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Aurantii Fructus: a systematic review of ethnopharmacology, phytochemistry and pharmacology

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Abstract Aurantii Fructus (called Zhiqiao, ZQ in Chinese), the dried unripe fruit of *Citrus aurantium* L. or its cultivated variety, is a common traditional edible-medicinal herb in regulating visceral functions for thousands of years. As a widely used ethnomedicine in Asia including China, Japan and Korea, ZQ possesses ideal therapeutic effect on digestive system diseases, and is also used as a condiment in food for regular consumption to benefit health. Amounts of investigations on different aspects have been done for ZQ in the past decades. However, there has no literature systematic comparison on the similarity concerning research achievements of ZQ. Herein, this review comprehensively presents the up-to-date information on botany, ethnopharmacology, phytochemistry, pharmacological activity, clinical use, quality control and toxicology of ZQ to identify their therapeutic potential and directs future research opportunities. So far, about 62 compounds has been isolated and identified from ZQ, in which flavonoids, alkaloids and coumarins would be the main bioactive ingredients for its pharmacological properties, such as regulating gastrointestinal motility, anti-gastric ulcer effect, regulating blood pressure, cardioprotective effects, anti-atherosclerotic activity, anti-vascular damage activity, anti-depression activity, anti-obesity activity, anti-inflammatory, anti-oxidant, anti-tumor, immunomodulatory activity and affecting enzyme activities. Even so, the variety of sources and origins, ZQ has defects in quality control and clinical application.

Keywords Aurantii Fructus · Botany and ethnopharmacology · Phytochemistry · Pharmacological activity · Quality control

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Introduction

Aurantii Fructus (called Zhiqiao, ZQ in Chinese), the dried unripe fruits of *C. aurantium* L. or its cultivars

gathered from July, is one of the most important and commonly used drugs for qi-regulating in the clinical practice of traditional Chinese medicine (TCM). Meanwhile, ZQ is widely used as a health food product in China, for the benefits to relax the bowels and protect gastric mucosa damage. In 2002, it was recorded on the herbal list declared by National Health Commission of China, in which 101 herbs can be employed for medicinal drugs and health products. In terms of the data of National Medical Products Administration (NMPA, https://www.nmpa.gov.cn/), there are 14 types of domestic health food contained ZQ extract in Chinese market. Furthermore, it is also very popular in other countries. For instance, the ripe fruit is consumed as an edible fruit in Iran (Hosseinimehr and Tavakoli 2003) or eaten with salt and chili paste in Mexico (Adriane 2004), and the fruit juice is commonly used as flavoring and acidifying agent for vegetable salads and appetizers in Turkey (Karabıyıklı et al. 2014). Its blossom is frequently used to make tea, with positive effects on losing weight (Ting et al. 2017). In addition, in the Mediterranean basin, eating fresh citrus fruits is thought to protect against many diseases due to the richest dietary sources of health-promoting compounds (Barreca et al. 2012a). Traditionally, it is believed that ZQ can improve stagnation of dyspepsia and gastrointestinal function, reduce chest pain and cure organ prolapse, by means of using alone or in combination with other herbs. Statistically, ZQ is found in a total of 1903 classic prescriptions of Chinese medicine according to ancient documents. So far, 351 Chinese patent medicines (CPMs) containing ZQ have been developed on basis of the data of NMPA. ZQ has been recorded in the *Chinese Pharmacopoeia* (ChP) since 1963. In addition to itself, the processed products—stir-baking ZQ with bran is also accepted by ChP for milder effects on improving digestion (Zhu et al. 2020b).

ZQ is mainly used for the auxiliary treatment of indigestion, poor appetite, abdominal distension, abdominal pain, chest pain, organ prolapse, and other diseases. Modern pharmacological studies have confirmed that ZQ possesses wide pharmacological actions such as effects on gastrointestinal and cardiovascular system, anti-depression, anti-inflammatory (Li et al. 2018a), anti-oxidation (Liu et al. 2017) and immunomodulatory (Su et al. 2008). Due to extensive pharmacological effects and universal folk use, the researches on ZQ chemical components get more and more attention. Until now, more than 60 compounds have been isolated and identified from ZQ, including flavonoids (Zhou et al. 2007), alkaloids (Peng et al. 2006), coumarins (Chen et al. 2012), volatile oil (Md Othman et al. 2016) and other less abundant ingredients such as polysaccharides, organic acids and steroids. Among them, flavonoids have been the most studied and possess the notable bioactivity. In 2015 Edition ChP, naringin (**1**) and neohesperidin (**6**) are now used as the official marker to monitor the quality of the unripe fruit.

Although many researchers have conducted extensive studies on the chemical composition and pharmacological effects of ZQ in the past decades, it's still not clear that the mechanism of qi-regulating effects based on the compatibility theory of TCM. On the other hand, because of the numerous origins and varieties, there are also many counterfeit species of ZQ in clinical use, which are often confused consumers and disrupted market prices. Herein, in this review, we have a detailed description on ZQ with compiling a variety of literature and websites to provide comprehensive insights into the ethnopharmacology, phytochemistry, pharmacological activity, clinical use, quality control and toxicology of ZQ for further in-depth development and applications.

Botany and ethnopharmacology

Botany

Rutaceae is a large family of dicotyledons with seven subfamilies. There are 180 genera and about 1300–1600 species in the Rutaceae family in the world. It is distributed in tropical and subtropical regions, with a few in temperate zones (Luo et al. 2010a). About 29 genera with 151 species (including both introduced and cultivated species) are found in the southwest and south of China mainly. Plants of this family have great economic value (Appelhans et al. 2018). Among them, genus *Citrus* is important sources of medicinal herbs (Gui et al. 2016). It has been classified according to two different systems: Swingle firstly defined 16 species, further subdivided into varieties and hybrids. Then, Tanaka reorganized the entire genus into 156 species, distributing most varieties and cultivars their own species (Barreca et al. 2020). In China, *C. aurantium* L. is a very

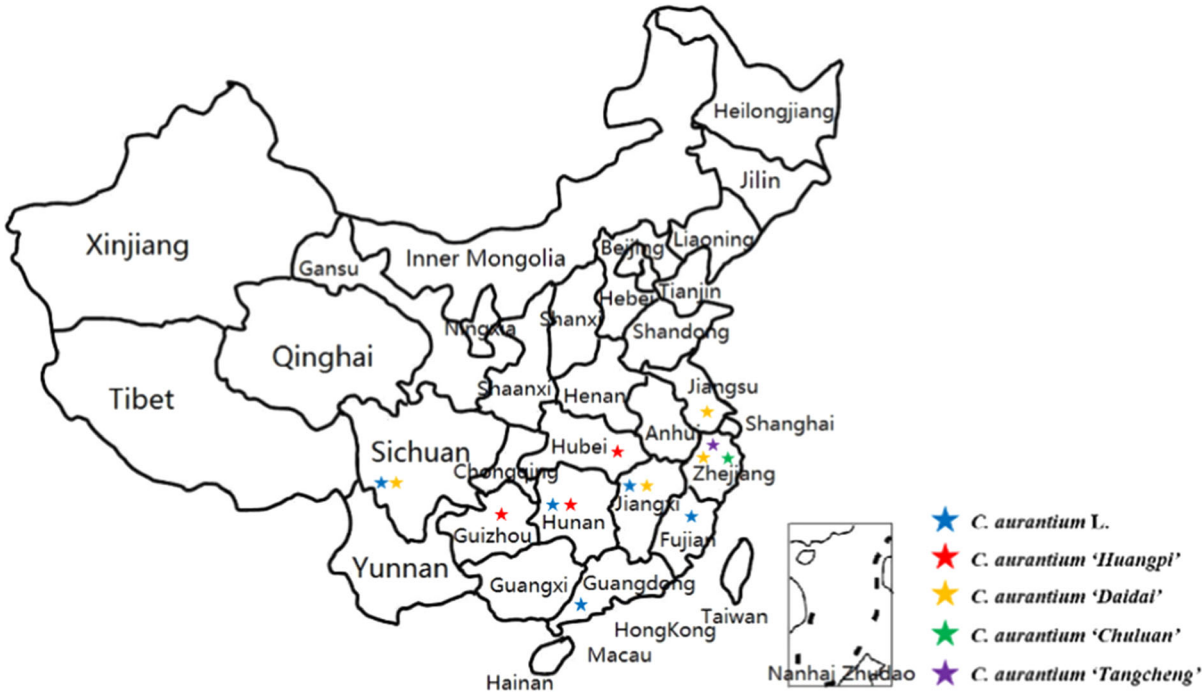


Fig. 1 Climatic and ecological adaptability distribution in China

important medicinal species, generally distributed in Hunan, Jiangxi, Fujian, Guangdong, and Sichuan provinces of China (Xue et al. 2017). Among them, Li Shi Zhen (1596 a.d.) in *Ben Cao Gang Mu* reported that ZQ produced in Jiangxi province was the authentic source and had the superior quality. Among different cultivated regions in China, Zhangshu of Jiangxi province produces the best quality of ZQ, which could be due to its specific geographical location. Zhangshu is 30 m above sea level and receives > 1500 mL of annual rainfall, and the average temperature in a year is about 17.5 °C, the climate is suitable for the growth of medicinal plants. Besides the geographical properties, farmers in Zhangshu have experience of cultivating ZQ for over 1000 years. Indeed, Zhangshu produces > 60% of the total production of ZQ in China (Peng et al. 2006) (Fig. 1).

The cultivars of *C. aurantium* L. primarily contain *C. aurantium* 'Huangpi' (*C. aurantium* L. CV.Huangpi-Suanchen), *C. aurantium* 'Daidai' (*C. aurantium* L. *var. amara* Engl.), *C. aurantium* 'Chuluan' (*C. aurantium* L. *var. decumana* Bonar.) and *C. aurantium* 'Tangcheng' (*C. aurantium* L. CV. Tangcheng) (Table 1). It is recorded that *C. aurantium* 'Huangpi' is mainly distributed in Hunan, Hubei and Guizhou provinces of China (Li et al. 2015a), while *C. aurantium* 'Daidai' commonly cultivate in the south of QinLing, such as Jiangxi and Sichuan province (Yan et al. 2018), and is popularly consumed as tea and food because of the health-promoting effect. Additionally, Zhejiang province is an essential source of *C. aurantium* 'Chuluan'(Chen 1998), which has more than 200 years of history in the local with the annual output of nearly 80% of the province (Wang et al. 2010). As for *C. aurantium* 'Tangcheng', there is no detailed literature report on it so far (Cai et al. 1999). In addition to the varieties specified in 2015 Edition ChP, there are many other sources of ZQ currently in circulation on the market, such as *C. aurantium* 'Xiucheng', *C. aurantium* 'Xiangcheng', *Poncirus trifoliata* (L.) Raf., *C. aurantium* 'Changshan-huyou', *C. grandis* and *C. sinensis*. Some of them are collected by local standards (Li et al. 2018a), while others are circulated as fake ZQ (Cai et al. 1999), which brings great inconvenience to the clinical application of ZQ (Fig. 2).

From the appearance, ZQ is semi-spherical, but with a diameter of 3–5 cm. On the brown epicarp, there remains obvious style remnants or fruit stalk marks and granular projections as well, while the

Table 1 Botanical traits comparison of five origins of ZQ

Botanical traits	*C. aurantium* L. (A)	*C. aurantium* 'Huangpi' (B)	*C. aurantium* 'Daidai' (C)	*C. aurantium* 'Chuluan' (D)	*C. aurantium* 'Tangcheng' (E)
Carpopodium	Dented into the peel	No distinguishing feature	Protruding from the peel	Dented into the peel	Protruding from the peel, radial wrinkles all around
Vascular bundle	Apparently arranged in concentric rings	Dotted and not obvious	Dotted and not obvious	Apparently arranged in concentric rings	Dotted and not obvious
Endocarp	White	Yellowish-white or brownish yellow	Yellowish-white	Off white	Yellowish-white
Exocarp	Brownish red or tan	Green brown, tan, black brown, or reddish brown	Green brown	Orange red	Surface coarse
Transverse section	Thick and slightly outward	Flat or concave	Slightly bulging	Thick and bulging	Poor thickness

