2011)
Fortunellin	5,7-Dihydroxy-4′-methoxyflavone-7-*O*-neohesperidoside	$C_{28}H_{32}O_{14}$	592.55	20633-93-6	(Barreca et al. 2011)
Acacetin-8-*C*-neohesperidoside	5,7-Dihydroxy-4′-methoxyflavone-8-*C*-neohesperidoside	$C_{28}H_{32}O_{14}$	592.55	\	(Barreca et al. 2011)
Lonicerin	5,7,3′,4′-Tetrahydroxyflavone-7-*O*-neohesperidoside	$C_{27}H_{30}O_{15}$	594.52	25694-72-8	(Barreca et al. 2011)
Vicenin-2	5,7,4′-Trihydroxyflavone-6,8-di-*C*-glucoside	$C_{27}H_{30}O_{15}$	594.52	23666-13-9	(Wang et al., 2020)
Saponarin	5,7,4′-Trihydroxyflavone-6-*C*-glucoside-7-*O*-glucoside	$C_{27}H_{30}O_{15}$	594.52	20310-89-8	(Zhao et al., 2017a)
Acacetin-3,6-di-*C*-glucoside	5,7-Dihydroxy-4′-methoxyflavone-3,6-di-*C*-glucoside	$C_{28}H_{32}O_{15}$	608.54	\	(Barreca et al., 2011)
Neodiosmin	5,7,3′-Trihydroxy-4′-methoxyflavone-7-*O*-neohesperidoside	$C_{28}H_{32}O_{15}$	608.55	38665-01-9	(Brito et al., 2014)
Diosmin	5,7,3′-Trihydroxy-4′-methoxyflavone-7-*O*-rutinoside	$C_{28}H_{32}O_{15}$	608.55	520-27-4	(Gil-Izquierdo et al., 2004)
Chrysoeriol-7-*O*-neohesperidoside	5,7,4′-Trihydroxy-3′-methoxyflavone-7-*O*-neohesperidoside	$C_{28}H_{32}O_{15}$	608.55	\	(Gattuso et al., 2006)
Chrysoeriol-7-*O*-rutinoside	5,7,4′-Trihydroxy-3′-methoxyflavone-7-*O*-rutinoside	$C_{28}H_{32}O_{15}$	608.55	32061-83-9	(Zhao et al., 2018)
Lucenin-2	5,7,3′,4′-Tetrahydroxyflavone-6,8-di-*C*-glucoside	$C_{27}H_{30}O_{16}$	610.52	29428-58-8	(Gattuso et al., 2006)

(Continues)

TABLE 1 (Continued)

Name	Chemical name	Molecular formula	Molecular weight (g/mol)	CAS	References
Luteolin-7,3′-di-*O*-glucoside	5,7,3′,4′-Tetrahydroxyflavone-7,3′-di-*O*-glucoside	$C_{27}H_{30}O_{16}$	610.52	52187-80-1	(Wang et al., 2020)
Luteolin-7-*O*-rutinoside	5,7,3′,4′-Tetrahydroxyflavone-7-*O*-rutinoside	$C_{27}H_{30}O_{16}$	610.52	\	(Marin et al., 2002)
Stellarin-2	5,7,4′-Trihydroxy-3′-methoxyflavone-6,8-di-*C*-glucoside	$C_{28}H_{32}O_{16}$	624.54	\	(Gil-Izquierdo et al., 2004)
Diosmetin-6,8-di-*C*-glucoside	5,7,3′-Trihydroxy-4′-methoxyflavone-6,8-di-*C*-glucoside	$C_{28}H_{32}O_{16}$	624.55	\	(Barreca et al., 2010)
Rhoifolin-4′-*O*-glucoside	5,7,4′-Trihydroxyflavone-7-*O*-neohesperidoside-4′-*O*-glucoside	$C_{33}H_{40}O_{19}$	740.67	\	(Zhao et al., 2015)
Luteolin-7-*O*-rutinoside-4′-*O*-glucoside	5,7,3′,4′-Tetrahydroxyflavone-7-*O*-rutinoside-4′-*O*-glucoside	$C_{33}H_{40}O_{20}$	756.66	\	(Wang et al., 2019a)

and variety specific in distribution (Wang et al., 2022). PMFs are concentrated in the flavedo part of fruit peels and are also distributed in leaves and flowers. The content of PMFs was lower in the pulp of the fruit and almost no PMFs were distributed in the roots of citrus (Zhao et al., 2021). In terms of varieties, PMFs are abundant in the fruits of tangerines, mandarins, oranges, and some hybrid citrus (Wang et al., 2022).

2.2.2 | Flavanones

Flavanones are another class of flavonoids that are highly abundant in citrus. Compared with flavonoids, relatively few flavanones have been identified in citrus, with about 35 species (Table 2). The distribution of flavanones is more extensive than PMFs, which can be detected in all varieties of citrus fruits, leaves, and flowers (Barpeled et al., 1993). However, the abundance of flavanones in different parts of citrus fruits were slightly different (Durand-Hulak et al., 2015). The content of the peel is higher than that of the pulp, and the relative abundance of the albedo is higher than that of the flavedo (Wang et al., 2017). Like flavones, citrus flavanones also exist in many isomers. Interestingly, in the same citrus fruit, the content of some flavanone isomers has a "teeter-totter" expression pattern, that is, when a certain substance has a high expression advantage, the other is in a low expression state. This phenomenon is particularly evident in the selection of the glycoside substituents on the 7th position of the A ring, and two glycosides, neohesperidoside and rutinoside, compete for aglycones (Brito et al., 2014, Wang et al., 2022, Wang et al., 2017). The dominant expression substance of ponkan, mandarin and orange fruits was hesperidin, and its 7th position glycoside was rutinoside (Khan et al., 2014, Xi et al., 2014). The dominant expression substance of grapefruit and ougan fruits was neohesperidin, and its glycoside at position 7 was neohesperidoside (Durand-Hulak et al., 2015, Khan et al., 2014, Wang et al., 2017). A similar phenomenon exists for other flavanones such as naringin and naringenin (Liu et al., 2017, Zhao et al., 2017b).

2.2.3 | Flavonols and flavanols

The structural characteristics of flavonols and flavanols are that there is a hydroxyl group attached to the 3rd position of the C ring. In previous studies on citrus flavonoids, 45 and 5 of them were identified, respectively (Tables 3 and 4). However, these two flavonoids are uncommon and low in citrus cultivars, and quite a few are only found in citrus leaves or flowers (Miyashita et al., 2018, Wang et al., 2019a). Unless used for special purposes, citrus was rarely used as a raw material for the extraction of these two flavonoids.

2.2.4 | Isoflavones

The structural feature of isoflavones is that the B ring is connected to the 3rd-carbon atom of the C ring. In citrus, 15 isoflavones have been identified (Table 5). Most of the substance information was derived from the metabolomic analysis of the citrus fruit peel, and its substance content was relatively low in citrus flavonoids.

2.2.5 | Anthocyanins

Anthocyanins are a class of citrus substances with color-rendering properties. The structure of the C-ring is different from other citrus flavonoids. The C-ring double bond is located between the positively charged oxygen ion on the 1st and the carbon atom on the 2nd, and between the carbon atoms on the 3rd and 4th. In previous studies, a total of four kinds of anthocyanidins and 11 kinds of anthocyanins with glycosides were identified (Table 6).

To sum up, citrus flavonoids have their own characteristics in structure, distribution, and function. Through targeted selection of high-content varieties and high-abundance expression parts, the natural product treasure house of citrus flavonoid resources can be utilized more efficiently.

