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Phytochemistry and bioactivity of *Citrus* flavonoids: a focus on antioxidant, anti-inflammatory, anticancer and cardiovascular protection activities

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Abstract Epidemiological studies have suggested an inverse relationship between increased consumption of fruits and reduced risk of chronic diseases, such as cardiovascular diseases, cancer, and diabetes. *Citrus* fruit is one of the mostly consumed fruits worldwide, and numerous studies have revealed its remarkable health-promoting activities, such as antioxidant, anticancer, anti-inflammatory, and cardiovascular protection activities. These activities largely depend upon the diverse chemical constituents of *Citrus* fruits, including vitamins, minerals, terpenoids, and flavonoids. Notably, dietary flavonoids occurring in *Citrus* fruits have attracted growing interest due to their distinct beneficial effects on human health. In this review, we outlined the main health-related properties of *Citrus* flavonoids, with a focus on antioxidant, anticancer, anti-inflammation, and cardiovascular protection activities. Also the bioavailability, a critical factor that influences the biological efficacy, of *Citrus* flavonoids was discussed. It was believed that insights about these advances may encourage researchers to discover new phytochemical components and further study specific bioactivities from *Citrus* fruits.

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Keywords *Citrus* flavonoids · Bioavailability · Health-promoting effects · Anticancer · Cardioprotective

Abbreviations

ACF	Aberrant crypt foci
AOM	Azoxymethane
AMPK	Adenosine monophosphate activated protein kinase
AP-1	Activator protein-1
apoB	Apolipoprotein B100
B(*a*)P	Benzo(*a*)pyrene
CDK	Cyclin-dependent kinases
CE	Capillary electrophoresis
COX-2	Cyclooxygenase-2
DM	Dried material
DMBA	Dimethylbenz[*a*]anthracene
DMH	1,2-Dimethylhydrazine
DSS	Dextran sodium sulfate
EGF	Epidermal growth factor
EMT	Epithelial–mesenchymal transition
eNOS	Endothelial nitric oxide synthase
ERK	Extracellular signal-regulated kinase
FM	Fresh material
HDL	High-density lipoprotein
HGF	Hepatocyte growth factor
HPLC	High performance liquid chromatography
HPT	3,5,6,7,8,3′,4′-Heptamethoxyflavone

HSCCC	High speed counter-current chromatography
HUVEC	H human umbilical vein endothelial cells
ICAM-1	Intracellular adhesion molecule-1
IκB	Inhibitor of NF-κB
IL	Interleujin-1β
*i*NOS	Induced nitric oxide synthase
JNK	Jun N-terminal kinase
LDL	Low-density lipoprotein
LOX	Lipoxygenase
LPS	Lipopolysaccharide PGE2: prostaglandins E2
MAPK	Mitogen-activated protein kinase
MMP	Metalloproteinase
MS	Mass spectrometry
NADPH	Nicotinamide adenine dinucleotide phosphate
NF-κB	Nuclear factor κB
NMR	Nuclear magnetic resonance
XO	Xanthine oxidase
PGE2	Prostaglandins E2
PI3K	Phosphatidyl inositol 3-kinase
PKC	Protein kinase C
PLA_2	Phospholipase A_2
PMFs	Polymethoxylated flavones
ROS	Reactive oxygen species
SHRs	Spontaneously hypertensive rats
SOCS-3	Suppressors of cytokine signaling-3
SOD	Superoxide dismutase
SR	Scavenger receptors
TGF	Tumor growth factor
TLC	Thin-layer chromatography
TNF-α	Tumor necrosis factor-α
TPA	12-*O*-tetradecanoylphorbol 13-acetate
UHPLC	Ultra-high performance liquid chromatography
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor
VLDL	Vascular low-density lipoprotein
VSMC	Vascular smooth muscle cells

Introduction

In the past two decades, considerable attention has been given to phytochemicals discovered in edible fruits and vegetables for their health-promoting effects (Cheynier 2012; Xiao 2015b). The daily ingested fruits and vegetables are rich sources of both nutrients, such as carbohydrate, vitamins, and minerals, and non-nutritive constituents, particularly polyphenols including flavonoids and phenolic acids (Patil et al. 2009a; Zhang et al. 2016b). Numerous investigations have suggested an inverse association between increased consumption of fruits and vegetables and reduced risk of inflammation and oxidative stress related to chronic diseases, such as cardiovascular diseases, cancer, and diabetes (Shukla et al. 2010; Testa et al. 2016; Turati et al. 2015).

Citrus fruit is one of the most popular fruits worldwide, and its remarkable nutrition and health-promoting values have been revealed in several studies (Khan et al. 2014; Tripoli et al. 2007). Health-promoting effects of *Citrus* fruits largely depend on their diverse chemical composition, including vitamins, minerals, flavonoids, phenolic compounds, terpenoids. These phytochemicals, ingested through fresh fruits or their derived products, have exhibited some important in vitro or in vivo biological activities including antioxidant, anti-inflammation, anti-mutagenicity, anti-carcinogenicity and anti-aging to human health (Li and Schluesener 2016; Parhiz et al. 2015; Zou et al. 2016).

Among the diverse chemical components in *Citrus* fruits, flavonoids belonging to phenolics are particularly important (Liu et al. 2012). Significantly, numerous in vitro and in vivo studies suggested that *Citrus* flavonoids possess biological effects against chronic-degenerative disorders such as cancer and cardiovascular diseases (Benavente-Garcia and Castillo 2008; Chanet et al. 2012a). Thus far, more than 60 types of *Citrus* flavonoids have been detected, and new flavonoids are gradually being discovered via existing advanced techniques (Lv et al. 2015). These reported flavonoids can be divided into five groups, including flavones, flavanones, flavonols, flavans and anthocyanins (only in blood oranges) (Tripoli et al. 2007). Flavanones are the predominant flavonoids found in *Citrus* fruits in terms of content level. It was noteworthy that polymethoxylated flavones (PMFs) such as nobiletin and tangeretin, even though presented in *Citrus* fruits with low concentration, are attracting more and more attention due to their specific and effective biological activities (Li et al. 2009).

To provide a better understanding on the biological activities of *Citrus* fruits, flavonoids as the major chemical compounds in *Citrus* fruits were systematically reviewed. This review mainly deals with

structures and classification, dietary source and distribution, separation and identification, bioavailability, and biological activities of *Citrus* flavonoids. In the parts dealing with biological properties, this review was focused on health-related properties including antioxidant, anti-inflammatory, anticancer and cardiovascular protection activities. Most importantly, the mechanisms of health-promoting and disease preventive effects of *Citrus* flavonoid would be summarized in current work. The accumulated knowledge in this review may provide useful information and ideas in the discovery of new phytochemical components from *Citrus* fruits and their specific bioactivities.

In this paper, literatures published since 1995 were reviewed. All of the relevant databases, including Web of Science, ScienceDirect, SpringerLink, and Pubmed et al. were searched for related key words, such as "*Citrus* flavonoid", "bioavailability", "antioxidant", "anti-inflammatory", "anticancer", "atherosclerosis" and "cardiovascular diseases".

Structures and classification of *Citrus* flavonoids

Flavonoids are a major class of phytochemicals discovered in *Citrus* fruits, especially in peels, pulp, and seeds. *Citrus* flavonoids are classified into three principal types, namely, flavanone, flavone, and flavonol (Nogata et al. 2006). In addition, anthocyanin, which is found only in blood orange, has also been determined (Lee 2002). PMFs are sometimes considered as an individual type of flavonoids because of their special structure (polymethoxylated) and high biological activity (Li et al. 2009). *Citrus* flavonoids are present in glycoside or aglycone forms, and usually do not occur naturally as aglycones but rather as glycosides, in which the aglycones are linked to a sugar moiety (Tripoli et al. 2007). For glycoside forms, *O*-glycosides, *C*-glycosides, rutinosides, glucosides and neohesperidosides are common. In Fig. 1, the classification of *Citrus* flavonoids and the chemical structures of major flavonoids are presented.

Flavanones are the predominant flavonoids in *Citrus* fruits (Khan et al. 2014). Either the number or content of flavanone glycosides is much higher than that of free flavanones. For free flavanones, hesperetin (4′-methoxy-3′,5,7-trihydroxyflavanone) and naringenin (4′,5,7-trihydroxyflavanone) are the two most observed compounds in *Citrus* fruits. In addition, isosakuranetin (4′-methoxy-5,7-dihydroxyflavanone) and eriodictyol (3′,4′,5,7-tetrahydroxyflavanone) are also found in *Citrus* species. These free flavanones share a common skeleton of which two hydroxyls are located at the C-5 and C-7 positions, respectively. In *Citrus* fruits and *Citrus*-derived products, flavanones are generally glycosylated by a disaccharide at C-7 position: either a neohesperidose, which imparts a bitter taste, such as naringin in grapefruit, or a flavorless rutinose, such as hesperidin in oranges (Gattuso et al. 2006). The large number of flavanone glycosides could be due to the combination of different sugar moieties bound to the aglycone.

In *Citrus* fruits, flavone and its glycosides are the second major group of flavonoids, followed by flavanones (Tripoli et al. 2007). Unlike flavanone, the C-2 and C-3 positions of flavones are linked by a double bond. The most commonly detected free *Citrus* flavones are apigenin, luteolin, diosmetin, and chrysoeriol. These flavones have also been detected in many other plants, suggesting that they are not unique to *Citrus* fruits. For flavone glycosides, the most common sugar moieties include glucose, rutinose, and neohesperidose (Silberberg et al. 2006). *O*-glycosides and *C*-glycosides are the two main forms of flavone glycosides. Both the *C*-6 and *C*-8 positions can be *C*-glycosylated, whereas the C-7 position is the most favorable for *O*-glycosides. Given that the glycosylation at C-6, C-7, and C-8 can simultaneously occur with different combinations of sugar moieties, a large number of flavone di-/tri-glycosides have been detected in *Citrus* aside from flavone mono-*C*/*O*-glycosides (Silberberg et al. 2006).

Compared with flavanones and flavones, the contents of flavonol are much lower in *Citrus* fruits (Nogata et al. 2006). The distinct characteristic of flavonol is that the C-3 position is hydroxylated. Kaempferol and quercetin are the most commonly detected flavonols in *Citrus*. The flavonol glycosides derived from the *O*-glycosylation of the C-3 or C-7 position with glucose and rutinose. Sometimes, both the C-3 and C-7 positions can be *O*-glycosylated simultaneously (Silberberg et al. 2006).

PMFs is a general term for flavones bearing two or more methoxy groups on their basic benzoc-pyrone (15-carbon, C6–C3–C6) skeleton with a carbonyl group at the C-4 position (Zhang et al. 2013). PMFs are of great importance in *Citrus* fruits, even though they occur in much lower contents than flavanones and

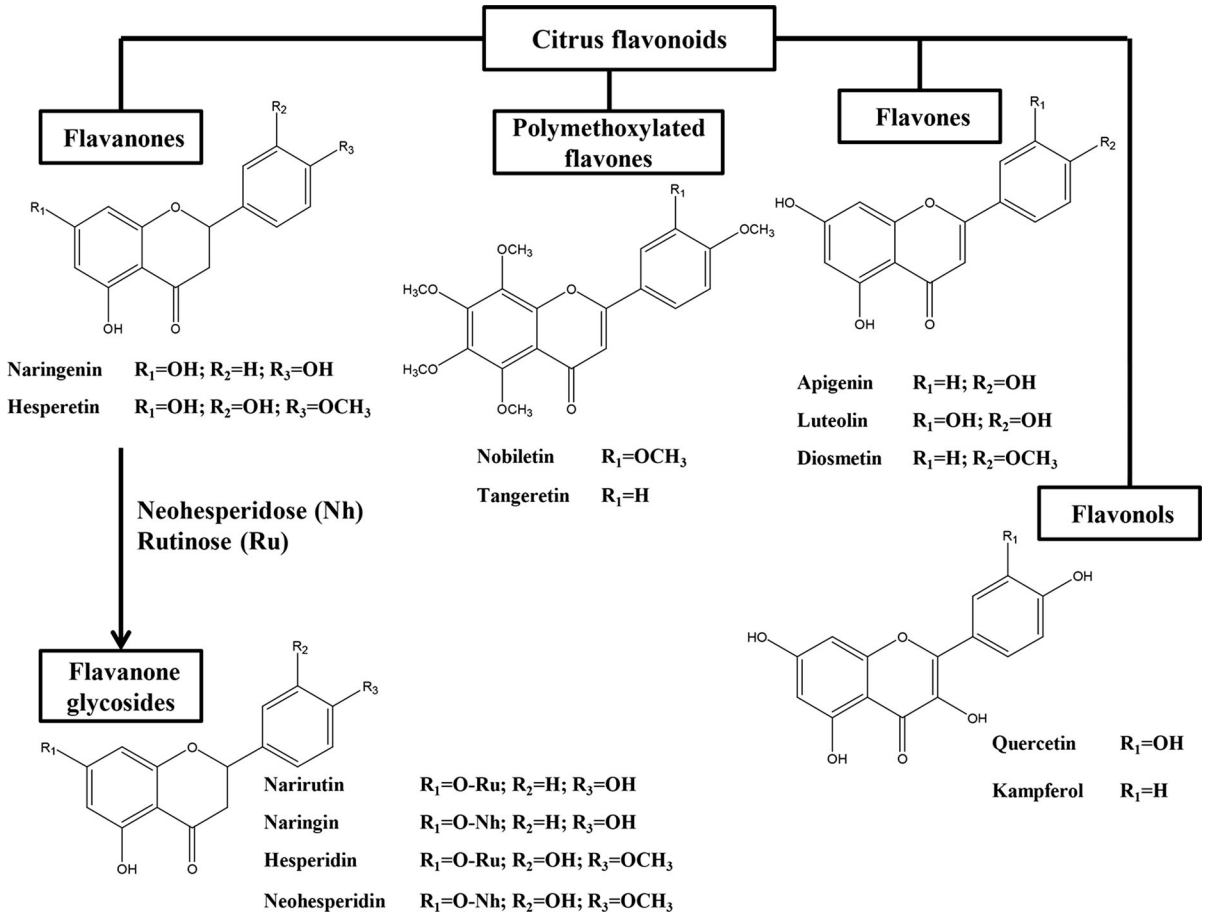

Fig. 1 Classification of *Citrus* flavonoids and the chemical structures of major flavonoids

flavones. Thus far, several PMFs have been identified in *Citrus* fruits, of which nobiletin and tangeretin were determined as the majority of PMFs (Li et al. 2009). The special chemical structures of PMFs may be responsible for several interesting biological properties, such as neuroprotective activity (Li et al. 2014).