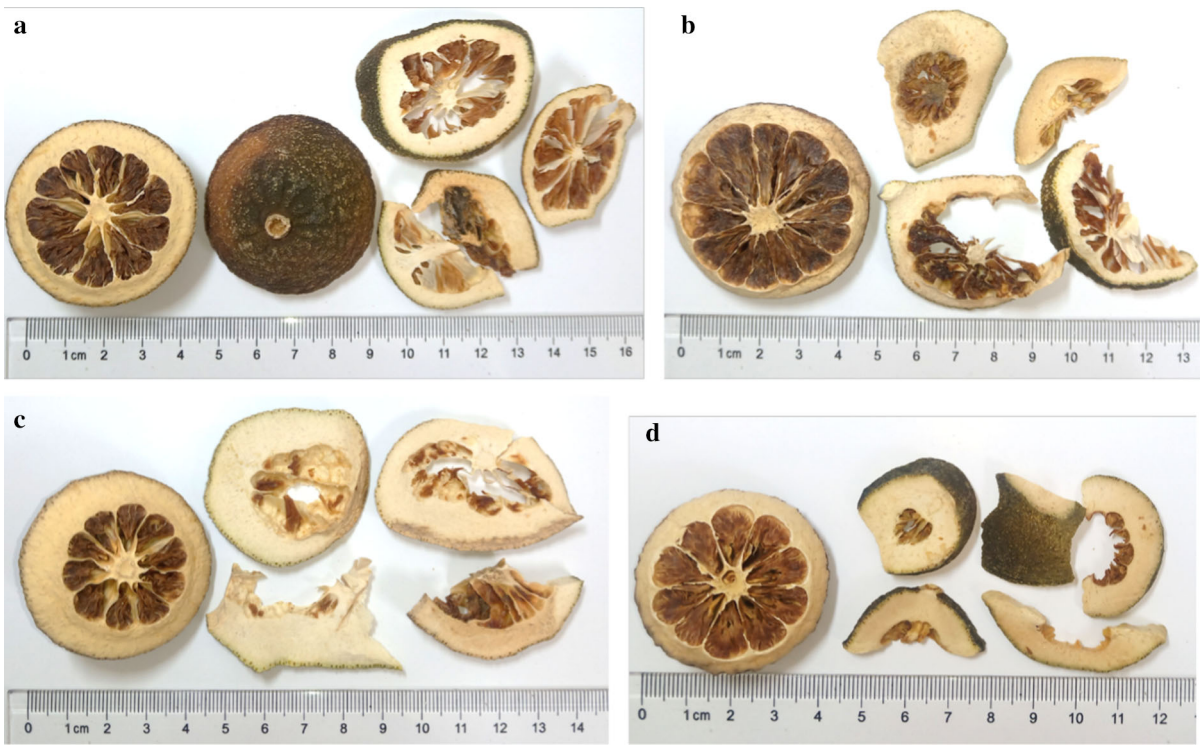


Fig. 2 **a** ZQ, **b** *C. aurantium* 'Xiucheng', **c** *C. aurantium* 'Changshan-huyou', **d** LYZQ

pitted oil chambers are at the tip of the projections. In the cut surface, the pericarp is yellowish white, smooth and slightly raised, 0.4–1.3 cm thick, with 1–2 rows of oil chambers scattered at the edge. Generally, the pulp sac has 7–12 petals, a few of which may have 15 petals. The juice sac shrinks to brown to tan, and contains seeds. ZQ is also unbreakable and smells pleasant, with bitter, slightly acidic taste (Pharmacopoeia 2015). Besides, another young fruit of *C. aurantium* L., collected from May to June, is considered a second medicine in TCM clinic, named Aurantii

Fructus Immaturus (called Zhishi, ZS in Chinese). It looks smaller than ZQ, with a diameter of 0.5–2.5 cm.

Except for the 5 sources specified in 2015 Edition ChP, other sources of ZQ currently exist on the market such as Poniciri Trifoliatae Fructus (called Lvyizhiqiao, LYZQ in Chinese), the unripe fruits of *Poncirus trifoliate* (L.) Raf.. In fact, ZQ was taken the ripe fruits of *Poncirus trifoliate* (L.) Raf. as authentic products before the Tang Dynasty (A.D. 618–907), then it gradually took *C. aurantium* L. as salable goods after the Song Dynasty (A.D. 960–1279) for better efficacy (Hu et al. 2019). Nowadays, LYZQ has been exported to Taiwan, South Korea and Southeast Asia for a long time, and is promising genuine regional drugs for Fujian province that can be used for export to earn foreign exchange (Xiao et al. 2009). It is precisely because of the many origins and varieties of ZQ that counterfeit and shoddy goods are easy to appear on the market. And more and more researchers are gradually concerned about the quality control of ZQ, which needs further relevant study.

Ethnopharmacology

ZQ has been traditionally applied in TCM for centuries. It was first recorded in '*Lei Gong Pao Zhi Lun*' which is the earliest extant Chinese medicine processing monograph published in the Northern and Southern Dynasties (A.D. 420–589). It is bitter, pungent and soreness in taste, coolness in nature, and acts on the spleen, and stomach channels. Based on '*Ben Cao Gang Mu*' (the Ming Dynasty, A.D. 1552–1578), ZQ has functions of promoting flow of Qi, reliving asthma, removing phlegm, relieving pain, and treating dysentery. At present, people gradually accept that ZQ can alleviate chest pain and improve gastrointestinal functions such as alleviating dyspepsia in a gentle yet efficient manner (Bai et al. 2018).

In traditional applications, there are many clinical cases of using ZQ alone to treat diseases. "*Jing Yan Fang*" written in the Qing Dynasty (A.D. 1777) records the usage of single ZQ for the treatment of rectal prolapse after childbirth. In the treatment of patients with gastroptosis, Tan used ZQ alone to relief symptom, and the cure rate is up to 100% (Tan 1998). Zhang also took advantage of ZQ alone for treating vertebral artery type of cervical spondylosis, ureteral calculus and gallstone, and the results were remarkable (Zhang 2005). Moreover, ZQ can help other herbs work better such as treating chest distress and asthma paired with Platycodonis Radix (called Jiegeng, JG in Chinese) (Wang 2002), and regulating functions of the internal organs to disperse the stagnation of liver-qi and uplift yang-qi when meeting Bupleuri Radix (called Chaihu, CH in Chinese) (Qiu et al. 2011). Some experiments have also proved that ZQ and Magnoliae Officinalis Cortex (called Houpo, HP in Chinese) could play the role of antidepressant, prokinetic, anti-inflammatory and anti-oxidative (Shi et al. 2020).

In 2018, National Administration of TCM announced 100 ancient classic prescriptions, of which 4 prescriptions contain ZQ. Interestingly, both these 4 prescriptions were recorded in medical books after the Song Dynasty. Before this, the classic prescriptions only included ZS rather than ZQ (Table 2). This is because the division of ZQ and ZS gradually appeared from the Tang Dynasty due to different medical sections, harvesting time, processing method and so on. Scholars believed that there was a mixed use of ZQ and ZS in ancient China (Hu et al. 2019; Zhao et al. 2020). Although the names of medicines in the classic prescriptions are the same in different ages, their connotations have changed a lot. For example, transformations have occurred in the plant origins, producing areas, harvesting time and processing methods of ZQ in different historical periods, which directly affect the collection of research and development samples. Therefore, the key information about ZQ in the classical prescriptions need to be investigated carefully to provide bases for development and clinical use.

Phytochemistry

Researchers have used a variety of methods for extraction, separation, characterization and identification to study the multiplicate compositions of ZQ. To date, a total of 62 compounds have been isolated and assuredly identified from ZQ, predominantly containing flavonoids, coumarins, alkaloids and limonoids. Compounds presenting in ZQ are summarized in Table S1, and the major ones are illustrated in Tables 3, 4, 5, 6 and Figs. 3, 4, 5.

Table 2 Application of ZQ and ZS in classical prescriptions of TCM

Prescription name	Main herbs	Traditional use	References	Dynasty
Huaihua Powder	Sophorae Flos, Platycladi Cacumen, Schizonepetae Spica, Aurantii Fructus	Curing hemorrhoidal bleeding	Pu Ji Ben Shi Fang	Song (A.D. 960–1279)
Ganlu Yin	Eriobotryae Folium, Rehmanniae Radix Praeparata, dried root of *Asparagus cochinchinensis*(Lour.) Merr, Aurantii Fructus	Clearing heat in stomach	Tai Ping Hui Min He Ji Ju Fang	Song (A.D. 960–1279)
Jichuan Jian	Angelicae Sinensis Radix, Achyranthis Bidentatae Radix, Aurantii Fructus	Treating senile constipation and habitual constipation	Jing Yue Quan Shu	Ming (A.D. 1368–1644)
Liangxue Dihuang Decoction	Angelicae Sinensis Radix, Rehmanniae Radix, Coptidis Rhizoma, Aurantii Fructus	Curing hemorrhoidal bleeding	Wai Ke Da Cheng	Qing (A.D. 1636–1921)
Xiaochengqi Decoction	Aurantii Fructus Immaturus, Rhei Radix Et Rhizoma, Magnoliae Officinalis Cortex	Reliving chronic constipation and food stagnation	Shang Han Lun	Han (B.C. 202-A.D. 220)
Zhishi Xiebai Guizhi Decoction	Aurantii Fructus Immaturus, Allii Macrostemonis Bulbus, Cinnamomi Ramulus	Reducing heart and chest pain	Jin Gui Yao Lue	Han (B.C. 202-A.D. 220)
Houpo Qiwu Decoctoin	Magnoliae Officinalis Cortex, Glycyrrhizae Radix Et Rhizoma, Rhei Radix Et Rhizoma, Aurantii Fructus Immaturus	Dissipating cold and painful abdominal mass	Jin Gui Yao Lue	Han (B.C. 202-A.D. 220)
Wendan Decoction	Pinelliae Rhizoma, Bambusae Caulis In Taenias, Aurantii Fructus Immaturus	Dissipating stagnant qi and eliminating sputum in gallbladder	Bei Ji Qian Jin Yao Fang	Tang (A.D. 618–907)
Sanhua Decoction	Magnoliae Officinalis Cortex, Rhei Radix Et Rhizoma, Aurantii Fructus Immaturus, Notopterygii Rhizoma Et Radix	Treating stroke	Su Wen Bing Ji Qi Yi Bao Ming Ji	Jin (A.D. 1115–1234)

Flavonoids

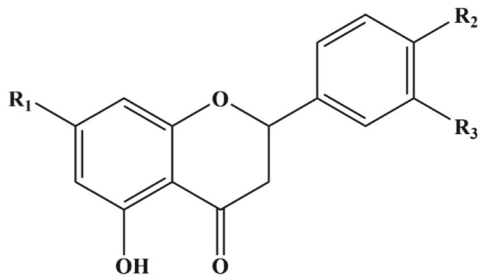
According to different oxidation conditions and distinctive types and positions of substituents, flavonoids in ZQ are mainly divided into four types: flavanones, polymethoxy flavonoids (PMFs), flavones and flavonols.

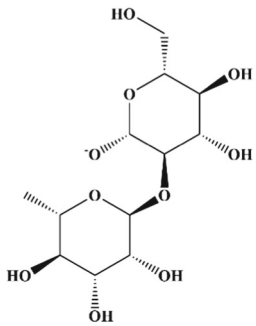
Flavanones

ZQ flavanones are present in the glycoside or aglycone forms. Among the aglycone forms, naringenin (**9**) and hesperetin (**11**) are the most important flavanones (Tripoli et al. 2007). Among the glycoside forms, two types are classified: neohesperidoside and rutinoside. Narirutin (**4**), hesperidin (**5**), eriocitrin (**2**) and didymin (**7**) have a flavanone and a rutinose (ramnosyl-α-1,6 glucose) and they are without taste, while naringin (**1**), neohesperidin (**6**), neoeriocitrin (**3**) and poncirin (**8**) consist of a flavanone with neohesperidose (rhamnosyl-α-1,2 glucose) and they have a bitter taste (Gattuso et al. 2007). Especially naringin (**1**) and neohesperidin (**6**) are the most abundant components of flavanones in *C. aurantium* L., and are also the quality markers stipulated in 2015 Edition ChP. However, naringin (**1**) and neohesperidin (**6**) are not detected in *C. sinensis* (L.) Osbeck which called sweet orange.

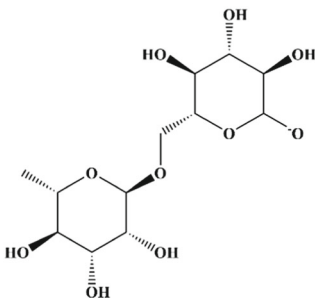
Studies found that the glycosylation of hydroxyl at the C7 reduced the biological activity of flavanones. For cytotoxic investigation, naringenin (**9**) and hesperetin (**11**) exhibited more significant cytotoxic effect in HL-60 cells ($p < 0.01$) than that of naringin (**1**) and hesperidin (**5**) accompanied by the dose- and time-dependent appearance of characteristics of apoptosis including an increase in DNA ladder intensity, morphological changes, appearance of apoptotic bodies, and an increase in hypodiploid cells by flow cytometry analysis (Chen et al. 2003). For anti-inflammation study, naringenin (**9**) and hesperetin (**11**) induced heme oxygenase 1 (HO-1) protein expression in the presence or absence of lipopolysaccharide (LPS), and

Table 3 Molecular structure of flavanones





Neohesperidoside

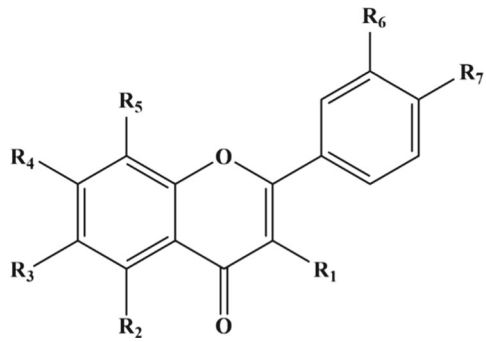


Rutinoside

Name	R_1	R_2	R_3
Naringin (**1**)	Neohesperidoside	H	OH
Neohesperidin (**6**)	Neohesperidoside	OH	OCH_3
Neoeriocitrin (**3**)	Neohesperidoside	OH	OH
Poncirin (**8**)	Neohesperidoside	H	OCH_3
Narirutin (**4**)	Rutinoside	H	OH
Hesperidin (**5**)	Rutinoside	OH	OCH_3
Eriocitrin (**2**)	Rutinoside	OH	OH
Didymin (**7**)	Rutinoside	H	OCH_3
Naringenin (**9**)	OH	H	OH
Hesperetin (**11**)	OH	OH	OCH_3
Eriodictyol (**10**)	OH	OH	OH
Naringenin-7-*O*-β-D-glucopyranside (**12**)	Glucopyranside	H	OH
(2S) -6″-*O*-acetylprunin (**13**)	5-Acetyl-glucopyrans	H	OH
(2R) -6″-*O*-acetylprunin (**14**)	5-Acetyl-glucopyrans	H	OH

showed time- and dose-dependent inhibition of LPS-induced nitric oxide (NO) production ($p < 0.01$) and inducible nitric oxide synthase (iNOS) expression in RAW264.7, J774A.1, and thioglycolate-elicited peritoneal macrophages. Furthermore, by using reverse transcription-polymerase chain reaction (RT-PCR) assay, hesperetin (**11**) and naringenin (**9**), but not hesperidin (**5**) and naringin (**1**), decreased LPS-induced iNOS mRNA expression at the dose of 200 μM respectively (Lin et al. 2005). It suggested that neohesperidoside and rutinoside at C7 in