TABLE 2 Flavanones detected in Citrus

Name	Chemical name	Molecular formular	Molecular weight (g/mol)	CAS	References
7-Hydroxyflavanone	7-Hydroxyflavanone	$C_{15}H_{12}O_3$	240.25	6515-36-2	(Calabro et al., 2004)
Liquiritigenin	7,4′-Dihydroxyflavanone	$C_{15}H_{12}O_4$	256.25	578-86-9	(Wang et al., 2020)
Pinocembrin	5,7-Dihydroxyflavanone	$C_{15}H_{12}O_4$	256.25	480-39-7	(Wang et al. 2020)
Butin	7,3′,4′-Trihydroxyflavanone	$C_{15}H_{12}O_5$	272.25	492-14-8	(Wang et al. 2020)
Naringenin	5,7,4′-Trihydroxyflavanone	$C_{15}H_{12}O_5$	272.25	480-41-1	(Barpeled et al., 1993)
Isosakuranetin	5,7-Dihydroxy-4′-methoxyflavanone	$C_{16}H_{14}O_5$	286.28	480-43-3	(Robards et al., 1997)
Sakuranetin	5,4′-Dihydroxy-7-methoxyflavanone	$C_{16}H_{14}O_5$	286.28	2957-21-3	(Durand-Hulak et al., 2015)
Eriodictyol	5,7,3′,4′-Tetrahydroxyflavanone	$C_{15}H_{12}O_6$	288.25	552-58-9	(Xi et al., 2014)
Hesperetin	5,7,3′-Trihydroxy-4′-methoxyflavanone	$C_{16}H_{14}O_6$	302.28	520-33-2	(Berhow & Smolensky, 1995)
Homoeriodictyol	5,7,4′-Trihydroxy-3′-methoxyflavanone	$C_{16}H_{14}O_6$	302.28	446-71-9	(Abad-Garcia et al., 2012a)
Sterubin	7-Methoxy-5,3′,4′-trihydroxyflavanone	$C_{16}H_{14}O_6$	302.28	51857-11-5	(Wang et al., 2020)
Persicogenin	5,3′-Dihydroxy-7,4′-dimethoxyflavanone	$C_{17}H_{16}O_6$	316.31	28590-40-1	(Wang et al. 2020)
5,6,7,4′-Tetramethoxyflavanone	5,6,7,4′-Tetramethoxyflavanone	$C_{19}H_{20}O_6$	344.36	2569-77-9	(Li et al., 2006b)
5-hydroxy-3,6,7,4′-Tetramethoxyflavanone	5-Hydroxy-3,6,7,4′-tetramethoxyflavanone	$C_{19}H_{18}O_7$	358.34	14787-34-9	(Zhao et al., 2018)
5,6,7,3′,4′-Pentamethoxyflavanone	5,6,7,3′,4′-Pentamethoxyflavanone	$C_{20}H_{22}O_7$	374.38	66074-98-4	(Xing et al., 2017)
5,7,8,3′,4′-Pentamethoxyflavanone	5,7,8,3′,4′-Pentamethoxyflavanone	$C_{20}H_{22}O_7$	374.39	78225-00-0	(Chen & Montanari, 1998)
6,7,8,3′,4′-Pentamethoxyflavanone	6,7,8,3′,4′-Pentamethoxyflavanone	$C_{20}H_{22}O_7$	374.39	\	(Xing et al., 2017)
5-Demethylcitromitine	5-Hydroxy-6,7,8,3′,4′-pentamethoxyflavanone	$C_{20}H_{22}O_8$	390.39	15512-52-4	(Xing et al. 2017)
Flavanone-7-*O*-glucoside	7-Hydroxyflavanone-7-*O*-glucoside	$C_{21}H_{22}O_8$	402.4	\	(Sentandreu et al., 2007)
5,6,7,8,3′,4′-Hexamethoxyflavanone	5,6,7,8,3′,4′-Hexamethoxyflavanone	$C_{21}H_{24}O_8$	404.41	67549-69-3	(Chen and Montanari, 1998)
Isohemiphloin	5,7,4′-Trihydroxyflavanone-8-*C*-glucoside	$C_{21}H_{22}O_{10}$	434.39	3682-02-8	(Wang et al., 2020)
Prunin	5,7,4′-Trihydroxyflavanone-7-*O*-glucoside	$C_{21}H_{22}O_{10}$	434.39	529-55-5	(Wang et al. 2020)
Hesperetin-7-*O*-rhamnoside	5,7,3′-Trihydroxy-4′-methoxyflavanone-7-*O*-rhamnoside	$C_{22}H_{24}O_{10}$	448.43	\	(Ledesma-Escobar et al., 2015)
Eriodictyol-7-*O*-glucoside	5,7,3′,4′-Tetrahydroxyflavanone-7-*O*-glucoside	$C_{21}H_{22}O_{11}$	450.39	38965-51-4	(Guedon & Pasquier, 1994)
Flavanomarein	7,8,3′,4′-Tetrahydroxyflavanone-7-*O*-glucoside	$C_{21}H_{22}O_{11}$	450.39	577-38-8	(Venturini et al., 2014)
Hesperetin 5-*O*-glucoside	5,7,3′-Trihydroxy-4′-methoxyflavanone-5-*O*-glucoside	$C_{22}H_{24}O_{11}$	464.42	69651-80-5	(Wang et al., 2020)
Hesperetin-7-*O*-glucoside	5,7,3′-Trihydroxy-4′-methoxyflavanone-7-*O*-glucoside	$C_{22}H_{24}O_{11}$	464.42	31712-49-9	(Castillo et al., 1993)
Persicoside	5,3′-Dihydroxy-7,4′-dimethoxyflavanone-5-*O*-glucoside	$C_{23}H_{26}O_{11}$	478.45	28978-03-2	(Wang et al., 2020)

(Continues)

TABLE 2 (Continued)

Name	Chemical name	Molecular formular	Molecular weight (g/mol)	CAS	References
Naringin	5,7,4′-Trihydroxyflavanone-7-*O*-neohesperidoside	$C_{27}H_{32}O_{14}$	580.53	10236-47-2	(Wang et al., 2016)
Narirutin	5,7,4′-Trihydroxyflavanone-7-*O*-rutinoside	$C_{27}H_{32}O_{14}$	580.54	14259-46-2	(He et al., 1997)
Didymin	5,7-Dihydroxy-4′-methoxyflavanone-7-*O*-rutinoside	$C_{28}H_{34}O_{14}$	594.53	14259-47-3	(Berhow et al., 1996)
Poncirin	5,7-Dihydroxy-4′-methoxyflavanone-7-*O*-neohesperidoside	$C_{28}H_{34}O_{14}$	594.56	14941-08-3	(Wang et al., 2020)
Eriocitrin	5,7,3′,4′-Tetrahydroxyflavanone-7-*O*-rutinoside	$C_{27}H_{32}O_{15}$	596.53	13463-28-0	(Kanes et al., 1993)
Neoeriocitrin	5,7,3′,4′-Tetrahydroxyflavanone-7-*O*-neohesperidoside	$C_{27}H_{32}O_{15}$	596.53	13241-32-2	(Roowi & Crozier, 2011)
Hesperidin	5,7,3′-Trihydroxy-4′-methoxyflavanone-7-*O*-rutinoside	$C_{28}H_{34}O_{15}$	610.56	520-26-3	(Wang et al., 2020)
Homoeriodictyol-7-*O*-rutinoside	5,7,4′-Trihydroxy-3′-methoxyflavanone-7-*O*-rutinoside	$C_{28}H_{34}O_{15}$	610.56	\	(Gil-Izquierdo et al., 2004)
Neohesperidin	5,7,3′-Trihydroxy-4′-methoxyflavanone-7-*O*-neohesperidoside	$C_{28}H_{34}O_{15}$	610.56	13241-33-3	(Wang et al., 2020)
Eriodictyol-7-*O*-rutinoside-4′-*O*-glucoside	5,7,3′,4′-Tetrahydroxyflavanone-7-*O*-rutinoside-4′-*O*-glucoside	$C_{33}H_{42}O_{20}$	758.68	\	(Brito et al., 2014)

TABLE 3 Flavonols detected in Citrus

Name	Chemical name	Molecular formula	Molecular weight (g/mol)	CAS	References
4′-Methoxyflavonol	3-Hydroxy-4′-methoxyflavone	$C_{16}H_{12}O_4$	268.26	6889-78-7	(Owens & McIntosh, 2009)
Kaempferol	3,5,7,4′-Tetrahydroxyflavone	$C_{15}H_{10}O_6$	286.24	520-18-3	(Doostdar et al., 1995)
Fisetin	3,7,3′,4′-Tetrahydroxyflavone	$C_{15}H_{10}O_6$	286.24	528-48-3	(Zheng et al., 2020)
3′,4′-Dimethoxyflavonol	3-Hydroxy-3′,4′-dimethoxyflavone	$C_{17}H_{14}O_5$	298.29	6889-80-1	(Owens & McIntosh, 2009)
Quercetin	3,5,7,3′,4′-Pentahydroxyflavone	$C_{15}H_{10}O_7$	302.23	117-39-5	(He et al., 1997)
Herbacetin	3,5,7,8,4′-Pentahydroxyflavone	$C_{15}H_{10}O_7$	302.24	527-95-7	(Wang et al., 2020)
Isorhamnetin	3,5,7,4′-Tetrahydroxy-3′-methoxyflavone	$C_{16}H_{12}O_7$	316.26	480-19-3	(Butryee et al., 2009)
Tamarixetin	3,5,7,3′-Tetrahydroxy-4′-methoxyflavone	$C_{16}H_{12}O_7$	316.26	603-61-2	(Butryee et al., 2009)
Quercetagetin	3,5,6,7,3′,4′-Hexahydroxyflavone	$C_{15}H_{10}O_8$	318.23	90-18-6	(Ooghe & Detavernier, 1997)
Myricetin	3,5,7,3′,4′,5′-Hexahydroxyflavone	$C_{15}H_{10}O_8$	318.23	529-44-2	(Swatsitang et al., 2000)
3-Hydroxy-5,7,8-trimethoxyflavone	3-Hydroxy-5,7,8-trimethoxyflavone	$C_{18}H_{16}O_6$	328.32	103393-10-8	(Xing et al., 2017)
Spinacetin	3,5,7,4′-Tetrahydroxy-6,3′-dimethoxyflavone	$C_{17}H_{14}O_8$	346.29	3153-83-1	(Klimek-Szczykutowicz et al., 2020)
Limocitrin	3,5,7,4′-Tetrahydroxy-8,3′-dimethoxyflvaone	$C_{17}H_{14}O_8$	346.29	489-33-8	(Klimek-Szczykutowicz et al., 2020)
3-Hydroxy-5,6,7,4′-tetramethoxyflavone	3-Hydroxy-5,6,7,4′-tetramethoxyflavone	$C_{19}H_{18}O_7$	358.35	5867-71-0	(Li et al., 2006b)
5,7,3′,4′-Tetramethylquercetin	3-Hydroxy-5,7,3′,4′-tetramethoxyflavone	$C_{19}H_{18}O_7$	358.35	1244-78-6	(Zhao et al., 2018)
3,5,6-Trihydroxy-7,3′,4′-trimethoxyflavone	3,5,6-Trihydroxy-7,3′,4′-trimethoxyflavone	$C_{18}H_{16}O_8$	360.32	99499-83-9	(Chu et al., 2012)
3-Hydroxytangeretin	3-Hydroxy-5,6,7,8,4′-pentamethoxyflavone	$C_{20}H_{20}O_8$	388.38	50461-91-1	(Li et al., 2006b)
Natsudaidain	3-Hydroxy-5,6,7,8,3′,4′-hexamethoxyflavone	$C_{21}H_{22}O_9$	418.40	35154-55-3	(Park et al., 2014)
Astragalin	3,5,7,4′-Tetrahydroxyflavone-3-*O*-glucoside	$C_{21}H_{20}O_{11}$	448.38	480-10-4	(Miyashita et al., 2018)
Quercitrin	3,5,7,3′,4′-Pentahydroxyflavone-3-*o*-rhamnoside	$C_{21}H_{20}O_{11}$	448.38	522-12-3	(Abad-Garcia et al., 2012a)
Trifolin	3,5,7,4′-Tetrahydroxyflavone-3-*O*-galactoside	$C_{21}H_{20}O_{11}$	448.38	23627-87-4	(Miyashita et al., 2018)
Kaempferol-7-*O*-glucoside	3,5,7,4′-Tetrahydroxyflavone-7-*O*-glucoside	$C_{21}H_{20}O_{11}$	448.38	16290-07-6	(Molina-Calle et al., 2015)
Isorhamnetin-3-*O*-rhamnoside	3,5,7,4′-Tetrahydroxy-3′-methoxyflavone-3-*O*-rhamnoside	$C_{22}H_{22}O_{11}$	462.41	\	(Brito et al., 2014)
Hyperoside	3,5,7,3′,4′-Pentahydroxyflavone-3-*O*-galactoside	$C_{21}H_{20}O_{12}$	464.38	482-36-0	(Venturini et al., 2014)
Isoquercitrin	3,5,7,3′,4′-Pentahydroxyflavone-3-*O*-glucoside	$C_{21}H_{20}O_{12}$	464.38	482-35-9	(Bilbao et al., 2007)
Isorhamnetin-3-*O*-glucoside	3,5,7,4′-Tetrahydroxy-3′-methoxyflavone-3-*o*-glucoside	$C_{22}H_{22}O_{12}$	478.4	5041-82-7	(Wang et al., 2020)
Gossypitrin	3,5,7,8,3′,4′-Hexahydroxyflavone-7-*O*-glucoside	$C_{21}H_{20}O_{13}$	480.38	489-34-9	(Wang et al. 2020)
Flavoyadorinin A	3,5,4′-Trihydroxy-7,3′-dimethoxyflavone-3′-*O*-glucoside	$C_{23}H_{24}O_{12}$	492.43	20486-38-8	(Brito et al., 2014)
Limocitrin-3-*O*-glucoside	3,5,7,4′-Tetrahydroxy-8,3′-dimethoxyflvaone-3-*O*-glucoside	$C_{23}H_{24}O_{13}$	508.43	\	(Wang et al., 2019a)
Kaempferitrin	3,5,7,4′-Tetrahydroxyflavone-3,7-di-*O*-rhamnoside	$C_{27}H_{30}O_{14}$	578.52	482-38-2	(Zeng et al., 2016)
Kaempferol-3-*O*-rhamnoside-7-*O*-glucoside	3,5,7,4′-Tetrahydroxyflavone-3-*O*-rhamnoside-7-*O*-glucoside	$C_{27}H_{30}O_{15}$	594.52	\	(Oliveras-Lopez et al., 2016)
Nicotiflorin	3,5,7,4′-Tetrahydroxyflavone-3-*O*-rutinoside	$C_{27}H_{30}O_{15}$	594.52	17650-84-9	(Abad-Garcia et al., 2007)
Kaempferol-7-*O*-neohesperidoside	3,5,7,4′-Tetramethoxyflavone-7-*O*-neohesperidoside	$C_{27}H_{30}O_{15}$	594.52	17353-03-6	(Smeriglio et al., 2019)