Dietary source and distribution

Citrus flavonoids, either the high content flavanones or the low content flavones and PMFs, have been detected in almost all the parts of *Citrus* fruits in different species. *Citrus* juice is also an important source of flavonoids, particularly flavonoids glycosides. However, the types and concentration of *Citrus* flavonoids vary among different species and fruit parts (Khan et al. 2014). The stages of maturity and the post-harvest processing technique also affect the levels of *Citrus* flavonoids (Xu et al. 2008).

First of all, the flavonoids content varies greatly depending on their types in *Citrus* fruits. For example, flavanones account for approximately 95% of the total flavonoids in *Citrus* fruits, while flavones, flavonols and PMFs present at lower concentration (Peterson et al. 2006a). Among flavanones, naringenin, hesperetin, and their glycosides hesperidin and naringin, present at high levels. Hesperidin is the predominant flavonoid, primarily in sweet orange and lemon (up to 14% of the fresh fruit weight), and consequently in these *Citruses*-derived juices (Kuntic et al. 2014). In lemons, limes, sweet oranges, tangerine and tangor species, hesperidin is present in high levels (28.5–73.8 mg/g FM), while neohesperidin, another glycoside of hesperetin, is absent in these species (Cano et al. 2008). Naringin (16.6 mg/g FM) and

narirutin (4.9 mg/g FM), glycosides of naringenin, are especially more abundant than naringenin in grapefruit (Peterson et al. 2006a).

Moreover, the compositions and content of different parts, such as seed and peel, are not always the same in *Citrus* fruits. The *Citrus* flavonoids are richer in peels than in seeds. For example, the lemon peel contains higher amounts of neohesperidin (4.37 mg/g DM) and naringin (6.06 mg/g DM) than other parts (Bocco et al. 1998). In addition, the lemon seed mainly contains hesperidin (0.50 mg/g DM), while the peel is rich in naringin and neohesperidin (Bocco et al. 1998). The highest concentrations of flavanones are found in peel as compared to the fleshy part of *Citrus* fruit (Nogata et al. 2006). Flavanone glycosyl compositions of peels and seeds are quite unlike those of juices. The solid parts of the fruit, particularly the albedo and the membranes separating the segments, are richest in flavanones compared to juice vesicles (pulp), which explains the higher content of flavanones in the whole fruit than in the juice (Tomás-Barberán and Clifford 2000). Low hydrophilicity of flavanones may explain its lower concentration in *Citrus* juices. Naringin has been found in lemon peel and seed as well as in mandarin seed, but it is absent in the juices of these fruits (Tripoli et al. 2007). Nobiletin and tangeretin, both exclusively present in the *Citrus* peels, rather than other parts (Li et al. 2009).

At last, the contents of flavonoids vary among different *Citrus* species. For example, hesperetin and its glycosides (hesperidin and neohesperidin) are characteristic flavanones of sweet orange, tangelo, lemon, and lime, whereas naringenin and its glycosides (narirutin and naringin) are those of grapefruit and sour orange (Peterson et al. 2006a, b). Significant amounts of hesperetin also occur in grapefruits while tangelo and sour orange are especially abundant in neohesperidin (Peterson et al. 2006a, b). Naringin was the predominant flavanone in pummelo varieties (4.63 mg/g FM) which have higher levels of flavones when compared with the grapefruit (Zhang et al. 2011). In grapefruit and sour orange, naringin present with different contents according to varieties (Igual et al. 2013). Compared to grapefruit and sour orange, other *Citrus* species like sweet orange, tangelo, lemon and lime exhibit lower quantities of naringin (Peterson et al. 2006a, b). Neohesperidoside flavanones, naringin, neohesperidin and neoeriocitrin, are mainly present in bergamot, grapefruit and bitter orange juices. In contrast, rutinoside flavanones, hesperidin and narirutin, are present in bergamot, orange, mandarin and lemon juices (Tripoli et al. 2007).

Separation and identification of *Citrus* flavonoids

Separation of *Citrus* flavonoids

Sample isolation and purification is the basis and precondition for the purpose of measuring the concentration and biological activity of individual *Citrus* flavonoids. For the separation purpose, advanced technique with superior performances, such as short analysis time, low cost, high reproducibility and sensibility, and highly automated operation, are preferred (Pereira-Caro et al. 2016). High performance liquid chromatography (HPLC), Ultra-high performance liquid chromatography (UHPLC), gas chromatography, and capillary electrophoresis (CE) are mostly used for analytical purpose. In contrast, preparative HPLC, open column chromatography, and High speed counter-current chromatography (HSCCC) are used for preparative isolation purpose. The flowchart of isolation and analysis of Citrus flavonoids was shown in Fig. 2.

HPLC is an automatable technique with high resolution, selectivity and sensitivity. So far, HPLC has been successfully used for analysis of a great variety of flavonoids in *Citrus* sample (Pingili et al. 2016; Yang et al. 2016). Sometimes, certain pretreatments, such as solid-phase extraction, on the *Citrus* samples are required for reducing the effects of interfering substances and obtaining clean chromatograms (Saeidi et al. 2011). UHPLC, using very small particles (<2 μm) and short columns (<100 mm), is a faster separation technique with higher sensitivity and resolution than HPLC (Gruz et al. 2008). By using a validated UHPLC method, only 5.5 min was required for the simultaneous separation and quantification of 11 selected flavonoids from *Citrus* fruit extracts (Actis-Goretta et al. 2015). By optimized UHPLC, the flavonoids in the peels and pulp of 28 Chinese local pummelos and four grapefruits were determined (Possemiers et al. 2015). The sensitivity of the validated UHPLC method (LDQ: 0.05–0.13 μg/mL; LOQ: 0.05–0.46 μg/mL) represented a significant improvement for most of the analytes when compared with a previously published

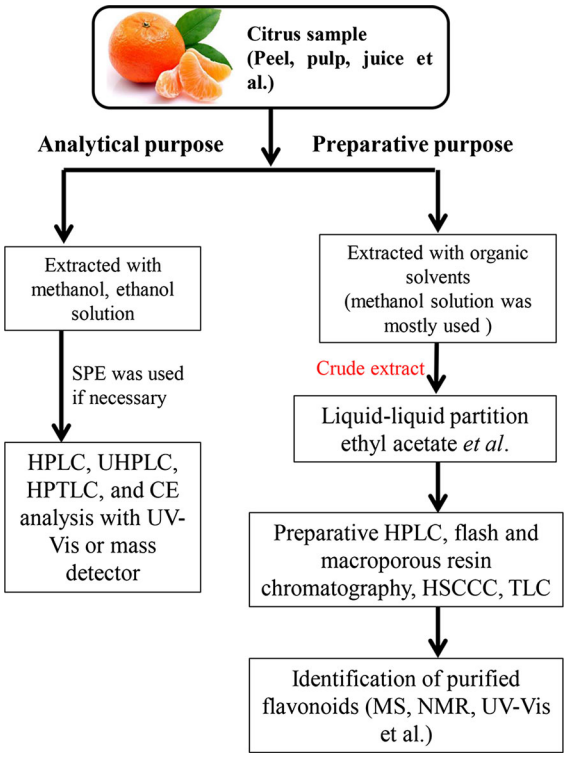

Fig. 2 The flowchart of isolation and analysis of *Citrus* flavonoids

HPLC methods (LDQ: 1.5–5 μg/mL; LOQ: 3.9–15.6 μg/mL) (Possemiers et al. 2015). In the future, UHPLC will be a perfect alternative to HPLC.

Thin-layer chromatography (TLC), the simplest and the most cost-effective chromatographic technique, has also been used for analysis of flavonoids for a long time. As examples, *Citrus* flavonoids including hesperidin, hesperetin, eriodictyol, naringin and naringenin were separated and analyzed by high-performance TLC coupled with mass spectrometry (Pereira-Caro et al. 2015). Nowadays, capillary electrophoresis (CE) has attracted increasing attention for analyzing flavonoids in different plant samples including *Citrus* fruit because of its high separation efficiency, short analysis time and low consumption of solvent (Amaretti et al. 2015). Sawalha et al. determined the main phenolic compounds (including hesperetin and hesperidin, neohesperidin, naringin and narirutin) in sweet and bitter orange peel using CE-MS/MS (Sawalha et al. 2009). In addition, CE was used to determine five flavonoids, i.e., hesperidin, naringin, hesperidin, naringenin, and rutin, in grapefruit peel and juice with electrochemical detection (Gimenez-Bastida et al. 2016).

High speed counter-current chromatography (HSCCC) is a support-free liquid–liquid partition chromatographic process in which both the mobile and stationary phases are liquids (Silveira et al. 2014). HSCCC has been demonstrated as a very useful technique for separating flavonoids from plant sources (Tomas-Navarro et al. 2014; Vallejo et al. 2010). By using HSCCC with a suitable biphasic liquid system, several PMFs were successfully isolated from *Citrus* peel (Bredsdorff et al. 2010; Zhang et al. 2014a). The separated compounds including nobiletin, 3,5,6,7,8,3′,4′-heptamethoxy flavone, tangeretin, and 5-hydroxy-6,7,8,3′,4′-pentamethoxy flavone et al. In order to enhance the separation capability, HSCCC was combined with other techniques such as preparative HPLC and macroporous resin chromatography (Londono-Londono et al. 2010; Zhang et al. 2012). By using HSCCC combined with other techniques, several flavonoids, including sinensetin, nobiletin, naringin, and neohesperidin et al., were successfully separated. HSCCC was also used for initial fractionation and enrichment of *Citrus* components, and then assisted the subsequent structural identification by LC–MS analysis (Li et al. 2015a).

Identification of *Citrus* flavonoids

UV–Vis spectra have been used for qualification and quantification of flavonoids for a long history. The UV spectra of flavones and related glycosides show two strong absorption peaks at band I (300–380 nm) and band II (240–280 nm) (de Rijke et al. 2006). In modern analytical platforms, UV–Vis detector was always coupled with separation technique such as HPLC, thus achieving online detection of target compounds. For analysis of *Citrus* flavonoids, the identification was performed based on their UV–Vis spectra and retention times compared with chemical standards (Chinapongtitiwat et al. 2013; Habauzit et al. 2009). Due to the lack of commercial standards, only a few components such as hesperidin and naringin, for which the standards are easily obtained, are usually quantitatively determined.

