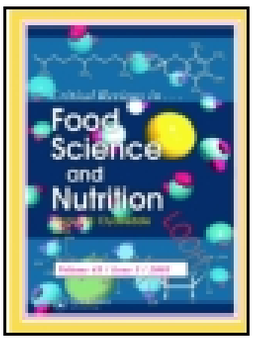

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Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Yue Wang , Xiao-Juan Liu , Jie-Biao Chen , Jin-Ping Cao , Xian Li & Chong-De Sun (2021): Citrus flavonoids and their antioxidant evaluation, Critical Reviews in Food Science and Nutrition

To link to this article: https://doi.org/10.1080/10408398.2020.1870035

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1870035

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REVIEW

Citrus flavonoids and their antioxidant evaluation

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ABSTRACT

The antioxidant ability is the link and bridge connecting a variety of biological activities. Citrus flavonoids play an essential role in regulating oxidative stress and are an important source of daily intake of antioxidant supplements. Many studies have shown that citrus flavonoids promote health through antioxidation. In this review, the biosynthesis, composition and distribution of citrus flavonoids were concluded. The detection methods of antioxidant capacity of citrus flavonoids were divided into four categories: chemical, cellular, animal and clinical antioxidant capacity evaluation systems. The modeling methods, applicable scenarios, and their relative merits were compared based on these four systems. The antioxidant functions of citrus flavonoids under different evaluation systems were also discussed, especially the regulation of the Nrf2-antioxidases pathway. Some shortcomings in the current research were pointed out, and some suggestions for progress were put forward.

KEYWORDS

Citrus; flavonoids; antioxidant; evaluation systems

Introduction

Citrus originated in the Himalayas region about 8 million years ago, which origin center may be the southwestern Yunnan in China and Assam area in India (Wu et al. 2018). The long natural evolution process and artificial selection formed various types of citrus, which had bred abundant citrus germplasm resources (Saunt 1990). At present, the citrus used for eating or processing mainly includes pomelos (*Citrus maxima*), sweet oranges (*Citrus sinensis*), sour oranges (*Citrus aurantium*), mandarins (*Citrus reticulata*), lemons (*Citrus limon*), limes (*Citrus aurantiifolia*), citrons (*Citrus medica*), grapefruits (*Citrus paradisi*), kumquat (*Citrus japonica*), and hybrids.

Flavonoids are an important class of natural products in citrus fruits. Their basic skeleton structure comprises 15 carbon atoms and contains two benzene rings (A ring and B ring) and one heterocycle (C ring). The substitution of different sites and quantities of hydroxyl, methoxy, glycosides and other functional groups on the basic skeleton of C6-C3-C6 constitutes a series of flavonoids with various types and isomers (Nogata et al. 2006).

Antioxidant ability, also known as oxidative stress resistance ability, is an important biological activity of citrus flavonoids. Simultaneously, the antioxidant capacity is also one of the internal mechanisms of citrus flavonoids exerting other biological activities. There have been reports of citrus flavonoids exerting biological activity functions such as inhibiting cancer development, inhibiting inflammation, controlling blood sugar and blood lipids, and inhibiting drugs' side effects of drugs through oxidative stress regulation (Bussmann et al. 2019; He et al. 2019; Jain et al. 2014; Lewinska et al. 2017).

According to the different carriers, the evaluation methods of citrus flavonoids antioxidant abilities could be divided into the following four types: chemical-based evaluation method (Da Pozzo et al. 2018), cellular-based evaluation method (Castro-Vazquez et al. 2016), animal-based evaluation method (Clavo et al. 2019), and clinical-based evaluation method (Salden et al. 2016). The four kinds of evaluation methods have their characteristics and application scenarios. In general, as the carrier system's complexity increased, the reliability of the research results also raised. Nevertheless, what followed was simultaneously climbing of the experimental difficulty and cost.

In this review, the biosynthesis pathway and the composition and distribution of citrus flavonoids were condensed. The characteristics of the antioxidant ability of citrus flavonoids under different evaluation systems were summarized. The mechanisms of citrus flavonoids in response to the threat of different oxidative stress were outlined. Suggestions on the selection of evaluation methods of antioxidant ability in the follow-up research were put forward.

Biosynthesis, composition and distribution of citrus flavonoids

According to the skeleton structure and B ring connection position, the flavonoids in citrus can be divided into the

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Supplemental data for this article is available online at https://doi.org/10.1080/10408398.2020.1870035.

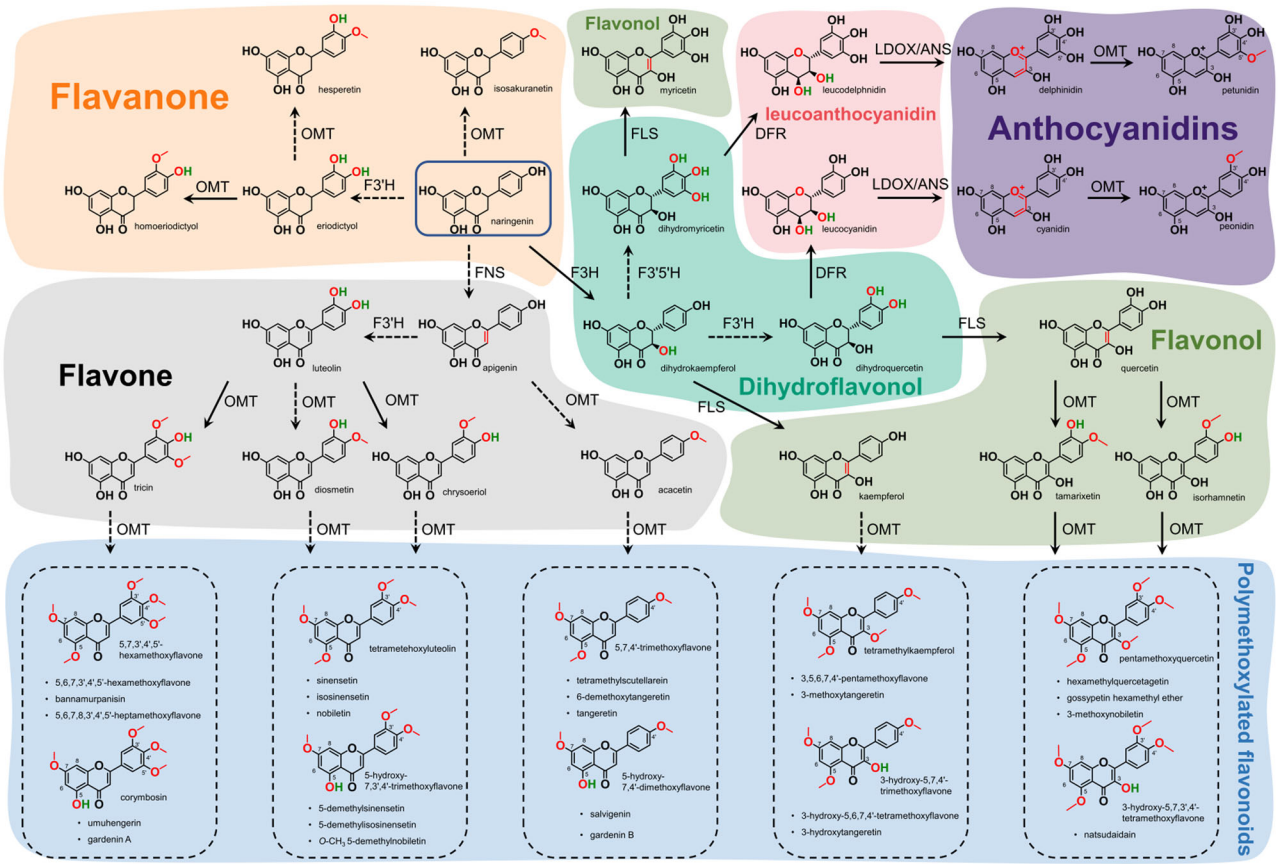

Figure 1. Biosynthesis pathway of citrus flavonoids.

following five categories: flavanones, flavones, flavonols, anthocyanins, and intermediate flavonoids including dihydroflavonols, isoflavones, and leucoanthocyanidins.

The biosynthesis of flavonoids in citrus fruits was generally started with 3 molecules of malonyl coenzyme A and 1 molecule of *p*-coumaroyl coenzyme A (Figure S1). Those starting substrates were decarboxylated and cyclized to naringenin chalcone under the catalysis of chalcone synthetase (CHS) (Austin and Noel 2003). Then the stereotactic cyclization took place under the action of chalcone isomerase (CHI) to form naringenin (Zhao et al. 2020). As shown in Figure 1, naringenin was converted into apigenin by flavone synthase (FNS) (Martens and Mithofer 2005), or transformed to dihydroflavonols under the catalysis of flavanone 3-hydroxylase (F3H) (Yonekura-Sakakibara, Higashi, and Nakabayashi 2019). Dihydroflavonols could further produce flavonols under the catalysis of flavonol synthase (FLS). Alternatively, in some special citrus varieties, the dihydroflavonols could be catalyzed to form leucoanthocyanidins under the action of dihydroflavonol 4-reductase (DFR) (Piero, Puglisi, and Petrone 2006). The leucoanthocyanidins were then converted to anthocyanidins through leucoanthocyanidin dioxygenase/anthocyanidin synthase (LDOX/ANS). Glycosyltransferases (GT) connect glycosides at specific sites of flavanone aglycone, flavone aglycone, or flavonol aglycone to form stable flavonoid glycoside structures (Wilson and Tian 2019) (Table 1). On the other hand, hydroxylases and *O*-methyltransferases (OMT) connected hydroxyl and methoxy groups to flavone aglycone or flavonol aglycone to form polymethoxylated flavonoids (Berim and Gang 2016; Liu et al. 2020a; Liu et al. 2020b).

Flavanones

Flavanones are a kind of flavonoid with high content in citrus. There are about 35 flavanones in 5 categories in citrus (Figure S2). Flavanones are converted from naringenin and generally have hydroxyl groups at positions 5 and 7 of A ring, and hydroxyl or methoxy substituents at 3′ or 4′ position of B ring. Flavanone glycosides are the products of the substitution of glycosides at position 7 of flavanone aglycone, usually in an *O*-glycoside mode (Table 1, Figure S2). The substituents of flavanone glycosides include glucoside, rhamnoside, rutinoside, and neohesperidoside.