(Continues)

TABLE 3 (Continued)

Name	Chemical name	Molecular formula	Molecular weight (g/mol)	CAS	References
Kaempferol-7-*O*-rutinoside	3,5,7,4′-Tetrahydroxyflavone-7-*O*-rutinoside	$C_{27}H_{30}O_{15}$	594.52	\	(Miyashita et al., 2018)
Kaempferol-3,7-diglucoside	3,5,7,4′-Tetrahydroxyflavone-3,7-di-*O*-glucoside	$C_{27}H_{30}O_{16}$	610.52	25615-14-9	(Oliveras-Lopez et al., 2016)
Quercetin-3-*O*-neohesperidoside	3,5,7,3′,4′-Pentahydroxyflavone-3-*O*-neohesperidoside	$C_{27}H_{30}O_{16}$	610.52	32453-36-4	(Ledesma-Escobar et al., 2016)
Rutin	3,5,7,3′,4′-Pentahydroxyflavone-3-*O*-rutinoside	$C_{27}H_{30}O_{16}$	610.52	153-18-4	(Roowi and Crozier, 2011)
Sophoraflavonoloside	3,5,7,4′-Tetrahydroxyflavone-3-*O*-sophoroside	$C_{27}H_{30}O_{16}$	610.52	19895-95-5	(Wang et al., 2019a)
Isorhamnetin-3-*O*-neohesperidoside	3,5,7,4′-Tetrahydroxy-3′-methoxyflavone-3-*O*-neohesperidoside	$C_{28}H_{32}O_{16}$	624.54	55033-90-4	(Ledesma-Escobar et al., 2016)
Isorhamnetin-3-*O*-rutinoside	3,5,7,4′-Tetrahydroxy-3′-methoxyflavone-3-*O*-rutinoside	$C_{28}H_{32}O_{16}$	624.54	604-80-8	(Abad-Garcia et al., 2007)
Isorhamnetin-3,7-di-*O*-glucoside	3,5,7,4′-Tetrahydroxy-3′-methoxyflavone-3,7-di-*O*-glucoside	$C_{28}H_{32}O_{17}$	640.54	6758-51-6	(Wang et al., 2019a)
Limocitrin-3-*O*-rutinoside	3,5,7,4′-Tetrahydroxy-8,3′-dimethoxyflvaone-3-*O*-rutinoside	$C_{29}H_{34}O_{17}$	654.57	\	(Girones-Vilaplana et al., 2014)
Robinbin	3,5,7,4′-Tetrahydroxyflavone-3-*O*-robinoside-7-*O*-rhamnoside	$C_{33}H_{40}O_{19}$	740.66	301-19-9	(Abad-Garcia et al., 2012a)
Quercetin-3-*O*-rutinoside-7-*O*-glucoside	3,5,7,3′,4′-Pentahydroxyflavone-3-*O*-rutinoside-7-*O*-glucoside	$C_{33}H_{40}O_{21}$	772.66	30311-61-6	(Gil-Izquierdo et al., 2004)
Isorhamnetin-3-*O*-rutinoside-7-*O*-glucoside	3,5,7,4′-Tetrahydroxy-3′-methoxyflavone-3-*O*-rutinoside-7-*O*-glucoside	$C_{34}H_{42}O_{21}$	786.7	\	(Lu et al., 2018)

TABLE 4 Flavanols detected in Citrus

Name	Chemical name	Molecular formula	Molecular weight (g/mol)	CAS	References
Aromadendrin	3,5,7,4′-Tetrahydroxyflavanone	$C_{15}H_{12}O_6$	288.25	480-20-6	(Zheng et al., 2020)
Taxifolin	3,5,7,3′,4′-Pentahydroxyflavanone	$C_{15}H_{12}O_7$	304.25	480-18-2	(Doostdar et al., 1995)
3-*O*-acetylpinobanksin	3-Acetoxy-5,7-dihydroxyflavanone	$C_{17}H_{14}O_6$	314.3	52117-69-8	(Wang et al., 2020)
Dihydroisorhamnetin	3,5,7,4′-Tetrahydroxy-3′-methoxyflavanone	$C_{16}H_{14}O_7$	318.28	55812-91-4	(Abad-Garcia et al., 2012b)
Astilbin	3,5,7,3′,4′-Pentahydroxyflavanone-3-*O*-rhamnoside	$C_{21}H_{22}O_{11}$	450.39	29838-67-3	(Wang et al., 2020)

3 | METHODS OF EXTRACTION AND PURIFICATION OF CITRUS FLAVONOIDS

The brief process of extraction and purification of citrus flavonoids includes: solvent extraction, removal of impurities, adsorption and elution, partition separation, collection. Solvent extraction is the process of dissolving flavonoids into solvent by changing the structure of raw materials. The solvent is generally an organic solvent or a mixture of an organic solvent and water. Depending on the extracted substance, organic solvents with different polarities can be selected, such as n-hexane, petroleum ether, acetone, methanol, ethanol, chloroform, and so on (Liu et al., 2016, Uckoo et al., 2015). Sometimes auxiliary methods such as heating, ultrasonic or reflux extraction are used to increase the extraction rate, and other auxiliary pH regulators such as formic acid are added to prevent the degradation of pH-sensitive substances such as anthocyanins (Fabroni et al., 2016). To remove impurities, the general strategy is to adsorb on a resin or silica gel column, and then elute with water or a low-concentration organic solvent. The purpose is to remove sugars, acids, pigments, or other flavonoids (Wang et al., 2019b). This process is realized by the principle of similarity compatibility and different binding degree between material and adsorbent. In addition to removing impurities, the enrichment of flavonoids was also completed, which was convenient for the subsequent purification process. Adsorption elution refers to the process of desorption of