Mass spectrometry (MS) has been accepted as an outstanding technique for analyzing compounds in food samples due to its high sensitivity and specificity (Li et al. 2008). The development of atmospheric

pressure ionization techniques, including electrospray ionization and atmospheric pressure chemical ionization, makes HPLC perfectly compatible with MS detector (Peacock et al. 2017; Yi et al. 2016). UHPLC coupled to high resolution mass spectrometry (UHPLC-HRMS) has been one of the best analytical techniques to study flavonoids in *Citrus* samples, which combines the high separation efficiency of UHPLC and the excellent structure identification capability of MS. By using high-resolution mass spectrometers, the accurate mass of parent and fragment ions can be measured, which is very helpful to determine elemental compositions and confirm chemical structure without available standards (Li et al. 2008). Moreover, tandem mass spectrometry is able to provide valuable fragment information used to deduce the chemical structures of unknown compounds (Li et al. 2008). Benefited from these advantages, UHPLC-HRMS has been used to separating and identify flavonoids without prior purification in different parts of *Citrus* fruits, including juices, peels, and pulp (Barreca et al. 2013; Brand et al. 2007; De Pascual-Teresa et al. 2007). By employing tandem MS (MS^n) with collision-induced dissociation, MS^n spectra of several *Citrus* flavonoids have been investigated and compared. Abad-Garcia et al. developed a general strategy for characterization of phenolic compounds in *Citrus* juices based on HPLC–DAD–ESI–MS/MS by investigating the fragmentation pattern of 72 standards (Scholz and Williamson 2007). By using the established strategy, the authors successfully identified a large number of flavonoids in *Citrus* juices (Kanaze et al. 2007; Silberberg et al. 2006). According to the characteristic fragmentation information provided by tandem MS, the structure of unknown flavonoids could be directly deduced even without available standards.

Nuclear magnetic resonance (NMR) and two-dimensional NMR techniques (COSY, OESY, HMQC and HMBC) are powerful techniques that can be used for the structural elucidation and the complete H and C assignments (Franke et al. 2000). Prior to NMR elucidation, isolation and purification of compounds are required. In several studies, NMR technique has been successfully used to identify the chemical structures of isolated *Citrus* flavonoids. The chemical structures of purified compounds were always identified by using NMR technique combined with mass spectrometry. For example, ten PMFs isolated from the peel of miaray mandarin were identified by spectral analysis using MS and NMR (Manach et al. 2003). By using HPLC–MS and NMR technique, two di-*C*-glycosyl flavones, a series of flavones, flavanone 7-*O*-neohesperidosides and two methoxyflavones (nobiletin and tangeretin), commonly present in *Citrus*, were identified in *Citrus aurantium* var. *amara* L. peel (Mencherini et al. 2013). Several combined utilization of NMR and mass technique can be found in literatures, and not listed in this review.

Bioavailability of *Citrus* flavonoids

From a nutritional point of view, bioavailability represents the overall effects of absorption, distribution, metabolism and excretion of a nutrient present in food. It is a key step in ensuring the biological efficacy of *Citrus* flavonoids. However, only the high content flavanones, namely hesperidin, hesperetin, naringin, and naringenin, have been studied mostly, while the bioavailability study of PMFs, nobiletin and tangeretin, has been scarcely performed.

After consumption of *Citrus* fruits or juices, glucuronides and sulfates were identified as the main metabolites of *Citrus* flavonoids (Pereira-Caro et al. 2015). The chemical structure would directly affect the metabolism of each flavonoid. Naringenin and hesperetin can be hydrolyzed in the small intestine and absorbed directly by intestine (Roohbakhsh et al. 2014). Both aglycones are absorbed by transcellular transport, which occurs mainly via proton-coupled active transport, and passive diffusion (Kobayashi et al. 2008). However, the glycosides of naringenin and hesperetin, namely naringin and hesperidin, are rutinosides that cannot be hydrolyzed by the bacterial β-glucosidases in the small intestine (Nielsen et al. 2006). Hence, naringin and hesperidin need to be hydrolyzed by the microflora of the colon, and then form naringenin and hesperetin that can be absorbed by the intestine. These results indicate the presence of sugar moiety restricts the colonic absorption and bioavailability of the glycosylated forms of *Citrus* flavonoids (Amaretti et al. 2015). Removal of either rutinose or rhamnose from hesperidin could improve its colonic absorption and bioavailability (Nielsen et al. 2006). The high bioavailability of aglycones possibly due to their better interaction with membranes (Londono-Londono et al. 2010). In addition,

flavonoids glucosides appear to possess a higher absorption and bioavailability than rutinosides (Actis-Goretta et al. 2015). In human subjects, the bioavailability naringenin and hesperidin were increased by conversion from rutinoside to glucoside (Bredsdorff et al. 2010; Habauzit et al. 2009). Glucosyl hesperidin, a water-soluble derivative of hesperidin, presents the same metabolic profile as hesperidin in sera, and is absorbed more rapidly and efficiently than hesperidin, because of its high water solubility (Yamada et al. 2006).

According to numerous reports, the bioavailability is not significantly affected by food matrix. After consuming two kinds of orange juice obtained from fresh-squeezing and commercially processing, no significant differences of the pharmacokinetic parameters, including T_{max}, AUC, C_{max}, and percent absorption, were observed for metabolites of the main flavanone glycosides hesperidin and narirutin present in juices (Silveira et al. 2014). In another study, the bioavailability and colonic catabolism of flavanones from orange juice to a 2.4-fold higher dose from fresh oranges were compared (Aschoff et al. 2016). Despite 2.4-fold higher doses, excretion of flavanones from ingested fresh orange fruit did not differ from that following orange juice consumption. However, the bioavailability of *Citrus* flavonoids is influenced by different physiological conditions. An in vivo study indicated that the bioavailability of hesperidin and naringin was higher in healthy (Sham-operated) rats compared with tumor-bearing rats (Silberberg et al. 2006). In contrast, the hesperetin conjugates (essentially glucuronides) was raised in tumor-bearing rats.

Solubility is a crucial factor that affects the bioavailability of certain compounds. Hence, enhancing the solubility by a certain method is a useful strategy to improve the bioavailability of *Citrus* flavonoids. By complexation with hydroxypropoyl-β-cyclodextrin, the solubility of naringenin was enhanced by over 400-fold, leading to improved bioavailability (Shulman et al. 2011). Solid dispersion technique, defined as a dispersion of active ingredients in molecular, amorphous and or microcrystalline forms into an inert carrier, has been applied in order to enhance the in vivo adsorption and bioavailability of naringenin (Khan et al 2015). Naringenin-loaded mixed micelle formulation can enhance its solubility and intestinal permeability and, thereby, overcome its low bioavailability (Song et al. 2015). There are also other strategies to improve the *Citrus* flavonoids bioavailability. For example, co-administration of hesperetin with other flavonoids, including quercetin, rutin, daidzein, and chrysin, increased the bioavailability of hesperetin (Thilakarathna and Rupasinghe 2013). Encapsulation and micronization are also effective strategy to improve hesperetin bioavailability (Takumi et al. 2012; Tomas-Navarro et al. 2014). Nanoemulsions may increase the bioavailability of highly hydrophobic bioactivities such as 5-hydroxy tangeretin, one of the PMFs (Zheng et al. 2012). Also utilizing mixed colloidal systems consisting of both lipid nanoparticles and protein nanoparticlesmay improves the bioavailability of hydrophobic bioactive agents, such as tangeretin (Chen et al. 2015a).

Antioxidant activities

Antioxidant activity has been recognized as an important marker for fruits and vegetables possessing diverse bioactive substances. It is also a foundation of many other biological activities (such as anti-cancer and anti-inflammation) of specific compounds (Gulcin 2012). As one major type of constituents in fruits and vegetables, flavonoids possess significant antioxidant activity that has been demonstrated over the past decades. Flavonoids exhibit their antioxidant activity by scavenging free radicals, modulating damage effects of reactive oxygen species, chelating metal ions, inhibiting lipid peroxidation reactions, inhibiting the activity of oxidant enzyme in body, and enhancing the activity of antioxidant enzyme (Zou et al. 2016).

Over the past decades, the antioxidant capacity of *Citrus* flavonoids has been demonstrated by performing various in vitro free radical scavenging assays, such as DPPH and ABTS radical scavenging ability tests (Zou et al. 2016). *Citrus* fruit and its derived parts (pulps, peels and juices) also show strong radical scavenging capacity, suggesting the presence of antioxidants. In fact, *Citrus* fruit and its derived parts contain high content of flavonoids that shows a positive correlation with their antioxidant capacity (Islam et al. 2015). Indeed, the antioxidant activity of *Citrus* flavonoids increases in a dose-dependent manner (Yu et al. 2014).

Citrus flavonoids exert their antioxidant capacity by decreasing the generation of reactive oxygen

species (ROS) and inhibiting lipid peroxidation. High concentrations of ROS, including hydrogen peroxide (H_2O_2), superoxide anion (O^{2-}), hydroxyl radical (·OH), $^1O_2$, and peroxyl radical (ROO·), play a pivotal role in the pathogenesis of a lot of human diseases. *Citrus* flavonoids may prevent the accumulation of ROS and eliminate them from biological system. For example, flavonoids-rich extracts obtained from both orange and bergamot juices can reduce the generation of reactive oxygen species and membrane lipid peroxidation, and thus prevent DNA-oxidative damage in A549 cells incubated with H_2O_2 and exposed to iron (Fe^{3+}) (Ferlazzo et al. 2015). In current literatures, pure *Citrus* flavonoids, including naringin, naringenin, hesperidin, hesperetin and tangeretin, have shown inhibitory effects on the production of ROS (Manna et al. 2016; Yoon et al. 2011). These flavonoids act as preventatives as well as chain scission factors at the same time, efficiently destroying the reactive oxygen species (Zou et al. 2016). *Citrus* flavonoids-containing extracts or pure *Citrus* flavonoids also show potential lipid peroxidation inhibitory ability, since they are able to inhibit the accumulation of ROS or eliminate them from biological system (Arul and Subramanian 2013a; Paul et al. 2015; Singh et al. 2014). Hesperetin, but not hesperidin, is able to inhibit lipid peroxidation initiated in rat brain homogenates by Fe^{2+} and L-ascorbic acid (Cho 2006). In an animal model, naringenin prevented lipid peroxidation and hepatic cell damage, and also protected the antioxidant system in *N*-nitrosodimethylamine-induced hepatocarcinogenesis (Arul and Subramanian 2013a).

Moreover, *Citrus* flavonoids exert their antioxidant capacity by modulating the activity of enzymes involved in the oxidation process. On the one hand, *Citrus* flavonoids have inhibition effects on oxidant enzyme, such as xanthine oxidase (XO), lipoxygenase, and nitric oxide synthase (de Souza et al. 2016; Singh et al. 2014; Yoon et al. 2011). These oxidant enzymes play important roles in redox reactions of biological systems, and also are the main promoters of cellular ROS. In *Citrus*, hesperetin was found to directly decrease cellular free radical generation by inhibiting XO. Recent studies indicated that hesperetin showed more potent XO inhibitory activity (IC_{50} = 16.48 - μM) than other *Citrus* flavonoids, such as its glycosylated derivatives hesperidin, and PMFs (de Souza et al. 2016). On the other hand, *Citrus* flavonoids are capable of improving the activity of the antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (de Souza et al. 2016; Ferlazzo et al. 2016). For example, naringin exhibited a comparable antioxidant capacity to probucol, a very potent antioxidant increasing endogenous antioxidant defenses (Jeon et al. 2002). It was concluded that ingestion of naringin supplement could increase the gene expressions of antioxidant enzymes, enhance the hepatic SOD and catalase activities, and reduce the hepatic mitochondrial H_2O_2 content (Jeon et al. 2002).

The antioxidant activities of flavonoids largely depend on their chemical structures, such as the degree of hydroxylation, other substitutions and conjugations and degree of polymerization. Di Majo et al. performed a comparative study on the antioxidant properties of nine different flavanones (naringin, neohesperidin, neoeriocitrin, hesperidin, narirutin, naringenin, hesperetin, eriodictyol and isosakuraternin) using the crocin bleaching inhibition assay (Di Majo et al. 2005). Surprisingly, the presence of a catechol nucleus (30,40-dihydroxy substitution on the B-ring) and its *O*-methylation have no significant effect on the antioxidant activity of aglycones. By contrast, the antioxidant activity was increased with the glycosides having a catechol nucleus while *O*-methylation of the catechol has an opposite effect (Di Majo et al. 2005). In addition, the glycosylation of hesperetin on the C_7-OH group by neohesperidose affects the antioxidant activity while the glycosylation by rutinose has no effect, suggesting that the antioxidant activity varied with different glycosyl moieties (Di Majo et al. 2005; Xiao 2015a).

Anti-inflammatory activity

Inflammation is the result of host response to external stimuli, such as tissue injuries, bleeding, and pathogenic infection. It is typically characterized by edema, redness, fever, pain, and loss of function. Normal inflammatory response is a self-controlled process that helps to restore tissue structure and function, while dysregulation of the inflammatory mechanism may lead to irreversible damage to host tissues and cause disease progression (Hotamisligil 2006). Several studies have revealed that numerous pathologies, such as cancer, type 2 diabetes, cardiovascular disease, and metabolic syndrome, are associated with chronic

inflammation (Balkwill and Mantovani 2001; Libby 2002). Thus, discovery of potential anti-inflammatory agents from plant origin, including fruits and vegetables, has attracted growing interests (Chen et al. 2016; Kim et al. 2004b). In this regard, *Citrus* flavonoids have shown anti-inflammatory activity in various in vivo and in vitro tests.