Flavanone glycosides were distributed in both peel and pulp of citrus, but the content was higher in peel (Wang et al. 2017). Flavanone aglycones have variety-specific. There are different dominant aglycones in different citrus varieties, for example, the content of naringin glycoside is higher in pomelos, while the content of hesperidin glycosides is higher in oranges or tangerines (Proteggente et al. 2003; Zhao et al. 2017). The expression of glycoside ligands also has variety preference, most of the glycosides in grapefruit, pomelos and 'Ougan' (*Citrus reticulata* cv. *Suavissima*) are neohesperidosides (Wang et al. 2017), while oranges and 'Chachi' (*Citrus chachiensis* Hort.) are mostly rutinosides (Zheng et al. 2019).

Table 1. Common flavonoid glycosides in citrus.

Aglycon	-Rut (7-*O*)	-Nhp (7-*O*)	-Glu
Flavanones			
Naringenin	Narirutin	Naringin	
Eriodictyol	Eriocitrin	Neoeriocitrin	
Isosakuranetin	Didymin	Poncirin	
Hesperetin	Hesperidin	Neohesperidin	
Flavones			
Apigenin	Isorhoifolin	Rhoifolin	Vitexin (8-*C*) Vicenin-2 (6,8-*C*)
Diosmetin	Diosmin	Neodiosmin	
Anthocyanidins			
Cyanidin			Cyanidin-3-*O*-glucoside (3-*O*) Cyanidin-3-*O*-(6″-dioxalyl)-glucoside (3-*O*)

The number in parentheses after the substance represents the link site, and *O* or *C* represents the connection mode.

Flavones

The aglycones of flavone glycosides are more abundant than flavanones. In addition to the substituted modes of flavanone aglycones, there are also aglycones with substituents at 3′, 4′ and 5′ position of B ring (Figure S3).

More than 120 kinds of flavonoids have been detected in citrus, which can be divided into 6 categories. The types and substitution positions of flavone glycosides are also more diverse than those of flavanones. Glycosides can be substituted at positions 5, 6, 7, 8 on ring A and 3′ and 4′ on ring B. There are not only *O*-glycosides but also *C*-glycosides. The types of glycosides include rutinoside, neohesperidoside, glucoside, rhamnoside, arabinoside, and xyloside. Although flavone glycosides are more diverse than flavanone glycosides, the content of flavone glycosides in citrus is significantly lower than that of flavanone glycosides (Gattuso et al. 2006). The reason may be that flavones are converted into polymethoxylated flavonoids (PMFs) rather than being glycosylated.

PMFs are a type of unique flavonoids in citrus, divided into 5 categories according to the methoxy substitution position of B ring and whether there is a methoxy substituent in C ring (Figure S4). PMFs includes both apigenin-sourced flavones, and dihydrokaempferol-sourced dihydroflavonols. PMFs with no substituent in C ring can be divided into the following three types according to the methoxy substitution on B ring: single methoxy substitution at position 4′, represented by tangeretin (5,6,7,8,4′-pentamethoxyflavone); 3′ and 4′ methoxy substitution, represented by sinensetin (5,6,7,3′,4′-pentamethoxyflavone), isosinensetin (5,7,8,3′,4′-pentamethoxyflavone) and nobiletin (5,6,7,8,3′,4′-hexamethoxyflavone); 3′, 4′ and 5′ methoxy substitution, which the content is less in citrus, the representative substances is 5,6,7,8,3′,4′,5′-heptamethoxyflavone. The PMFs, with methoxy substitution in C ring, could also be divided into two types: single methoxy substitution at 4′ position and 3′ and 4′ dimethoxy substitution. In addition to the methoxy group, the substituent of PMFs is often accompanied by hydroxyl substitution at position 5. The representative substances are 5-demethylnobiletin (5-hydroxy-6,7,8,3′,4′-pentamethoxyflavone) and 5-demethylsinensetin (5-hydroxy-6,7,3′,4′-tetramethoxyflavone). The distribution of PMFs in citrus fruit has tissue specificity and variety specificity. PMFs is concentrated in the flavedo of oranges, tangerines, mandarins, lemons and limes. In contrast, the PMFs content is shallow in the albedo, segment membrane and juice sacs of citrus fruits, and in the whole fruits of pomelos and grapefruits (Wang et al. 2017). It has been found that PMFs has low polarity and low water solubility, but it has strong cell membrane permeability and can penetrate the blood-brain barrier (Saigusa et al. 2011).

Flavonols

Compared with flavone and flavanone aglycone, the main feature of flavonol aglycone is the existence of a hydroxyl group at position 3 in C ring (Figure S5). The four main flavonol glycosides were kaempferol, quercetin, limocitrin, and isorhamnetin. Unlike flavones and flavanones, flavonol glycosides are substituted at position 7 of ring A and position 3 of ring C, and the main mode of substitution is *O*-glycoside. The content of flavonol glycosides in citrus is low, and it has tissue and variety specificity. For example, astragalin (3,5,7,4′-tetrahydroxyflavone-3-*O*-glucoside) and trifolin (3,5,7,4′-tetrahydroxyflavone-3-*O*-galactoside) were only identified in citrus flowers (Miyashita et al. 2018). Limocitrin-3-*O*-glucoside (3,5,7,4′-tetrahydroxy-8,3′-dimethoxyflvaone-3-*O*-glucoside) and isorhamnetin-3,7-di-*O*-glucoside (3,5,7,4′-tetrahydroxy-3′-methoxyflavone-3,7-di-*O*-glucoside) exist only in finger lime (*Citrus australasica*) originating from Australia (Wang et al. 2019).

Anthocyanins

Anthocyanins are flavylium cation derivatives with chromogenic properties in citrus, and the structure of its C ring is different from that of other citrus flavonoids (Figure S6). In previous studies, four anthocyanidins and various anthocyanins substituted by rutinoside, glucoside, rhamnoside and sophoroside were identified. Among them, the most abundant anthocyanins were cyanidin-3-*O*-glucoside and cyanidin-3-*O*-(6″-dioxalyl)-glucoside (Sommella et al. 2017). The distribution of anthocyanins is also variety-specific, which is commonly found in orange fruits with red flesh (Proteggente et al. 2003) and some unique grapefruit fruits (Huang et al. 2018).

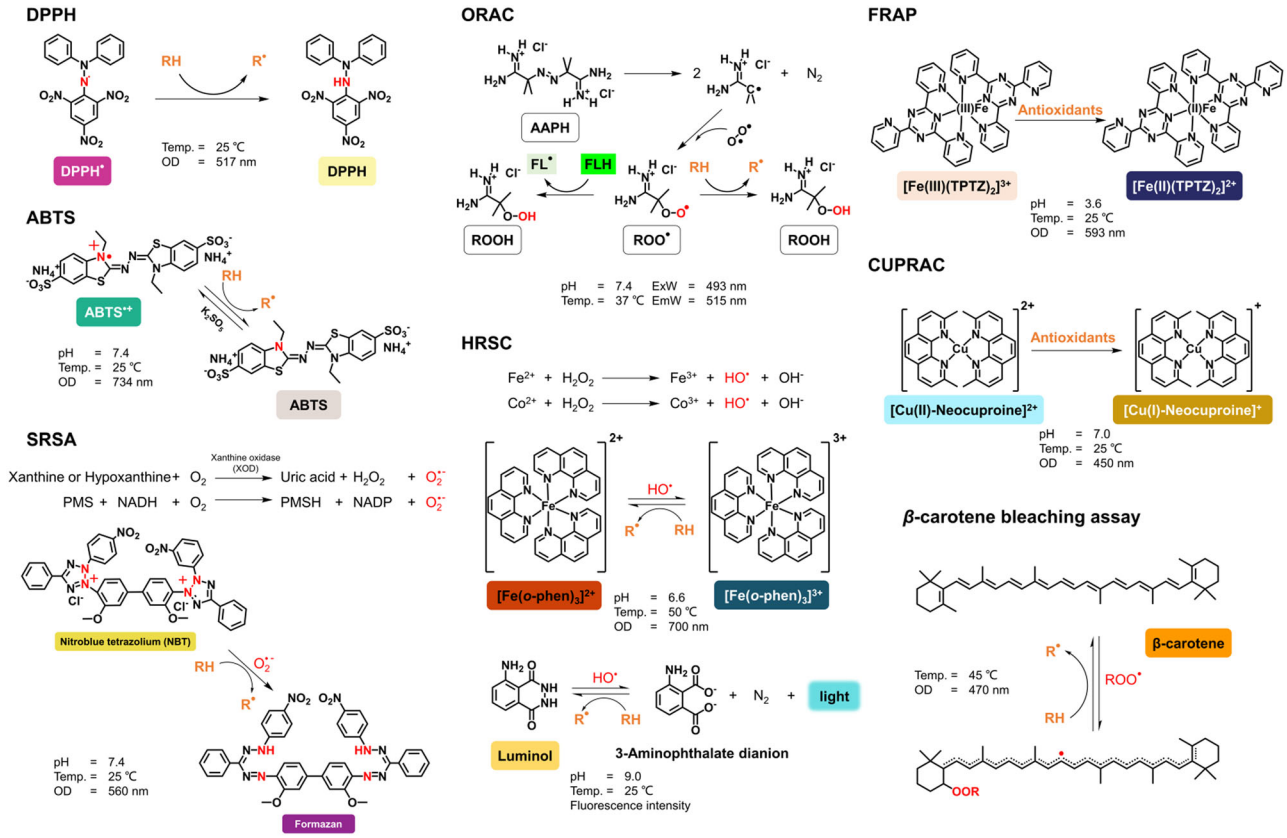

Figure 2. Methods for chemical antioxidant evaluation of citrus flavonoids.

Intermediate flavonoids

The species of intermediate flavonoids including isoflavones, dihydroflavonols, and leucoanthocyanidins in citrus are very few and the distribution abundance is very low. Among dihydroflavonols, only aromadendrin (3,5,7,4′-tetrahydroxyflavanone) and taxifolin (3,5,7,3′,4′-pentahydroxyflavanone) were found in oranges (Doostdar et al. 1995), while dihydroisorhamnetin (3,5,7,4′-tetrahydroxy-3′-methoxyflavanone) was identified in the metabonomic analysis of 'Shatangju' mandarin (*Citrus reticulata* Blanco) (Wang et al. 2020). For isoflavones, genistein (5,7,4′-trihydroxyisoflavone) was found in 'Shatangju' and 'CaraCara', while orobol (5,7,3′,4′-tetrahydroxyisoflavone) was only found in 'Shatangju' (Lu et al. 2018; Wang et al. 2020).