TABLE 5 Isoflavones detected in Citrus

Name	Chemical name	Molecular formula	Molecular weight (g/mol)	CAS	References
Formononetin	7-Hydroxy-4′-methoxyisoflavone	$C_{16}H_{12}O_4$	268.26	485-72-3	(Molina-Calle et al., 2015)
2′-hydroxydaidzein	7,2′,4′-Trihydroxyisoflavone	$C_{15}H_{10}O_5$	270.24	7678-85-5	(Wang et al., 2020)
6-hydroxydaidzein	6,7,4′-Trihydroxyisoflavone	$C_{15}H_{10}O_5$	270.24	17817-31-1	(Wang et al. 2020)
Genistein	5,7,4′-Trihydroxyisoflavone	$C_{15}H_{10}O_5$	270.24	446-72-0	(Wang et al. 2020)
Biochanin A	5,7-Dihydroxy-4′-methoxyisoflavone	$C_{16}H_{12}O_5$	284.26	491-80-5	(Wang et al. 2020)
Calycosin	7,3′-Dihydroxy-4′-methoxyisoflavone	$C_{16}H_{12}O_5$	284.26	20575-57-9	(Wang et al. 2020)
Prunetin	5,4′-Dihydroxy-7-methoxyisoflavone	$C_{16}H_{12}O_5$	284.26	552-59-0	(Wang et al. 2020)
2′-hydroxygenistein	5,7,2′,4′-Tetrahydroxyisoflavone	$C_{15}H_{10}O_6$	286.24	1156-78-1	(Wang et al. 2020)
Orobol	5,7,3′,4′-Tetrahydroxyisoflavone	$C_{15}H_{10}O_6$	286.24	480-23-9	(Wang et al. 2020)
Tectorigenin	5,7,4′-Trihydroxy-6-methoxyisoflavone	$C_{16}H_{12}O_6$	300.26	548-77-6	(Wang et al. 2020)
Daidzin	7,4′-Dihydroxyisoflavone-7-*O*-glucoside	$C_{21}H_{20}O_9$	416.38	552-66-9	(Wang et al. 2020)
Ononin	7-Hydroxy-4′-methoxyisoflavone-7-*O*-glucoside	$C_{22}H_{22}O_9$	430.41	486-62-4	(Wang et al. 2020)
Genistin	5,7,4′-Trihydroxyisoflavone-7-*O*-glucoside	$C_{21}H_{20}O_{10}$	432.38	529-59-9	(Wang et al. 2020)
Puararin	7,8,4′-Trihydroxyisoflavone-8-*C*-glucoside	$C_{21}H_{20}O_{10}$	432.38	100272-46-6	(Wang et al. 2020)
Glycitin	7,4′-Dihydroxy-6-methoxyisoflavone-7-*O*-glucoside	$C_{22}H_{22}O_{10}$	446.4	40246-10-4	(Wang et al. 2020)

different components in the enrichment product successively after the enrichment product of flavonoids is closely combined with the adsorption material in the early stage and eluted with a specific concentration or ratio of solvent. The specific gradient change of solvent ratio can further separate the target component from the enrichment product (Wang et al., 2019b). Collection refers to the process in which the separated and purified products are recovered, rationally combined, the solvent is removed and the final component or monomer purified products are obtained (Figure 4).

3.1 | Materials preparation and components enrichment

3.1.1 | Drying method

Although drying is not a method for extracting flavonoids from raw materials, it is crucial in the overall extraction system. First, in the process of preparation and processing of raw materials, dried raw materials are more conducive to processing, transportation, storage, and use. The other is to obtain the powder-like extract through a certain drying method after obtaining the solution containing a relatively pure target extract, which is convenient for further use or biological activity evaluation. When selecting a drying method, the following factors should be considered: the nature of the raw material to be dried, the stability of the target extract, the temperature, humidity, and flow rate of the drying medium (Elmeligy et al., 2021, Kumar et al., 2021, Senevirathne et al., 2009). The drying methods used in the extraction of citrus flavonoids include hot air drying, freeze drying, and spray drying (Elmeligy et al., 2021, Papoutsis et al., 2017). Hot air-drying method is generally used for the drying of fresh raw materials, using hot air-drying citrus peel and other citrus flavonoid raw materials. Due to the good thermal stability of flavanone and PMF components in citrus, the use of hot air drying has no effect on most citrus flavonoids. Zhang et al. (2019) found that desiccation induced demethylation of polymethoxyl flavones at 5th position. Further mechanism study found that this reaction was carried out under acid hydrolysis and enzyme mediated catalysis, and temperature was not completely proportional to the degree of demethylation reaction (Zhang et al., 2019). Freeze drying is to freeze the dry object into solid and dehydrate the material at low temperature by sublimation of ice under the condition of low temperature and decompression. It is characterized by low drying temperature, suitable for thermally unstable components such as citrus anthocyanins (Papoutsis et al., 2018, Tsai et al., 2007). At the same time, the dried products are generally loose and porous and easy to dissolve. Spray drying is to atomize liquid materials into fine mist droplets through nozzles. In the hot air with a certain flow rate, the raw material contacts with the heat medium in the drying tower and is dried into powder. The feed state of spray drying can be solution, suspension, or paste, which is generally used for drying of crude extract or drying of extract (Shofinita et al., 2015). The advantage of spray drying is that powdery solid particles can be obtained directly from the extraction liquid (Sansone et al., 2011). Compared with drying and freeze drying, the drying time is shorter, and the particle size and water content of the final dried product can be controlled by changing the process parameters (Elmeligy et al., 2021). Hu et al. (2018) used gum arabic/whey protein concentrate as wall material to encapsulate total flavonoids extracted from Ponkan, and microencapsulated

TABLE 6 Anthocyanins detected in Citrus

Name	Chemical name	Molecular formula	Molecular weight (g/mol)	CAS	References
Pelargonidin chloride	3,5,7,4′-Tetrahydroxyflavylium chloride	$C_{15}H_{11}ClO_5$	306.71	134-04-3	(Fuzfai & Molnar-Perl, 2007)
Cyanidin chloride	3,5,7,3′,4′-Pentahydroxyflavylium chloride	$C_{15}H_{11}ClO_6$	322.71	528-58-5	(Sorrenti et al., 2004)
Peonidin chloride	3,5,7,4′-Tetrahydroxy-3′-methoxyflavylium chloride	$C_{16}H_{13}ClO_6$	336.74	134-01-0	(Butryee et al., 2009)
Malvidin chloride	3′,5′-Dimethoxy-3,5,7,4′-tetrahydroxyflavylium chloride	$C_{17}H_{15}ClO_7$	366.77	643-84-5	(Fuzfai & Molnar-Perl, 2007)
Callistephin chloride	3,5,7,4′-Tetrahydroxyflavylium-3-*O*-glucoside chloride	$C_{21}H_{21}ClO_{10}$	468.87	18466-51-8	(Wang et al., 2020)
Cyanidin-3-*O*-glucoside	3,5,7,3′,4′-Pentahydroxyflavylium-3-*O*-glucoside chloride	$C_{21}H_{21}ClO_{11}$	484.87	7084-24-4	(Proteggente et al., 2003)
Peonidin 3-*O*-glucoside chloride	3,5,7,4′-Tetrahydroxy-3′-methoxyflavylium-3-*O*-glucoside chloride	$C_{22}H_{23}ClO_{11}$	498.9	6906-39-4	(Wang et al., 2020)
Delphinidin-3-*O*-glucoside chloride	3,5,7,3′,4′,5′-Hexahydroxyflavylium-3-*O*-glucoside chloride	$C_{21}H_{21}ClO_{12}$	500.87	6906-38-3	(Sommella et al., 2017)
Petunidin 3-*O*-glucoside chloride	3,5,7,3′,4′-Pentahydroxy-5′-methoxyflavylium-3-*O*-glucoside chloride	$C_{22}H_{23}ClO_{12}$	514.9	6988-81-4	(Wang et al., 2020)
Cyanidin-3-*O*-(6′′-malonylglucoside) chloride	3,5,7,3′,4′-Pentahydroxyflavylium-3-*O*-(6′′-malonylglucoside) chloride	$C_{24}H_{23}ClO_{14}$	570.92	\	(Sommella et al., 2017)
Delphinidin-3-*O*-(6′′-malonylglucoside) chloride	3,5,7,3′,4′,5′-Hexahydroxyflavylium-3-*O*-(6′′-malonylglucoside) chloride	$C_{24}H_{23}ClO_{15}$	586.92	\	(Fabroni et al., 2016)
Cyanidin-3-*O*-rutinoside chloride	3,5,7,3′,4′-Pentahydroxyflavylium-3-*O*-rutinoside chloride	$C_{27}H_{31}ClO_{15}$	631.03	18719-76-1	(Wang et al., 2020)
Cyanidin-3,5-di-*O*-glucoside chloride	3,5,7,3′,4′-Pentahydroxyflavylium-3,5-di-*O*-glucoside chloride	$C_{27}H_{31}ClO_{16}$	647.03	2611-67-8	(Lo Piero, 2015)
Cyanidin-3-*O*-sophoroside chloride	3,5,7,3′,4′-Pentahydroxyflavylium-3-*O*-sophoroside chloride	$C_{27}H_{31}ClO_{16}$	647.03	18376-31-3	(Lo Piero 2015)
Peonidin-3,5-di-*O*-glucoside chloride	3,5,7,4′-Tetrahydroxy-3′-methoxyflavylium-3,5-di-*O*-glucoside chloride	$C_{28}H_{33}ClO_{16}$	661.06	132-37-6	(Wang et al., 2020)