During inflammation, several proinflammatory mediators, including nitric oxide (NO), prostaglandins E2 (PGE2), tumor necrosis factor-α (TNF-α), and interleujin-1β (IL-1β), are produced (Kim et al. 2004b). Overproduction of these molecules plays a pivotal role in further onset of inflammation. Various in vitro and in vivo studies have shown that anti-inflammatory properties of *Citrus* flavonoids are due to their inhibition of synthesis and activities of these proinflammatory mediators (Khan et al. 2014). Several regulatory enzymes, including phospholipase A_2 (PLA_2), cyclooxygenase-2 (COX-2), nitric oxide synthase (*i*NOS), and lipoxygenase (LOX), play critical roles in the production of proinflammatory mediators, such as PGE_2 and NO (Kim et al. 2004b). *Citrus* flavonoids are able to down-regulate the expression of COX-2 and *i*NOS, and thus suppress the production of corresponding proinflammatory mediators (Benavente-Garcia and Castillo 2008). In addition, *Citrus* flavonoids suppress inflammation by directly decreasing the expression of proinflammatory cytokines, mainly TNF-α and IL-1β (Benavente-Garcia and Castillo 2008; Sridharan et al. 2016).

It is worth pointing out that the antioxidant properties of *Citrus* flavonoids may be the foundation of their inhibition effects on inflammation. Oxidative stress, caused by the imbalance between free radical production and antioxidant defense, may be involved in in the pathogenesis of various diseases, such as inflammation and cancer (Li and Schluesener 2016). During inflammatory process, ROS was over produced near the damaged tissues or cells. In turn, overproduction of ROS would lead to oxidative stress and deterioration of inflammation. As mentioned in "antioxidant activity" part, *Citrus* flavonoids are able to decrease the generation of ROS or directly eliminate ROS, which is helpful to modulate oxidative stress and inhibit inflammation. Additionally, *Citrus* flavonoids exerts anti-inflammatory activity by inhibiting oxidant enzymes, including COX-2, *i*NOS, and LOX. These oxidant enzymes played important roles in the production of proinflammatory mediators such as PEG2 and NO, and are also the main promoters of cellular ROS/RNS.

In an early study, hesperidin was proven to inhibit the lipopolysaccharide (LPS)-induced overexpression of COX-2 and *i*NOS, overproduction of PGE2 and NO in macrophage cells (Sakata et al. 2003). Hesperidin can effectively mitigate LPS-induced acute lung inflammation in vivo by inhibiting the expression of proinflammatory mediators, including TNF-α, IL-1β, and *i*NOS (Yeh et al. 2007). An ex vivo investigation demonstrated that hesperetin metabolites are effective inhibitors compared to hesperetin and hesperidin (Yang et al. 2012). Hesperetin metabolites inhibited LPS-induced expression of COX-2 and *i*NOS through suppression of nuclear factor κB (NF-κB) activation in macrophages or smooth muscle cells (Yang et al. 2012). The results suggest a great potential of hesperetin metabolites to be novel chemopreventive agent for the treatment of inflammatory disorders.

Similar anti-inflammatory effects were also found for naringenin and its glycosides, naringin. Naringenin showed inhibitory effects on LPS-induced proinflammatory cytokines in macrophage and ex vivo human whole-blood models to prevent periodontitis (Bodet et al. 2008). A later study indicated that naringenin more effectively inhibits LPS-induced inflammatory status, including NO production and *i*NOS and COX-2 expression in macrophages (50 μM/L) than that in microglia (100 μM/L) (Chao et al. 2010). In glial and microglia cells, naringenin inhibits the release of NO, the expression of *i*NOS and COX-2, as well as the production of proinflammatory cytokines, TNF-α and IL-1β. The attenuation of inflammatory responses caused by naringenin mainly through the NF-κB, mitogen-activated protein kinases (MAPK) signaling pathways (Vafeiadou et al. 2009). And a very recent study suggested that naringenin-inhibited *i*NOS and COX-2 expression is mediated by suppressors of cytokine signaling (SOCS)-3 activation through Adenosine monophosphate activated protein kinase (AMPK)-α and Protein kinase C (PKC)-δ signaling pathways (Wu et al. 2016). Naringenin reduced production of nitrate and nitrites (indicators of inflammatory process) in dextran sodium sulfate (DSS)-induced ulcerative colitis mice model to control the formation of intestinal edema (Amaro et al. 2009). Targeted inhibition of the TLR4/NF-κB signaling pathway might be an important mechanism for naringenin in protecting intestinal inflammation. Naringenin also shows other

anti-inflammatory activities, such as protect airway, liver and lung inflammation (Bodduluru et al. 2016; Jayaraman et al. 2012; Shi et al. 2009). Thus, naringenin may be utilized as an effective agent for the treatment of many inflammatory diseases.

PMFs seem to possess stronger anti-inflammatory activities than other *Citrus* flavonoids. In a comparative study, nobiletin and tangeretin are more effective than other compounds (naringin, naringenin, hesperidin, hesperetin, and rutin) in terms of inhibiting NO production (Choi et al. 2007). In both rabbit and human synovial fibroblasts, nobiletin effectively suppressed production and gene expression of promatrix metalloproteinases (proMMP-1 and proMMP-3) and PGE2 (Lin et al. 2003). The inhibitory effects on PGE2 production are achieved by selectively down-regulating COX-2 gene expression. A very recent report further suggested that nobiletin inhibited the expression of inflammatory mediators (NO, PGE2, IL-6, *i*NOS, COX-2) and regulated jun N-terminal kinase (JNK)/extracellular signal-regulated kinase (ERK)/p38 MAPK and phosphatidyl inositol 3-kinase (PI3K)/Akt (also known as protein kinase B) pathways in human osteoarthritic chondrocytes (Liu et al. 2016). Tangeretin, another abundant PMF occurring in *Citrus* fruits, also effectively suppressed MMPs, COX-2, and PGE2 expression in synovial fibroblasts (Li et al. 2015b). These results suggest that nobiletin and tangeretin is able to inhibit matrix degradation of the articular cartilage and pannus formation in osteoarthritis and rheumatoid arthritis. In addition, the gene expression of proinflammatory cytokines, such as IL-1α, IL-1β, TNF-α and IL-6, can be down-regulated by nobiletin, tangeretin, and 3,5,6,7,8,3′,4′-heptamethoxyflavone (Ho and Kuo 2014; Lee et al. 2016; Okuyama et al. 2015). In LPS-induced RAW264.7 macrophage, nobiletin and its metabolites, 3′-demethylnobiletin, 4′-demethylnobiletin, and 3′,4′-dimethylnobiletin moderately attenuated *i*NOS and COX-2 gene expression, and NO production (Li et al. 2007). Through the down-regulation of *i*NOS and COX-2 expression, nobiletin exerted anti-inflammatory effects in 2,4,6-trinitrobenzene sulfonic acid-induced colitis (Xiong et al. 2015). Several PMFs, including nobiletin, tangeretin, 4′-demethylnobiletin, 3,5,6,7,8,3′,4′-heptamethoxyflavone, and 5-demethyltangeretin, effectively inhibited 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-induced skin inflammation (Lai et al. 2007, 2008; Wu et al. 2015b). This inhibitory effect may be associated with suppression on TPA-induced up-regulation of proinflammatory cytokines IL-1β, IL-6, and TNF-α, and decreased expression levels of *i*NOS, COX-2, and MMP-9.

Anticancer activities

Cancer is a multifactorial heterogeneous disease that has become one of the leading causes of death worldwide. Over the past decades, researchers have been devoted to searching for novel and efficient drugs for the treatment of cancer. Phytochemicals and dietary compounds have been used for the treatment of cancer throughout history due to their safety, low toxicity, and general availability (Arroo et al. 2009; Pratheeshkumar et al. 2012). Epidemiological studies suggest that long-term consumption of diets rich in fruits and vegetables reduces the risk of chronic diseases especially cancer (Key 2011). *Citrus* fruits are a major winter fruits consumed all over the world, and their anticancer effects have attracted increasing attention. Also evidences for the anticancer property of *Citrus* flavonoids, such as flavanones and PMFs, have been provided by numerous in vitro and in vivo studies (Cirmi et al. 2016). *Citrus* flavonoids can be effective in fighting carcinogenesis by minimizing DNA damage, inhibiting tumor development and progression (Benavente-Garcia and Castillo 2008). Molecular mechanisms, including stimulation of DNA repair following damage, inhibition of chemical-induced carcinogenesis, induction of apoptosis and cell cycle arrest, inhibition of proliferation and angiogenesis, and inhibition of cell invasion and metastasis, have been proposed as relevant pathways for *Citrus* fruits and its flavonoids (Cirmi et al. 2016). An overview of the anticancer effects *Citrus* flavonoids, and the underlying mechanisms or related pathways were presented in Fig. 3. The anticancer properties of *Citrus* flavonoids have been investigated in almost all types of cancer, resulting in plenty of published literatures. In this review, only the anticancer activities against some of the most common cancer types, including skin, liver, lung, breast, gastric, colon, prostate, pancreatic, and bladder cancers, were summarized and discussed in detail.

Skin cancer

The activity of *Citrus* flavonoids on the inhibition of skin carcinogenesis has been studied by using in vitro

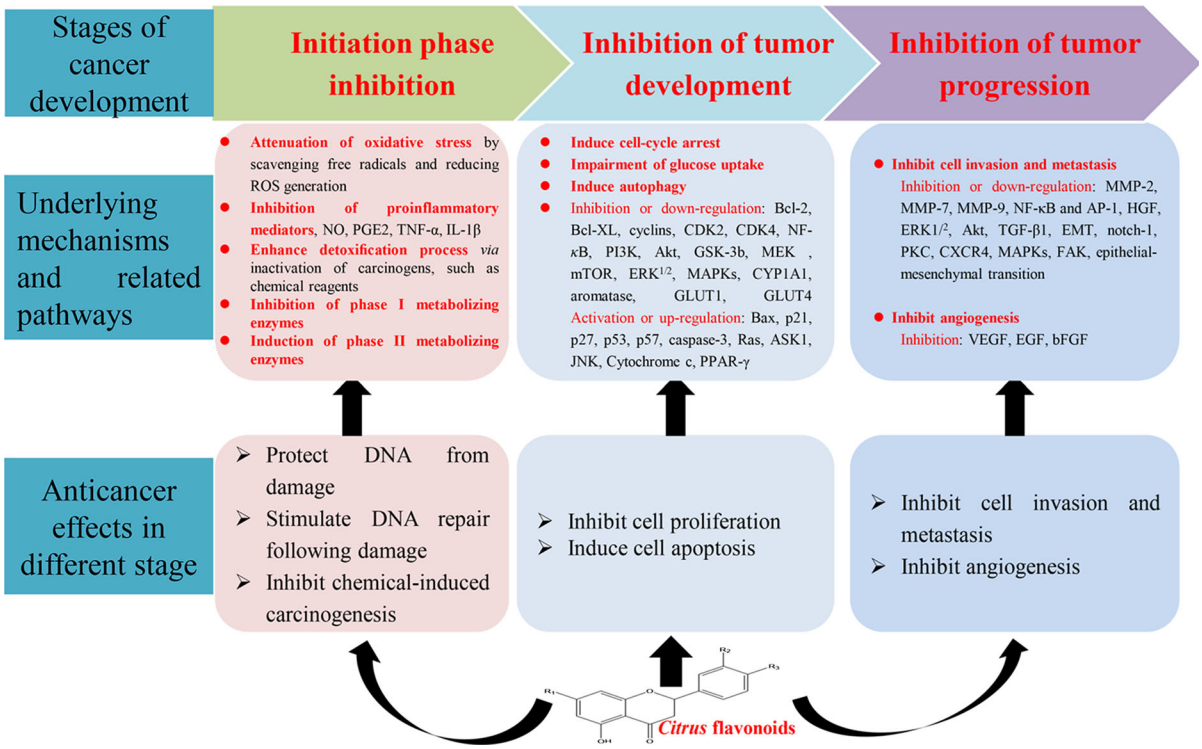

Fig. 3 An overview of the anticancer effects *Citrus* flavonoids, and the underlying mechanisms or related pathways

and in vivo models. An early study reported that hesperidin inhibited TPA-induced tumor promotion in the skin of a two-stage skin tumorigenesis protocol in CD-l mice (Berkarda et al. 1998). Using a similar two-stage carcinogenesis model, Murakami et al. found that nobiletin (160 and 320 nmol) inhibited dimethylbenz[*a*]anthracene (DMBA)/TPA-induced skin tumor formation by reducing the number of tumors per mouse by 61.2 and 75.7%, respectively (Murakami et al. 2000). The authors also reported that 3,5,6,7,8,3′,4′-heptamethoxyflavone (HPT) showed remarkable inhibitory effects on mouse skin tumor promotion (Iwase et al. 2000). The same group further compared nobiletin and HPT for the antitumor-initiating activity against skin tumor (Iwase et al. 2001). Both nobiletin and HPT are effective for inhibiting carcinogenesis on mouse skin, and the anti-tumor-initiating activity of HPT is comparatively stronger than that of nobiletin (Iwase et al. 2001). Other PMFs, such as tangeretin, 3′,4′-didemethylnobiletin, 5-demethyltangeretin, and 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone, also showed significant inhibitory effects on DMBA/TPA-induced skin tumor formation evidenced by decreased tumor numbers, incidence and size of papillomas (Lai et al. 2007).