Antioxidant evaluation of citrus flavonoids in different systems

Chemical-based antioxidant abilities of citrus flavonoids

The chemical-based antioxidant evaluation was generally based on the redox reaction, using chemical reagents to model the free radicals or other oxides. After reacting with the test samples, the free radical scavenging or metal ion reduction abilities of the samples were calculated according to the number of products or substrates detected by color reaction or fluorescence (Figure 2).

The previously reported methods for evaluating the chemical antioxidant capacity of citrus flavonoids mainly include the following three categories: evaluation of free radical scavenging ability, evaluation of metal ion reduction ability and evaluation of lipid peroxy radical scavenging ability.

Free radical scavenging ability methods

Methods for evaluation of free radical scavenging ability mainly include 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay (DPPH) (Wang et al. 2017), 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical scavenging assay (ABTS) (Tarozzi et al. 2006), superoxide radical scavenging activity (SRSA) (Barreca et al. 2010), oxygen radical absorbance capacity (ORAC) (Yoo et al. 2009), and hydroxyl radical scavenging capacity (HRSC) (Yu et al. 2015). Among these methods, the free radicals of DPPH and ABTS were added directly, while the other three methods produced free radicals through the reactions in the system. The reaction condition of ORAC method is pH 7.4 and the temperature is 37 °C, which is close to that of body fluids. The reaction temperatures of DPPH and ABTS are mostly 25 °C, close to the room temperature. The pH of two detection HRSC methods are 6.6 and 9.0, which may lead to deviation in the test of substances sensitive to pH conditions.

Ion reduction ability methods

The principle of metal ion reduction ability is that antioxidants can change the valence of ions in metal ion complexes, which changes the color of the original metal ion complexes. The degree of valence change of metal ionization can be determined by optical density, which can be used to express the reducing ability of metal ions of antioxidants. The two conventional methods for evaluating the metal ion

reduction ability of citrus flavonoids are ferric ion reducing antioxidant power (FRAP) (Gonzalez-Molina, Moreno, and Garcia-Viguera 2008) and cupric ion reducing antioxidant capacity (CUPRAC) (Papoutsis et al. 2016). The main difference between the two reaction systems is pH, FRAP needs an acidic environment, while CUPRAC is more suitable for a neutral environment.

β-carotene bleaching assay

The principle of β-carotene bleaching assay is based on the breaking of π conjugation due to the addition reaction of lipid peroxy radicals and carbon-carbon double bond of β-carotene (Loizzo et al. 2012). This leads to the discoloration of β-carotene solution. Free radicals are produced by self-oxidation of heated linoleic acid. The antioxidants added to the system compete with β-carotene for free radicals, thus retarding the discoloration of the β-carotene solution.

Applications of chemical-based antioxidant ability evaluation

Under the chemical evaluation system, the experiment has the advantages of simple operation, fast reaction and sensitive response. Therefore, it was often used in rapid screening of antioxidant activity of citrus extract or fruit juice (Table 2), or preliminary detection of the activity of natural products. Previous studies have found differences in antioxidant capacity among different citrus varieties (Da Pozzo et al. 2018) and different tissue parts (Xi et al. 2017). Planting mode, such as organic cultivation (Tarozzi et al. 2006) and harvest time (Gonzalez-Molina, Moreno, and Garcia-Viguera 2008), would affect the fruit quality and maturity, which could be reflected in citrus' antioxidant capacity. When citrus flavonoids were not consumed directly, they need to be further processed and preserved. Processing techniques such as drying method, drying time (Lou et al. 2015) and drying temperature (Castro-Vazquez et al. 2016) would also affect the antioxidant capacity of citrus. In addition, during the evaluation, the extraction method (Butryee, Sungpuag, and Chitchumroonchokchai 2009) and extraction solvent (Karimi et al. 2012) could also affect the antioxidant activity of the samples.

Cellular-based antioxidant abilities of citrus flavonoids

Cellular-based antioxidant evaluation refers to using in vitro cultured cells as carriers to evaluate flavonoids' protective effects on cells under oxidative stress. Compared with chemical methods, the cellular model considered the interaction between the carrier cells' antioxidant system and the exogenous antioxidants. The binary relationship between "antioxidant" and "oxidant" was changed to the ternary relationship among "antioxidant" - "cell" - "oxidative stress", which made the evaluation more reasonable.

In this ternary relationship, antioxidants mainly exert four functions: (a) Binding effect: antioxidants directly bind free radicals to eliminate oxidative stress. (b) Blocking effect: antioxidants prevent the occurrence of cell damage by blocking reactive oxygen species (ROS) signal transmission. (c) Inducing effect: antioxidants induce cell resistance by regulating antioxidant enzymes and other cellular active substances. (d) Repairing effect: antioxidants repair the cells after oxidative damage has occurred (Sies, Berndt, and Jones 2017).

Cellular oxidative stress detection indicators

There are mainly the following indicators to evaluate cellular-based antioxidant abilities of citrus flavonoids. Cell viability assay: it was mainly used to reflect the harm of high dose ROS to the whole cell, and it can also be supplemented by the determination of apoptosis state and cell cycle state (Shukla et al. 2018). Determination of cellular ROS. ROS could be captured by probe and then visually observed by fluorescence microscopy or flow cytometry (Hwang and Yen 2008). Determination of cellular antioxidant enzymes. The antioxidant capacity of cells could be judged by measuring the activity, gene expression and protein expression of specific antioxidase in cells (Kulasekaran and Ganapasam 2015). Evaluation of organelle function, mainly for the determination of mitochondrial function. The functional status of mitochondria could be judged by measuring the mitochondrial membrane potential and the fluidity of Ca^{2+} ions (Hwang and Yen 2008).

Cellular oxidative stress modeling agent

Under the evaluation of the cellular oxidative stress model, hydrogen peroxide (H_2O_2) was the most commonly used oxidative stress modeling agent (Da Pozzo et al. 2017; Kanno et al. 2003; Liu and Wu 2018; Lu et al. 2010; Su et al. 2012; Wijesinghe et al. 2011; Yoo et al. 2009). H_2O_2 is a small molecular substance that can directly penetrate the cell membrane and produce hydroxyl radicals during decomposition, triggering free radical chain reactions, causing damage to a variety of substructures in cells (Hwang and Yen 2008; Hwang and Yen 2009). In addition, other reagents used for oxidative stress modeling were as follows: neurotoxic reagents amyloid β-protein (Aβ) (Cho 2006; Curro et al. 2016; Heo et al. 2004), inflammation inducer lipopolysaccharide (LPS) (Guo et al. 2018; He et al. 2019; Lee et al. 2016; Liu and Wu 2018; Risitano et al. 2014) and high glucose (Chen et al. 2014a; Chen et al. 2014b; Liu et al. 2017a; Shukla et al. 2018), oxidative damage toxic reagents *tert*-butyl hydroperoxide (*t*-BHP) (Johnson, Maher, and Hanneken 2009; Liang et al. 2018; Shaik, Zbidah, and Lang 2012; Yang et al. 2020), Ca^{2+} influx inducer ionomycin, carcinogenic reagents phorbol myristate acetate (PMA) (Ali et al. 2019; Zielinska-Przyjemska and Ignatowicz 2008), environmental toxins, including heavy metal Cadmium (Cd) (Yilmaz et al. 2012) and ultraviolet (UV) (Cimino et al. 2007; Li et al. 2016; Yoon et al. 2011).

Table 2. Chemical antioxidant ability evaluations of citrus extracts.