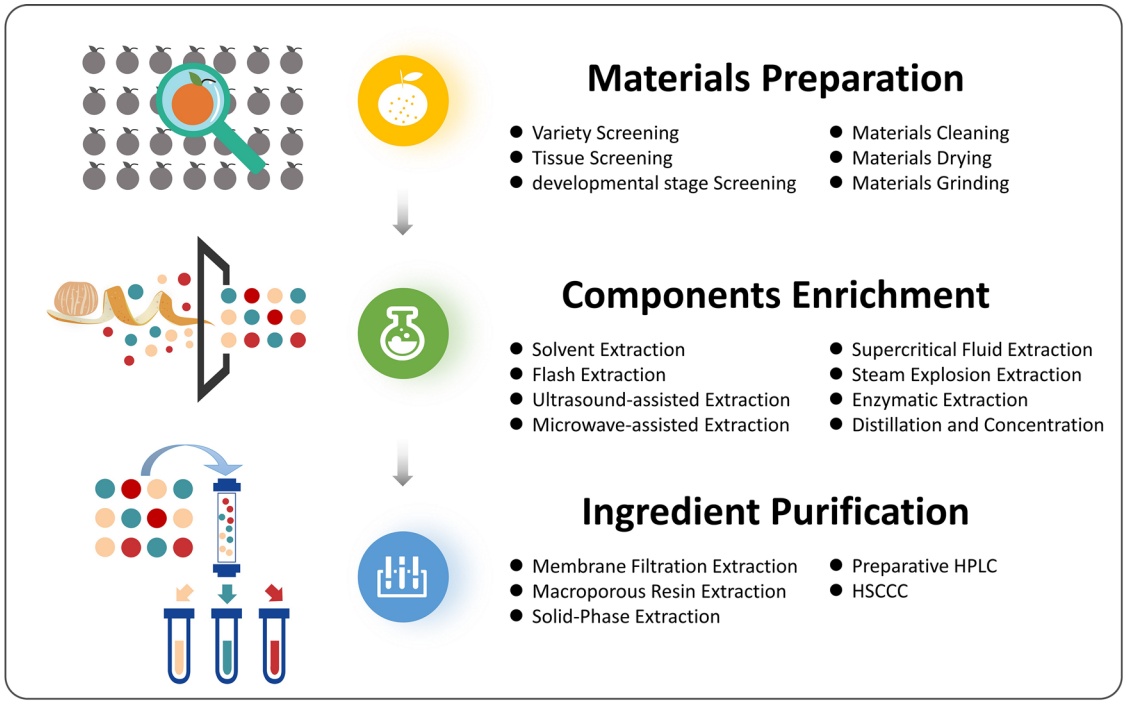


FIGURE 4 Process of citrus flavonoids extraction.

powder was produced by preparing oil-in-water emulsion and spray drying techniques. The microencapsulated flavonoids were characterized by stable structure, high powder yield (72.74%), high encapsulation rate (97.60%), and the retention rate of flavonoids reached 63.39%, which was higher than that of unencapsulated flavonoids (19.29%). Islam et al. (2017) employed two new technologies, micro wet milling and vacuum spray drying (VSD), to produce *Citrus unshiu* powder concentrate. The VSD method involved vacuum drying at low temperature (40–60°C) with superheated steam (200°C) as the heating medium and maltodextrin (maltodextrin) as the carrier. The powder produced had lower water activity (0.20), lower hygroscopicity (0.0597 gH_2O/solid) and higher retention of ascorbic acid (73.97%), flavonoids (93.90%), and phenolic compounds (93.50%). Papoutsis et al. (2018) encapsulated the aqueous extract of lemon by-products by spray drying and freeze drying techniques using maltodextrin, soy protein and *ι*-carrageenan as coating agents. It was found that the retention of total phenolics, total flavonoids, and antioxidant capacity of the freeze-dried particles was higher, and the water content (1.15–2.15%) and water activity (0.13–0.14) were lower than those of the spray-dried particles.

3.1.2 | Solvent extraction

Solvent extraction method is a method to extract flavonoids from raw materials according to the principle of similarity compatibility and the solubility difference of components in different solvents. Solvent extraction method is the most commonly used method to extract flavonoids in laboratory and factory because of its low equipment cost, wide extraction range, and simple operation. Solvent extraction is also the basic step of other extraction methods, and more precise or efficient extraction methods could be formed through the assistance of other equipment or processes. Due to the dissolution characteristics of flavonoids, alcohol or alcohol–water mixture is often used in the selection of extraction solvent. Flavonoid enriched components obtained by solvent extraction often contain other lipid soluble components, so they are called crude extracts. The crude extract is suitable for the detection of citrus flavonoids, and further separation and purification are required to obtain monomers of citrus flavonoids.

3.1.3 | Flash extraction

Flash extraction is also called plant tissue fragmentation extraction. Under a certain temperature and solvent system, the raw material is crushed to proper size by using flash extractor. The extraction efficiency was improved by external forces such as rapid stirring, vibration, and negative pressure filtration. The cutter head and the power part provided by the high speed electromotor are the key parts of the flash extractor (Qin and Xi, 2021). The cutter head is composed of inner edge and outer edge, with a gap of 0.5–1 mm between the two edges, connected by a precise concentric shaft. The outer edge is fixed, and the inner edge rotates at a high speed driven by the electromotor, crushing raw materials at a speed of 15,000–30,000 r/min (Fan et al., 2014). In the process of cutting between the inner edge and the outer edge, a strong vortex is formed in the center of the inner edge, which drives the crushed material to react inside and outside, thus forming a violent stirring effect and making the whole system in a rapid concentration change (Lin et al., 2020). With the process of

crushing, the distribution of chemical composition between the extraction solvent and the material particles is in a dynamic change system of equilibrium and nonequilibrium, and eddy current negative pressure is generated between the inner and outer edges. Under the action of eddy current negative pressure, molecular infiltration occurs inside and outside the outer edge (Yin et al., 2020). The extracted flavonoids are surrounded, dissociated and replaced by solvent molecules under the action of negative pressure, and finally separated from the raw material into the solvent. At the same time, the high-speed rotation will produce a vibration equivalent to 1/60 ultrasonic wave, which also has a promoting effect on the extraction of the solution. Xie et al. (2010) obtained hesperidin from *pericarpium citri reticulatae* by flash extraction method. The optimum process conditions were 70% ethanol concentration, 42.1 mL/g liquid to material ratio, 2.6 min extraction time, and flash extraction twice. Compared with ethanol thermal reflux method, the yield of hesperidin was increased by 6.35% and the extraction time was shortened greatly. Han et al. (2011) obtained flavonoids from *Citrus* Chang shan-huyou Y.B. Chang with an ethanol concentration of 78%, a liquid to material ratio of 31 mL/g, and an extraction time of 95 s as the optimal process conditions, with an extraction rate of 4.37%. Flash extraction method has the characteristics of short extraction time (generally within 30 s to 1 min), small space occupied by equipment, wide range of applicable materials, simple operation, energy saving, environmental protection, and so on. It should be noted that the solvent selection of flash extraction method is generally aqueous solvent. Flammable organic solvents such as ether and ethyl acetate should be carefully used, and the pH value of the solvent should also be paid attention to avoid corrosion of cutter head.

3.1.4 | Ultrasound-assisted extraction

Ultrasonic vibration frequency is between 20 and 50 kHz, with high frequency, strong direction, strong penetration, and energy concentration. It can increase the penetration of solvent, increase the molecular movement speed and frequency of extracted chemical components, and improve the extraction rate of these components (Soria & Villamiel, 2010). Ultrasonic-assisted extraction depends on cavitation, mechanical, and thermal effects. Cavitation effect is the phenomenon that when the negative pressure in the liquid exceeds the critical value, the liquid will break off and form a local cavity. When the ultrasonic wave propagates in the liquid, the average distance of the solvent changes with the vibration, and the generated negative pressure forms local cavities in the liquid (Yusoff et al., 2022). These cavitation bubbles undergo compression and collapse instantly, creating a huge jet that rushes toward the surface of the material and breaks down the cell wall. The solvent thus infiltrates into the internal cells of the raw material, and the mutual infiltration of flavonoids promotes extraction (Singla & Sit, 2021). Ultrasonic wave can form effective agitation and flow in the liquid, destroy the structure of the medium, smash the particles in the liquid. Combined with the pressure generated by the cavitation effect, the cell wall and the organism are broken, and the vibration effect generated by the mechanical effect enhances the release, diffusion, and dissolution of intracellular substances (Chemat et al., 2011). The thermal effect is due to the mutual friction of the medium after absorbing the ultrasonic energy. The molecules vibrate violently, and the mechanical energy of the ultrasonic wave is converted into the internal energy of the medium, causing the temperature of the medium to rise (Chen et al., 2020). The intensity of the ultrasonic waves is proportional to the thermal action produced. By controlling the ultrasonic intensity, the temperature inside the raw material tissue can be increased instantly, and the flavonoids dissolution can be accelerated. The factors that affect ultrasonic extraction efficiency include ultrasonic frequency, ultrasonic intensity, extraction time, and system temperature (Rao et al., 2021). For citrus flavonoids, ultrasonic-assisted extraction can greatly improve the extraction efficiency. Due to the strong stability of flavanones and PMFs, the selection range of ultrasonic-assisted extraction conditions is relatively wide. Khan et al. (2010) separated orange peel extract using ultrasonic-assisted extraction method. The optimal extraction conditions were the temperature of 40°C, the ultrasonic power of 150 W, and the ratio of alcohol to water of 4:1 (v/v). Compared with the traditional solvent extraction method, the total phenolic content (275.8 mg GAE/100 g FW) and flavanone concentration (naringin 70.3 mg/100 g FW and hesperidin 205.2 mg/100 g FW) obtained by this method were higher, and the extraction rate was 10.9%. Garcia-Castello et al. (2015) applied ultrasonic-assisted extraction method to separate flavonoids from grapefruit peel, and 80.0 mg GAE/g DW total phenols could be obtained at the optimal process conditions of 25°C, 40% of ethanol concentration and 55 min of extraction time. Compared with solvent extraction, this method could achieve higher extraction rates at lower temperatures and shorter extraction times (average 50% higher total phenolics and 66% higher total antioxidant capacity). Interestingly, treatment without organic solvents at 25°C and short time (t = 3 min) led to similar results (753 mg GAE/g DW of total phenolics), emphasizing its higher economic and environmental benefits. Ultrasonic-assisted extraction has the characteristics of high extraction efficiency, short extraction time (generally 20–60 min), low extraction temperature, wide adaptability, convenient for rapid detection with analytical instruments, and significant comprehensive economic benefits. Additionally, ultrasound-assisted extraction can be combined with other methods such as pulsed electric fields to further improve the extraction performance in mild conditions (Gao et al., 2022).