In A431 human epidermoid skin carcinoma cells, hesperetin exerted apoptotic effect by regulating MAPKs and cyclins (Smina et al. 2015). Also in the same cell line, naringenin showed ability to induction of cell apoptosis by inducing ROS generation and cell cycle arrest in G0/G1 phase (Ahamad et al. 2014). Naringenin exhibited significant anti-proliferative activity against B16F10 melanoma cells after 24 and 48 h of incubation (Bouzaiene et al. 2016).

Liver cancer

Citrus flavonoids can exhibit their anticancer activity by inducing cell apoptosis and inhibiting proliferation. In a rat model of hepatocarcinogenesis induced by *N*-nitrosodiethylamine, the ability of naringenin to inhibit cell proliferation and induce apoptosis was demonstrated by Arul et al. (Arul and Subramanian 2013a). Down-regulation of NF-κB, vascular endothelial growth factor (VEGF), and MMPs and modulation of mitochondrial pathway, such as decreased

expression of Bcl-2 and increased expression of Bax and caspase-3, may account for the molecular mechanism of naringenin-induced cell proliferation and apoptosis (Subramanian and Arul 2013). Naringenin also showed an inhibitory effect on the growth of human hepatoma cell line HepG2 cells (IC_{50} = 100 - μM) through inhibition of cell proliferation and induction of apoptosis (Arul and Subramanian 2013b). The molecular mechanism of the effect of naringenin involves induction of HepG2 cell cycle arrest at the Go/G1 and G2/M phase and mediation of mitochondrial signaling pathway by regulating the expression of apoptosis-related proteins, such as p53, Bcl-2, Bax, and caspase-3 (Arul and Subramanian 2013b). By regulating the expression of these apoptosis-related proteins, the ability of nobiletin to induce apoptosis and cell cycle arrest in hepatic cancer cells was demonstrated by in vitro and in vivo results (Ma et al. 2014). Three *Citrus* flavonoids, including neohesperidin, hesperidin and naringin, were identified as active compounds in *Citrus* seed that show cytotoxic effect of on human HepG2 cells, and hesperidin (IC_{50} = 150.43 μM) is the most effective compound of three (Banjerdpongchai et al. 2016). Hesperidin induced human hepatocellular carcinoma HepG2 cell apoptosis via both mitochondrial and death receptor pathways (Banjerdpongchai et al. 2016). Even though the inhibitory activity is lower than hesperidin, naringin is also able to induce human hepatocellular carcinoma HepG2 cell apoptosis via mitochondria-mediated activation of caspase-9 and caspase-8-mediated proteolysis of Bid (Banjerdpongchai et al. 2016). Hesperetin, the aglycone of hesperetin, inhibited the proliferation and induced the apoptosis of hepatocellular carcinoma via triggering the activation of the mitochondrial pathway by increasing levels of intracellular ROS, ATP and Ca^{2+} (Zhang et al. 2015b).

Though induction of apoptosis by caspases has been observed as the classical event in cancer cell death, caspases independent non-apoptotic mechanisms like autophagy, mitotic catastrophe, paraptosis etc., can also mediate programmed cell death in cancer cells. Paraptosis is a non-apoptotic programmed cell death that is morphologically and biochemically different from apoptosis (Wang et al. 2004). In the recent year, paraptosis has been a new area of interest in cancer research. Apoptotic characteristics like pyknosis, DNA fragmentation and caspase activation is absent in paraptosis, whereas it is characterized by cytoplasmic vacuolation with swelling of mitochondria or endoplasmic reticulum (Wang et al. 2004). Yumnam firstly reported the hesperidin-induced paraptosis like cell death in HepG2 cells with the activation of $ERK^{1/2}$ (Yumnam et al. 2014). The authors further revealed that hesperidin-induced mitochondrial Ca^{2+} overload caused increase ROS production and loss of membrane potential, which finally led to paraptotic cell death in HepG2 cells (Yumnam et al. 2016).

Matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases, are intimately involved in the invasion and metastasis of various tumor cells. In an early study, hesperidin effectively suppressed the expression of MMPs activated by nicotine, suggesting the potential ability of hesperidin to prevent invasion or metastasis of human cancers, such as human hepatocellular carcinoma cells (Balakrishnan and Menon 2007). Hesperidin, through inhibition of the expression of MMP-9, showed inhibitory effects on chemical agents, including acetaldehyde and TPA-induced invasion or metastasis of human hepatocellular carcinoma cells (Lee et al. 2010b; Yeh et al. 2009). The molecular mechanism of suppression of MMP-9 expression by hesperidin involves inhibition of both NF-κB and activator protein-1 (AP-1) activity by the inhibitor of NF-κB (IκB), JNK, and p38 signaling pathways (Lee et al. 2010b; Yeh et al. 2009). Similar to hesperidin, naringenin suppressed TPA-induced cell invasion and migration of human hepatocellular carcinoma cells by reducing MMP-9 expression (Yen et al. 2015). Hepatocyte growth factor (HGF), a paracrine cellular growth, motility and morphogenic factor, and its receptor c-Met play an important role in the control of tumor growth and invasion. In a comparative study, nobiletin was found to possess stronger inhibitory effects on HGF-induced cell invasion/migration of HepG2 liver cancer cells than other three flavones, namely apigenin, tricetin, and tangeretin (Shi et al. 2013). The inhibition of HGF-induced cell invasion/migration by nobiletin is mainly occurring through inhibition of the ERK^2 or Akt signaling pathway.

Lung cancer

As reported by Du et al., naringenin significantly reduced lung metastases in mice with bleomycin-

induced pulmonary fibrosis that promote a high incidence of lung cancer (Du et al. 2009). Naringenin can improve the microenvironment of pulmonary fibrosis and suppresses lung metastasis by directly down-regulating TGF-β1 in the mice lungs (Du et al. 2009). The chemopreventive nature of naringenin against benzo(*a*)pyrene (B(*a*)P)-induced lung carcinogenesis was demonstrated in Swiss albino mice (Bodduluru et al. 2016). Administration of naringenin (50 mg/kg body weight) significantly ameliorated cell proliferation in B(*a*)P-induced pulmonary carcinogenesis by modulating CYP1A1, NF-κB and PCNA expression (Bodduluru et al. 2016). Hesperidin, as well as its aglycone hesperetin, also showed protective effects against B(*a*)P-induced lung cancer by using mouse model (Bodduluru et al. 2015; Kamaraj et al. 2009, 2010, 2011). In B(*a*)P-induced lung cancer cells, hesperidin supplementation (25 mg/kg body weight) effectively attenuated mast cell density as well as alleviated the mitochondrial dysfunction (Kamaraj et al. 2009, 2010, 2011). In A549 human lung cancer cell lines, naringin (23 μM) suppressed the enhancing effect of β-carotene on DNA damage induced by nicotine-derived nitrosamine ketone, a potent tobacco-related carcinogen in humans (Yeh et al. 2006). In the same cell line, naringin (100 μM) also reduced epidermal growth factor (EGF)-induced MUC5AC secretion through the inhibition of MAPKs/AP-1 and IKKs/IκB/NF-κB signaling pathways (Nie et al. 2012).

Citrus flavonoids showed effective anticancer effect in A549 human lung cancer cells via induction of G2/M cell cycle arrest and apoptosis (Nagappan et al. 2016; Park et al. 2012; Uesato et al. 2014). Recently, Cincin further demonstrated the anti-proliferative and apoptotic effects of hesperidin on non-small cell lung cancer cells, including NCI-H358 and A549 cells (Cincin et al. 2015). The mechanisms underlying hesperidin-induced growth arrest and apoptosis are modulation of immune response-related pathways, namely fibroblast growth factor and NF-κB signal transduction pathways (Cincin et al. 2015). Also in a very recent study, naringin suppressed HeLa and A549 cell growth through the alteration of glycolipids, which may largely arise from the attenuation of EGF receptor (EGFR) signaling through GM3 ganglioside (Yoshinaga et al. 2016). Both in vitro and in vivo tests indicated that nobiletin showed antiproliferative activity on lung cancer cells in a dose-dependent manner through the activation of the apoptotic process and cell cycle arrest at G2/M phase due to decreased Bcl-2 and increased Bax expression (Luo et al. 2008). Tangeretin also inhibited the growth and invasion of A549 cells and promotes the cell apoptosis by potentially inhibiting PI3K/Akt signaling pathway activation (Shi 2015). 5-Hydroxylated PMFs seem to exhibit more potent antiproliferative activities in lung cancer cells than their PMF counterparts (Xiao et al. 2009). It was showed that 5-demethyltangeretin exhibited much higher cytotoxicity against three human non-small cell lung cancer cell lines than its counterpart, and the IC_{50} values of 5-demethyltangeretin were 79-, 57- and 56-fold lower than those of tangeretin in A549, H460 and H1299 cells, respectively (Charoensinphon et al. 2013). Similar to 5-demethyltangeretin, the antiproliferative activity of 5-demethylnobiletin against human lung cancer cells was also confirmed in in vitro and in vivo studies (Chen et al. 2015b). In human lung cancer cells, both 5-demethyltangeretin and 5-demethylnobiletin showed preventive effects by inducing G2/M cell cycle arrest and apoptosis (Charoensinphon et al. 2013; Chen et al. 2015b). A recent study confirmed the inhibitory effects of metabolites of 5-demethylnobiletin on human non-small cell lung cancer cells (Song et al. 2016b).

Epithelial–mesenchymal transition (EMT) is a critical cellular process in cancer metastasis, during which epithelial polarized cells become motile mesenchymal cells (Da et al. 2016). Transforming growth factor-β (TGF-β) is a potent inducer of EMT, thus blocking of TGF-β/Smad signaling has become a promising cancer therapy. Nobiletin was found to notably attenuate hypoxia/TGF-induced EMT, invasion and migration in H1299 and A549 cells (Da et al. 2016; Gao et al. 2015). Suppression of notch-1 and TGF-β1/Smad3 signaling and promotion of re-expression of miR-200b underlie the mechanism of this inhibitory effect of nobiletin on EMT (Da et al. 2016; Gao et al. 2015). Nobiletin also inhibited tumor growth and reversed EMT in mice bearing A549-Luc xenografts (Da et al. 2016).

Breast cancer

Citrus flavonoids are able to inhibit chemical-induced carcinogenesis of breast cancer. Nandakumar et al. reported that daily administration of hesperidin (30 mg/kg body weight) for 45 days prevented DMBA-induced experimental breast cancer formation, presumably by the regulation of both phase I and

phase II metabolizing enzymes, and through its strong antioxidant activity (Nandakumar and Balasubramanian 2012). Regulation of these key metabolizing enzymes by hesperidin thus significantly ameliorated the changes in carbohydrate metabolism, lipid profile, and ATPases during DMBA-induced breast carcinogenesis (Nandakumar and Balasubramanian 2011, 2012; Nandakumar et al. 2014).

In breast carcinoma MCF-7 cells, hesperetin was found to markedly inhibit cell proliferation by inducing cell cycle arrest at G1 phase that involving regulation of CDK4 and p2l (Choi 2007). Hesperidin was reported suppress proliferation human breast cancer by a possible interaction with androgenic receptors (Lee et al. 2010a). Tangeretin and nobiletin inhibited the proliferation of both human breast cancer cell lines (MDA-MB-435 and MCF-7) in a concentration-dependent manner, by blocking cell cycle progression at the G1 phase without inducing cell death (Morley et al. 2007). Naringenin (10 μM) can inhibit the proliferation of MCF-7 cells via impaired glucose uptake. Indeed, naringenin is a potential of PI3K and MEK inhibitor that blocks basal and insulin-stimulated glucose uptake in breast cancer cells (Harmon and Patel 2004). Hesperetin is also able to decrease basal and insulin-induced glucose uptake in MDA-MB-231 breast cancer cells, and thus inhibits cellular proliferation (Yang et al. 2013). Hesperetin-induced suppression of glucose uptake is mainly caused by down-regulation of glucose transporters including GLUT1 and GLUT4, as well as inhibition of the phosphorylation of IR-β and Akt. In human mammary carcinoma cell line MCF-7, hesperidin (80 μM) effectively induced cell apoptosis that may be due to DNA damage and increased expression of apoptotic protein p53 and caspases-3 (Natarajan et al. 2011). In the same cell line, hesperetin also induced cell apoptosis (Palit et al. 2015). Hesperetin can mediate inhibition of growth and induction of intrinsic mitochondrial apoptotic cascade by triggering generation of cytosolic ROS and activating downstream Apoptosis signalregulating kinase 1 (ASK1)/JNK signaling pathway (Palit et al. 2015).