Methods/ Citrus extracts	Antioxidant abilities	Influencing factors	References
DPPH			
Orange peel extracts	18 – 131 mg GA/ mg extracts	Extract fraction	(Manthey 2004)
Lemon juice	2.35 – 5.09 mM Trolox	Genotype; Harvest time; Planting year	(Gonzalez-Molina, Moreno, and Garcia-Viguera 2008)
Citrus hystrix leaf extracts	11 – 64% RSA/ 8 mg DW	Extraction method; Extraction solvent	(Butryee, Sungpuag, and Chitchumroonchokchai 2009)
Different citrus extracts	0.6 – 3.9 mg/mL (IC_{50})	Variety; Fruit tissue	(Ghasemi, Ghasemi, and Ebrahimzadeh 2009)
Orange peel extracts	0.12 – 12.13 mg/mL (EC_{50})	Extract fraction	(Kanaze et al. 2009)
Citrus myrtifolia Raf. fruit juice	8.9 – 13.1 μM Trolox	Mature stage	(Barreca et al. 2010)
Citrus limetta Risso fruit juice	261 ± 9 μM Trolox/ 1 mL extract	\	(Barreca et al. 2011)
Clementine fruits juice	6.77 – 26.48 mg RE/ mL Juice (IC_{50})	Cultivar	(Milella et al. 2011)
Citrus aurantium petals extracts	50.46 – 55.32% RSA/ 1 mL extracts	Extraction solvent	(Karimi et al. 2012)
Citrus flavonoid extracts	58.4 – 283.3 mg/L (EC_{50})	Variety	(Kim et al. 2012)
Citrus aurantifolia peel and leaves extracts	75. 4 – 162.3 mg/L (IC_{50})	Tissue; Extraction solvent	(Loizzo et al. 2012)
Citrus grandis Osbeck extracts	29.31 – 58.13% RSA/50 μL	Variety; Fruit tissue	(Xi et al. 2014)
Citrus reticulata Blanco extracts	29.04 – 50.46 μM TEAC/ g DW	Cultivar	(Zhang et al. 2014)
Immature kumquat extracts	12.07 – 34.64% RSA/ (mg/mL sample)	Drying time; Drying temperature	(Lou et al. 2015)
Grape fruit extracts	11.52 – 83.87% RSA/50 μL	Variety; Fruit tissue	(Xi et al. 2015)
Citrus grandis Osbeck extracts	444.45 – 836.81 mg/L (EC_{50})	Maturity; Tissue	(Yu et al. 2015)
Citrus extracts	0.4 – 10.4 mg dry extracts/ 10 mL (IC_{50})	Cultivar; Extraction solvent	(Assefa et al. 2016)
Grape fruit peel extracts	25.18 – 122.83 mg TEAC/ g DW	Cultivar; Drying temperature	(Castro-Vazquez et al. 2016)
Lemon waste extracts	0.02 – 0.15 mg TEAC/ g DW	Extraction solvent	(Papoutsis et al. 2016)
Citrus extracts	0.51 – 0.68 mg/L (IC_{50})	Variety	(Chen, Tait, and Kitts 2017)
Orange peel extracts	333.76 – 568.39 μg/mL (IC_{50})	Variety	(Sommella et al. 2017)
Lemon extracts	0.22 – 8.20 RE/ g FW	Cultivar; Tissue	(Xi et al. 2017)
Orange peel extracts	11.61 – 18.20 TEAC/ g DW	Extraction solvent	(Liew et al. 2018)
Citrus aurantium flower extracts	96.07 – 393.71 μg/mL (IC_{50})	Extraction solvent	(Degirmenci and Erkurt 2019)
ABTS			
Red orange extracts	669 – 741 μmol TEAC/ 100 g edible pulp	Planting mode	(Tarozzi et al. 2006)
Lemon juice	2.33 – 4.15 mM Trolox	Genotype; Harvest time; Planting year	(Gonzalez-Molina, Moreno, and Garcia-Viguera 2008)
Citrus flavedo extracts	11.0 – 46.1 umol TEAC/ g FW	Cultivar	(Ramful et al. 2010)
Citrus limetta Risso fruit juice	1446 ± 30 μM Trolox/1 mL extract	\	(Barreca et al. 2011)
Citrus flavonoid extracts	132.2 – 261.1 mg/L (EC_{50})	Variety	(Kim et al. 2012)
Citrus aurantifolia peel and leaves extracts	18.7 – 91.6 TEAC values	Tissue; Extraction solvent	(Loizzo et al. 2012)
Citrus reticulata Blanco extracts	65.62 – 108.60 μM TEAC/ g DW	Cultivar	(Zhang et al. 2014)
Grape fruit extracts	1.50 – 7.99 mM VC/ g DW	Variety; Fruit tissue	(Xi et al. 2015)
Citrus grandis Osbeck extracts	137.91 – 851.50 mg/L (EC_{50})	Maturity; Tissue	(Yu et al. 2015)
Grape fruit peel extracts	99.46 – 537.48 mg TEAC/ g DW	Cultivar; Drying temperature	(Castro-Vazquez et al. 2016)
Lemon waste extracts	0.27 – 0.46 mg TEAC/ g DW	Extraction solvent	(Papoutsis et al. 2016)
Citrus extracts	189.5 – 256.2 μM TEAC/ g DW	Variety	(Chen, Tait, and Kitts 2017)
Lemon extracts	0.42 – 14.40 RE/ g FW	Cultivar; Tissue	(Xi et al. 2017)
SRSA			
Citrus extracts	Inhibition rate of 2 – 53%/ 500 μg/ mL sample	Variety; Tissue	(Murakami et al. 2000a)
Orange peel extracts	20.5 – 86.4 ppm (IC_{50})	Flavonoid fraction	(Manthey 2004)
Citrus extracts	18.66 – 40.44 mg/L (IC_{50})	Variety; Tissue	(Yoo et al. 2009)
Citrus myrtifolia Raf. fruit juice	144 – 184 μM Trolox	Mature stage	(Barreca et al. 2010)
Citrus grandis Osbeck. extracts	30.55 – 50.31%	Variety; Fruit tissue	(Xi et al. 2014)
Citrus bergamot juice	1.01 – 4.77 mg/mL (IC_{50})	Cultivar	(Da Pozzo et al. 2018)
ORAC			
Citrus hystrix leaf extracts	105.11 – 680.21 μM TEAC / g DW	Extraction method; Extraction solvent	(Butryee, Sungpuag, and Chitchumroonchokchai 2009)
Citrus extracts	227.1 – 1221.1 μmol TEAC/g FW	Variety; Tissue	(Yoo et al. 2009)
Citrus reticulata Blanco extracts	395.66 – 834.37 μM TEAC/ g DW	Cultivar	(Zhang et al. 2014)
Citrus extracts	1033.8 – 1331.7 μM TEAC/ g DW	Variety	(Chen, Tait, and Kitts 2017)
Orange peel extracts	0.31 – 0.92 mol TEAC/ g DW	Extraction solvent	(Liew et al. 2018)
HRSC			
Orange peel extracts (Co(II)/EDTA-Luminol)	0.02 – 0.30 mg/mL (IC_{50})	Extract fraction	(Kanaze et al. 2009)
Citrus flavonoid extracts (Reducing power)	28.1 – 112.5 OD_{700} value (sample concentration 0.1)	Variety	(Kim et al. 2012)
Citrus grandis Osbeck extracts (Reducing power)	571.67 – 883.3 OD_{700} value (sample concentration 0.3)	Maturity; Tissue	(Yu et al. 2015)

(*continued*)

Table 2. Continued.

Methods/ Citrus extracts	Antioxidant abilities	Influencing factors	References
FRAP			
Lemon juice	2.63 – 4.65 mM Trolox	Genotype; Harvest time; Planting year	(Gonzalez-Molina, Moreno, and Garcia-Viguera 2008)
Citrus hystrix leaf extracts	7.20 – 115.63 μmol Fe^{2+}/ g DW	Extraction method; Extraction solvent	(Butryee, Sungpuag, and Chitchumroonchokchai 2009)
Citrus flavedo extracts	14 – 81.3 umol TEAC/ g FW	Cultivar	(Ramful et al. 2010)
Citrus limetta Risso fruit juice	318 ± 8 μM Trolox/1 mL extract	\	(Barreca et al. 2011)
Citrus aurantium petals extracts	43.5 – 51.7% reductive potential/ 1 mL extracts	Extraction solvent	(Karimi et al. 2012)
Citrus aurantifolia peel and leaves extracts	112.1 – 205.4 μM Fe^{2+}/ 1 g extract	Tissue; Extraction solvent	(Loizzo et al. 2012)
Citrus grandis Osbeck. extracts	0.87 – 1.76 mM	Variety; Fruit tissue	(Xi et al. 2014)
Citrus reticulata Blanco extracts	26.50 – 46.98 μM TEAC/ g DW	Cultivar	(Zhang et al. 2014)
Grape fruit extracts	0.35 – 6.52 mM	Variety; Fruit tissue	(Xi et al. 2015)
Citrus extracts	19.4 – 185.2 mg TEAC/ g DW	Cultivar; Extraction solvent	(Assefa et al. 2016)
Grape fruit peel extracts	44.82 – 207.74 mg TEAC/ g DW	Cultivar; Drying temperature	(Castro-Vazquez et al. 2016)
Lemon extracts	0.07 – 6.60 RE/ g FW	Cultivar; Tissue	(Xi et al. 2017)
Citrus bergamot juice	6.85 – 9.83 mg TEAC/g DW	Cultivar	(Da Pozzo et al. 2018)
Orange peel extracts	139.94 – 296.61 mmol Fe^{2+}/ g DW	Extraction solvent	(Liew et al. 2018)
CUPRAC			
Citrus extracts	16.1 – 208.7 mg TEAC/ g DW	Cultivar; Extraction solvent	(Assefa et al. 2016)
Lemon waste extracts	10 – 57 mg TEAC/ g DW	Extraction solvent	(Papoutsis et al. 2016)
β-carotene bleaching assay			
Citrus aurantifolia peel and leaves extracts	8.5 – 31.5 mg/L (30 min, IC_{50}) 12.4 – 52.9 mg/L (60 min, IC_{50})	Tissue; Extraction solvent	(Loizzo et al. 2012)

GA: gallic acid; %RSA: percentage of DPPH radical scavenging activity; DW: dried weight (of samples); FW: fresh weight (of samples); IC_{50}: half maximal inhibitory concentration; EC_{50}: concentration for 50% of maximal effect; RE: rutin equivalents; TEAC: Trolox equivalent antioxidant capacity.

Alleviating effect of citrus flavonoids on cellular oxidative stress

Studies on cellular antioxidant capacity of citrus flavonoids mainly focused on flavanones and flavones, including didymin (Ali et al. 2019; Shukla et al. 2018), eriodictyol (He et al. 2019; Johnson, Maher, and Hanneken 2009; Lee et al. 2015), hesperetin (Hwang and Yen 2008; Liu et al. 2017b), hesperidin (Cho 2006; Li et al. 2016), naringenin (Da Pozzo et al. 2017; Zielinska-Przyjemska and Ignatowicz 2008), naringin (Chen et al. 2014a; Kulasekaran and Ganapasam 2015), neohesperidin (Hwang and Yen 2008), nobiletin (Jayakumar et al. 2017; Liu and Wu 2018), tangeretin (Lee et al. 2016; Liang et al. 2018), and diosmetin (Poor et al. 2014). Citrus flavonoids inhibited the production and accumulation of ROS (Ali et al. 2019; Liu and Wu 2018), inhibited lipid peroxidation (He et al. 2019; Li et al. 2016), and induced the activities of antioxidant enzymes including glutathione peroxidase (GSH-Px) (Hwang and Yen 2008), glutathione reductase (GR) (Kulasekaran and Ganapasam 2015), catalase (CAT) (Hwang and Yen 2009), superoxide dismutase (SOD) (Liu et al. 2017b) and so on. By relieving oxidative stress, citrus flavonoids also inhibited ROS-induced DNA damage (Da Pozzo et al. 2017; Hwang and Yen 2008; Kanno et al. 2003; Yilmaz et al. 2012), prevented Ca^{2+} influx (Hwang and Yen 2009; Shaik, Zbidah, and Lang 2012), reduced the content of cytochrome c in the cytoplasm and increased the membrane potential of mitochondria (Liu et al. 2017a; Liu et al. 2017b). As a result, the proportion of apoptotic cell decreased (Chen et al. 2014a; Liu et al. 2017b; Shukla et al. 2018), the cell cycle transited smoothly (Da Pozzo et al. 2017) and the cell viability improved (Cho 2006; Liu and Wu 2018; Shukla et al. 2018). Citrus extracts, including bergamot peel extract (Curro et al. 2016; Risitano et al. 2014; Trombetta et al. 2010) or citrus juice (Murakami et al. 2000a), also showed the cellular antioxidant abilities, including enhancing cell vitality, inhibiting lipid peroxidation, promoting the expression of cell antioxidant enzymes.