Table. 4 Molecular structure of PMFs



Name	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Nobiletin (**15**)	H	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
Tangeretin (**16**)	H	OCH_3	OCH_3	OCH_3	OCH_3	H	OCH_3
Sinensetin (**26**)	H	OCH_3	OCH_3	OCH_3	H	OCH_3	OCH_3
Isosinensetin (**24**)	H	OCH_3	H	OCH_3	OCH_3	OCH_3	OCH_3
5,6,7,4′-Tetramethoxyflavone (**18**)	H	OCH_3	OCH_3	OCH_3	H	H	OCH_3
5,7,8,4′-Tetramethoxyflavone (**28**)	H	OCH_3	H	OCH_3	OCH_3	H	OCH_3
4′-Hydroxy-5,6,7-trimethoxyflavone (**27**)	H	OCH_3	OCH_3	OCH_3	H	H	OH
5-Hydroxy-6,7,8, 3′,4′-Pentamethoxyflavone (**17**)	H	OH	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
5-Hydroxy-6,7,8,4′-tetramethoxyflavone (**20**)	H	OH	OCH_3	OCH_3	OCH_3	H	OCH_3
5-Hydroxy-6,7,3′,4′-tetramethoxyflavone (**19**)	H	OH	OCH_3	OCH_3	H	OCH_3	OCH_3
Eupatilin (**22**)	H	OH	OCH_3	OH	H	OCH_3	OCH_3
5,6-Dihydroxy-7,4′-dimethoxyflavone (**30**)	H	OH	OH	OCH_3	H	H	OCH_3
Natsudaidain (**21**)	OH	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
3′,4′,3,5,6,7,8-Heptamethoxyflavone (**25**)	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
Vitexicarpin (**23**)	OCH_3	OH	OCH_3	OCH_3	H	OH	OCH_3

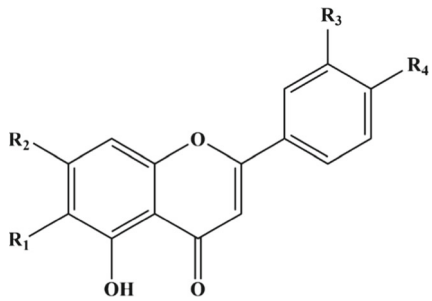
flavanones prevented the induction of apoptosis and the inhibition of LPS-induced NO production.

It is reported that naringenin (**9**) (100 μM) dramatically inhibited the active tension on spontaneous contractions of intestine smooth muscle, but hesperetin (**11**) had no significant effect at the same concentration (He et al. 2018a). From a chemical structure perspective, the only difference between naringenin (**9**) and hesperetin (**11**) is the hydroxy substitution in the B cycle, which is 4′-hydroxy in naringenin (**9**) and 3′-hydroxy-4′-methoxy in hesperetin (**11**). This indicated that 4′-hydroxy was the essential group for inhibitory effects on jejunum contraction. Nevertheless, evaluations involving a series of homologues should be performed to validate the structure–activity relationship.

PMFs

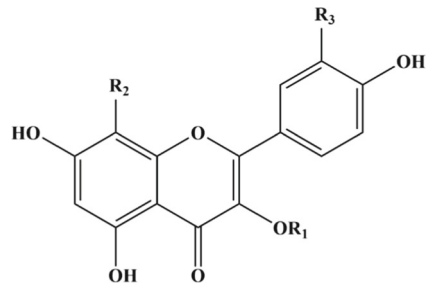
PMFs refer to a class of natural products containing 4 or more methoxy groups on the molecular skeleton of flavonoids, which is a unique bioflavonoid in *Citrus* plants. According to literature, PMFs have exceptional pharmacologic activity such as antioxidant,

Table 5 Molecular structure of flavones



Name	R_1	R_2	R_3	R_4
Diosmin (**31**)	H	Rutinoside	OH	OCH_3
Saponarin (**32**)	*C*- Glucoside	*O*- Glucoside	H	OH
Apigenin (**33**)	H	OH	H	OH
Rhoifolin (**34**)	H	Neohesperidoside	H	OH

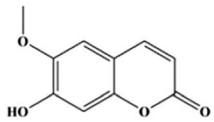
Table 6 Molecular structure of flavonols



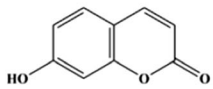
Name	R_1	R_2	R_3
5,7,4′-Trihydroxy-8,3′-dimethoxyflavone-3-*O*-6″ -(3-hydroxyl-3-methylglutaroyl)-β-*D*-glucopyranoside (**29**)	6″-(3-hydroxyl-3-ethylglutaroyl)-β-*D*-glucopyranoside	OCH_3	OCH_3
Rutin (**35**)	Rutinose	H	OH

antimicrobial (Mokbel and Suganuma 2006) and gastric mucosal protective properties (Takase et al. 1994a). PMFs are considerably less polar and assume planar structures. These features of the polymethoxylated flavones influence their biological properties, including their permeabilities to biological membranes, metabolic fates, and binding properties.

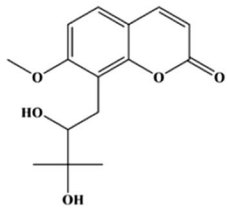
The number and position of methoxy groups of PMFs are important factors for their efficacy. 3′,4′,3,5,6,7,8-heptamethoxyflavone (**25**) which has largest number -7 of methoxy groups showed better permeability of the serum and brain tissues than those of other PMFs (nobiletin (**15**), tangeretin (**16**), and natsudaidain (**21**)). For the suppressive effect of PMFs on MK-801-induced locomotive hyperactivity, 3′,4′,3,5,6,7,8-heptamethoxyflavone (**25**) significantly decreased the total distance traveled (117% ± 27.3%, $p < 0.05$), nobiletin (**15**) and tangeretin (**16**) had a tendency to suppress the MK-801-induced increase in locomotive activity (159% ± 19.0% and 167% ± 20.2%, respectively), but natsudaidain (**21**) treatment had no obvious effect (207% ± 22.7%) (Okuyama et al. 2017). Moreover, the increase of total number of methoxy side groups in PMFs was



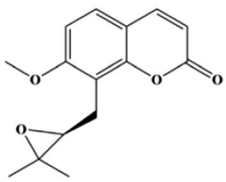
Scopoletin (**43**)



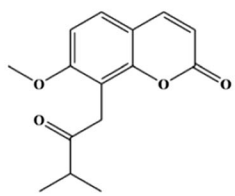
Umbelliferone (**47**)



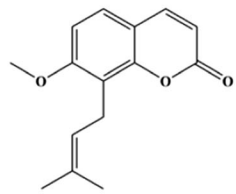
Meranzin hydrate (**36**)



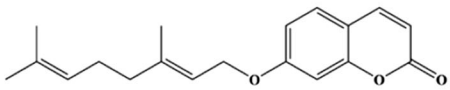
Meranzin (**38**)



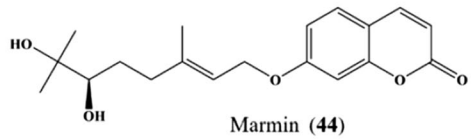
Isomeranzin (**39**)



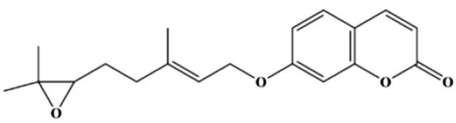
Osthole (**40**)



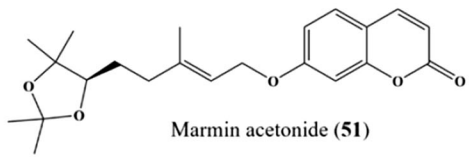
Auraptene (**45**)



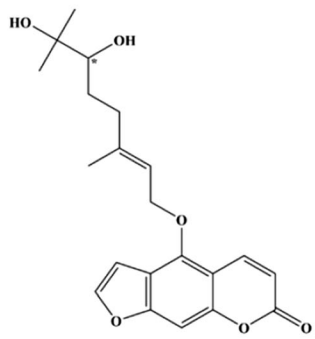
Marmin (**44**)



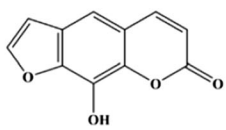
Epoxyaurapten (**50**)



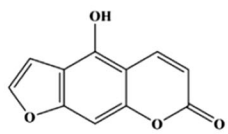
Marmin acetonide (**51**)



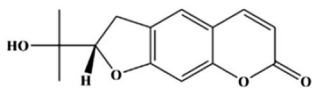
6′,7′-Dihydroxybergamottin (**48**)



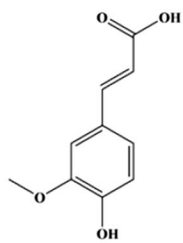
Xanthotoxol (**41**)



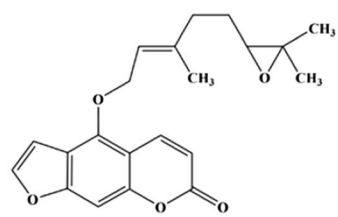
Bergaptol (**49**)



Marmesin (**46**)

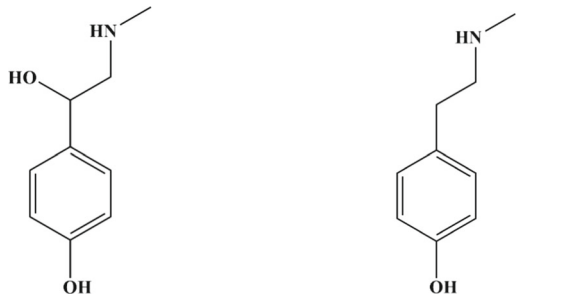


Ferulic acid (**52**)



Epoxybergamottin (**53**)

◀ **Fig. 3** The major coumarins presenting in ZQ



Synephrine (**54**) *N*-methyltyramine (**55**)

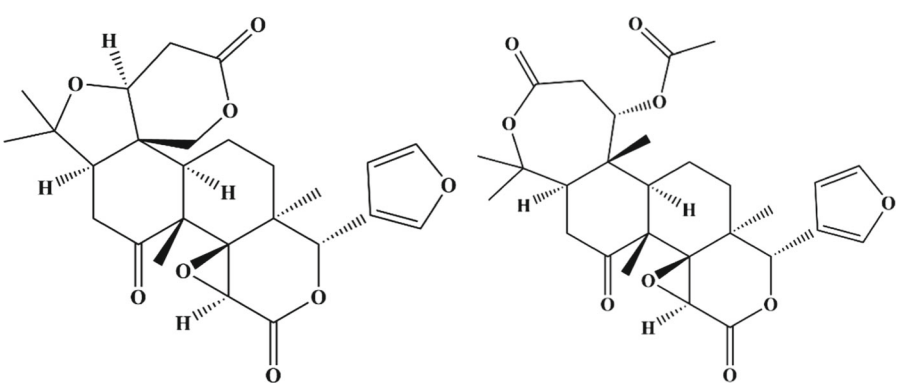
Fig. 4 The major alkaloids presenting in ZQ

positively correlated with the overall anti-proliferative activity of compounds in HL-60 cell lines. IC_{50} rapidly decreased in a row of sinensetin (**26**) < nobiletin (**15**) < 3,5,6,7,8, 3′,4′-heptamethoxyflavone (> 100, 41.50 ± 7.01, 13.31 ± 1.28 μM, respectively) (Li et al. 2007a).

The substituents at the C3 and C5 also play a key role in the efficacy of PMFs. Nobiletin (**15**) (64 μM), but not natsudaidain (**21**), directly inhibited mitogen-activated protein/extracellular signal-regulated kinase (MEK) activity compared with 12-*O*-tetradecanoyl phorbol 13-acetate (TPA)-treated cells in vitro ($p < 0.001$). And natsudaidain (**21**) (16, 32, 64 μM) which attaches a hydroxy in C3 exhibited no or less inhibitory effect than that of nobiletin (**15**) on the proMMP-9/progelatinase B production in HT-1080 cells (Miyata et al. 2008). However, substitution of the methoxy groups with hydroxyls in 5-position is linked to significant increase in bioactivity. 5-hydroxy-6,7,8,3′,4′-pentamethoxy flavone (2.07 ± 2.56 μM) was more than 20-fold effective in suppressing HL-60 cell growth compared to nobiletin (**15**) (41.50 ± 7.01 μM). Additionally, lack of either the 3′- or 8-methoxy group renders hydroxylated PMF inactive, such as 5-hydroxy-6,7,8,3′,4′-pentamethoxyflavone (5.87 ± 0.13 μM) showed stronger activity induced apoptosis of HL-60 cells than 5-hydroxy-6,7,3′,4′-tetramethoxyflavone (**19**) (> 100 μM) and 5-hydroxy-6,7,8,4′-tetramethoxyflavone (**20**) (> 100 μM) (Li et al. 2007a).