Triple-negative breast cancer, characterized by a lack of expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER)-2, showed a tendency toward early metastasis and poor prognosis (Seal and Chia 2010). Triple-negative (ER−/PR−/HER2−) breast cancer is an aggressive cancer with a poor prognosis and a lack of targeted therapies. In this kind of tumor, naringin was able to inhibit cell proliferation and promoted cell apoptosis and G1 cycle arrest (Li et al. 2013). These effects were accompanied by increased p21 levels and decreased survival by modulation of the β-catenin pathway (Li et al. 2013). Aromatase is a key enzyme in estrogen synthesis, and aromatase inhibitors have been developed for treating estrogen-responsive breast cancer. In vivo study has demonstrated that hesperetin is effective in blocking estrogen synthesis by suppressing expression of aromatase, and thus exerts inhibitory effects on cell proliferation (Ye et al. 2012). In vitro investigation further confirmed that both hesperetin and naringenin showed effective anti-tumor activity against HER2 positive tumors by serving as HER2 tyrosine kinase inhibitors (Chandrika et al. 2016).

Metastasis and invasion are the main causes of death in cancer patients. By using a breast cancer resection model, Qin et al. found that orally administered naringenin significantly decreased the number of metastatic tumor cells in the lung and extended the life span of tumor resected mice (Qin et al. 2011). A recent study indicated that naringenin effectively blocked TGF-β1 secretion by inhibiting phosphorylation of PKC, and then suppressed TGF-β1-induced migration and pulmonary metastasis of breast tumor cell (Zhang et al. 2016a). Nobiletin exerts antimetastatic effects on human breast cancer cells through down-regulation of both CXC chemokine receptor type 4 (CXCR4) and MMP-9 via NF-κB inhibition and MAPKs activation (Baek et al. 2012).

Dietary administration of hesperetin (1000 and 5000 ppm) significantly inhibited xenograft growth in athymic mice ovariectomized and transplanted with aromatase-overexpressing MCF-7 cells (Ye et al. 2012). The mechanism involves down-regulating the expression of cyclin D1, CDK4 and Bcl-xL and up-regulating $p57^{Kip2}$ expression (Ye et al. 2012).

Gastric cancer

Citrus flavonoids have been found to inhibit gastric carcinogenesis, cell proliferation, invasion, and metastasis. In gastric cancer, naringenin showed inhibitory effects on β-catenin/Tcf signaling that plays an important role in the early events of gastric

carcinogenesis (Lee et al. 2005; Park et al. 2005). A series of in vivo experiments were carried out to study the antitumor effects of naringenin (Ekambaram et al. 2008a, b; Ganapathy et al. 2008). These found that naringenin showed efficacy against *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine-induced gastric carcinogenesis by reducing tumor size and weight loss, regulating glycoprotein levels, and protecting the glutathione-metabolizing enzymes, phase I and phase II xenobiotic enzymes (Ekambaram et al. 2008a, b; Ganapathy et al. 2008). These results demonstrated the chemopreventive potential of naringenin against gastric carcinogenesis. A comprehensive study was performed to investigate the antitumor effects and mechanism of naringenin using human gastric cancer cells SGC-7901 (Bao et al. 2016). It was concluded that naringenin inhibited SGC-7901 cell proliferation, migration, and invasion, and induced apoptosis by down-regulation of the Akt pathway.

Nobiletin, both alone and in combination with cisplatin, showed growth-inhibitory effects on various human gastric cancer cells (TMK-1, MKN-45, MKN-74, and KATO-II), through the induction of apoptosis and cell cycle arrest (Yoshimizu et al. 2004). In human gastric p53-mutated SNU-16 cells, nobiletin effectively inhibited cell proliferation, induced apoptosis, and enhanced the efficacy of 5-fluorouracil, an anticancer drug (Cho et al. 2013). Further study revealed that nobiletin induced apoptosis in SNU-16 cells mediated by pathways involving intracellular ER stress-mediated protective autophagy (Moon and Cho 2016). Tangeretin also induced apoptosis of human gastric cancer AGS cells through the activation of both extrinsic and intrinsic signaling pathways and thus up-regulation of pro-apoptotic proteins, such as caspase-3 and p53 (Lan et al. 2011). In AGS gastric adenocarcinoma cells, naringin showed growth-inhibitory activity by suppressing the PI3K/Akt/mTOR cascade via induction of autophagy with MAPKs activation (Raha et al. 2015). Hesperidin showed apoptotic effect on human gastric cancer cells SNU-668, possibly by regulation of the expression of related proteins, such as up-regulation of Bax and caspase-3, and down-regulation of Bcl-2 (Park et al. 2007). Both in vitro and in vivo results indicated that hesperetin was able to inhibit proliferation and induce the apoptosis of gastric cancer cells via activating the mitochondrial pathway by increasing ROS (Zhang et al. 2015a).

In severe combined immune deficient mice model, nobiletin effectively inhibited the activity of pro-MMP-9 and the formation of peritoneal dissemination nodules from TMK-1 (a poorly differentiated human-stomach adenocarcinoma cell line) (Minagawa et al. 2001). The results suggest nobiletin as a candidate anti-metastatic drug for the prevention of peritoneal dissemination of gastric cancer (Minagawa et al. 2001). Moreover, nobiletin has a distinct ability to highly suppress adhesion, invasion, and migration of human gastric adenocarcinoma AGS cells by inhibiting the activation of focal adhesion kinase and PI3 K/Akt signals, which in turn down-regulates MMP-2 and-9 expression and activity (Lee et al. 2011). Zhang et al. documented that tangeretin enhanced radiosensitivity of gastric cancer cells and attenuated radiation-induced EMT, invasion and migration, accompanied by down-regulation of notch-1 and up-regulation of miR-410 (Zhang et al. 2015c).

Colon cancer

Citrus flavonoids are capable of inhibiting chemical-induced colon carcinogenesis. Hesperidin, alone or in combination with diosmin, suppressed colon carcinogenesis in azoxymethane (AOM)-treated male F344 rat, may be partly due to suppression of cell proliferation in the colonic crypts (Tanaka et al. 1997). It was suggested that nobiletin (100 ppm) significantly suppressed the serum leptin level related to colon carcinogenesis, thereby inhibiting the proliferation of HT-29 colon cancer cells in AOM- and DSS-treated male ICR mice (Miyamoto et al. 2008). These results suggested the potential of nobiletin for chemoprevention of early changes associated with carcinogenesis colon. In AOM-treated rats, naringenin was reported to suppress colon carcinogenesis through the aberrant crypt stage (Leonardi et al. 2010). Aranganathan et al. carried out a number of experiments to investigate the antitumor effects of hesperetin on 1,2-dimethylhydrazine (DMH)-induced colon carcinogenesis in male Wistar rats (Aranganathan et al. 2008, 2009a, b; Aranganathan and Nalini 2009). Hesperetin supplementation (20 mg/kg) effectively suppressed the formation of aberrant crypt foci (ACF) and reduced the activity of bacterial enzymes in DMH-induced colon carcinogenesis (Aranganathan et al. 2008; Aranganathan and Nalini 2009). Also, hesperetin was able to modulate ACF and xenobiotic-metabolizing

enzymes during DMH-induced colon carcinogenesis (Aranganathan et al. 2009b). Moreover, hesperetin supplementation significantly released the antioxidant enzymes activities and effectively decreased lipid peroxidation level (Aranganathan et al. 2009a). These results indicate that hesperetin may be a potential chemopreventive agent against chemical-induced colon carcinogenesis.

Citrus flavonoids also exert anticancer effects on colon cancer through induction of apoptosis and inhibition of proliferation. In human colorectal carcinoma cells COLO 205, tangeretin induced cell cycle arrest at G1 phase through inhibiting cyclin-dependent kinases (CDK2and CDK4) activities as well as elevating CDK inhibitors p21 and p27 (Pan et al. 2002). Tangeretin and nobiletin inhibited the proliferation of a human colon cancer cell line (HT-29) in a concentration- and time-dependent manner, by blocking cell cycle progression at the G1 phase (Morley et al. 2007). Nobiletin also showed a distinct ability to highly suppress MMP-7 expression and production in both concentration- and time-dependent manner by blocking AP-1 activity, suggesting it as an effective agent to suppress cancer cell invasion and metastasis (Kawabata et al. 2005). Nobiletin, as well as its colon metabolites, significantly inhibited colitis-associated colon carcinogenesis in mice (Wu et al. 2015a). 5-Hydroxy PMFs, including 5-hydroxy-6,7,8,3′,4′-pentamethoxyflavone, 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone, and 5-hydroxy-6,7,8,4′-tetramethoxyflavone, showed much stronger inhibitory effects on the growth of the colon cancer cells in comparison with their counterparts, nobiletin and tangeretin (Qiu et al. 2010). Frydoonfar et al. demonstrated the ability of naringenin to inhibit cell proliferation in HT-29 colon cancer cell line (Frydoonfar et al. 2003). A very recent study reported that naringenin induced apoptosis in human colon cancer cells involving the mechanism of activation of transcription factor 3 (ATF3) (Song et al. 2016a). Naringin, a glycoside of naringenin, prevented intestinal tumorigenesis likely through a collection of activities including anti-proliferation, induction of apoptosis, modulation of glycogen synthase kinase (GSK)-3β and APC/β-catenin pathways and anti-inflammation (Zhang et al. 2016c). These suggest naringin as a potential chemopreventive agent for reducing the risk of colonic cancers. Hesperetin possessed apoptosis-inducing and antiproliferative ability in DMH-induced colon cancer (Aranganathan and Nalini 2013; Sivagami et al. 2012). It induced apoptosis via the Bax-dependent mitochondrial pathway, involving oxidant/antioxidant imbalance (Sivagami et al. 2012). Hesperidin exhibited cytotoxic and pro-apoptotic effects on SNU-C4 human colon cancer cells through activation of capase-3 (Park et al. 2008). Hesperidin treatments significantly suppressed cell proliferation markers, and reduced ACF in AOH-induced colon carcinogenesis of Swiss albino mice (Saiprasad et al. 2013). Also hesperidin supplementation induced apoptosis via targeted inhibition of constitutively activated Aurora-A mediated PI3 K/Akt/GSK-3βand mTOR pathways coupled with autophagic stimulation against AOM-induced colon carcinogenesis (Saiprasad et al. 2014).

Prostate cancer

Naringenin at low doses (10–80 μM) can stimulate DNA repair following oxidative damage in a human lymph node prostate cancer cell line (LNCaP), leading to a significant increase in the levels of several major enzymes in the DNA base excision repair pathway (Gao et al. 2006). Nobiletin has been reported to counteract prostate carcinogenesis both in vitro and in vivo (Tang et al. 2007). Particularly, nobiletin inhibited the growth of several prostate cancer cell lines with IC_{50} values of around 100 μM, by a mechanism involving apoptosis and cell cycle arrest at the G0/G1 phase, as well as inhibited development of prostate adenocarcinomas in a transgenic rat model (Tang et al. 2007). Nobiletin also showed inhibitory effects on PhIP-induced prostate carcinogenesis in F344 rats (Tang et al. 2011). Hesperidin suppressed the proliferation of androgen-dependent prostate cancer cells through mechanisms other than antimitotic ones, suggesting a possible interaction with androgenic receptors (Lee et al. 2010a). Using in silico and in vitro methods, the underlying mechanism of hesperetin-induced apoptosis in prostate cancer PC-3 cells was investigated by Sambantham et al. (2013). It was shown that hesperetin induced apoptosis by inhibiting NF-κB signaling that regulates the expression of apoptosis-related proteins (Sambantham et al. 2013). In human prostate cancer cells (DU145, PC-3, LNCaP), tangeretin showed inhibitory effects on cell proliferation and induced apoptosis via activation of notch signaling and regulating the androgenic

receptors and PI3K/Akt/mTOR pathways (Guo et al. 2015). Nobiletin reduced cell viability in both PC-3 and DU-145 prostate cell lines through the Akt pathway, with more profound effect against the more metastatic PC-3 line (Chen et al. 2014). In the same cell lines, naringenin was observed to be effective in reducing the viability and migratory percentage of PC-3 and DU145 cells, by down-regulating the MMP-2/-9 via ROS/ERK$^{1/2}$ pathways (Lin et al. 2014).