Regulation of Nrf2-Keap1 pathway by citrus flavonoids

Citrus flavonoids regulated the cellular-antioxidant ability mainly through the Nrf2-Keap1 pathway (Figure 3). Nuclear factor erythroid 2-related factor 2 (Nrf2) is a basic leucine zipper protein (bZIP) and is also a transcriptional factor regulating oxidative stress (Ge et al. 2017; Ishii et al. 2000). Under the silent situation, Nrf2 was located in the cytoplasm, binds to Kelch-like ECH-related protein 1 (Keap1) (Kang et al. 2004), and was degraded by ubiquitin ligase Cullin 3 (Cul3) (Kobayashi et al. 2004). When cells were subjected to oxidative stress, Nrf2 dissociated from Keap1 and transferred to the nucleus. Nrf2 then interacted with other bZIP proteins to form a heterodimer, which bound to the antioxidant response element (ARE) (Nioi et al. 2003). ARE activated the expression of antioxidant enzymes, including CAT, SOD, nicotinamide adenine dinucleotide phosphate (NADPH) quinone oxidoreductase 1 (NQO1), glutamate-cysteine ligase catalytic subunit (GCLC), glutamate-cysteine ligase regulatory subunit (GCLM), heme oxygenase-1 (HO-1) (Kwak, Wakabayashi, and Kensler 2004). The regulation of citrus flavonoids on the Nrf2-Keap1 pathway was mainly to promote the expression of Nrf2 and nuclear transport (Ali et al. 2019; He et al. 2019; Johnson, Maher, and Hanneken 2009; Kulasekaran and Ganapasam 2015), promote the expression of *ARE* (Lee et al. 2015; Lee

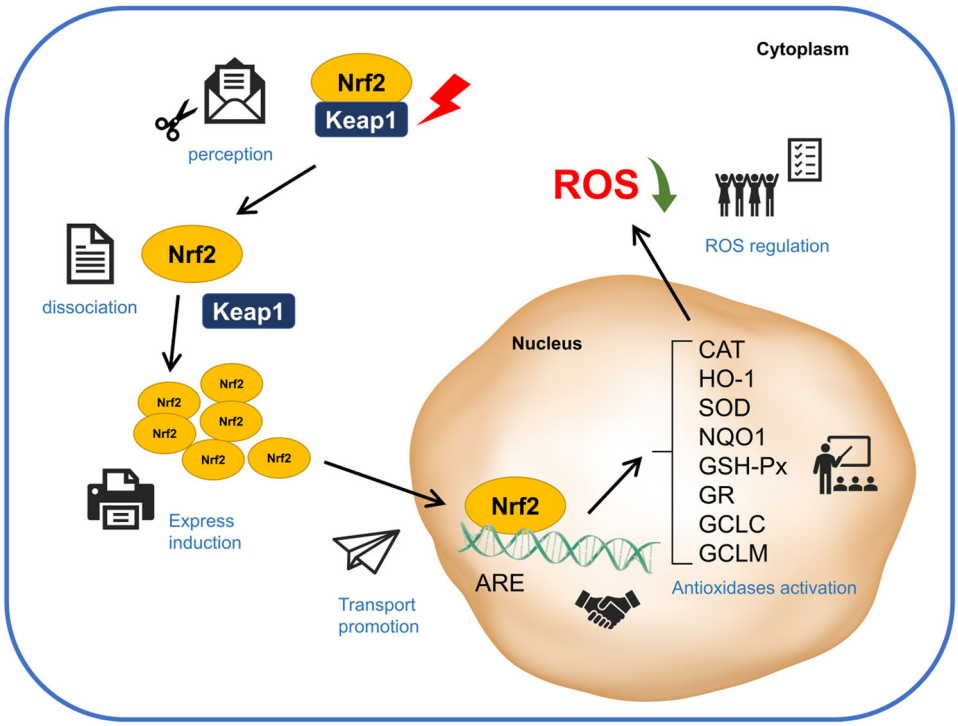

Figure 3. Regulatory effect of citrus flavonoids on antioxidation pathway.

et al. 2016; Liang et al. 2018) and inhibit the expression of Keap1 (He et al. 2019).

The other side of the coin, the activation of citrus flavonoids on oxidative stress

It is worth noting that the oxidative stress regulation of citrus flavonoids is a double-edged sword, which needs to be discussed on a case-by-case basis. On the one hand, as we described earlier, flavonoids could protect cells from oxidative stress-induced cell damage. On the other hand, under different cell lines and different treatment doses, especially in the tumor cell lines, citrus flavonoids could induce ROS production, thus inhibiting the excessive proliferation of cells. For example, in prostate cancer cell line PC3, naringin inhibited cell viability and cell migration by inducing ROS production and induced apoptosis by increasing the proportion of Bax/Bcl-2 (Lim et al. 2017). Diosmin inhibited the excessive proliferation of three kinds of breast cancer cells MCF-7, MDA-MB-231 and SK-BR-3 through ROS-mediated cell cycle arrest and apoptosis (Lewinska et al. 2017). In some harmful cell proliferation processes caused by internal inducers, such as the excessive proliferation of vascular smooth muscle cells (VSMCs) induced by platelet-derived growth factor-BB (PDGF-BB) or angiotensin II, naringenin and nobiletin could reduce cell viability and cell mobility by inhibiting the production of ROS and the activation of NF-κB (Guan et al. 2014; Xu et al. 2013).

In summary, citrus flavonoids could regulate cellular oxidative from multiple levels. Interestingly, citrus flavonoids exhibited a "big vision", which could regulate cellular oxidative stress positively or negatively from an overall point of view, and maintain the health of the organism.

Animal-based antioxidant abilities of citrus flavonoids

Compared with the cellular model, the animal-based antioxidant evaluation system is more systematic. The study object changed from relatively a single cell population to tissues, organs, and even the whole biological individual. The change of the study object was helpful to test the response of antioxidants to oxidative stress in the complex system and contributed to verify the interaction between antioxidants and the characterization of the biological disease model. In terms of the selection of animal model, rats and mice were most commonly used, and there were reports about the antioxidant activity of citrus flavonoids in fruit flies (Abolaji et al. 2017) and rabbits (Jeon et al. 2001; Jeon et al. 2002).

Oxidative stress detection indicators in animal models

Under the evaluation of in vivo model, the detection indexes of antioxidant ability are more diversified. In addition to ROS content and antioxidant enzyme expression detection, animal safety indicators, health indicators and specific disease-related markers were also carried out in the detection. For example, in the hypertension model, blood pressure could be measured to observe the effect of flavonoids on blood pressure recovery by inhibiting ROS (Wunpathe et al. 2018). In the diabetic model, blood glucose index and insulin content could also reflect the inhibition of citrus flavonoids on the incidence of diabetes (Wojnar, Zych, and Kaczmarczyk-Sedlak 2018). In the osteoporosis model, bone mineral density and other related indicators could show the effect of flavonoids on bone health (Morrow et al. 2009). Besides, body weight, organ weight, organ index, and food intake also explained the health situation of mice.

In vivo *oxidative stress modeling methods*

The in vivo oxidative stress model mainly includes the pathological models, the toxicological models, and the physiological models (Figure 4). The pathological models include disease models such as hypertension (Wunpathe et al. 2018), spinal cord injury (Heo et al. 2020), ischemia-reperfusion (Bayomy et al. 2014), diabetes (Samie et al. 2018), Alzheimer's disease (Nakajima et al. 2015), osteoporosis (Morrow et al. 2009). Drugs that can cause side effects of oxidative stress include cisplatin (Kamisli et al. 2015), isoproterenol (Al-Yahya et al. 2013), zymosan (Bussmann et al. 2019), kainic acid (Golechha et al. 2011), daunorubicin (Carino-Cortes et al. 2010), doxorubicin (Abdel-Raheem and Abdel-Ghany 2009). The toxicological models include reagents harmful to health, such as LPS (He et al. 2019; Kaur, Tirkey, and Chopra 2006; Khajevand-Khazaei et al. 2018; Muhammad et al. 2019), arsenic trioxide (As_2O_3) (Mershiba, Dassprakash, and Saraswathy 2013; Roy et al. 2014; Xie et al. 2017), 2,4,6-trinitrobenzene sulfonic acid (TNBS) (Xiong et al. 2018), sodium fluoride (NaF) (Nkpaa and Onyeso 2018), methylmercury (Krishna Chandran et al. 2019). Mutagens such as radiation (Pradeep, Park, and Ko 2008; Pradeep et al. 2012; Said et al. 2012), carbon tetrachloride (CCl_4) (Esmaeili and Alilou 2014; Hermenean et al. 2014; Kim et al. 2016; Tirkey et al. 2005), 2,2′-Bis(hydroxymethyl)butyric acid (DMBA) (Lakshmi and Subramanian 2014a; Lakshmi and Subramanian 2014b), Benzoapyrene (BaP) (Arafa et al. 2009; Bodduluru et al. 2016; Islam et al. 2020; Kamaraj et al. 2009), and 12-*O*-tetradecanoylphorbol-13-acetate (TPA) (Murakami et al. 2000a; Murakami et al. 2000b). Heavy metal pollution, such as cadmium (Agir and Eraslan 2019; Pari and Shagirtha 2012; Prabu, Shagirtha, and Renugadevi 2011; Qu et al. 2018; Renugadevi and Prabu 2009; Renugadevi and Prabu 2010; Shagirtha and Pari 2011). The physiological models were mainly used to simulate bad living habits such as high-fat diet (De Leo et al. 2020; Ferreira et al. 2016; Ling et al. 2020; Rapavi et al. 2007; Shen et al. 2019), high-cholesterol diet (Jeon et al. 2001; Jeon et al. 2002), and excessive alcohol intake (Arab et al. 2015; Choi et al. 2015; Selmi et al. 2017). There are also reports of using aging models to explore physiological oxidative stress (Elavarasan et al. 2012; Miler et al. 2016; Nakajima et al. 2013).

Regulatory effect of citrus flavonoids on oxidative stress in vivo

Citrus flavonoids alleviated the pathological damage. In tissue injury models, citrus flavonoids improved organisms' health from different levels such as cells, tissues or organs by inhibiting oxidative stress. Nobiletin inhibited lipid peroxidation, increased antioxidant enzymes activity, and enhanced the survival of random pattern skin flaps (Jiang et al. 2020). By increasing the expression and transport of Nrf2, hesperidin increased the expression of HO-1 and the activity of SOD, reduced the inflammation and improved the motor ability of rats with spinal cord injury (Heo et al. 2020). Hesperidin also showed the accelerating effect of healing gastric ulcer by regulating oxidative stress (da Silva et al. 2019). Ischemia-reperfusion (IR) is the injury caused by free radical outbursts when the body is flush with blood in the case of spontaneous or artificial ischemia. IR injury was a severe side effect of some surgical operations, in which intestine, lung, brain and heart were organs sensitive to IR (Eltzschig and Eckle 2011). As a relief, citrus flavonoids extracts (from bergamot juice) and the monomers (hesperidin, neohesperidin, naringenin) showed the effect of reducing cell damage or organ morphological damage by inhibiting oxidative stress and inflammation (Bayomy et al. 2014; Impellizzeri et al. 2016; Wang and Cui 2013; Yu et al. 2019).