Flavones and flavonols

Flavones are based on 2-phenyl chromone without substituent at C3. While the structural feature of flavonols is that there are hydroxyl groups or other oxygen-containing groups at C3 of the structure of the flavonoids. Both flavones and flavonols have a C2–C3 double bond structure of C ring. This is the active structure that induces tumor cytotoxicity. Studied found that TNF-α induction was totally abrogated after incubation with apigenin (**33**), while naringenin (**9**) and hesperetin (**11**) only inhibited the TNF-α surge by 50% or less (Lopez-Posadas et al. 2008). Apigenin (**33**) was the effective vascular endothelial growth factor (VEGF) inhibitor, with IC_{50} values 5.9 ± 0.1 μM, while naringenin (**9**) was inactive in this assay (Anso et al. 2010). Additionally, C2–C3



Limonin (**56**) Nomilin (**58**)

Fig. 5 The major limonoids presenting in ZQ

double bond is beneficial to the resonance stability of the formed free radicals (Barreca et al. 2020) and has a certain effect on the oxidation resistance (Modak et al. 2005; Cai et al. 2006). The hydroxyl group at C3′ has also been proved to possess closely relation to the scavenging activity of free radicals. The antioxidant activity of rutin (**35**) was significantly higher than that of the similar structure of morin, IC_{50} value was 2.22 and 76 μg/mL, respectively (Hui et al. 2019).

To sum up, these structures of flavonoids ensure that they can support and enhance the body's defenses against oxidative stress and help the organism in the prevention of cardiovascular diseases, atherosclerosis, and cancer (Barreca et al. 2017). In addition to ZQ, there are also a large number of biologically active flavonoids in ripe fruits of *C*. aurantium L. Barreca' team firstly discovered new ingredients (lucenin-2, vicenin-2, lucenin-2, 4′-methyl ether, rhoifolin 4′-glucoside, narirutin 4′-glucoside, melitidin and brutieridin) in fresh sour orange juice via reverse-phase LC–DAD–ESI–MS–MS analysis (Barreca et al. 2011). These components can be responsible for antioxidant activity (Barreca et al. 2014). This has a positive impact on the development of new drugs led by flavonoids.

Coumarins

Coumarins derived from a branch of the phenylalanine metabolism pathway mainly include meranzin hydrate (**36**), marmin (**44**), auraptene (**45**), umbelliferone (**47**), etc. in ZQ. Coumarins are another major class of bioactive compounds found in *Citrus* herbs (Yamada et al. 1987).

Scopoletin (**43**) and umbelliferone (**47**) have the hydroxyl group at C7, which is important for their antioxidant and antimicrobial activities. Scopoletin (**43**) inhibited the release of superoxide anion more efficiently than that of hydrogen peroxide or substrate oxidation. The inhibition of three-specific aldehyde oxidase substrates containing phthalazine, indole-3-adehyde and phenanthridine was significant in the presence of 10, 50 and 100 μM scopoletin (**43**) compared with the control values ($p < 0.05$, $p < 0.01$, $p < 0.005$) (Al-Omar and Al-Arifi 2005). In addition to antioxidant capacity, umbelliferone (**47**) also had good inhibitory of *Staphylococcus aureus* ATCC-29213 (MIC = 500 μg/mL), *Pseudomonas aeruginosa* ATCC-9027 (MIC = 500 μg/mL) (Shakeel et al. 2010), *Enterobacter aerogenes* CM 64 (MIC = 128 μg/mL) and *Escherichia coli* AG 100 (MIC = 256 μg/mL) (Fouotsa et al. 2013).

C7 is often replaced by methoxy as well. For osthole (**40**), the methoxy group at C7 and the 3-methyl-2-butenyl group at C8 were necessary for its anti-hepatitis C virus activity. Intraperitoneal injection of osthole (**40**) at the dose of 100 mg/kg (n = 10) inhibited 85% of the Con A-induced elevation of plasma alanine transaminase (ALT). In contrast, osthenol, the product of the hydroxyl group substituted for the 7-methoxy group of osthole (**40**), showed inhibition of 32%, 7-hydroxycoumarin without substitution in C8 shows inhibition of 9% (Wu and Xu 2010; Mazzei et al. 2008; Okamoto et al. 2007). However, it has other pharmacological effects after being replaced by other substitutions in C8, such as meranzin hydrate (**36**). Meranzin hydrate (**36**) induced similar effect to ZQ. In healthy rats, meranzin hydrate (**36**) (7, 14, and 28 mg/kg) and ZQ (3.3, 10, and 20 g/kg) both promoted intestinal transit and gastric emptying in a dose-dependent manner when gavaged acutely (Huang et al. 2011). Meranzin hydrate (**36**) (28 mg/kg) significantly accelerated gastric emptying and intestinal transit (72.9 ± 3.8% and 75.2 ± 3.1%) compared with the control (55.45 ± 3.7% and 63.51 ± 5.1%, $p < 0.05$) (Qiu et al. 2011). It is also a key component in the anti-depressive effects of ZQ and prescriptions containing ZQ (Xie et al. 2013a; Fan et al. 2012; Choi et al. 2017). Studies suggested that the isolation of meranzin hydrate (**36**) by thin layer chromatography is considered to be a consequence of hydration of meranzin (**38**) during chromatograph (Mchalce et al. 1987). Besides, isomeranzin (**39**) dose-dependently inhibited mRNA and protein expression of IL-1β, IL-6 and TNF-α in M1-polarized BMDMs and Raw264.7 cells. And also significantly raised the mice survival rate to 40% in LPS-induced shock at 30 mg/kg. It indicated that isomeranzin (**39**) specifically reduced the M1 macrophage-associated pro-inflammatory cytokines to suppress inflammatory diseases (Xu et al. 2016). Meranzin hydrate (**36**), meranzin (**38**) and isomeranzin (**39**) are structurally similar, the structure–activity relationship between them is worthy of further study.

The C7 of auraptene (**45**), marmin (**44**), epoxyauraptenen (**50**) and marmin acetonide (**51**) are also substituted by various substitutions. Auraptene (**45**) has a variety of biological activities, such as tumor

inhibition and nerve cell protection. Treatment with auraptene (**45**) decreased the levels of both intracellular and extracellular proMMP-7 production in the human colorectal adenocarcinoma cell line HT-29, with IC_{50} values of 2.8 and 3 μM, respectively. In contrast, umbelliferone (**47**) had no effect even at 100 μM (Kawabata et al. 2006). On the other hand, auraptene (**45**) exerted a good dose-dependent manner protective effect against *N*-methyl-D-aspartate (NMDA)-induced neurotoxicity in particular at concentrations ranging from 1 to 10 μM (Epifano et al. 2008). Marmin (**44**) had a strong activity against gastric ulcer. Except for inhibiting the appearance of ethanol-induced gastric hemorrhagic lesions with ED_{50} values 17.2 mg/kg, marmin (**44**) significantly prevented the gastric transmucosal potential difference (PD) reduction induced by ethanol at a dose of 25 mg/kg intragastrically (Takase et al. 1994b). Both are likely to be new drug candidates. However, the content of auraptene (**45**) and marmin (**44**) in ZQ is very low. Therefore, some scholars studied the synthesis of auraptene (**45**) and marmin (**44**). As raw materials, geraniol and umbelliferone (**47**) were taken to synthesize auraptene (**45**) by the reaction of chlorination and ether formation. And then marmin (**44**) was synthesized from auraptene (**45**) via Sharpless asymmetric alkene hydroxylation reaction (Zhang et al. 2010). Furthermore, Su used the transforming strain RR1 in the transforming system with pH of 7.5 and temperature of 30 °C to bioconvert auraptene (**45**) into marmin (**44**) (Su et al. 2010).

ZQ also contains a certain amount of furanocoumarins including xanthotoxol (**41**), bergaptol (**49**), 6′,7′-dihydroxybergamottin (**48**), marmesin (**46**). Besides, Barreca et al. isolated a new furocoumarin called epoxybergamottin (**53**) which was quantified as 0.27 ± 0.010 mg/L in *C.* aurantium L. fruit juice (Barreca et al. 2012b). Furanocoumarin is a kind of photosensitizer of natural plants. Especially, it has the linear structure of furanocoumarin ring, which has a strong absorption effect on all wavelengths of light and can increase the sensitivity of ultraviolet A (UVA) in organisms. Therefore, it can be used as a photosensitizer to enhance the sensitivity of skin to light. Among them, xanthotoxol (**41**) had strong photosensitive activity and could be used in the treatment of psoriasis, vitiligo, mortis and other skin diseases (Xiong et al. 2010). At the same time, xanthotoxol (**41**) showed good antioxidant activity in lipid peroxidation test and hemolysis test. In brain and kidney homogenates, the inhibitions for malondialdehyde (MDA) formation of xanthotoxol (**41**) were 71.31% and 61.94%, respectively ($p < 0.05$). And xanthotoxol (**41**) had effects of natural products on hemolysis of rat erythrocytes with inhibition being 79.85% (Ng and Wang 2000). By using 2,2′-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) and 1,1-diphenyl-2-picrylhydrazyl (DPPH) method, Girennavar et al. found that bergaptol (**49**) also showed very good radical scaenging activity at all the tested concentrations (200, 400, 800 ppm) in dose-dependent manner (Girennavar et al. 2007). It suggested that phenolic hydroxyl groups might be the pivotal to the antioxidant activity of coumarins. 6′,7′-dihydroxybergamottin (**48**) has been identified as potent inhibitors of CYP3A4 in vitro (Edwards et al. 1999). Grapefruit juice significantly reduced CYP3A activity in contrast to orange juice ($p < 0.05$), which contained no measurable 6′,7′-dihydroxybergamottin (**48**) (28.6% vs. 62.2% of control activity). After added 30 μM 6′,7′-dihydroxybergamottin (**48**), orange juice would decrease CYP3A activity to values comparable to those observed with grapefruit juice (Edwards et al. 1996). Marmesin (**46**) was a novel angiogenesis inhibitor. Marmesin (**46**) treatment (0.1, 1, 10 μM) dose-dependently suppressed cell proliferation in response to VEGF-A stimulation and did not alter cell viability (Kim et al. 2015). In a word, furanocoumarins are a treasury of natural medicine, which should be further studied and explored.

Alkaloids

As the highest content of alkaloids in ZQ, synephrine (**54**) is a highly water-soluble sympathomimetic amine, and the stability of which can be affected by prolonged heat and light (Pellati and Benvenuti 2007). Synephrine (**54**) exist in three different positional isomeric forms (*ortho o-, meta m-, and para p-*) and each positional isomer is also found in two enantiomeric forms (Haaz et al. 2006). Most studies stated that only p-synephrine can be found in *Citrus* fruits, whereas others claimed that *m*-synephrine is also present (Adriane 2004; Arbo et al. 2008; Andrade et al. 2009). However, *o*-synephrine cannot be obtained from natural sources up to now (Santana et al. 2008; Penzak 2001; Bent et al. 2004). Synephrine (**54**) are closely related to endogenous neurotransmitters and

ephedrine in structure. It is an adrenergic agonists not only has a vasoconstrictive effect but also has a strong expansion function in the trachea and bronchi. It is characterized to have a rapid action and fast elimination. In addition, synephrine (**54**) could improve metabolism, increase calorie consumption, oxidation of fats through an increased thermogenesis, and stimulate lipolysis presumably by means of β−3 adrenergic receptors (Mattoli et al. 2006). It is often incorporated into supplements designed to lose body weight or improve general performance (Haaz et al. 2006; Di Lorenzo et al. 2014; Rossato et al. 2011).

Synephrine (**54**) is formed in *Citrus* by a pathway involving *N*-methyltyramine (**55**) (Wheaton and Stewart 1969) which has numerous pharmacological activities such as raising blood pressure, increasing blood flow, and enhancing the contractive strength of heart muscle (Kusu et al. 1992). Compared with synephrine (**54**), *N*-methyltyramine (**55**) has one less hydroxyl substitution. This may lead to differences in pharmacological effects between them. In rats, synephrine (**54**) (0.01–1000 μg/mL) was clearly stimulatingthe lipolysis in a dose-dependent manner ($p < 0.001$), reaching around 80% of the maximal response to isoprenaline, while *N*-methyltyramine (**55**) was not lipolytic. In human adipocytes which were obtained from ten overweight women, although both synephrine (**54**) and *N*-methyltyramine (**55**) increased lipolysis, the lipolysis of synephrine (**54**) (33%) was still more than that of *N*-methyltyramine (**55**) (20%) (Mercader et al. 2011).

Limonoids

Limonoids are often reported in *Citrus* plants (He et al. 2018b). Limonoids are a group of chemically related, highly oxygenated, tetracyclic triterpenoids in aglycone and glucosidic forms (Tian and Stewart 2003). Both limonin (**56**) and nomilin (**58**) are limonoid aglycones. The *Citrus* bitter principle limonin (**56**) was first isolated in 1841, and the structure of limonin (**56**) was confirmed by chemical and X-ray diffraction in the 1960s (Arigoni et al. 1960). Nomilin (**58**) is a limonoid first isolated from the seeds of oranges and lemons (Emerson 1948). It is bitter and is reported to be about twice as bitter as limonin (**56**) (Emerson 1951; Dreyer 1965). Limonin (**56**) followed by nomilin (**58**) are the most abundant aglycones (Andrew and Breksa 2006). Nomilin (**58**) is the initial precursor of all the limonoids known to be present in *Citrus* and *Citrus* hybrids (Hasegawa et al. 1986a), and limonin (**56**) are considered the terminal points in the aglycone biosynthetic pathway (Hasegawa et al. 1986b).