Other cancers

Lou et al. demonstrated that naringenin inhibited pancreatic cancer cell migration and invasion through the down-regulation of TGF-β-induced EMT markers, including vimentin, *N*-cadherin, MMP-2 and MMP-9 (Lou et al. 2012). In a recent study, naringenin induced apoptosis of pancreatic cancer cells SUN-213 by activation of ASK1 via a Prdx-1 pathway inhibition resulting in increased ROS levels (Park et al. 2017). Patil et al. found that hesperidin inhibited cell cycle progression in Panc-28 human pancreatic carcinoma cells (Patil et al. 2009b). In pancreatic cancer cell line PANC-1, nobiletin caused both time-and dose-dependent inhibition of proliferation by inducing apoptosis and cell cycle arrest at the G0/G1 phase (Zhang et al. 2014b). Nobiletin induced apoptosis in these cells via up-regulation of the pro-apoptotic protein Bax and down-regulation of the anti-apoptotic protein Bcl-2.

An early study found that diosmin and hesperidin, both individually and in combination, were effective in inhibiting *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine-induced carcinogenesis of the bladder, and that such inhibition might be partly related to suppression of cell proliferation (Yang et al. 1997). In urinary bladder cancer cells, 100 μM naringin showed growth-inhibitory effects on 5637 bladder cancer cells in a concentration-dependent manner together with of cell-cycle blocking (Kim et al. 2008). In this cell line, the naringin-induced anti-proliferative effect seems to be linked to the activation of Ras/Raf/ERK-mediated p21WAF1 induction, which in turn leads to a decrease in the levels of cyclin D1/CDK4 and cyclin E-CDK2 complexes, causing G1-phase cell-cycle arrest (Kim et al. 2008). Liao et al. provided the first evidence that naringenin inhibits migration of bladder cancer cells through down-regulation of Akt and MMP-2 (Liao et al. 2014).

Cardiovascular protection activities

Cardiovascular disease (CVD) represents one of the leading causes of death worldwide, considering 17.3 million deaths per year, a number that is anticipated to rise to over 23.6 million over 2030 (Smith et al. 2012). The onset of CVD depends on many factors, such as obesity, type 2 diabetes mellitus, metabolic syndrome, high blood pressure, and plasma dyslipidemia, which can be modulated by dietary components (Toh et al. 2013). Epidemiological studies have revealed an association between the intake of flavonoid-containing foods and a decreased incidence of cardiovascular disease (Yamada et al. 2011). In this regard, numerous in vitro and in vivo studies have shown that *Citrus* flavonoids, mainly flavanones including hesperidin, hesperetin naringin, and naringenin as well as PMFs, can exert vasoprotective, antihypertensive and anti-atherosclerotic effects (Bharti et al. 2014; Li and Schluesener 2016; Orhan et al. 2015). These beneficial effects of *Citrus* flavonoids are achieved by modulating the expression of inflammation-related molecules, preventing the formation of foam cells, reducing the area of atherosclerotic plaques, improving the lipid profile, inhibiting the adhesion of monocytes to the endothelium, and modulating cell migration (Chanet et al. 2012a; Roohbakhsh et al. 2015). The cardiovascular effects of *Citrus* flavonoids are summarized in Fig. 4.

Vasorelaxant and vasoprotective effects

In normal coronary functions, the vascular endothelial cells play critical roles, such as regulation of vascular tone and blood flow to organs. Notably, cardiovascular complications result primarily from endothelial dysfunction, manifested as impaired endothelium-dependent vasodilator actions secondary to decreased production and/or bioavailability of NO (Tang and Vanhoutte 2010). The vascular endothelial cells are able to produce endothelium-derived relaxing factors, such as NO, and potent contracting factors, such as endothelin (ET)-1. Endothelium-derived NO plays a critical role in the regulation of endothelium-dependent vasodilatation, blood pressure, platelet aggregation, leukocyte adhesion, and migration and proliferation of smooth muscle cells. In human umbilical vein endothelial cells (HUVEC), hesperidin (10 and 100 μM/L) inhibited strain-induced ET-1

secretion and enhances NO production, suggesting the protective effects of hesperidin in vascular vessels (Chiou et al. 2008). It was demonstrated that hesperetin was able to promote both NO production and endothelial nitric oxide synthase (eNOS) expression (Rizza et al. 2011). Hesperetin acutely induced phosphorylation of Akt, AMPK, and eNOS, which mediated NO production in endothelial cells. In addition, hesperetin may also affect NO production in endothelial cells through ER-α activation (Liu et al. 2008). Naringin showed potent effects against LPS-induced damage in HUVEC through the modulation of oxidative stress, inflammation, apoptosis and MAPK pathways (Bi et al. 2016). Hesperetin and its derived metabolites, at physiologically relevant concentrations (1–10 μM), significantly attenuated TNF-α induced human aortic endothelial cell migration, which perhaps mediated by a significant decrease in levels of the thrombogenic plasminogen activator inhibitor-1 (Gimenez-Bastida et al. 2016).

The vasorelaxant potential of certain *Citrus* flavonoids, such as hesperidin, hesperetin and naringenin, has been demonstrated in animal models. In rat aorta, activation of tetraethylammonium-sensitive K^+ channels was suggested being involved in hesperetin-induced vasorelaxation (Calderone et al. 2004). Myogenic studies in vitro showed that both hesperetin and naringenin relaxed rat aorta (Orallo et al. 2004, 2005). This vasorelaxant effect seems to be resulted from the inhibition of different phosphodiesterase isoenzymes (Orallo et al. 2004, 2005). Human studies on endothelial cells proposed that vasodilation effect of hesperetin might be mediated via enhancement of endothelial NO production (Takumi et al. 2012). Another study using the patch clamp technique suggested that vasospasmolysis after hesperetin is mediated through the enhancement of K_v current in coronary artery (Liu et al. 2014). A recent study indicated that hesperidin might improve the endothelium-dependent vasodilation during hypertension, possibly through the enhancement of K_v channels function (Dobias et al. 2016). In vascular smooth muscle cells, Saponara et al. reported the vasorelaxant effect of the naringenin on endothelium-denuded vessels, which were due to the activation of BK_{Ca} channels in myocytes (Saponara et al. 2006). Based on abovementioned results, the results on the mechanisms underlying the vasorelaxant effect are inconsistent, probably because of different experimental models and conditions. Hence, the vasorelaxant effects of *Citrus* flavonoids might be attributed to more than one specific mechanism.

Antihypertensive or hypotensive effects

Some studies have examined the antihypertensive or hypotensive effects of *Citrus* flavonoids in spontaneously hypertensive rats (SHRs). In an early study, Galati et al. reported that oral administration of hesperidin at high dose (200 mg/kg) showed antihypertensive and weak hypotensive effects in SHRs and conscious normotensive rats, respectively (Galati et al. 1996). Long-term administration of hesperidin and glucosyl hesperidin effectively decreased the blood pressure and heart rate of SHRs, suggesting the antihypertensive effects of both flavonoids on hypertensive animals (Ohtsuki et al. 2002). The chronic administration of glucosyl hesperidin (50 mg/kg) over 8 weeks also resulted in a moderate reduction in systolic blood pressure in SHRs (Yamamoto et al. 2008b). In stroke-prone SHRs, both hesperidin and glucosyl hesperidin suppressed age-related increase in blood pressure and decreased thrombotic tendency after 4 weeks oral administration (Ikemura et al. 2012). Daily ingestion of hesperidin, glucosyl hesperidin and naringin promoted antihypertensive and antithrombotic effects in stroke-prone SHRs (Yamamoto et al. 2013a). The same antihypertensive effects were also observed in SHRs after short-term administration of hesperidin, glucocyl hesperidin, and hesperetin-7-*O*-glucuronide (Yamamoto et al. 2008b, 2013b). The antihypertensive mechanism of these *Citrus* flavonoids has also been explored. Yamamoto et al. suggested that the hypotensive effect of hesperetin in SHRs is associated with NO-mediated vasodilation (Yamamoto et al. 2008b). The researchers also reported that continuous ingestion of glucocyl hesperidin reduced oxidative stress by inhibiting nicotinamide adenine dinucleotide phosphate oxidase expression in the vasculature, thereby ameliorating endothelial dysfunction and hypertension in SHRs (Yamamoto et al. 2008a). The strong antioxidant properties of *Citrus* flavonoids could modulate the inactivation of NO and protect endothelial function from ROS (Yamamoto et al. 2013a). In this manner, the flavonoids could contribute beneficial effects on the mechanisms of hypertension and thrombosis by increasing the bioavailability of NO.

Continuous ingestion of hesperidin also alters the gene expression of vascular regulatory molecules, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and thromboxane A2 synthase in the aorta, which leads to prevention of hypertension in SHRs (Yamamoto et al. 2013a).

Anti-atherosclerotic effects

Atherosclerosis, the primary cause of CVDs, is a multifactorial disease characterized by lipid accumulation, monocyte infiltration, and foam cell formation that leads to the development of the atherosclerotic plaque. Atherosclerosis is mainly caused by deposition of low-density lipoprotein (LDL)-cholesterol in macrophages of arterial walls. Numerous evidences have demonstrated the anti-atherosclerotic effects of *Citrus* flavonoids. The abilities of *Citrus* flavonoids to protect endothelial cells, inhibit proliferation and migration of vascular smooth muscle cells (VSMC), regulate lipid metabolism, suppress LDL oxidation, inhibit adhesion molecule production, and reduce platelet aggregation are believed to have crucial roles against atherosclerosis.

Endothelial cell injury and dysfunction have been regarded as one of the key factors in the pathogenesis of atherosclerosis. Hence, protecting endothelium cell injury is quite important for the treatment of atherosclerosis. A recent study indicated naringin inhibited LPS-induced damage in HUVEC via attenuation of inflammation, apoptosis and MAPK pathways (Bi et al. 2016). In endothelial cells subjected to high glucose, naringenin ameliorated PKC-βII-associated endothelial dysfunction via regulating ROS/caspase-3 and NO pathway (Qin et al. 2016). Other beneficial effects of *Citrus* flavonoids on endothelial cell have been summarized in previous parts.

Abnormal VSMC proliferation and migration play fundamental roles in the pathogenesis of vascular diseases, especially atherosclerosis. *Citrus* flavonoids are able to inhibit the proliferation and migration of VSMC, which contributes to their inhibitory effects against atherosclerosis. Lee et al. reported the inhibitory effects of naringin (0–150 μM) on VSMCs growth, which seems to be linked to p21WAF1-mediated G1-phase cell cycle arrest in VSMCs via activation of the Ras/Raf/ERK signaling pathway (Lee et al. 2008). Both naringin and naringenin at 10–25 μM concentrations inhibited the invasion and migration of TNF-α-induced VSMCs by inhibiting MMP-9 expression and PI3K/Akt signaling pathway through suppression of NF-κB and AP-1 binding activities (Lee et al. 2009). Besides, Chen et al. further demonstrated the ability of naringenin to inhibit TNF-α-induced VSMCs proliferation and migration via induction of hemeoxygenase-1 (Chen et al. 2012). Platelet-derived growth factor and angiotensin II are two kinds of mitogenic stimuli that drive VSMC proliferation. Previous studies revealed that the platelet-derived growth factor—BB-induced VSMCs proliferation can be inhibited by hesperetin, naringenin, nobiletin and tangeretin (Guan et al. 2014; Jin et al. 2008; Lee et al. 2012; Seo et al. 2011). Such inhibitory effects are possibly attributed to cell-cycle arrest at G0/G1 phase in association with modulation of the expression or activation of cell-cycle regulatory proteins, such as cyclin D, cyclin E, CDK2, and CDK4 (Jin et al. 2008; Lee et al. 2012; Seo et al. 2011). On the other hand, both naringenin and nobiletin are able to inhibit angiotensin II-induced VSMC proliferation (Xu et al. 2013; Zhou et al. 2009). The preventing effect of nobiletin on angiotensin II-induced VSMCs proliferation is attributed, in part, to its inhibitory effect on Ca^{2+}-dependent JNK activation in VSMCs (Zhou et al. 2009). Naringenin significantly attenuated the ROS production, increased SOD activity and decreased NADPH oxidase activity, reduced phosphorylation of $ERK^{1/2}$ and p38 MAPK and NF-κB p65 in angiotensin II-treated VSMCs (Xu et al. 2013).