Citrus flavonoids inhibited the development of the disease. Under the animal assay, the related disease phenotype would gradually appear with the aggravation of the oxidative stress process. Diabetic animals produced weight loss, increased blood sugar, and increased total cholesterol and triglycerides. Citrus flavonoids (diosmin, hesperetin, hesperidin, and naringenin) could regulate the activity and expression of antioxidant enzymes to inhibit the rise of these undesirable indicators (Elshazly, Abd El Motteleb, and Ibrahim 2018; Jain et al. 2014; Samie et al. 2018; Srinivasan and Pari 2012; Wojnar, Zych, and Kaczmarczyk-Sedlak 2018). Alzheimer's disease is a neurodegenerative disease that leads to memory loss. Nobiletin blocked this process by inhibiting ROS production and activating GR enzymes (Nakajima et al. 2015). In the hypertension model, hesperidin inhibited the increase of ROS and MDA and decreased systolic blood pressure (Wunpathe et al. 2018). Within the

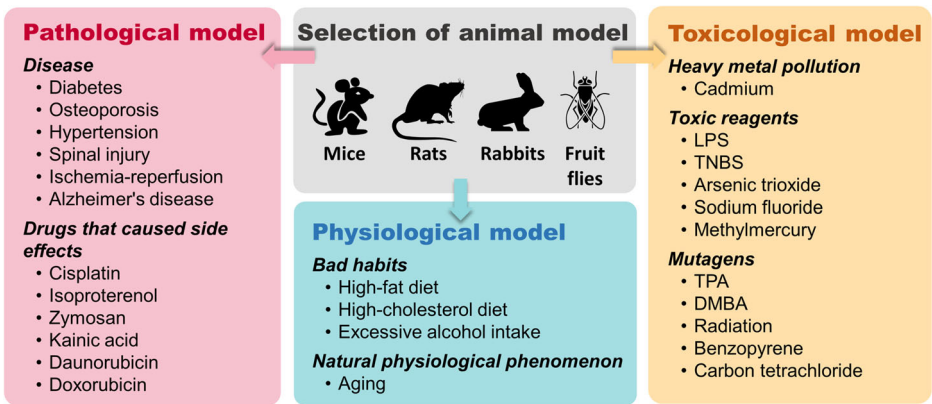

Figure 4. In vivo oxidative stress modeling method.

osteoporotic model rats, orange pulp significantly increased the bone mineral density area, improve the microarchitectural properties of vertebral bones and the cortical thickness of long bones (Wunpathe et al. 2018).

Citrus flavonoids reduced the drug side effects. Isoproterenol, a β-adrenoceptor agonist, is generally used in the treatment of bronchial asthma or atrioventricular block. However, excessive isoproterenol is cardiotoxic and can cause oxidative stress. In severe cases, it can lead to arrhythmias, cardiac hypertrophy, and even myocardial infarction (Allawadhi et al. 2018). Citrus flavonoids, including grapefruit extract, *Citrus medica* extract and hesperidin, inhibited lipid peroxidation and increased the activity of antioxidant enzymes such as SOD to restore normal heart rhythm and inhibit myocardial verification and morphological damage (Al-Yahya et al. 2013; Bhargava et al. 2019; Shaikh, Bhatt, and Barve 2019). Cisplatin is a broad-spectrum chemotherapy drug that binds to DNA, causing cross-linking that disrupts DNA function and inhibits mitosis. In clinical application, cisplatin could cause a severe burden on the nervous system and kidney of patients, which is related to the excessive ROS production in the body and the inhibition of the antioxidase system (Clavo et al. 2019; Holditch et al. 2019). It has been reported that hesperidin, nobiletin, rutin and tangeretin could alleviate the inhibition of cisplatin against oxidase activity and reduce the content of serum sodium and serum potassium (Kamel et al. 2014; Kamisli et al. 2015; Malik et al. 2015). The apoptosis and morphological damage of renal cells was reduced by inhibiting the inflammation associated with oxidative stress (Kamel et al. 2014). Other side effects alleviated by citrus flavonoids include cardiotoxicity induced by doxorubixin (Abdel-Raheem and Abdel-Ghany 2009), kainic acid-induced status epilepticus (Golechha et al. 2011), hyperalgesia and edema caused by zymosan (Bussmann et al. 2019), gentamicin-induced acute nephrotoxicity (Anandan and Subramanian 2012; Fouad et al. 2014), colchicine-induced cognitive dysfunction (Kumar, Dogra, and Prakash 2010), and oxytetracycline mediated liver oxidative damage (Pari and Gnanasoundari 2006).

Citrus flavonoids inhibited the health damage of mutagens. When organisms were exposed to mutagens, the accumulation of exposure dose would lead to signal disorder, oxidation pathways block, inflammatory markers increase, organ damage and even cancer. Supplementation of citrus flavonoids could reduce the damage of mutagen. Hesperidin could inhibit the BaP-induced lung carcinogenesis (Kamaraj et al. 2009), testicular toxicity (Arafa et al. 2009), diethylnitrosamine (DEN)-induced hepatocellular carcinoma (Mo'men, Hussein, and Kandeil 2019), γ-radiation-induced tissue damage (Pradeep et al. 2012), and CCl_4 induced liver and kidney damage (Tirkey et al. 2005). These functions of hesperidin were related to the regulation of the expression and activity of antioxidant enzymes. For polymethoxylated flavonoids, tangeretin showed chemotherapeutic effects in DMBA-induced mammary carcinoma through inhibition of Keap1 and upregulation of Nrf2, HO-1 and NQO1 (Lakshmi and Subramanian 2014a; Lakshmi and Subramanian 2014b). Nobiletin inhibited TPA-induced ROS generation, skin inflammation and tumor promotion (Murakami et al. 2000a; Murakami et al. 2000b).

Citrus flavonoids inhibited heavy metal environmental toxins. Cadmium pollution is a kind of heavy metal environmental pollution with high harmfulness, often around chemical fertilizer plants, smelters, and electroplating plants (Satarug et al. 2010). Accumulation of cadmium in the body could cause hepatotoxicity, nephrotoxicity and reproductive toxicity, all related to oxidative stress caused by cadmium (Prabu, Shagirtha, and Renugadevi 2011; Renugadevi and Prabu 2009; Shagirtha and Pari 2011). By giving full play to its antioxidant capacity, citrus flavonoids increased serum creatinine clearance (Renugadevi and Prabu 2009), inhibited the abnormal expression of ALT, AST and ALP (Prabu, Shagirtha, and Renugadevi 2011; Renugadevi and Prabu 2010), reduced the content of cadmium in testis (Shagirtha and Pari 2011), and inhibited neuronal apoptosis in rats (Qu et al. 2018).

Citrus flavonoids also have the following "detoxifying effects". Neuroprotective effects by regulating oxidative stress: citrus flavonoids inhibited neurological damage induced by 3-nitropropionic acid (3NP) (Gopinath and Sudhandiran 2012), LPS (He et al. 2019; Muhammad et al. 2019), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Mani et al. 2018), NaF (Nkpaa and Onyeso 2018), MeHg (Krishna Chandran et al. 2019), or $AlCl_3$ (Justin Thenmozhi et al. 2017). Digestive tract health enhancement by inhibiting inflammatory syndrome and oxidative stress disorders: fortunellin targeted the negative regulator of phosphatase and tensin homolog (PTEN) *miR-374a*, which contributed to the colitis amelioration (Xiong et al. 2018). Inhibition of liver damage caused by lipid peroxidation: citrus flavonoids attenuated oxidative-related hepatic pathological damage induced by As_2O_3 (Roy et al. 2014; Xie et al. 2017), LPS (Kaur, Tirkey, and Chopra 2006), STZ (Jayaraman et al. 2018), 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (Bentli et al. 2013).

Citrus flavonoids reduced the health risks of poor dietary habits. Poor dietary habits, such as high cholesterol intake, high fat intake, or excessive alcohol consumption, could increase the digest and circulatory system burden. Long-term accumulation of unhealthy conditions could lead to thickening of blood vessel walls, fatty liver, stomach ulcers and other diseases (Bastien et al. 2014; Hadi, Vettor, and Rossato 2018). In addition to correcting eating habits, supplementing the intake of citrus flavonoids also helped improve the healthy state. High cholesterol diet increased liver weight and serum total cholesterol content, while naringin could improve the health threat brought by high cholesterol through inhibiting mitochondrial H_2O_2 and enhancing the expression and activity of SOD and CAT (Jeon et al. 2001; Jeon et al. 2002). Long-term high fat intake led to oxidative stress and liver inflammation supplementation with citrus extracts (Arab et al. 2015; De Leo et al. 2020; Shen et al. 2019) or citrus flavonoid monomers (Ferreira et al. 2016) inhibited lipid peroxidation, reduce the overexpression of inflammatory factors, and control excessive weight gain. Excessive alcohol consumption is a health

threat to middle-aged and older people. Alcohol over intake is closely related to peptic ulcer development (Friedman, Siegelaub, and Seltzer 1974). Although not an excuse for excessive drinking, citrus flavonoid compounds could indeed inhibit the development of lipid peroxidation and gastric ulcer by up-regulating the expression of antioxidant enzymes induced by Nrf2 (Arab et al. 2015; Choi et al. 2015; Selmi et al. 2017).

Citrus flavonoids reversed the senescent induced antioxidases activity fading. Oxidative stress is closely related to the development of old-age diseases. During the aging process, the endogenous defense system's decline determines the need for dietary supplementation with exogenous antioxidants (Elavarasan et al. 2012). Citrus flavonoids improved the antioxidant system in mice, reversed age-related declines in learning and memory (Nakajima et al. 2013). In another report, citrus flavanones, including naringenin and hesperetin improved the antioxidant status and membrane phospholipid composition in the liver of elderly rats (Miler et al. 2016).