3.1.5 | Microwave-assisted extraction

Microwave is an electromagnetic wave with a frequency between 300 MHz and 300 GHz, which has the characteristics of strong penetration, good selectivity, and high heating efficiency. In the microwave field, some regions of the matrix or some components of the extraction system are selectively heated due to the difference in microwave absorption capacity. The extracted substance is separated from the matrix or system into a solvent with a small dielectric constant and relatively poor microwave absorption capacity (Zhang, Yang & Wang, 2011). Microwave heating is based on the time of dipole turning

polarization and interface polarization of microwave field, which is consistent with microwave frequency and promotes the rotational energy level transition of medium, intensifies thermal motion, and converts electric energy into heat energy (Ekezie et al., 2017). The active ingredients in citrus flavonoid raw materials are often embedded in the inner parenchyma cells or vacuoles protected by the epidermis, which are very difficult to break down. Microwave heating causes polar substances in cells, especially water molecules, to absorb microwave energy and generate a large amount of heat, which rapidly increases the temperature in cells (Inoue et al., 2010). The pressure of liquid water vaporizing breaks down cell membranes and cell walls, forming tiny holes. This results in reduced moisture in the cell interior and wall, cell shrinkage, and cracks on the surface. The presence of holes or cracks allows the solution to easily enter the cell, dissolving and releasing intracellular products such as flavonoids. Inoue et al. (2010) applied microwave-assisted extraction to rapidly purify hesperidin and naringenin from the immature *C. unshiu* peel. After the samples were exposed to microwave radiation at 140°C for 7 min in a closed system, the yields of hesperidin and naringenin reached 58.6 and 13.1 mg/g, which were 27 times and 2.5 times higher than those of the conventional extraction method. M'hiri et al. (2015) employed microwave-assisted extraction method to isolate flavonoids from *Citrus sinensis* fruit peel, which was heated at 200 W power for 180 s. The total phenolic content was 26.88 ± 0.78 g GAE/kg, and the hesperidin and neohesperidin contents reached 9.289 and 12.215 g/kg, respectively, which were significantly better than the conventional solvent extraction method (m/v: 5 g/50 ml, 80 min, 35°C, 80% ethanol). The microwave has strong penetrating power and can heat the reactants evenly and rapidly at the same time, so the extraction efficiency is high. Therefore, microwave-assisted extraction of plant active ingredients has the advantages of simple, rapid, efficient and uniform heating. Microwave-assisted extraction can be used in large-scale production, which is safe, reliable, pollution free, and belongs to green engineering. The production line is simple and saves investment. It should be noted that raw materials rich in volatile or heat-sensitive components are not suitable for microwave extraction. Raw materials rich in starch or gum will lead to deformation and gelatinization during microwave extraction, blocking the extraction channel, which is not conducive to the release of intracellular products. The active ingredient should have a high-water content in the area.

3.1.6 | Supercritical fluid extraction

Supercritical fluids refer to fluids whose temperature and pressure are both higher than the critical temperature and pressure. Its density is similar to that of liquid, its viscosity and diffusion coefficient are similar to that of gas. The dissolution process of substances includes intermolecular interaction and diffusion. The dissolution of substances is proportional to the density and diffusion coefficient of the solvent, and inversely proportional to the viscosity. Therefore, supercritical fluids have strong dissolving power for many substances (Sihvonen et al., 1999). When the supercritical fluid encounters the extraction material, it selectively dissolves certain components. The density and dielectric constant of supercritical fluids increase with the increase of the pressure of the closed system, and the components of different polarities can be extracted in parts by using the program boosting. After the extraction, the temperature or pressure of the system is changed to make the supercritical fluid become ordinary gas and escape, and the extracted components in the material are completely separated out to achieve the purpose of extraction and separation (Patil et al., 2021). Extraction pressure, extraction temperature, extraction time, flow rate of supercritical fluid, particle size of raw material, and loading amount all affect the efficiency of supercritical fluid separation (Wang & Weller, 2006). CO_2 is the most commonly used supercritical extraction agent. Supercritical CO_2 extraction instrument is mainly composed of heating system and pressurizing system, including CO_2 pump, entrainer pump, heater, cooler, extraction kettle, separation kettle, pressure controller, temperature controller, and low temperature constant temperature tank purification system, flow meter, safety protection device, cleaning system, and so on (Sihvonen et al., 1999). CO_2 with a certain flow rate can reach supercritical state under the action of CO_2 extractor and can be stably extracted through the extraction kettle under the set temperature, pressure, and flow rate. Lee et al. (2010) used supercritical CO_2 extraction to isolate PMFs from *Citrus depressa* Hayata fruit peel. The results showed that when using 85% ethanol was used as modifier and under the conditions of temperature 80°C, pressure 30 MPa, CO_2 flow rate 3.0 ml/min, and extraction time 80 min, the extraction yield of nobiletin and tangeretin was the highest. The yield was 7% higher than that of the conventional solid-liquid extraction method, and the purity (35.3%) was 7.2 times higher than that of the conventional solid-liquid extraction method (4.9%). He et al. (2012) extracted flavonoids from the peel of *Citrus grandis* (L.) Osbeck by supercritical CO_2 extraction. The conditions were as follows: 85% ethanol as modifier, temperature 80°C, pressure 39 MPa, static extraction time 49 min. Compared with the traditional solvent extraction method, the yield of flavonoids obtained by supercritical CO_2 extraction was higher (2.37 vs. 1.51%), the extraction time was shorter (49 vs. 120 min), and the flavonoids obtained had higher free radical scavenging ability. Supercritical CO_2 extraction has the following advantages: extraction ability, high extraction efficiency, extraction of selective, less impurities, low temperature, effective component is not damaged, short production cycle, easy operation parameters control, has the oxidation resistance and sterilization effect, stable quality, standards, easy to control, simple process, saving labor, pollution is small. However, the supercritical extraction unit needs high-pressure equipment, which has high initial investment and high maintenance cost. Therefore, cost control should be paid attention to before application.

3.1.7 | Steam explosion extraction

The steam explosion is an extraction method that destroys the raw material tissue and cell wall of the plant, so that the effective components in the plant tissue cells are dissolved (Wan et al., 2022). By wetting the raw materials, placing them in a closed container, and after pressurizing for a certain period of time, the pressure is suddenly released. After pressurization, there is a large pressure difference

between the inside and the outside of the raw material plant. Instantly releasing the pressure will generate a strong impact force, breaking through the cell wall, tearing the plant tissue, and making the raw material tissue structure loose (Chen & Liu, 2015). In this case, the contact area between the raw material and the solvent is greatly increased, which is conducive to accelerating the penetration of the solvent into the raw material particles and the dissolution of the active ingredient (Dorado et al., 2019, Putnik et al., 2017). Steam explosion extraction is generally divided into two stages. Stage one, pressure-maintaining stage. The wet raw materials are placed in an airtight container and pressurized with compressed air to maintain the pressure in the container for a period time. Under high pressure, water and air penetrate into the intercellular spaces and cells of plants, dissociating their various components (Wan et al., 2022, Zhao et al., 2014). The hydrogen bonds between fiber molecules were destroyed, and the fiber tissue and cell wall were softened. The adhesion strength of plant cell tissue decreased, and the transverse connection strength decreased (Peng et al., 2012). At the same time, under high pressure, a large amount of liquid water and compressed air gather inside the tissues and cells (Putnik et al., 2017). Stage two, blasting stage. In sudden pressure relief, a great pressure difference is instantaneously generated between the inside and outside of the plant tissue cells. The high-pressure liquid water in the tissue cells is instantly boiled and vaporized and is flushed out of the cells and plant tissues together with the compressed air (Duque et al., 2016). Plant tissue cells are broken and torn, and the tissue structure becomes very loose (Bousfield et al., 2018). The extraction efficiency of steam explosion is affected by the following factors: the texture and particle size of the raw material, the degree of wetness of the raw material, the pressure maintenance time, and the blasting time (Sharma et al., 2017, Wan et al., 2022). The steam explosion method is suitable for the extraction of multifiber raw materials such as roots, stems, bark, and leaves of plants (Bousfield et al., 2018, Zhao et al., 2014). However, this extraction technology is not suitable for raw materials with high short fiber and starch content, otherwise, the extract after blasting is too broken, which is not conducive to the subsequent process (Wan et al., 2022, Zhao et al., 2014). Cameron et al. (2016) completed a steam explosion process for adding value to citrus processing waste. That is, at a temperature of 150°C, steam was injected into waste biomass to release phenolic compounds, and 41.1% of PMFs and 11.4% of flavanones in waste were recovered. Dorado, compared the effects of different reaction temperatures (130, 150, and 170°C) and hold times (1, 2, 4, and 8 min) on the recovery of citrus flavonoids from citrus juice processing waste (Dorado et al., 2019). It was found that higher reaction temperature (170°C) and longer hold time (8 min) were more conducive to the recovery of hesperidin, nobiletin and tangeretin flavonoids from citrus juice processing waste. At the same time, PMFs were also be recoverable in the water washes after steam explosion.

3.1.8 | Enzymatic extraction

Enzyme reactions have the characteristics of high catalytic efficiency, strong specificity, mild reaction conditions, and strong controllability. Cellulase, hemicellulase, pectinase, and multienzyme complexes are used to remove plant cell walls and release cell contents during extraction (Chavez-Gonzalez et al., 2020, Gligor et al., 2019, Zhou, 2010). Protease, glucosidase, and glucosidase are used to remove impurities such as starch, pectin, mucinous, and protein, improve the clarity of the liquid, and improve the purity and stability of the extract (Gligor et al., 2019, Zhou, 2010). When extracting flavonoids by enzymatic hydrolysis, attention should be paid to the selection of enzyme type and corresponding enzymatic reaction conditions (temperature, pH, enzyme dosage, reaction time, etc.) (Anh et al., 2021, Hung et al., 2020, Mandalari et al., 2007, Rodríguez De Luna et al., 2020, Tomaz et al., 2016).