Shi found that with the increase of the ripeness of *C. aurantium* L. fruits, the content of limonin (**56**) peaked in mid-June (0.5%). Then it showed a decline followed by an increase and then a decrease. The content of limonin (**56**) in early September was the lowest (0.26%) (Shi 2012). Meanwhile, nomilin (**58**) concentrations were found to be greatest in early season juices and decrease rapidly with increasing fruit maturity. Nomilin (**58**) concentrations fell more rapidly than that of limonin (**56**). In November the nomilin (**58**)/limonin (**56**) ratio was 0.125, by January the level has fallen to 0.100 and the ratio for the April juices was 0.038 (Rouseff 1982). This suggested that the maturity of ZQ was an important factor affecting its quality.

Limonin (**56**) and nomilin (**58**) have a wide spectrum of pharmacological effects. A dose-dependent induction in rat liver GST activity was observed following dietary treatment with either limonin (**56**) or nomilin (**58**). Statistically significant induction was seen at the higher dose levels (5, 10 mg) of both limonin (**56**) ($977 \pm 37, 967 \pm 37$ nmol/min/mg) and nomilin (**58**) ($1653 \pm 162, 1410 \pm 24$ nmol/min/mg) ($p < 0.05$) (Kelly et al. 2003). In another study, limonin (**56**) and nomilin (**58**) were found to inhibit the HIV-1 replication in all cellular systems used. Incubation with limonin (**56**) and nomilin (**58**) would dose-dependently inhibit viral replication in peripheral blood mononuclear cell (PBMC) isolated from healthy donors and infected with HIV-1 strain (EC_{50} values: 60.0 μM and 52.2 μM, respectively) (Battinelli et al. 2003). This indicated that anti-HIV activities of limonin (**56**) and nomilin (**58**) were not drastically influenced by the structural difference between the two compounds. Furthermore, both limonin (**56**) and nomilin (**58**) could anti-oxidation (Sun et al. 2005) and liver protection properties (Fan et al. 2019). Although a lot of research has been done on the biological activity of limonoids, it was often concentrated on the study of several common compounds. Therefore, it is still necessary to conduct in-depth systematic biological activity research on limonoids.

Volatile oils

The volatile oils in ZQ were widely used as flavoring in foods, perfumes and pharmaceutical formulations (Sara 2004) due to their pharmacological activities like antifungal (Viuda-Martos et al. 2008), anticancer (Asamoto et al. 2002), antimicrobial and antioxidant (Fernandez-Lopez et al. 2005). Except for the fruit of *C. aurantium* L., other parts also have volatile oil. Volatile oils from the dried peel of unripe fruit flavors Curacao, Cointreau, and Triple Sec, and volatile oils from the flowers, called neroli, was used in perfumes, liqueurs, and orange-flower water, which was used to flavor sweets (Adriane 2004; Kenneth and Kiple 2000). Among them, the volatile oil from *C. aurantium* L. *var. amara* Engl. was one of the best *C. aurantium* oils. The bioactivities of it at 250 μg/mL showed greater anti-inflammation potential than that of antioxidant, anticancer, and 3T3-L1 proliferation inhibition (Shen et al. 2017). Most of volatile oils belonged to monoterpenes (98.0%) (Njoroge et al. 1994) and sesquiterpenes. In terms of reports (Li et al. 2016), the most predominant volatile constituent was D-limonene (94.7%) (Liu et al. 2014; Njoroge et al. 1994), followed by γ-terpinene, linalool, o-cymene, germacrene D, β-myrcene, β-pinene, α-pinene, trans-β-ocimene, terpinolene, α-terpineol, and δ-Cadinene.

Other chemical compositions

Citric acid (**59**), quinic acid (**60**), β-sitosterol (**61**) and daucosterolpalmitate (**62**) have been isolated from ZQ. ZQ is also rich in the nutrients necessary for human life, such as amino acids (He et al. 2018b), polysaccharides (Wang et al. 2014). All of these ingredients together form a large and complex material basis of ZQ.

Biological activities

Modern pharmacological studies have indicated that ZQ exhibits extensive range of biological activities in digestive system, cardio-cerebrovascular system and immune system. Furthermore, ZQ has the same therapeutic actions on digestive system in accordance with 2015 Edition ChP. These effects are inseparable from its antioxidant and anti-inflammatory properties. (Table S2.a-2.b).

Effect on the digestive system

Regulating gastrointestinal motility

In TCM, ZQ has been used for the treatment of indigestion and flatulence. Modern pharmacological studies have also shown that ZQ and its ingredients have a good role in exciting gastrointestinal smooth muscle and promoting gastrointestinal movement. Meranzin hydrate (**36**) had a significant dose-dependent stimulant effect of the amplitude of isolated rat jejunum by stimulation of H1 histamine (HA) receptors in part, it increased the mean amplitude of contractions in the longitudinal and circular strip in vitro (Huang et al. 2011). In vivo, experimental rats were administered 0.3 g/mL ZQ water decoction at 2.0 mL/100 g body weight per day for 7 days by gavage feeding, while control rats were gavage fed equal volumes of distilled water. The expression levels of 5-hydroxytryptamine (5-HT) and vasoactive intestinal peptide (VIP) were measured by immunohistochemical staining and microscopic image analysis of the gastrointestinal (GI) mucosa and myenteric nerve plexus. The results showed that ZQ could enhance gastrointestinal motility by increasing 5-HT content over a broad area of the mucosal layer and downregulating VIP expression in the myenteric plexus in the rat GI tract (Jiang et al. 2014). Wang investigated the effect of flavonoids isolated from ZQ on gastric emptyment and intestinal propulsion in mice. The mice were orally administered the solution of flavonoids (8.02 g/kg, 2.68 g/kg, 0.89 g/kg) once daily (control group with saline) for 7 days. After the formula calculation, the gastric residual rates of flavonoids groups were lower than that in control group and with significant differences ($p < 0.05$), the small intestinal propulsive rates were higher ($p < 0.05$), and the promotion effect was dose-dependent (Wang et al. 2017). When the main components of flavonoids, naringin (**1**) and neohesperidin (**6**), were given separately, there was no significant effect on intestinal propulsion in normal mice ($p > 0.05$). However, the combination of naringin (**1**) and neohesperidin (**6**) had obviously promoted the intestinal propulsion of normal mice ($p < 0.01$) (Yi et al. 2015). Naringin (**1**) and neohesperidin (**6**) could be broken down to their aglycon naringenin (**9**) and hesperetin (**11**) via the gut microflora, and absorbed from the gut (Choudhury

et al. 1999). Ma showed that the $AUC_{0\text{-}t}$ and C_{max} of naringenin (**9**) and hesperetin (**11**) in the combination of naringin (**1**) and neohesperidin (**6**) were increased compared with the monomer group of both (Ma et al. 2013). Wang also found that naringenin (**9**) was the component with the highest concentration among all constituents in rat plasma (Wang et al. 2018). Hence, whether naringin (**1**) and neohesperidin (**6**) played a role in promoting gastrointestinal movement or their aglycones remains to be further explored. Beyond that, other ingredients induced similar effect to ZQ on intestinal motility. Synephrine (**54**) promoted small intestinal propulsion in normal mice compared with the control ($p < 0.05$), and antagonized epinephrine induced inhibition of gastric emptation and intestinal propulsion in mice (Guan et al. 2002). Therefore, the traditional effects of ZQ on regulating qi and promoting digestion could be well explained.

On the other hand, ZQ has been proven to possess two-ways pharmacological effects on the gastrointestinal tract. In vitro, volatile oils (3 μL/mL, 10 μL/mL) extracted from ZQ could significantly slow down the frequency and amplitude of normal rat jejunal contraction (Hu et al. 1992). 10^{-8} to 10^{-3} mol/L of *N*-methyltyramine (**55**) significantly relaxed small intestinal smooth muscle in dose-dependently (Ni et al. 2019). Marmin (**44**) (10^{-7}–3×10^{-4} g/mL) and nobiletin (**15**) (10^{-7}–10^{-5} g/mL) exhibited concentration-dependent relaxations of contractions induced by acetylcholine, transmural electrical stimulation and HA in isolated guinea pig ileum, respectively (Hideki Takase 1994a). Similarly, in vivo experimental results of intestinal propulsion in mice showed that intragastric administration of volatile oil (10%, 20%) at 0.1 mL/10 g of body weight significantly inhibited intestinal propulsion (Hu et al. 1992). Ni also confirmed that intragastric administration of *N*-methyltyramine (**55**) (3, 9, 30 mg/kg) also inhibited small intestinal propulsion (Ni et al. 2019). According to Takase's study, both marmin (**44**) and nobiletin (**15**) given intragastrically at 10 mg/kg and 25 mg/kg inhibited gastric motor activity (Hideki Takase 1994a).

Traditional herbal formula which was consisted of HP and ZQ also induced bidirectional effects on gastric motility in rats. The in vitro experiments demonstrated that 3–10 μg/mL herb-pair concentration-dependently increased the mean amplitude of contractions in the antral circular strip compared to untreated controls ($p < 0.05$). While, the concentration of 30 μg/mL prohibited gastric antral smooth muscle contractility (Xiong et al. 2015). Similarly, lower dosage (10, 20 mg/kg) of them promoted gastric emptying in vivo, while higher dosage (30 mg/kg) produced inhibition (Xiong et al. 2015).

Anti-gastric ulcer effect

Hu studied that after administration of 1 mL/100 g of 20% volatile oils, it could prevent the formation of pyloric ligation ulcers in rats, and could significantly reduce the secretion of gastric juice and reduce pepsin activity compared with the control group ($p < 0.01$) (Hu et al. 1992). Furthermore, oral administration of marmin (**44**) and nobiletin (**15**) inhibited both the appearance of ethanol-induced gastric hemorrhagic lesions dose-dependently in a dose range of 10–50 mg/kg, with ED_{50} values for marmin (**44**) and nobiletin (**15**) being 17.2 and 8.0 mg/kg, respectively (Hideki Takase 1994a). Zhiqiao Jianwei Granules (ZQJWG) which regards ZQ as the Monarch herb, could significantly improve 75% ethanol-induced hyperemia, edema and inflammatory infiltration of gastric mucosa in rats. The dose of 5.4 g/kg and 10.8 g/kg could significantly reduce the ulcer index and the content of malondialdehyde (MDA) in the serum of rats in the model group, and increase the content of superoxide dismutase (SOD), nitric oxide (NO) and prostaglandinE_2 (PGE_2) in the serum with statistical significance (Liu et al. 2014).

Anti-depression activity

Depression, a common mental disorder, is often associated with gastrointestinal dysfunction such as abdominal discomfort, nausea, heartburn, bloating, diarrhea and constipation (Zou et al. 2004; Lu et al. 2017). But common antidepressants were discontinued because they inhibited gut movement (Xie et al. 2013b). Consequently, ZQ has become the research hotspots because they can promote gastrointestinal motility while exerting anti-depressant effects.

After oral administration of ZQ extracted by 70% ethanol (3, 9, 18 mg/kg) half an hour before the behavior test, the rats showed similar pharmacological effects to fluoxetine (20 mg/kg) such as producing a significant dose-dependent increase in locomotor activity of rats in open-field test (OFT) ($p < 0.01$)

and decreasing significantly the immobility time in forced swimming test (FST) ($p < 0.01$). The results of FST showed anti-immobility effect of ZQ was significantly prevented by pretreatment of rat with 5-HT receptor antagonist, dopamine receptor antagonist and α2-adrenoceptor. It could be speculated that ZQ antidepressive action might be rely on the serotonergic, noradrenergic and dopaminergic systems (Zhang et al. 2012). Besides, the chronic unpredicted mild stress (CUMS) model rats performed significantly increased sugar water preference ($p < 0.05$, $p < 0.01$) and immobility time in FST ($p < 0.05$, $p < 0.01$) at the dose of 10 g/kg and 20 g/kg 70% ethanol extract of ZQ. Meanwhile, gastric motility was also significantly increased at 20 g/kg ($p < 0.05$). Further study of the rats serum and brain tissue found that 10 g/kg and 20 g/kg 70% ethanol extract of ZQ could significantly up-regulates glucocorticoid receptors (GR) mRNA expression in hippocampus, decreased plasma corticosterone (COR) concentration, and up-regulated brain-derived neurotrophic factor (BDNF) mRNA expression levels in cerebral cortex and hippocampus ($p < 0.05$, $p < 0.01$) (Xu et al. 2013). In another study, CUMS rats were gavaged 20 mg/kg of synephrine (**54**) once a day in late 2 weeks. The results showed that synephrine (**54**) could enhance the weight of CUMS rats, the sucrose preference rate and the total distance of rats in OFT ($p < 0.01$, $p < 0.05$). Notably, synephrine (**54**) could reverse the change of 14 metabolites including ethanolamine phosphate, benzoic acid, cholesterol and glutamic acid in CUMS rat serum to make it tend to the normal group ($p < 0.05$) (Xie et al. 2019).

Pharmacokinetic study confirmed that naringenin (**9**), nobiletin (**15**), narirutin (**4**), naringin (**1**), hesperidin (**5**), neohesperidin (**6**), and especially meranzin hydrate (**36**) might be the main effective substances in ZQ water extract for the treatment of acute depression in rats in vivo (Zhang et al. 2018b). Xie measured that administration of meranzin hydrate (**36**) (9 mg/kg) decreased the immobility time during the FST from 180.62 ± 19.61 to 130.87 ± 14.95 after acute treatment ($p < 0.01$), and also promoted gastric emptying and intestinal transit in rats with or without FST ($p < 0.05$). Similarly, the immobility time of rats during the FST was decreased significantly by treatment with meranzin hydrate (**36**) (2.25 mg/kg) after 14 days chronic treatment (Xie et al. 2013b). Fan also found that meranzin hydrate (**36**) isolated from plasma after oral administration of Chaihu-Shugan-San (CSS) in depression patients could significantly reduce immobility time and increase locomotor activity ($p < 0.05$). The effect of meranzin hydrate (**36**) was similar to Fluoxetine at high doses (14 mg/kg) (Fan et al. 2012).