Clinical-based antioxidant abilities of citrus flavonoids

The treatment of clinical-based antioxidant evaluation was generally nutritional intervention with citrus flavonoids over a period of time through dietary supplementation. According to the physiological and pathological characteristics of the specific population, key indicators were compared with the control group, to evaluate the antioxidant activity ability of testing substances.

Clinical trial substances and detection indictors

To ensure the safety of clinical trials, the antioxidants consumed by volunteers were generally edible citrus juices or commercially available citrus flavone supplements (Cases et al. 2015; Ghanim et al. 2007; Ribeiro et al. 2019; Riso et al. 2005; Snyder et al. 2011). It may be due to toxicity and cost considerations, in terms of monomer compounds, only hesperidin and its suboptimal enantiomer hesperidin 2S have been reported (Morand et al. 2011; Salden et al. 2016).

The indicators of clinical trials were generally those related to oxidative stress in body fluids, such as blood and urine, and other indicators that could be tested nondestructive, such as weight, waist circumference, and hip circumference (Cases et al. 2015; Morand et al. 2011; Snyder et al. 2011).

Clinical trial population

The volunteers recruited for clinical trials could be divided into healthy volunteers, sub-healthy volunteers, and special physiological conditions (Table 3). For healthy volunteers, the trial's objective was to investigate whether citrus flavonoid-rich juices caused (Ghanim et al. 2007) or inhibited oxidative stress (Riso et al. 2005; Snyder et al. 2011). Some sub-healthy volunteers, such as overweight or obese adults or children (Cases et al. 2015; Codoner-Franch et al. 2010; Morand et al. 2011; Rangel-Huerta et al. 2015; Salden et al. 2016), hypercholesterolemic people (Constans et al. 2015), patients with hepatitis C (Goncalves et al. 2017) or prediabetes (Ribeiro et al. 2019) were also recruited for clinical antioxidant studies in citrus extract or monomer, primarily to test whether citrus flavonoids could help alleviate these conditions. Citrus flavonoids were also clinically tested in people with specific physiological stages or physiological functions such as postmenopausal women (Habauzit et al. 2015) or athletes (Overdevest et al. 2018). In clinical trials, individuals differ greatly in their living habits, so it is difficult to carry out a unified diet like animal models, and even operation like cell models. Correspondingly, it is difficult to obtain significant difference indicators such as animal models and cell models in clinical.

Unsatisfactory phenotype in clinical trials, inadequate antioxidant capacity or inappropriate testing?

Compared with the "triumphs" of animal experiments, clinical trials seem to have won only "sporadic battles". These include: in some experiments, citrus flavonoids did not achieve significant regulation of antioxidant enzyme activity (Constans et al. 2015; Rangel-Huerta et al. 2015). Indicators of diseases related to oxidative stress showed differences only in a few scattered indicators (Habauzit et al. 2015; Ribeiro et al. 2019). In fact, some indicators have appeared that were contrary to the expected effect, such as the decline of high-density lipoprotein cholesterol (HDL-C) (Codoner-Franch et al. 2010) and the rise of apolipoprotein B (Apo B) (Constans et al. 2015).

To sum up the above problems, this insufficiently bright result has objective reasons, namely the limitation of the clinical trial itself and subjective reason, namely the problem of experimental design and detection method. In clinical trials, individuals differ greatly in their living habits, so it was difficult to carry out the unified diet like animal models, let alone homogenization as in cell models. Therefore, it was challenging to get significant differences in clinical trials as in animal and cell models. On the other hand, some areas could be improved in the experimental design. For example, the intake of citrus flavonoids in clinical trials was generally low. Although 500 to 600 mL of fruit juice was recommended, it contained only 19.1 to 750 mg of citrus flavonoids per person per day (Habauzit et al. 2015; Overdevest et al. 2018; Rangel-Huerta et al. 2015; Riso et al. 2005; Salden et al. 2016), an order of magnitude difference compared with the intake in animal trials. Although the main trials were aimed at citrus flavonoids, the volunteers consumed more of mixtures, such as sugar-preserving fruit juices. It is not known whether the sugar in the juice has a counteracting effect on the antioxidant capacity of citrus flavonoids. The results of these studies showed was that intaking citrus flavonoid-rich juice did not seem to cause oxidative stress as much as eating sugar (Ghanim et al. 2007), and it was not clear that citrus juice had a direct inhibitory effect on oxidative stress in the body. In terms of the detection method, the present research also seems to have some improvement. Due to the high antioxidant capacity of the serum itself (Jansen and Ruskovska 2015; Stocker 2016; Tonin et al. 2015), it seems difficult to induce fluctuations in serum antioxidant capacity by oral

Table 3. Clinical-based evaluation of antioxidant abilities of citrus extracts/flavonoids.

Substances	Subjects	Design	Primary outcome	References
Blood orange juice	16 healthy female volunteers (BMI: 16.0 − 23.3)	600 mL/d, 3 weeks	VC↑; C3G↑; β-Cryptoxanthin↑; β-carotene↑; zeaxanthin↑; PAC\; MDA\; u-11-Dehydro TXB2\; DNA damage in lymphocytes↓	(Riso et al. 2005)
Orange juice	32 healthy volunteers (BMI:20 − 25)	300-kcal orange juice, single (300-kcal glucose as control)	glucose↓; insulin↑; ROS generation↓; NF-κB binding↓; CRP↓;	(Ghanim et al. 2007)
Orange juice	16 healthy volunteers (BMI: 20 − 27.4)	Placebo diet + 591 mL/d orange juice, 1 week	ORAC↑; LO↓; PP \	(Snyder et al. 2011)
A mixture of hesperidin, luteolin and naringenin	16 healthy volunteers (BMI: 20 − 27.4)	Placebo diet + mixture, 1 week	ORAC↑; LO \; PP↑	(Snyder et al. 2011)
Mandarin juice	40 children with severe obesity (BMI z-socre ≥ 2)	Low-cal diets +500 mL/d mandarin juice, 4 weeks	Weight↓; BMI↓; waist circumference↓; hip circumference↓; BP↓; HDL-C↓; HOMA-IR↓; insulin↓; folic acid↑; MDA↓; p-VC↑; α-tocopherol↑; GSH↑	(Codoner-Franch et al. 2010)
Orange juice	24 healthy male volunteers (BMI: 25.2 − 30.5)	500 mL/d orange juice, 4 weeks	DBP↓; uric acid↓; β-Cryptoxanthin↑; VC↑; endothelium-dependent vasodilation↑	(Morand et al. 2011)
Hesperidin	24 healthy male volunteers (BMI: 25.2 − 30.5)	292 mg/d hesperidin, 4 weeks	DBP↓; endothelium-dependent vasodilation↑	(Morand et al. 2011)
Citrus-based extract Sinetrol® XPur	25 overweight male volunteers (BMI: 26 − 29.9)	2 capsules/d, 12 weeks	Weight↓; abdominal fat↓; waist; hip↓; glycemia↓; NEFAs↑; Apo A1↑; fibrinogen↓; uric acid↓	(Cases et al. 2015)
Orange juice	25 mild hypercholesterolemic male volunteers (LDL-C: 130 − 190 mg/L)	600 mL/d orange juice, 4 weeks	VC↑; plasma hesperetin↑; urinary hesperetin↑; Apo A1↑; Apo B↑; erythrocyte catalase activity↓; FRAP↑; β-carotene↑; urinary 8-iso-PGF2α↓	(Constans et al. 2015)
Orange juice with high polyphenol concentration	100 obese volunteers (BMI: 32.5 − 33.7)	500 mL/d orange juice, 12 weeks	Weight↓; BMI↓; waist circumference↓; glucose↑; Apo A1↓; leptin↓; urine hesperetin↑; urine naringenin↑; erythrocyte catalase↓; erythrocyte SOD↑; erythrocyte GR↓; α-tocopherol↑; CoQ10↑; urine 8-iso-$PGF_{2\alpha}$↓; urine 8-OHdG↓	(Rangel-Huerta et al. 2015)
Hesperidin 2S	68 overweight volunteers (BMI: 25 − 35)	250 mg/d hesperidin 2S, 6 weeks	sVCAM-1↓; sICAM-1↓; FMD↑	(Salden et al. 2016)
Orange juice	43 patients with hepatitis C	500 mL/d orange juice, 8 weeks	TC↓; LDL-C↓; CRP↓; ABTS↑; TBARS↓; AST↓	(Goncalves et al. 2017)
Eriomin®	103 prediabetes patients (HbA1c ≥ 5.7%)	200, 400 or 800 mg/d, eriomin, 12 weeks	Glucose↓; OGGT↓; HOMA-IR↓; HbA1c↓; glucagon↓; C-peptide↓; GLP-1↑; hsCRP↓; IL-6↓; TNFα↓; lipid peroxidation↓; SBP↓; adiponectin↑	(Ribeiro et al. 2019)
Grapefruit juice	48 healthy postmenopausal female volunteers (BMI: 19 − 30)	340 mL/d grapefruit juice, 24 weeks	carotid-femoral pulse wave velocity↓	(Habauzit et al. 2015)
Citrus extract	39 healthy trained athletes (BMI ≈ 22.1)	500 mg citrus extract, 4 weeks	Absolute power output↑; oxygen consumption/ power ratio↓	(Overdevest et al. 2018)

8-iso-$PGF_{2\alpha}$: 8-isoprostane prostaglandin F2α; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; Apo A1: apolipoprotein A1; Apo B: apolipoprotein B; AST: aspartate transaminase; BP: blood pressure; CoQ: coenzyme Q; CRP: C-reactive protein; DBP: diastolic blood pressure; FMD: flow-mediated dilation; HbA1c: Glycated hemoglobin; GLP-1: glucagon-like peptide 1; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; NEFAs: non-esterified fatty acids; LO: lipoprotein oxidation; OGTT: oral glucose tolerance test; PAC: plasma antioxidant capacity; PP: plasma phenolics; SBP: systolic blood pressure; sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1; TC: total cholesterol; ↑: significant increase in detection; ↓: significant decrease in detection;\: no significant change.

administration of citrus flavonoids. Researchers seem to have focused too much on detecting serum antioxidant activity (Constans et al. 2015; Goncalves et al. 2017; Snyder et al. 2011) and not enough on the effects of antioxidant enzyme activity. Studies on the clinical metabolism of citrus flavonoids have also been biased. In juice, citrus flavanones are mostly in the form of glycosides. However, in some studies, researchers used Elisa and HPLC method to detect aglycones in plasma and urine (Constans et al. 2015; Rangel-Huerta et al. 2015). Since the content of these aglycones in the juice was already low, such tests may be unrepresentative.