The enzymatic extraction method can not only extract citrus flavonoids, but also induce the transformation of flavonoids and thus improve the biological activity of flavonoids. A tannase isolated from *Paecilomyces variotti* was used to catalyze the conversion of hesperidin and naringin in orange juice to hesperetin and naringenin, and thus enhanced its antioxidant capacity and cell proliferation inhibitory capacity (Ferreira et al., 2013). By combining cellulase and tannase to extract flavanone components from citrus residues, hesperetin and naringenin could be obtained, and these flavanone aglycones often exist in the form of glycosides (Madeira & Macedo, 2015). Ruviaro et al. (2019) compared pectinase, cellulase, tannase, and β-glucosidase, either alone or in combination, to study the effects on the release and transformation of phenolics in citrus juice by-products. It was found that β-glucosidase could improve the flavonoids extraction efficiency, promote the conversion of hesperidin and naringin to its aglycone, and improve the antioxidant activity. It should be noted that the enzyme extraction method cannot be used in conjunction with methods such as ultrasonic assistance extraction and microwave assistance extraction. which are destructive to enzyme activity. At the same time, after enzymolysis, how to remove the enzyme in the reaction system is also a factor to be considered.

3.1.9 | Distillation and concentration

In the process of separation and purification of citrus flavonoids, distillation is often used to remove the extraction solvent for further purification. The basic principle of distillation and concentration is to separate the components according to their different boiling points. The lower the boiling point of a liquid, the more volatile it becomes. When a liquid mixture is boiled and partially vaporized and partially condensed, the concentration of the more volatile components is higher in the gas phase than in the liquid phase. Correspondingly, the concentration of the less volatile components in the liquid phase is higher than that in the gas phase, so the separation of the light and heavy components can be achieved by separately collecting the gas and liquid phases. Distillation can be divided into simple distillation, balance distillation, and rectification (Starmans & Nijhuis, 1996, Wang & Weller, 2006). According to the operating pressure, distillation can be divided into atmospheric distillation, pressure distillation, and decompression distillation. In the extraction process of citrus flavonoids, vacuum distillation is often used, that is, the pressure of the system is

reduced by a vacuum pump to reduce the boiling point of the solvent, and the organic solvent is removed at a lower temperature (Gonzalez-Molina et al., 2010, Raman et al., 2004). Factors affecting distillation concentration include pressure, temperature, and relative volatility of materials. When extracting anthocyanins, attention should be paid to adjusting pH in the system and keeping away from light (Fabroni et al., 2016, Hillebrand et al., 2004, M'Hiri et al., 2014, Scordino et al., 2005). Distillation concentration has the advantages of simple equipment, easy operation, low equipment cost, and large output.

3.2 | Ingredient purification

3.2.1 | Membrane filtration extraction

The core component of membrane separation is a specially manufactured thin film with selective permeability. Under the action of external forces such as pressure difference, concentration difference and potential difference on both sides of the membrane, the mixture is separated, graded, purified, and concentrated under the action of the membrane to obtain the required product (Akin et al., 2012, Cassano et al., 2018, Castro-Munoz et al., 2016). Membrane separation is widely used in the separation of both liquid and gas mixtures. There are two principles of membrane separation. One is to rely on the micropores on the separation membrane. According to the difference in mass, volume, and geometry of the substance to be separated, the components larger than the micropores are difficult to pass through, while the components smaller than the micropores are easy to pass through, so as to achieve the purpose of separation. Microfiltration, ultrafiltration, nanofiltration, and dialysis generally use this principle (Cassano et al., 2018, Castro-Munoz et al., 2016, Tylkowski et al., 2017). The second is to rely on the physical and chemical properties of the separation membrane. According to the difference of the affinity of each component of the mixture to the membrane, the component with a high affinity to the membrane can dissolve in the membrane and diffuse from one side of the membrane to the other side. However, the components with low affinity to the membrane can hardly pass through the membrane by diffusion, so as to achieve the purpose of separation. Reverse osmosis, gas separation, liquid membrane separation, pervaporation, and other membrane separation processes generally belong to this principle (Sagehashi et al., 2007, Schell et al., 1989, Van der Bruggen et al., 2006). In the extraction of citrus flavonoids, membrane separation is generally used to extract flavonoids from industrial wastewater (Betoret et al., 2009, Cassano et al., 2014). The recovery rate of the membrane extraction method is related to the pore size of the membrane and the molecular weight of the target flavonoids. The high content of flavonoids in citrus has a molecular weight of 200–700 Da (Ali et al., 2015, Van der Bruggen et al., 2006, Wang et al., 2022). Conidi et al. (2011) clarified bergamot juice with 100 kDa polysulphone hollow fiber membrane modules and then employed ultrafiltration and nanofiltration membranes with molecular weight cut-off (MWCO) of 1000, 750, and 450 Da. The results showed that when the molecular weight of the interception was 450 Da and the average pore size was 0.9 nm, the separation effect of polyphenols and sugars was the best, the permeability measured at 25°C was 0.77 L/m^2 bar, and the recoveries of narirutin, naringin, hesperidin, and neohesperidin were the highest. Certain flavonoids, such as anthocyanins, are positively charged at low pH, so the effect of charge on rejection also needs to be considered in membrane filtration. Another study by Conidi et al. (2012) compared the retention rates of sugars and citrus flavonoids by spiral wound nanofiltration membranes with four different MWCOs (250, 300, 400, and 1000 Da) and different polymer materials (polyamide, polypiperazine amide, and polyethersulphone). The results showed that with the increase of the MWCO, the average rejection rate of sugars by the membrane decreased, while the rejection rate of anthocyanins remained above 89%. The factors affecting membrane separation also include membrane structure parameters (membrane material and pore diameter), system properties of raw material liquid (pretreatment degree, flavonoid concentration, water content after circulation), operation parameters (membrane surface flow rate, pressure on both sides of membrane, system temperature), and so on. Membrane separation technology has the advantages of low operating temperature, no phase change in the separation process, low energy consumption, and large separation coefficient.

3.2.2 | Macroporous resin extraction

Macroporous resin is an inert high molecular polymer with a three-dimensional spatial structure inside, which has a high porosity and a large pore size in the dry state. The macroporous resin relies on the van der Waals force between it and the adsorbed molecules (adsorbents) through their large specific surface area for physical adsorption. Macroporous resin contains many mesh pore structures with microspheres, the total surface area of particles is very large, with a certain polar group, so that macroporous resin has a greater adsorption capacity (dos Santos et al., 2022). The mesh pores have a range of pore sizes, so that they have a certain selectivity to the compound according to the molecular weight. According to the molecular sieve principle, organic compounds such as flavonoids are separated by a certain solvent elution according to the different molecular weights (Li & Chase, 2010). Macroporous resins can be divided into nonpolar and polar categories according to the different monomer composition of their polymerization. According to the polarity, it can also be divided into weak polarity, medium polarity, and strong polarity (Chang et al., 2012). The use of macroporous resin can be divided into static adsorption separation and dynamic adsorption separation according to the operation method (dos Santos et al., 2022, Jia & Lu, 2008, Ke et al., 2021). Static adsorption is to mix the macroporous resin and the treatment solution. Then separate the resin containing the extract from the solution by filtration, pouring, centrifugal sedimentation, and other methods. The macroporous resin was then statically eluted with a suitable eluent, and the eluent was dried to obtain the extract (Jamali et al., 2006). Dynamic adsorption requires packing the macroporous resin and then loading the treatment solution from above the column. The treatment solution is first in contact with the resins on the upper part of the

column, which are first saturated. This adsorption saturation state is then gradually moved downward to form the chromatographic band (Gao et al., 2019). When all resin adsorption to a certain extent, the adsorption is stopped, and the active ingredients such as flavonoids are eluted with a solvent. Compared with static adsorption, dynamic adsorption has higher adsorption efficiency, and more extracts can be obtained in a single sample loading (dos Santos et al., 2022, Gao et al., 2019, Li et al., 2018, Zhang et al., 2012). It should be noted that macroporous resin needs to be pretreated to remove unpolymerized organic residues. Zhang et al. (2012) compared six resins, including AB8, ADS17, D101, DM130, HPD100, and XAD16, by adsorption and desorption tests. The results showed that the two selected macroporous resins, D101 and AB8, were better for the adsorption and desorption of neohesperidin from the albedo of *C. reticulata* cv. *Suavissima*. The purity of neohesperidin eluted by 55% ethanol aqueous solution increased from 4.92% in the crude extract of albedo to 58.22% in the refined sample of the resin, which was an 11.83-fold increase with a recovery of 68.97%. Liu et al. (2017) loaded the crude extract into an AB-8 macroporous resin column and washed the column with double-distilled water to remove water-soluble pigments and impurities. After elution with 70% ethanol, the fractions with high flavonoid content were pooled, evaporated (50°C, 0.1 MPa) and freeze-dried to obtain the resin-refined extract. Then the purification was combined with HSCCC to obtain neoeriocitrin, naringin, hesperidin, and neohesperidin with purity of 95.47, 99.62, 99.21, and 98.45%, respectively. In the extraction of citrus flavonoids, D101, AB-8, S-8, HPD-450, NKA-9, XAD-2, and DM-130 are generally selected (Gao et al., 2019, He et al., 2012, Lv et al., 2018, Shen et al., 2020, Zhang et al., 2012). Macroporous resin extraction has the advantages of wide use, simple operation, renewable utilization, and safe eluent and is suitable for industrialization.