Except for CSS, other prescriptions containing ZQ also had favorable antidepressant effects as well. Such as so-ochim-tang-gamibang (SOCG) has been applied to treat depressive moods and depression associated somatoform pain in Korea. By using chronic restraint stress mice which were exposed to restraint stress 6 h per day and orally administrated SOCG (30, 100, 300 mg/kg/day) over 2 weeks, SOCG significantly reduced the serum level of corticosterone and expression of caspase-3, while increased expression of brain-derived nerve growth factor (Choi et al. 2017). Beyond that, ZQ-HP formula (10, 20 g/kg) could also produce a significant dose-dependent decrease compared to vehicle ($p < 0.05$, $p < 0.01$) in the FST (Shi et al. 2020). Due to the increase of herbs in prescription, the synergistic pharmacological effect of multiple ingredients makes it more difficult to study the mechanism of anti-depression, but it would be more significant in clinic use.

Effect on the cardiovascular system

Regulating blood pressure (BP)

ZQ has elevated BP in a variety of animal models. When the decoction and ethanol extract of ZQ was injected intravenously into rabbits and dogs models, the BP increased significantly (Wang 1955). Many studies have shown that synephrine (**54**) and *N*-methyltyramine (**55**) were the dominant components to elevate BP. Synephrine (**54**) affected adrenergic receptors directly, while *N*-methyltyramine (**55**) worked mainly through the indirect mechanism of catecholamine release (Zhang et al. 2009). Huang studied that ZQ (2.8–280 μg/mL) and synephrine (**54**) (10–6–10–4.5 μg/mL) induced dose-dependent contractile responses in aorta and mesenteric artery in vitro. ZQ (1.25, 2.5, 5.0 mg/kg/min) and synephrine (**54**) (0.095, 0.19, 0.38 mg/kg/min) dose-dependently reduced portal pressure and elevated mean arterial pressure in partial portal vein ligation (PVL) rats in vivo (Huang et al. 1995). This demonstrated that ZQ

reduced portal pressure through arterial vasoconstriction possibly.

Cardioprotective effects

As a qi-regulating drug, ZQ treatment for chest discomfort and pain is partly similar with those of myocardial ischemia and myocardial infarction (Yu et al. 2018). ZQ played an anti-ischemic effect on ischemic and reperfuse rat heart by recovery of contractile dysfunction. ZQ treatment (50 mL of 3 mg/mL) significantly prevented decreases in perfusion pressure, aortic flow, coronary flow, and cardiac output on ischemia induced isolated rat heart in vitro ($p < 0.01$) (Kang et al. 2007). Yang confirmed that polysaccharide purified from ZQ played an important role in cardioprotective effects. CALB-3 was a purified acidic hetero-polysaccharide isolated from ZQ. CALB-3 (1, 2.5, 5, 10, 20, 40, 80 μg/mL) dose-dependently protected H9c2 cardiomyocytes against oxidative stress in vitro. Pretreatment with CALB-3 (50, 100, and 200 mg/kg, i.g.) daily for 21 days could prevent isoproterenol (ISO)-induced myocardial damage in vivo (Yang et al. 2019). Shu also found that CALB-3 exerted its cardioprotective effects via protein kinase B (Akt) signaling (Shu et al. 2020).

On one study, rats were treatment with 10 or 20 mg/kg osthole (**40**) via daily gavage for 28 days. The results suggested that osthole (**40**) remarkably decreased right ventricle pressure and improved myocardial hypertrophy and mitochondrial swelling, vacuolization, and sarcoplasmic reticulum enlargement when compared with the model rats induced by monocrotaline ($p < 0.05$) in vivo (Li et al. 2018b). Oral administration of naringin (**1**) (10, 20, 40 mg/kg) to ISO-induced rats daily for 56 days showed a significant decrease in the levels of thiobarbituric acid reactive substances (TBARS) and hydroperoxides (HP), a significant increase the activities of SOD, catalase, myocardial glutathione peroxidase (GPX) and glutathione-*S*-transferase (GST), and the levels of glutathione (GSH), vitamin C and E ($p < 0.05$) in vivo. Histopathological findings of the myocardial tissue also showed the cardioprotective role of naringin (**1**) in ISO-induced rats (Rajadurai and Prince 2006).

Anti-atherosclerotic (AS) activity

Dietary consumption of flavonoids correlated positively with lower risk of cardiovascular disease (Basu et al. 2016). The flavonoids in the blossoms of ZQ decreased oxidized low-density lipoprotein (ox-LDL)-induced foam cell formation (Shen et al. 2020). 25 μmol/L hesperetin (**11**) attenuated the rate of ox-LDL-induced cell death, substantially diminished the ox-LDL-induced $2^{\#}$, $7^{\#}$-dichlorofluorecein staining, suggesting that hesperetin (**11**) inhibited intracellular accumulation of ox-LDL-triggered reactive oxygen species and consequent apoptosis in vitro (Choi et al. 2008). Nevertheless, naringenin (**9**), hesperetin (**11**), tangeretin (**16**) and nobiletin (**15**) were pretreated (100 μM) with murine J774A.1 macrophages. Among them, only nobiletin (**15**) inhibited (50–72%) acLDL metabolism. Nobiletin (**15**) might prevent atherosclerosis at the level of the vascular wall by inhibiting macrophage foam-cell formation in vitro (Whitman et al. 2005). In another experiment in vivo, the rabbits were supplemented with 1% cholesterol diet containing either 0.1% naringin (**1**) or 0.05% naringenin (**9**) for 8 weeks. Then the percentage area of occupied by atherosclerotic lesions on the inner surface between the second and seventh intercostal arteries significantly reduced in the naringin (**1**)- and the naringenin (**9**)-supplemented groups compared to control group (only 1% cholesterol diet) ($p < 0.001$). Semiquantitative analysis of the intimal thickening of each group via subendothelial macrophages content, showed significantly lower scores in the naringin (**1**)- and the naringenin (**9**)-supplemented group than in the control ($p < 0.001$). The hepatic acyltransferase (ACAT) activities of the naringin (**1**)- and naringenin (**9**)-fed groups were slightly lowered 5.0% and 15.0% ($p < 0.05$). And the expression levels of vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemotactic protein-1 (MCP-1) were significantly lower in the naringin (**1**)- and naringenin (**9**)-supplemented animals ($p < 0.01$) (Lee et al. 2001).

Antithrombotic activity

In the antithrombotic experiment of rabbit in vitro, the aqueous phase of ZQ water decocotion extracted by ethyl ether had a certain inhibitory effect on thrombosis (Zhang et al. 2013). 12.5, 25, 50 and 100 μM nobiletin (**15**) exhibited a clear reduction in thrombus

volume and fluorescence intensity in human blood in vitro (Vaiyapuri et al. 2015). Nobiletin (**15**) reduced platelet aggregation in a concentration-dependent manner at 5 min in vitro with 95% inhibition achieved at 100 μM. 200 μM nobiletin (**15**) showed maximal inhibition of approximately 50% P-selectin exposure (Vaiyapuri et al. 2015). The experiments in vivo showed that administration of 50 μM nobiletin (**15**) extended the bleeding time in C57BL/6 mice to between 278 and 1200 s, whereas vehicle-treated mice bled between 98 and 372 s (Vaiyapuri et al. 2015). Intragastric administration of nobiletin (**15**) to rats could inhibit platelet aggregation. 3.2 mg/kg nobiletin (**15**) produced obvious antithrombotic effect, which was better than heparin (132 U/kg) (Zhang et al. 2013).

Anti-adipogenic activity

Obesity is a major health problem facing the developed and developing world. *C. aurantium* L, which contains synephrine (**54**) alkaloids, has been suggested as a safe dietary supplements to reduce obesity (Haaz et al. 2006). Synephrine (**54**) was clearly stimulating the lipolysis in a dose-dependent manner (Mercader et al. 2011). Synephrine (**54**) inhibited adipocyte differentiation and lipid accumulation in vitro, reduced the CCAAT/enhancer-binding protein α (C/EBPα) and peroxisome proliferator-activated receptors γ (PPARγ) expression, reduced the activity of glycogen synthase kinase 3β (GSK3β), activated the protein kinase B (PKB/Akt) pathway (Guo et al. 2019).

The flavonoid-rich ZQ extract also prevented obesity. Nobiletin (**15**) at concentrations of 10, 25, 50 and 100 μM potently suppressed triacylglycerol (TG) accumulation in 3T3-L1 preadipocytes as compared to TG accumulation in the vehicle-control group in vitro ($p < 0.05$). The glycerol-3-phosphate dehydrogenase (GPDH) activity was significantly lower than the GPDH activity in untreated control cells ($p < 0.05$) after added nobiletin (**15**) (10–100 μM) to 3T3-L1 cells for 4 days. Samples treated with nobiletin (**15**) (100 μM) showed markedly attenuated levels of adipogenic transcription factors ($p < 0.05$), including peroxisome proliferator-activated receptors (PPARγ) and CCAAT/enhancer binding proteins (C/EBPα) compared with the control group. In addition, nobiletin (**15**) at concentrations of 25, 50, and 100 μM increased phosphorylation of AMP-activated protein kinase (AMPK) ($p < 0.05$), which was a major regulator of cellular energy balance, phosphorylation, and intracellular reactive oxygen species (ROS) generation (Choi et al. 2011). The in vivo experimental results indicated that high-fat diet (HFD)-fed mice treated with ZQ flavonoids (300 mg/kg/day) for 12 weeks significantly reduced weight gain, inflammation and liver steatosis ($p < 0.05$, $p < 0.01$). Flavonoids also elevated the expression of tight junction proteins and reduced metabolic endotoxemia. In addition, flavonoids treatment reversed HFD-induced gut dysbiosis, as indicated by the reduction of *Firmicutes* to *Bacteroidetes* ratio, the increase of genera *Akkermansia* and *Alistipes*, and the decrease of genera *Dubosiella*, *Faecalibaculum*, and *Lactobacillus* (Bai et al. 2019).

Shen studied that the extract of ZQ blossoms feeding mitigated weight gain in a dose-dependent manner for HFD-fed mice, decreased the diameter of adipocytes, the contents of total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and lipopolysaccharide (LPS), normalized Leptin level in vivo. It also decreased triglyceride (TG) content, and reduced expression levels of genes involved in lipid and glucose metabolism such as *mdt-15*, *tub-1*, *cebp-2*, *nhr-80*, *fat-7*, *fat-6*, *fat-5*, *fat-4*, *fat-2*, *fat-1* and *sbp-1* in wild type *Caenorhabditis elegans* (*C. elegans*) in vivo (Shen et al. 2019). It indicated that ZQ blossoms could be explored into a health care product for the intervention of gut dysbiosis and obesity-related metabolic disorders.

Anti-inflammatory activity

In LPS-induced RAW 264.7 cells, Zhao confirmed that ethanol extraction of ZQ (160 μg/mL) led to a significant inhibition of interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α production ($p < 0.05$, $p < 0.001$), and decreased expression and protein levels of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase kinase 3 (MEKK3), apoptosis signal-regulating kinase 1 (ASK1), p38 mitogen-activated protein kinase (p38 MAPK), phosphorylation protein kinase B (pAkt) and p65 ($p < 0.001$) (Zhao et al. 2018). Li compared the inflammatory activities of water extractions of ZQ with 25 μg/mL indometacin as positive control in vitro. ZQ (5 mg/mL) resulted in a clear decrease on the levels of IL-6, interferon-γ (IFN-γ),

monocytechemoattractantprotein-1 (MCP-1), and IL-12p70. However, it did not significantly suppress the levels of TNF. In addition, the level of anti-inflammatory cytokine IL-10 was apparently enhanced after treatment with ZQ (5 mg/mL) compared with that of the LPS group (Li et al. 2018a). Moreover, both ethanol extracts of ZQ (250 mg/kg i.g.) and water decoction of ZQ (2.5, 7.5, 25 g/kg) decreased the level of CRP, IL-1β, IL-6 and TNF-α in rats treated with LPS in vivo (Zhao et al. 2018; Li et al. 2018a). Water decoction of ZQ also reduced the neutrophil number of zebrafish treated with $CuSO_4{\cdot}5H_2O$ in a dose-dependent manner (222, 667, 2000 μg/mL) in vivo (Li et al. 2018a).

PMFs in ZQ have also been shown to have good anti-inflammatory activity, especially nobiletin (**15**) (Li et al. 2007b). Nobiletin (**15**) (1.5 and 5.0 mg/kg given intraperitoneally) significantly reduced ovalbumin (OVA)-induced increases in eosinophils, remarkably lowered the level of Eotaxin in blood and broncho-alveolar lavage fluid (BALF) of asthmatic rats in vivo ($p < 0.05$, $p < 0.001$). On the other hand, a significant increase in expression of Fas mRNA was observed after treatment with 1×10^{-7}, 1×10^{-6}, 1×10^{-5} mol/L nobiletin (**15**) ($p < 0.05$, $p < 0.001$). Meanwhile, the apoptosis index of cultured eosinophils was significantly elevated after treatment with different doses of nobiletin (**15**) ($p < 0.05$, $p < 0.01$) (Wu et al. 2006).