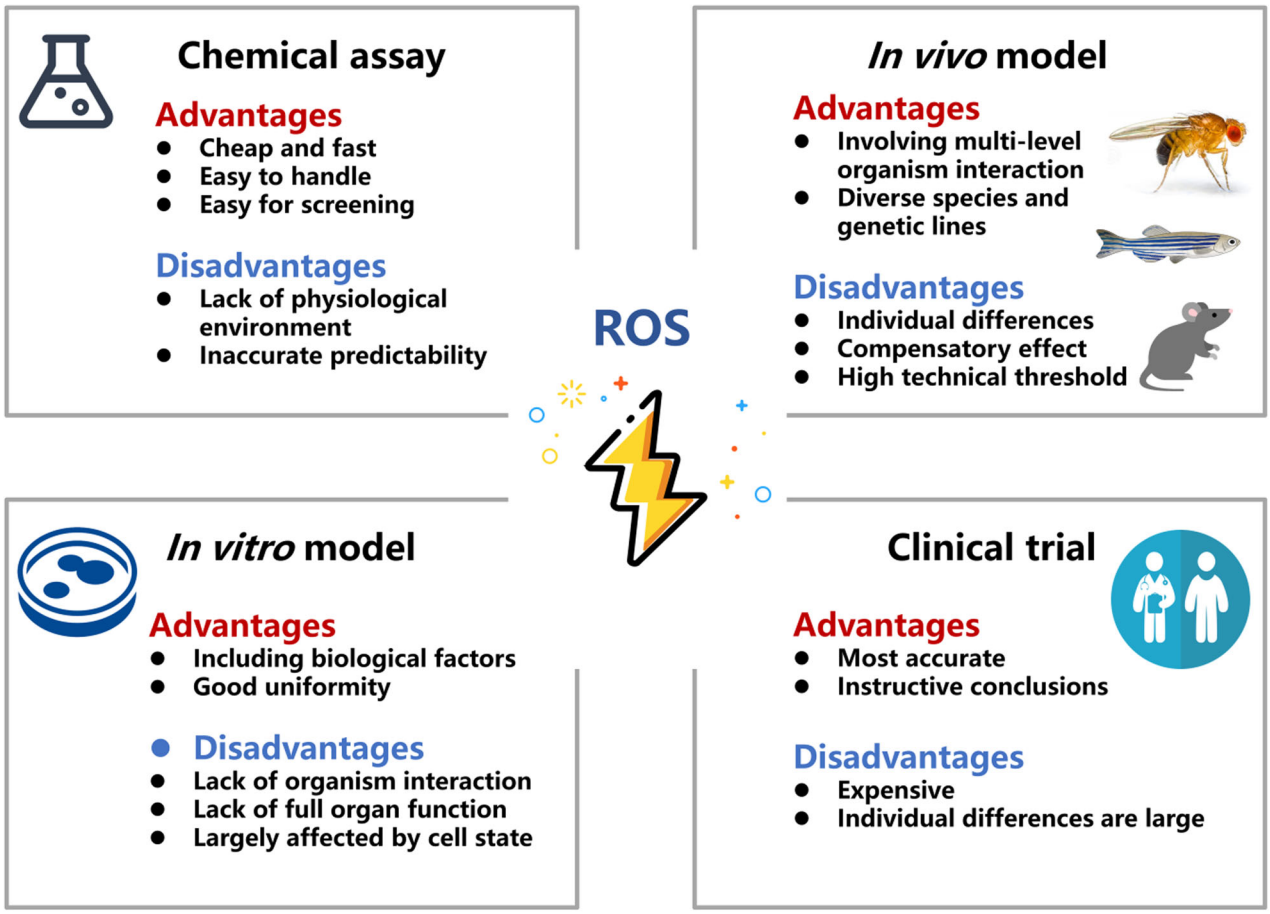

Figure 5. Advantages and disadvantages of different antioxidant evaluation systems.

Although there are many problems, promoting health indicators under the complex interaction between the human body and the environment was helpful to confirm further the positive effect of citrus flavonoids on the body's antioxidant capacity.

To summarize the four antioxidant evaluation systems, different antioxidant evaluation systems have their own advantages and disadvantages due to their different evaluation objects, detection methods and experimental costs (Figure 5). While evaluating the antioxidant capacity of citrus flavonoids, the detection system should be selected according to the experimental purpose. Chemical assays were suitable for rapid screening of citrus varieties or crude extracted products. The in vitro evaluation systems were generally used to detect the regulation of oxidative stress caused by the interaction between citrus flavonoids and in vitro organisms. In addition to screening for cytoprotective or toxic effects of flavonoids, in vitro evaluation systems were often used to explore and verify antioxidant mechanisms. As it involves multiple levels of organ interaction, in vivo evaluation systems were suitable for the study of disease-related oxidative stress phenotype and mechanism. The results of the clinical trials were more precise and could provide consumers with guidance on their daily consumption of citrus flavonoids. However, due to the high cost, clinical trials were relatively independent from the other three antioxidant evaluation systems, and more trials are needed to enlighten researchers.

Outlook

Seek the application of citrus flavonoids in more oxidative stress scenarios

Improve isolation and purification technology

The utilization of citrus flavonoids, especially monomer substances, were abundant in the middle and sparse at both ends in the present study. In other words, in the chemical antioxidant evaluation and clinical trials, citrus crude extracts or citrus juice were mostly used as research objects. In contrast, in cellular and animal antioxidant models, the experimental objects were more abundant, including various citrus flavone monomers. The reason for this may be that individual citrus flavonoid monomers were not available in sufficient quantities, especially for clinical trials. This problem brings us a new challenge, which requires us to develop an efficient, low cost and high safety separation and purification process for citrus flavonoids.

Explore more application scenarios

Although previous studies have already put in the citrus flavonoid to participate in numerous oxidative stress scenarios, there are still other conceivable or operational applications. For example, the interaction of citrus flavonoids with other antioxidants could be studied by simulating the serum's antioxidant content in vitro. Another situation that remains to be

studied is the "causal relationship" between the oxidative stress effects of citrus flavonoids and other biological activities. Were flavonoids biologically active because they resisted oxidative stress, or vice versa because they regulated other biological activities and thus inhibited oxidative stress? In some overproliferated cells, such as cancer cells, citrus flavonoids played an effect of inducing oxidative stress, which is contrary to its effect of inhibiting oxidative stress. The mechanism underlying this phenotype is also worth investigating.

Clarify the function of citrus flavonoids in Nrf2-Keap1 pathway

Pay attention to Nrf2 negative feedback loop

The activation and induction of antioxidation pathways have been widely reported, but studies on the inhibition and degradation of Nrf2 are lacking. The Nrf2-Keap1 pathway is the main pathway regulating the antioxidant function of organisms. The main steps for this pathway function include the dissociation and expression of Nrf2, the nucleation of Nrf2, and the combination of Nrf2 and ARE to activate the expression of antioxidant enzymes. Current reports have shown that citrus flavonoids had regulatory activities for the above steps. However, it should be noted that Nrf2 is also ubiquitinated by Keap1 and Cul3 after completing the regulatory action. This process is related to the regulating duration of citrus flavonoids, which has not been reported yet.

The other side of the coin, the dark side of Nrf2 continual activation

Long-term activation of Nrf2 is harmful to organisms and may cause cell canceration. It has been reported that some small molecules such as IASSP can continuously activate Nrf2 by competitively combining Keap1 (Ge et al. 2017). This led to harmful phenomena, such as promoting tumor growth and drug resistance. Do citrus flavonoids circumvent this problem? Citrus flavonoids can not only regulate oxidative stress, but also inhibit the development of tumors, which is a thought-provoking problem.

Selectivity in the regulation of antioxidant enzymes

The antioxidant enzymes regulated by the Nrf2-Keap1 pathway include CAT, SOD, GCLC, GCLM, HO-1, NQO1 and so on. In cell and animal studies, citrus flavonoids seem to regulate most antioxidant enzymes, but in clinical trials, they failed to regulate certain enzymes (Constans et al. 2015; Rangel-Huerta et al. 2015). Does this reflect the selectivity of citrus flavonoids in the regulation of antioxidant enzymes? What is its internal mechanism? This point needs to be studied.

Eliminate the design defects of the experiment

Did "experimental convenience" lead to "sexism"?

In antioxidant experiments with citrus flavonoids, males were selected more often, while females participated in only a few experiments. Does this mean that the antioxidant capacities of citrus flavonoids in oxidative stress models without female animals cannot be applied to women? The reason for this gender bias may be that the periodic hormonal fluctuations of female animals may lead to unstable experimental data, but this cannot be used as an interface for the design of animal models that only use males. In follow-up studies, we need to increase the number of female-participated experiments, or at least balance the sex ratio in animal studies. Also, there is an urgent need to see studies comparing the antioxidant capacity of animals of different sexes.

By age, are the existing animal model representative?

In addition to the aging model, the selection of mice in the animal model did not consider the age factor, which was taken into account in clinical trials. The incidence of some diseases is related to age factors, such as adolescent obesity (Lobstein et al. 2015), juvenile diabetes (Dabelea et al. 2014), and childhood leukemia (Bhojwani and Pui 2013). In order to better simulate these diseases, we should select animals at the corresponding age to discuss in more detail whether citrus flavonoids play different oxidative stress in different age groups.

For the care of healthy people, does citrus flavonoid further improve physical functions?

Some models set up in the current study did not match the expectation of daily intake of citrus flavonoids. In current studies, the hypothesis and purpose of citrus flavonoids function were mostly saving and redemption, reducing the degree of disease through antioxidant bioactivities. While in daily intake, people's expectation of citrus flavonoids is mostly to maintain and improve, and retain their own healthy state. It is undeniable that "icing on the cake" experiments are painful. Existing experimental models and statistical methods seem difficult to quantify from "good" to "better". More efforts are needed to develop new evaluation models and indicators to assess health status. However, isn't that the meaning and fun of scientific research?

Conflicts of interest

The authors declare no conflict of interest.

Funding

This research was supported by the Natural Science Foundation of Zhejiang Province (LR17C200001), National Natural Science Foundation of China (32072132), the Fundamental Research Funds for the Central Universities (2020XZZX003-03), the Agricultural Outstanding Talents and Innovation Team of the State Agricultural Ministry on Health and Nutrition of Fruit, National Key R&D Program of China (2017YFD040020) and the 111 project (B17039).

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