3.2.3 | Solid-phase extraction

SPE is based on the separation principle of selective adsorption and elution and is a solid–liquid two-phase physical extraction process (Bucar et al., 2013, Martins et al., 2021). When the sample solution passes through the stationary phase containing the adsorbent, the separated components are selectively adsorbed to the stationary phase, and after the impurities are washed away, the eluent is used to desorb them from the stationary phase, so as to achieve the purpose of separation (Zeng et al., 2016). SPE sorbents commonly used in citrus flavonoid extraction are porous silica particles bonded with octadecyl silane (C18), which are nonselective sorbents (Kanaze et al., 2004, Sammani et al., 2019, Sharma et al., 2019). At present, there are commercial SPE applications, such as the Sep-Pak C18 series produced by Waters corporation, and the corresponding specifications can be selected according to the amount of extraction (Ishii et al., 1997, Li et al., 2006a). The influencing factors of SPE include packing material, type and concentration of elution solvent, retention volume, flow rate of sample loading, and elution (Bucar et al., 2013, Sammani et al., 2019). The operation of SPE generally goes through the following processes: pretreatment (column activation), the purpose of which is to remove the impurities remaining in the filler and solvate the filler to improve the reproducibility of SPE; sample loading, which is loading liquid or dissolved sample into the SPE column. The sample passes through the SPE column under the action of gravity, vacuum, and centrifugation (Wang et al., 2019b). It should be noted that the loading solvent should not contain eluent solution. For example, when using a C18 SPE column, it is necessary to avoid organic solvents such as methanol and ethanol in the solution to prevent simultaneous adsorption and desorption. Washing, when the sample enters the SPE column, the target compound is adsorbed by the adsorbent, through deionized water or a certain concentration of alcohol-aqueous solution at a certain flow rate through the SPE column to remove impurities. For example, in the extraction of citrus flavonoids, a large amount of water (10–50 BV) is needed to remove organic acids, sugars, and so on. Removal of these impurities avoids interference with subsequent refining or detection processes (Wang et al., 2019b). Elution, after removing impurities, substances such as flavonoids can be desorbed from the column by elution with an organic solution such as methanol. Varies of concentrations of organic solvents eluted different products. Saeidi et al. (2011) employed SPE coupled with high-performance liquid chromatography (HPLC) for the simultaneous determination of hesperidin, diosmin, and eriocitrin in Iranian lime juice samples. The optimum SPE elution conditions were found to be 8 mL of water/methanol (85:15, v/v, pH = 3) as the washing solution and 4 mL of methanol as the eluent, and the yields of several citrus flavonoids were more than 93%. Wang et al. (2019b) performed the separation and purification of PMFs from ougan using a Sep-Pak C18 SPE column. After the crude extract of citrus peel was sampled, it was eluted with aqueous 12 BV 35% methanol solution, and then collected PMF fraction with 100% methanol. This operation not only removed the sugars and acids but also the flavanone components. The SPE extract could be better purified using HSCCC for targeted purification.

3.2.4 | Preparative HPLC

Chromatography is an efficient method for the separation of complex mixtures. It is generally used as a high-precision and fast analytical tool for the analysis and quantification of natural products. However, the column of analytical HPLC generally has less packing, and the sample load is only microliter level, so it is difficult to meet the requirements of the sample volume for separation (Zeng et al., 1998). Unlike analytical HPLC, which prioritizes maximum separation efficiency per unit time, preparative HPLC pursues the amounts of pure components per unit time (Brandt & Kueppers, 2002, Latif & Sarker, 2012). The high-efficiency and high-capacity liquid chromatography columns used in preparative HPLC are generally used in the state of overloading the liquid chromatography column (Majors, 2004, Queiroz et al., 2019). According to the preparation scale, preparative chromatography can be divided into: semi-preparative chromatography, generally used in the laboratory, processing capacity in 10–50 mg; gram grade, processing capacity can reach 1 g; industrial grade, the capacity can reach 20 g (Brandt & Kueppers, 2002, Mazzei & d'Avila, 2003, Van der Vorst et al.,

2009, Wellings, 2011). PREP-HPLC has the advantage of "what you see is what you get." It can perform single-component high-precision separation and recovery of purified products for the sample (Uckoo et al., 2012, Wang et al., 2019b). By optimizing the experimental system, the single purification time can be shortened, and it has the characteristics of high recovery rate (Li et al., 2018). Ko et al. (2010) obtained six PMFs and two demethyl PMFs using semi-PREP-HPLC separation of crude extracts of *Citrus sunki* Hort. ex Tanaka obtained by hot water and organic solvent extraction. Russo et al. (2015) isolated flavonoids in bergamot juice by PREP-HPLC, and attempted to completely purify all flavonoids contents in bergamot juice by collecting the fractions of the first dimension, reinjecting them into the second dimension and conducting automatic collection. Since the automated collection of flavonoids in this method is based on the signal intensity generated by the mass spectrometer detector and only specific products can be detected by localization, the purity and yield were improved. A total of eight citrus flavonoids were obtained, and their purity was over 97% with a recovery of more than 85%. However, PREP-HPLC also has limitations, such as low sample loading and fixed mobile phase, when acetonitrile is used as mobile phase, the time cost of organic solvent removal is high.

3.2.5 | High-speed countercurrent chromatography

HSCCC is a separation method based on liquid–liquid distribution principle, which is unique in that it is based on unidirectional hydrodynamic equilibrium system (Sticher, 2008, Winterhalter, 2007). HSCCC can be efficiently separated and prepared in a short time. Since HSCCC system does not include solid phase carrier, it can completely eliminate the effects of sample nonadsorption, peak tailing, contamination, inactivation, and denaturation of the sample caused by solid phase (Hu & Pan, 2012, Huang et al., 2016, Li et al., 2022). The crude flavonoid extract can be used for direct separation, and high-efficiency, rapid, and large-scale preparative separation can be performed, and high-purity separation of components in complex mixtures can be achieved (Wang et al., 2019b, Zhang et al., 2012). As the HSCCC system works, the spiral tube in the chromatograph makes planetary motions (Li et al., 2022). Due to gravity and the force of the helical tube, the stationary phase moves towards the inlet of the helical tube, so that the stationary phase is retained. Two-phase solvents are mixed in a spiral tube. Due to the difference of the distribution coefficient of different solutes in the two-phase solvent, the solutes are balanced in the two-phase solvent and elute in order of the distribution coefficient (Ito, 2005). For different raw materials, or even the same target substance in different raw materials, the solvent system should be tested, screened, and remanufactured. It is generally required that the two-phase solvent can be layered up and down, and the partition coefficient (*K* value) of the target substance in the solvent is between 0.5 and 2 (Ito, 2005). At the same time, HSCCC extraction is also related to the rotation speed of the high-speed countercurrent chromatograph, the flow rate of the mobile phase and the injection volume. After the solvent system is determined, it is necessary to test the three instrument parameters at the same time to determine the optimal separation conditions (Gong et al., 2020, Ito, 2005). Zhang et al. (2014) extracted citrus peel crude extract with n-hexane, chloroform, n-butanol, and other solvents. Then flavanones and PMFs were purified with ethyl acetate-n-butanol-water (4:1:5) and n-hexane-ethyl acetate-methanol (1:0.8:1:1), respectively. Finally, seven citrus flavonoids were obtained by HSCCC purification process for about 300 min, with a purity of over 97% (Zhang et al., 2014). On this basis, Wang et al. screened different solvent systems and determined n-hexane–ethyl acetate–methanol–water (1.1:0.8:1.1:0.9) as HSCCC solvent system. Finally, three PMF monomers were obtained within 100 min with purity of 99.87% to nobiletin, 99.76% to tangeretin, and 98.75% to 5-demethylnobiletin (Wang et al., 2019b).

4 | OUTLOOK

4.1 | Rethink the source of raw materials

Citrus as raw materials for flavonoid extraction can be divided into three categories. One is the by-products in citrus processing industry, such as peel after juice extraction, pomace after essential oil extraction, and wastewater from juice or canning production. The second is the fallen fruit or secondary fruit in the citrus planting industry. The third is the citrus ripe fruit peel and traditional Chinese medicine. In general, citrus fruit is the main raw material.

There are two problems with such a source of raw materials. The first is that it is difficult to guarantee annual supply. In industrial production, the maximum efficiency of the assembly line must be guaranteed to make effective profits. This leads to the need to adjust the assembly line parameters to adapt to different varieties of citrus fruits or different flavonoids extraction processes. There are two potential solutions. One is to consider the use of citrus leaves as a source of raw material for nonfruit supply periods. As evergreen trees, citrus leaves are available every year and contain similar flavonoid products as fruit. The other is to establish storage methods of fruit raw materials, such as drying fallen fruits and extending the supply period of raw materials by preserving raw materials.

4.2 | Find new citrus flavonoids

Finding new citrus flavonoids is an important goal of the efforts of researchers and flavonoid-related practitioners. The relatively stable backbone of flavonoids means that more modifications are required to find new flavonoids. At present, there are three ways to try: one is to use specific enzymes in the process of citrus extraction to change the structure of functional groups; the other is to cultivate new citrus varieties and find new raw materials through hybridization or transgenic breeding; the third is to use the help of microorganisms, It is known that intestinal flora has a transformation effect on citrus flavonoids, and specific microorganisms can be added to citrus raw materials to search for new flavonoids.

4.3 | Modularization of extraction process to accommodate rapid conversion of flavonoid extraction

Due to the imbalance of supply and demand, the change of purification purpose or the instability of raw material sources, flavonoid extraction methods, and technological processes often need to be iteratively converted for different requirements. This transformation mainly focuses on the following three types: transformation for different extracts, transformation for different extraction amounts, and transformation for different extraction requirements. Considering the profitability and cost of extracts, both laboratory and factory extraction processes require the establishment of modular extraction processes to facilitate the combination or process optimization between different extraction methods. At present, there is no standard establishment method for modularization of extraction process, which still needs to be explored.

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CONFLICT OF INTEREST STATEMENT

The authors confirm that they have no conflict of interest to declare for this publication.

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