Anti-oxidant activity

Compared with other three *Citrus* (ZS, Citri Reticulatae Pericarpium and Citri Reticulatae Viride Pericarpium), methanol extracts of ZQ showed the highest antioxidant activity. In the test of scavenging of DPPH radical in vitro, the activities of ZQ extracts (EC_{50} = 0.10 ± 0.01) were 49% at 0.1 mg/mL and 78% at 1.0 mg/mL. In hydrogen peroxide-scavenging assay, ZQ (EC_{50} = 0.08 ± 0.01) exhibited 77.3 ± 0.92% scavenging activities toward hydrogen peroxide at a concentration of 1.0 mg/mL. In metal ion-chelating assay in vitro, ZQ (EC_{50} = 0.80 ± 0.07) exhibited 52.3 ± 1.53% ion-chelating activities at a concentration of 1.0 mg/mL. But in ferric-reducing antioxidant power (FRAP) assay in vitro, at a concentration of 0.3 mg/mL, reducing powers of ZQ was 2.12, ZQ had the lowest EC_{50} value of reducing power (EC_{50} = 0.12 ± 0.01) among the four *Citrus* herbs extracts. This indicated that ZQ extracts might not have good reducing power (Su et al. 2008).

Flavonoids, which contain a chromanol ring system, have stronger antioxidant activity in ZQ (Lin et al. 2012). By using the DPPH method in vitro, limonin (**56**) and neoeriocitrin (**3**) showed 0.5% and 17.2% free radical scavenging activity. In the superoxide model in vitro, limonin (**56**) inhibited the production of superoxide radicals by 2.5–10%, while the flavonoids such as neoeriocitrin (**3**) and neohesperidin (**6**) inhibited superoxide formation by 48.3% and 37.7%, respectively. However, limonin (**56**) offered some protection against LDL oxidation, increasing lag time for LDL incubated to 345 min (threefold) and 160 min (33% increase), respectively, while neoeriocitrin (**3**) increased lag time to 2800 min (23-fold) (Yu et al. 2005). Another study investigated that hesperidin (**5**) played an antioxidant properties in nicotine-induced lung toxicity. Hesperidin (**5**) was administered orally for the lung damaged rats induced by nicotine at a dose of 25 mg/kg body weight. Results showed that hesperidin (**5**) decreased the activities of enzymes including alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), and lactate dehydrogenase (LDH), and brought back the levels of glutathione (GSH), glutathione peroxidase (GPX), SOD and catalase (CAT) to near normal in vivo (Balakrishnan and Menon 2007).

Wang has been identified polysaccharides as free radical or active oxygen scavengers. In vitro experiments, the DPPH radical scavenging activity of CALB (6.4 mg/mL) was 89.4%, more than the positive group VC (89.3%). The hydroxyl radical scavenging activity was 98.6%, also more than the positive group VC (98.4%). The superoxide radical scavenging activity was 97.4% and the H_2O_2 scavenging activity was 83.2%, stronger than VC at 6.4 mg/mL. Among them, CALB-3 had a stronger antioxidant activities than CALB-1, CALB-2, and CALB-4. In vivo experiments, compared with the model group which was administered with 0.2 mL of 140 mg/kg D-galactose s.c., CALB evidently enhanced the enzyme activities of SOD, CAT, and GSH-Px in blood, heart, and liver, whereas CALA enhanced only SOD, CAT, and GSH-Px activity in blood. CALC showed no effect in blood, heart, and liver. Furthermore, CALA (200 mg/kg) and CALB (100 and 200 mg/kg) significantly reduced MDA formation in blood, heart, and liver (Wang et al. 2014).

Neuroprotective activity

Flavonoids derived from *Citrus* such as nobiletin (**15**) and tangeretin (**16**) have been shown to exhibit neuroprotective effects in several studies (Braidy et al. 2017), especially in vivo experiments. Nobiletin (**15**) protected the brain mainly by attenuating the cerebral ischemia–reperfusion (IR) injury and by improving the motor and cognitive impairment. On cerebral ischemia–reperfusion (I/R) injury in transient middle cerebral artery-occluded (t-MCAO) rats, nobiletin (**15**) treatment (30 mg/kg) significantly reduced the infarct volume ($p < 0.001$), suppressed the brain edema ($p < 0.05$) and neutrophil invasion into the ischemic region ($p < 0.05$, $p < 0.01$), and decreased the apoptosis of brain cells in the ischemic hemisphere ($p < 0.05, p < 0.01$) (Yasuda et al. 2014).

Akira found that nobiletin (**15**) (10, 50 mg/kg) reversed the impairment of recognition memory and context-dependent fear memory in SAMP8 mice, and could improve oxidative stress via restoring the decrease in the GSH/GSSG ratio in the brain. Furthermore, nobiletin (**15**) reduced tau phosphorylation in the hippocampus of SAMP8 mice (Nakajima et al. 2013). Nobiletin (**15**) rescued motor and cognitive dysfunction in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–induced Parkinson model mice, in part by enhancing dopamine release (Yabuki et al. 2014). In addition, nobiletin (**15**) might ameliorate isoflurane-induced cognitive impairment through antioxidant, anti-inflammatory and anti-apoptotic effects via modulation of Akt, Bax, p-CREB and BDNF in aging rats (Bi et al. 2016). This helped the prevention and treatment of Alzheimer's disease.

Anti-tumour activity

ZQ has already been confirmed anti-tumour activities on human colon carcinoma cell lines SW480 cell, HT-29 cell, Caco-2 cell, SNU-C4 (Park et al. 2008; Wang et al. 2000), human lung carcinoma cells A549, H1299 (Chen et al. 2007), human neuroblastoma SH-SY5Y cells (Akao et al. 2008). The volatile oils from ZQ showed different degrees of inhibitory activity against liver cancer cells (BEL-7402), gastric cancer cell (SGC-7901) and lung carcinoma cell (SPCA-1) and in dose-dependent manner in vitro (Xing et al. 2015). By inducing peroxisome proliferator-activated receptor-gamma (PPARγ) and downregulating nuclear factor-kappa B (NF-κB), hesperidin (**5**) (10, 25, 50, 100 μM) exhibited proapoptotic and antiproiferative actions in NALM-6 cells (Ghorbani et al. 2011). Hesperidin (**5**) (1, 10, 50, 100 μM) could induce apoptosis in human colon cancer cells SNU-C4 through caspase-3 (CASP3) activation in vitro (Park et al. 2008).

Additionally, nobiletin (**15**) has anti-angiogenic activity. Nobiletin (**15**) inhibited angiogenesis by regulating Src/FAK/STAT3-mediated signaling through PXN in estrogen receptor positive (ER^+) breast cancer cells in vitro (Sp et al. 2017). In human umbilical vein endothelial cells (HUVECs), nobiletin (**15**) (30–100 mM) inhibited endothelial cell proliferation and, to a greater extent, tube formation in a dose-dependent manner in vitro. In transgenic zebrafish-Tg (fli1:EGFP) embryos, nobiletin (**15**) (30–100 mM) inhibited the formation of intersegmental vessels (ISVs) in live transgenic zebrafish embryos expressing green fluorescent protein (GFP) in the vasculature in vivo (Lam et al. 2011). Therefore, hesperidin (**5**) and nobiletin (**15**) could be identified as a potential anticancer agent.

Immunomodulatory activity

Human peripheral blood mononuclear cells play an important role in immunomodulatory activity through the release of cytokines such as TNF-α, IL-1β, IL-6, NO and other inflammatory mediator (Adams and Hamilton 1984). Yet, the anti-inflammatory effect of ZQ is closely related to the regulation of these inflammatory factors. In this manner, then, it is not surprising that ZQ might also have immunomodulatory activity. A pectic polysaccharide (CALB-4) from ZQ exhibited the immune enhancement effects. By using human peripheral blood mononuclear cells (PBMCs), Shu studied that CALB-4 (20, 40 and 80 μg/mL) showed significant dose-dependent stimulation of PBMC proliferation ($p < 0.05, p < 0.01$) and clearly increased NO production via increasing iNOS expression. In addition, CALB-4 increased the cytoplasmic concentration of pro-IL-1 via the up-regulation of several mitogen-activated protein kinases (MAPKs) and the nuclear translocation of p65 (Shu et al. 2018).

In term of anti-allergy, in rat basophilic leukemia RBL-2H3 cells, 500 μM of nobiletin (**15**) significantly inhibited both HA ($p < 0.01$) and β-hexosaminidase ($p < 0.01$) release. 100 μM of hesperetin (**11**)

significantly inhibited both HA ($p < 0.001$) and β-hexosaminidase ($p < 0.05$) release (Shoko Kobayashi 2006). Nobiletin (**15**) and tangeretin (**16**) (25 μM) significantly inhibited phorbol 12′-myristate 13′-acetate (PMA)-induced IL-4 expression by 55% and 61%, respectively ($p < 0.05$), and TNF-α expression by 46% and 52%, respectively. They also inhibited the HA-induced activation of the transcription factors NF-κB, c-Jun, and p38. Furthermore, they (10 μM) inhibited purified protein kinase C (PKC) activity by 51% and 55%, respectively (Jang et al. 2013). In one study, neohesperidin (**6**) also suppressed IgE-mediated anaphylactic reactions and mast cell activation via Lyn-PLC-Ca^{2+} pathway. After LAD2 cells treated with 50–800 μM neohesperidin (**6**) for 24 h, it decreased the Ca^{2+} flux into cells in a dose-dependent manner, inhibited the secretion of β-hexosaminidase, HA, TNF-α, MCP-1 and IL-8 (Zhao et al. 2019). In vivo experiments, Jang investigated that nobiletin (**15**) (5, 10, 25 mg/kg) and tangeretin (**16**) (5, 10, 25 mg/kg) potently inhibited scratching behavior of mice ($p < 0.05$), as well as HA-induced vascular permeability ($p < 0.05$). additionally, different doses of neohesperidin (**6**) (5, 10, and 20 mg/kg) were orally administered to C57BL/6 mice injected with DNP-IgE, then neohesperidin (**6**) suppressed IgE-mediated passive cutaneous anaphylaxis and MCs degranulation, and reduced serum HA, TPS, CMA1, IL-8, MCP-1, and TNF-α levels (Zhao et al. 2019). In conclusion, ZQ flavoniods may be developed as a new agent for preventing mast cell-immediate and delayed allergic diseases.

Other pharmacological activities

In addition to the pharmacological activities described above, ZQ displayed other activities. Aqueous ZQ extracts (0.3, 0.7, 1.0 mg/mL) significantly prevented CaOx crystallization and promoted crystal dissolution in vitro ($p < 0.05$). In SD rats CaOx crystallization model induced by ethylene glycol (EG), aqueous ZQ extracts (220, 660 mg/kg) could significantly decreased urinary oxalate, the number of crystal deposits and the rates of urinary tract infection, increased urine output and citrate levels, and exhibited minimal OPN expression ($p < 0.05$) (Li et al. 2015b).

The Cytochrome P450 enzymes (CYP450) are involved in approximately 80% of oxidative drug metabolism and account for almost 50% of the overall elimination of commonly used drugs (Wilkinson 2005). In HepG2 cells cultured with ZQ-mediated serum, it seemed to increase CYP1A2 mRNA expression in a dose-dependent manner. The mRNA expression of CYP3A4 was significantly induced when HepG2 cells were treated with 10% low and medium dosage ($p < 0.05$). However, there was very small, not significant change in CYP2E1 mRNA expression. Employing Western Blotting, RT-PCR method, the cocktail method, Zhou determined the protein, mRNA expression and enzyme activity of CYP1A2, CYP3A4, and CYP2E1 in rat, after orally administration of ZQ water extracts (10, 20, 30 g/kg) in succession for 7 days. ZQ significantly accelerated the metabolisms of caffeine and dapsone ($p < 0.05$), and induced hepatic CYP1A2 and CYP3A4 activities. Thus, it should be careful when ZQ is administrated combined with CYP1A2 or CYP3A4 substrate to reduce adverse drug–drug interaction (Zhou et al. 2018).

Overall, experiments indicated that ZQ has remarkable effects on the digestive, cardiovascular and immune systems. This powerfully supported the traditional use of ZQ with characteristics such as regulating qi, relieving pain, eliminating phlegm, removing food retention, activating vital energy and circulation herbal medicine. In addition, modern pharmacological studies have shown that ZQ also plays broad roles in other systems, which provide a theoretical basis for the development of ZQ as a drug.

Clinical use

There are numerous clinical trials on ZQ products and most of them focus on decoction. The efficacy of ZQ decoction in the treatment of gastrointestinal diseases has been proved in the clinical practice for thousands of years. Gastrointestinal disorders require treatments that cause relaxation of intestinal smooth muscle, promote gastric emptying and regulate intestinal movement. The effects of TCM versus prokinetic agents in the treatment of functional dyspepsia (FD) of liver-stomach disharmony syndrome were compared by meta-analysis involving 1153 patients. TCM therapy showed a better clinical effect rate compared with that with prokinetic agents [odds ratio (*OR*): 3.2, 95% confidence interval (*CI*) (2.27, 4.51)]. The TCM group also had a better cure rate than that in the group of

prokinetic agents [Peto *OR*: 2.26, 95% *CI* (1.61, 3.18)]. Among the TCM, the frequency of use of ZQ ranked the top six, and no serious adverse effects were reported (Wang et al. 2012). Tan even used the decoction of single ZQ 200 g to treat 31 cases of gastroptosis (1 dose per day). After one course of treatment (2 weeks), 15 cases were markedly effective, 16 cases improved, and the total effective rate reached 100% (Tan 1998). Luo treated a major depressive disorder (MDD) complicated by FD patient with Zhiqiaochuanxiong (ZQCX) decoction (ZQ 40 g and Rhizoma Chuanxiong 40 g). 7 weeks after treatment, the patient felt significant improvements in appetite with reduced frequency of early satiety, epigastric fullness, and belching. His electroencephalogram (EEG) showed disappearance of T3-T4 asymmetry and with no excessive β waves. His mood was much more stable (Min et al. 2015). Another decoction contains ZQ called Simo Decoction (SMD), a representative of prokinetics in TCM, has been efficiently used to treat constipation and bloating for a long history in China (Dai et al. 2012). Zhu selected 60 patients with senile constipation and divided them into lactulose group (19 cases, 20 mL/time, 2 times/day, oral for 14 day), SMD group (14 cases, 20 mL/time, 3 times/day, oral for 14 day) and combined group (27 cases, lactulose and SMD were given the above dosage for 14 day). Results showed that The effective rates of the three groups were 79%, 71% and 96%, respectively, and the difference of effective rate between the combined group and each single drug group was statistically significant ($p < 0.05$). No adverse reactions were observed in all three groups (Zhu et al. 2020a).