Dyslipidemia, including hyperlipidemia and hypercholesterolemia, is one of the major risk factors for the development of atherosclerosis. Atherogenic dyslipidemia is characterized by increased plasma concentrations of vascular LDL (VLDL)-triglyceride and LDL-cholesterol and low levels of high-density lipoprotein (HDL). The hypolipidemic and hypocholesterolemic potentials of *Citrus* flavonoids have been evaluated in several studies. Both 0.1% naringin and naringenin reduced the cholesterol levels in liver and plasma via inhibition of 3-hyroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase and acyl-CoA: cholesterol acyl coenzyme a-cholesterol acyltransferase activity (ACAT) in high-cholesterol diet fed-rats (Lee et al. 1999; Shin et al. 1999). Naringin also lowered plasma cholesterol level in high-cholesterol diet-fed rabbits (Jeon et al. 2004) as well as LDL-receptor knockout mice (Kim et al. 2004a) through the

similar mechanism. In Sprague-Dawley rats, naringin (0.2 g/kg body weight) administration reduced the hepatic synthesis of cholesterol and, subsequently, the plasma lipid levels after 6 weeks administration (Kim et al. 2006). In a similar model, naringenin (0.02% wt/wt) decreased the hepatic cholesterol, plasma total-cholesterol, triglyceride, HMG-CoA and ACAT activity and atherogenic index, along with an increase of HDL-cholesterol (Jeon et al. 2007). Rats fed with naringenin (0.003, 0.006 and 0.012% wt/wt) were found to exhibit reduced plasma and hepatic triglyceride and cholesterol levels which may contribute to its hypolipidemic and anti-adiposity effects (Cho et al. 2011). In LDL receptor-null (Ldlr/) mice fed cholesterol-enriched diets, naringenin (3% wt/wt) significantly prevented metabolic dysregulation and atherosclerosis via attenuation of hepatic macrophage infiltration, foam cells formation and inflammatory markers expression in peritoneal macrophages (Assini et al. 2013). Naringenin, through induction of hepatic fatty acid (FA) oxidation and attenuation of FA synthesis, prevented hepatic steatosis, hepatic VLDL overproduction, and hyperlipidemia induced by cholesterol-rich diets (Assini et al. 2013). In fat-fed Ldlr2/2 mice, nobiletin attenuated dyslipidemia through a reduction in VLDL-triglyceride secretion (Mulvihill et al. 2011). Oral administration of hesperetin reduced the hepatic triacylglycerol and cholesterol levels in orotic acid-fed rats (Cha et al. 2001) and lowered cholesterol content in hypercholesterolemic hamsters (Kim et al. 2010). A hypolipidemic effect of hesperetin was also reported even during the high lipid concentrations (Kim et al. 2003). Hesperetin (200 μM) is likely to stimulate LDLr gene expression via increase phosphorylation of PI3K and $ERK^{1/2}$, which increased SREBP-1a and SREBP-2 mRNA levels and enhanced the maturation of the encoded proteins (Bawazeer et al. 2016). This may result in lower plasma LDL-cholesterol, which suggests diets supplemented with hesperidin might provide cardio-protective effects and reduce mortality and morbidity from coronary heart diseases.

Plasma concentration of apolipoprotein B (apoB)-containing particles directly correlates with plasma cholesterol levels. Hence, reduction in apoB secretion has been an attractive therapeutic target for treating atherosclerosis. The anti-atherosclerosis potential of *Citrus* flavanones, hesperetin and naringenin, may be attributed to their ability to reduce apoB secretion and cellular cholesterol homeostasis in human hepatoma cells line HepG2 (Wilcox et al. 2001). Naringenin (100 μM) also inhibited the secretion of apoB100 in HepG2 cells by activation of PI3K and MAPK pathway (Allister et al. 2005, 2008; Borradaile et al. 2003). The mechanism involved in naringenin anti-atherosclerosis activity is a reduced apoB secretion primarily due to the inhibition of microsomal triglyceride transfer protein and the enhancement of LDLr-mediated apoB-containing lipoprotein uptake (Borradaile et al. 2003). In high-fat fed Ldlr/mice, naringenin (1 or 3% wt/wt) also decreased progression of atherosclerosis and metabolic syndrome by ameliorating dyslipidemia, inhibiting apoB overproduction and hyperinsulinemia (Mulvihill et al. 2009, 2010). Nobiletin also decreased the secretion of apoB100 through activation of $MAPK^{erk}$, enhancement of LDLr expression, and attenuation of MTP activity and diacylglycerol acyltransferase expression (Mulvihill et al. 2011). Beneficial effects were also observed in humans in whom dietary naringin (0.4 g/kg) reduced plasma LDL-cholesterol levels along with apoB levels (Jung et al. 2003).

There is also strong evidence that oxidized LDL is a key factor in the initiation and progression of the pathology of atherogenesis. Naringin was found to prevent in vitro LDL oxidation and therefore may have beneficial effects on inhibition of atherosclerosis (Naderi et al. 2003). Oxidative modification of LDL alters its structure allowing LDL to be taken up by scavenger receptors (SRs) on macrophage, endothelial, and smooth muscle cells, leading to the formation of lipid-laden foam cells, the hallmark of early atherosclerotic lesions. Nobiletin could prevent atherosclerosis at the level of the vascular wall by inhibiting macrophage foam-cell formation, through selectively inhibited class A scavenger receptor (SR-A)-mediated metabolism of acetylated LDL (Whitman et al. 2005). In THP-1 human monocytic cells, nobiletin and its metabolites also effectively inhibited TPA-induced expression of LOX-1, a scavenger receptor, via AP-1 repression and thus blockaded acetylated LDL uptake, which suggests this flavonoid as a candidate to regulate the development of atherosclerosis (Eguchi et al. 2007).

Adhesion molecules, including endothelial selectin (E-selectin), vascular cell adhesion molecule-1 (VCAM-1), and intracellular adhesion molecule-1 (ICAM-1), are crucial pathogenic elements in

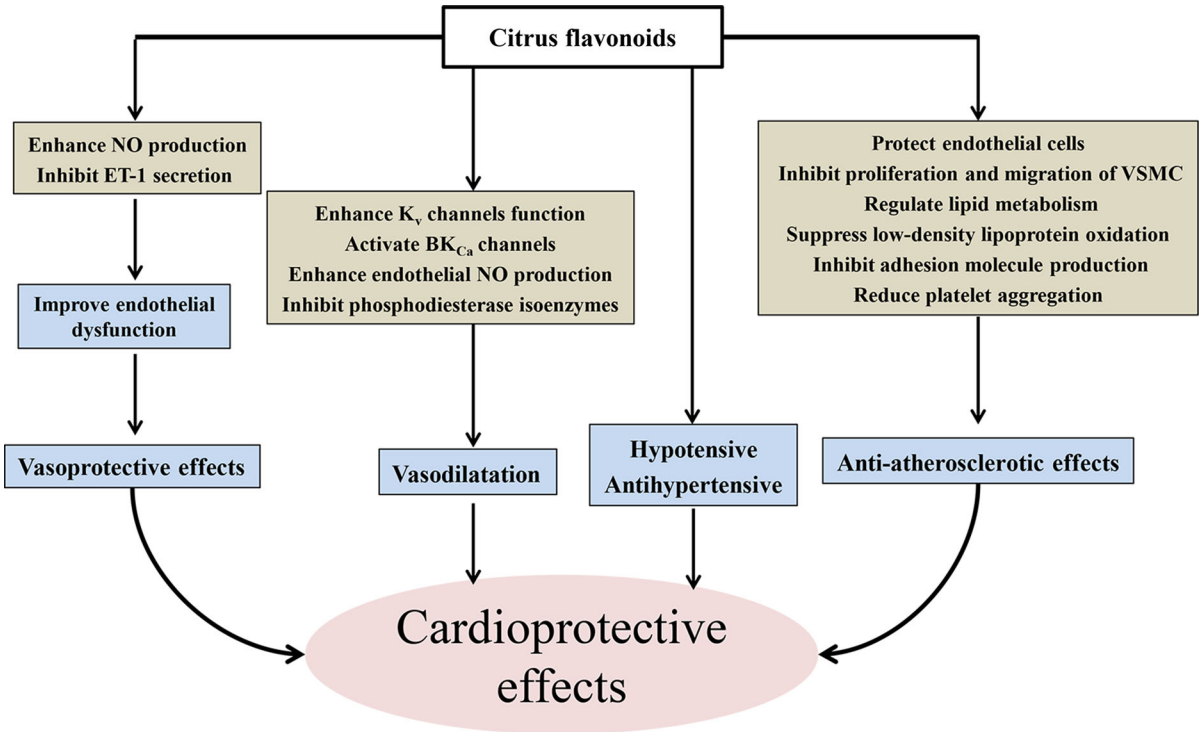

Fig. 4 An overview of the cardioprotective effects of *Citrus* flavonoids

atherosclerosis and have been reported to be up-regulated in the cells of atherosclerotic lesions (Blankenberg et al. 2003). Naringin (0.5 g/kg) could decrease the expression of ICAM-1 in endothelial cells, fatty streak formation, and neointimal macrophage infiltration in hypercholesterolemic rabbits (Choe et al. 2001). In high cholesterol-fed rabbits, the antiatherogenic effects of naringin (0.1%) and naringenin (0.05%) seems to be closely involved with a decreased hepatic ACAT activity and the down-regulation of VCAM-1 and MCP-1 genes (Lee et al. 2001). Naringin (0.2 g/kg) also prevented the adhesion of immune cells, their infiltration in the intima of the vascular wall, and subsequently, smooth muscle cell proliferation as observed in diet-induced hypercholesterolemic mice (Chanet et al. 2012b). In high glucose-induced HUVEC cultures, pretreatment with both naringin and hesperidin drastically inhibited ICAM-1 expression, but did not alter VCAM-1 and E-selectin expressions (Kim et al. 2011). Hesperidin and naringin reduced the ICAM-1 expression via the p38 MAPK signaling pathway, which contributed to the inhibition of monocyte adhesion to endothelial cells (Kim et al. 2011). Naringenin and hesperetin metabolites at physiologically relevant concentrations significantly reduced monocyte adhesion to TNF-α-stimulated endothelial cells by affecting the expression of related genes (Chanet et al. 2013). A recent study revealed that the anti-atherosclerotic effect of naringin was associated with reduced expressions of cell adhesion molecules, VCAM-1, ICAM-1 and E-selectin, and chemokines through NF-κB pathway (Hsueh et al. 2016). Also a recent clinical trial indicated that 6 weeks of hesperidin 2S supplementation in healthy, overweight individuals appeared to reduce circulating adhesion molecules and tended to lower both systolic and diastolic blood pressure (Salden et al. 2016).

Platelet aggregation is the critical event occurring during the initiation of atherosclerosis. Naringin (25 μM) was found to inhibit the transfer of an acetyl group from platelet-activating factor to lysophospholipids that prevented the activation of endothelial cells and, hence, retarded the development of an atherosclerotic plaque (Balestrieri et al. 2003). In hyperlipidemic rabbits, naringin inhibited platelet aggregation induced by arachidonic acid, adenosine diphosphate and collagen by reducing blood cholesterol levels and the

cytosolic free calcium concentration (Xiao et al. 2014). Through the inhibition of phospholipase C-γ2 phosphorylation, cyclooxygenase-1, and arachidonic acid-induced serotonin secretion, hesperetin potently inhibited collagen and arachidonic acid-induced platelet aggregation (Jin et al. 2007). Nobiletin inhibited collagen—and arachidonic acid—induced platelet aggregation in the washed human platelets, which may be associated with hydroxyl radical scavenge, inhibition of phospholipase C-γ2/PKC signaling, and suppression of MAPKs and Akt activation (Lu et al. 2016).

Conclusions and prospective

Numerous epidemiological studies have suggested an inverse relationship between increased consumption of *Citrus* fruits and lowered risk of chronic diseases. The extraordinary content of bioactive constituents seems to be responsible for the beneficial effects on human health. *Citrus* flavonoids, the major phytochemicals present in *Citrus* fruits, have shown a wide range of biological activities in various in vitro and in vivo studies. In this review, we highlighted the antioxidant, anti-inflammatory, anticancer, and cardioprotective activities of *Citrus* flavonoids. It was concluded that the antioxidant activity is the foundation of other biological activities, and that the bioavailability is a critical issue to be resolved for enhancing the biological efficacy of *Citrus* flavonoids. However, the role of *Citrus* flavonoids in human health is still an interesting area worth further exploration. Given the rapid advancement of separation and purification technologies, studies concerning more pure *Citrus* flavonoids and their biological activities will attract more and more attention in the future. Meanwhile, the biological activities of *Citrus* flavonoids mixture are worthy to investigate since the dietary form consumed in our daily life is complex food matrix containing several components. Moreover, in-depth studies need to be carried out to further explain and validate the molecular and cellular mechanisms of the biological activities of *Citrus* flavonoids as well as its metabolites in human body, especially the anticancer and cardioprotective effects. Significantly, further clinical studies in different populations using purified compounds should be performed to clarify the beneficial effects of *Citrus* flavonoids in humans.

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