Except for decoction, a lot of prescriptions containing ZQ also have been applied in the form of oral solution, granule, pill, and capsule. Their various clinical efficacy has been well documented (Table 7). For instance, Danhong Huayu Oral Solution is a modified Chinese prescription of Xuefu Zhuyu Decoction which has been used for the treatment of blood stasis syndrome for centuries. It was prescribed for the treatment of central retinal vein occlusion to 34 patients for 3 months, and the total effective rate was 94.10%. The difference was statistically significant compared with that in the control group ($p < 0.05$) (Jia and Wan 2015; Liu et al. 2019). Weichang'an pill (WCA) was used to treat 59 patients with postoperative metastasis of gastric cancer, the quality of life and tumor-bearing survival time after relapse were markedly better in the WCA group than those in the chemotherapy group ($p < 0.05$) (Yang et al. 2003). Besides, with regard to the respiratory system, Tongxuan Lifei pill has a significant therapeutic effect for exogenous cough and chronic cough. The total effective rate were 94.00% ($p < 0.05$) (Li 2018) and 91.67% ($p < 0.05$) (Deng and Lan 2011), respectively. There is also a famous CPM containing ZQ in China-Jizhi syrup (JZS). It is the eutherapeutic cough medicine and was approved for sale and use in Pakistan in November 2019 by the Health and Over-the-Counter Drugs Division of the Pakistan Drug Administration. This is the sixth country and territory where JZS has been registered, after Indonesia, Hong Kong, Singapore, the United States and Macao (Guo 2019).

The above results showed ZQ a high clinical application value. It could relieve the clinical symptoms effectively, and improve the quality of life. However, what is the specific mechanism of ZQ clinical efficacy? Are these satisfactory clinical traits a placebo effect? All these issues need further study.

Quality control

Quality control of herbs is essential to ensure their efficiency and safety. According to 2015 Edition ChP, the content of naringin (**1**) and neohesperidin (**6**) in ZQ must be no less than 4.0% and 3.0%. In Hong Kong Chinese Materia Medica (HKCMM) standards, in addition to stipulating the content standards of naringin (**1**) (≥ 4.0%) and neohesperidin (**6**) (≥ 3.0%), it also stipulates that the content of synephrine (**54**) should not be less than 0.083%. Taiwan Herbal Pharmacopeia only stipulates that the content of naringin (**1**) should not be less than 2.5%. Additionally, in terms of a warning letter sent to one health company by Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition in 2015, September 21, the natural p-synephrine content in dried *C. aurantium* L. ranges from 0.012%-0.25% and the content of p-synephrine in concentrated extracts or commercial products are standardized to 4–6% (Correll 2015). It can be seen from the above that different countries and regions have different requirements for quality control standards. Meanwhile, current studies suggested that

Table 7 Representative preparations of ZQ listed in 2015 Edition ChP

Name	Type	Main herbs	Function	Clinical research	References
Danhong huayu	Oral solution	Salviae Miltiorrhizae Radix Et Rhizoma, Angelicae Sinensis Radix, Chuanxiong Rhizoma, Aurantii Fructus	Curing blurred vision, Sudden blindness and central retinal vein occlusion	Number of patients: 34 Recovery rate: 94.10% Recovery cycle: 3 months	Jia and Wan (2015), Liu et al. (2019)
Weichang'an	Pill	Aucklandiae Radix, Aquilariae Lignum Resinatum, Aurantii Fructus	Curing dyspepsia	Number of patients: 59 Survival rate: 71.18% Postoperative survival time: 36 months	Yang et al. (2003)
Jizhi	Syrup	Houttuyniae Herba, Fagopyri Dibotryis Rhizoma, Ilicis Chinensis Folium, Aurantii Fructus	Curing cough induced by acute bronchitis (CAB) and acute exacerbation of chronic bronchitis (AECB)	Number of patients: 40 for CAB, 38 for AECB Recovery rate: 92.50% for CAB, 89.50% for AECB Recovery cycle: 1 week for CAB, 2 weeks for AECB	Zhang (2019)
Tongxuan lifei	Tablet	Perillae Folium, Peucedani Radix, Platycodonis Radix, Aurantii Fructus	Curing cold and cough	Number of patients: 50 for exogenous cough (EC), 70 for chronic cough (CC) Recovery rate: 94.00% for EC, 91.67% for CC Recovery cycle: 7 days for EC, 6 days for CC	Li (2018), Deng and Lan (2011)
Qizhi weitong	Granule	Bupleuri Radix, Corydalis Rhizoma, Aurantii Fructus	Curing liver Qi stagnation, chest pain and stomachache	Number of patients: 65 Recovery rate: 95.38% Recovery cycle: 8 weeks	Liu (2020)
Danshitong	Capsule	Taraxaciherba, Hedyotis Corymbosa, Artemisia Capillaris, Aurantii Fructus	Curing gall-stone and cholecystitis	Number of patients: 15 Recovery rate: 86.66% Recovery cycle: 2 weeks	Hu (2019)
Weichang fuyuan	Electuary	Aurantii Fructus, Pseudostellariae Radix, Rhei Radix Et Rhizoma	Curing abdominal distension after gastrointestinal surgery, decreased gastrointestinal activity and senile constipation	Number of patients: 112 Postoperative gastrointestinal decompression: 182 ± 4.5Ml ($P < 0.01$) Postoperative time: 24 h	Zhang et al. (2003)

Table 7 continued

Name	Type	Main herbs	Function	Clinical research	References
Guogong	Vinum	Angelicae Sinensis Radix, Notopterygii Rhizoma Et Radix, Achyranthis Bidentatae Radix, Aurantii Fructus	Curing arthralgia, numbness of limbs, hemiplegia and facial paralysis	Number of patients: 36 Recovery rate: 91.70% Recovery cycle: 1 week	Zhou et al. (2015)

geographical origins might bring about differences in quality of herbs to some extent.

Liu studied systematically the constituents in ZQ both growing in China and in Korea and found out a big difference in the composition and content of them. There was no neohesperidin and naringin detected in Korean ZQ, whereas there was no poncirin detected in Chinese ZQ. The content of hesperidin in Chinese ZQ is 6.75%, while the content of hesperidin in Korean ZQ is 1.10% (Liu et al. 2003). Scholars have performed comparative research on flavonoids found in ZQ collected from four regions in China: Zhangshu of Jiangxi, Suzhou of Jiangsu, Yibin of Sichuan, and Fuzhou of Fujian. The study found that the content of flavonoids in ZQ collected in different regions is not exactly the same, and the content of synephrine (**54**), naringin (**1**) and hesperidin (**5**) from ZQ in Zhangshu of Jiangxi was the highest (Peng et al. 2006). Guo also demonstrated that the contents of the two compounds (7.5% naringin (**1**), 5.6% neohesperidin (**6**)) were highest in ZQ from Jiangxi province (Guo et al. 2012). Li reported that the content of narigin in some batches of ZQ samples from Sichuan and Yunnan province was significantly higher than other compounds analyzed. Besides, the total flavonoids contents of samples from Jiangxi were relatively higher compared with other provinces (Li et al. 2016). Xing demonstrated that the relative content of limonene in ZQ was the highest from Jiangxi Zhangshu (Xing et al. 2015), which is in agree with the fact that Jiangxi province is the authentic source of ZQ. However, no naringin (**1**) and neohesperidin (**6**) were detected in ZQ (*C. aurantium* 'Chuluan') from Zhejiang province (Guo et al. 2012), although it is a variety included in the 2015 Edition ChP. The constituent is usually associated with the pharmacological activities, consequently, differences in ingredients will inevitably lead to distinctions in the quality of herbs, which still needs high attention of researchers.

Regional differences lead to different climatic conditions, and the growth and development of ZQ are also different. In Rongchang area of Chongqing, the contents of naringin (**1**) and neohesperidin (**6**) in ZQ harvested before mid-August were all in accordance with 2015 Edition ChP. However, the *pharmacopoeia* requires that ZQ should be collected in July. In addition, by measuring the diameter of ZQ in different harvesting periods, it was found that the diameter of fruits before mid-July ranged from 0.5 to 2.5 cm, while those between mid-July and early-August ranged from 3 to 5 cm, and those after mid-august all exceeded 5 cm. This also did not meet the requirements of 2015 Edition ChP (Shi et al. 2012). The content disparity might be explained by the different collection periods of ZQ, which caused the differences in the accumulation of secondary metabolites. The content of naringin (**1**) gradually increased with the extension of the growth cycle, while the content of hesperidin (**5**) and neohesperidin (**6**) gradually decreased. The three flavonoids in the nearly mature ZQ were all reduced, naringin (**1**) and neohesperidin (**6**) are relatively high, and the content of hesperidin (**5**) was very small (Kang and Deng 2012). Analysis of the biosynthetic pathway highlighted that the syntheses of flavone and flavone glycosides were deeply affected in *Citrus* ripening stages.

Moreover, Jiang concluded that different extraction methods might also lead to different yields of ingredients. The extract yields of essential oil from the bud of *C. aurantium* L. var. *amara* Engl. were 0.16%, 2.18%, and 2.34% by using steam distillation extraction (SDE), reflux extraction (RE), and ultrasound-assisted extraction (USE) respectively (Jiang et al. 2011).

As there are many factors affecting the quality of ZQ, the current research on quality control technology is becoming more and more urgent. With the development of modern separation and identify techniques, it is widely accepted that the quality of herb medicine cannot be measured by mono-content. Xu suggested that naringin (**1**), neohesperidin (**6**), narirutin (**4**) and synephrine (**54**) could be considered as the quality markers (Q-marker) of ZQ (Xu et al. 2018). Peng presented the first application of capillary electrophoresis with electrochemical detection (CE-ED) for the determination of syneprine, naringin (**1**), hesperidin (**5**) and naringenin (**9**) in ZQ of different geographical origin, which was more economical in comparison to HPLC (Peng et al. 2006). The plant origins of fifty ZQ commercial samples have been identified by multivariate analysis including principal component analysis (PCA), cluster analysis (CA), and linear discriminant analysis (LDA) were used as classification procedures (Chuang et al. 2007). Pan established the ensemble methods combined with partial least squares (bagging-PLS) and near-infrared (NIR) sensor use in the online quantitative monitoring of pilot-scale extraction processes in ZQ, which might also constitute a suitable strategy for online NIR monitoring of TCM (Pan et al. 2015). In another study, Luo used DNA barcoding, a molecular diagnostic technology identifying species by a short genomic sequence (Hebert et al. 2003), to identify 300 samples of 192 species from 72 genera of the family Rutaceae, and propose that ITS2 was a promising candidate barcode for plant species identification (Luo et al. 2010b). It would help non-professionals identify species quickly and accurately. It was reported that China launched the national standardization construction project of 10 herbs containing ZQ on January 7, 2017 in order to improve the quality standards of ZQ and optimize the technical specifications in all aspects of Chinese medicine production (Liu 2017). And the researches on quality control of ZQ is still developing.

Toxicology

To date, the toxicity studies on ZQ are seldom reported. According to 2015 Edition ChP, the clinical administrations of ZQ in an adult are suggested to be 3–10 g daily, indicating it low-toxicity herbs. Studies showed that the LD_{50} of volatile oil from ZQ was 4 234.38 mg/kg (Zhang et al. 2018a). It is low toxicity according to Classification Standard for Acute Toxicity of Drugs Administered Orally (Wang 2004).

To date, most of the controversies about the safety of using ZQ are focused on dietary supplement for weight loss. Since April 2004, ephedra products were banned by FDA in due to the unreasonable risk of illness or injury (Bent et al. 2004), weight loss dietary supplements containing *C. aurantium* L. extracts have rapidly become the new replacement (Stohs et al. 2020). The content of synephrine (**54**) was used as the quality evaluation index, which could replace ephedrine to reduce weight (Ratamess et al. 2016). However, as a fat decreasing agent, synephrine (**54**) is used in traditional medications, but it has been banned by the National Collegiate Athletic Association (NCAA), due to its risks such as cardiovascular hazards and alkaloid toxicity (Arbo et al. 2009). There is a published report of stroke in a 38-year-old man (Bouchard et al. 2005), variant angina in a 57-year-old man (Gange et al. 2006) and a possible case of myocardial infarction in a 55-year-old woman associated with use of dietary supplements containing bitter orange (Nykamp et al. 2004). Synephrine (**54**) has effects on the cardiovascular system through adrenergic stimulation indeed. Some studies suggested that it could cause the increasing arterial blood pressure, left ventricular pressure by strengthening cardiac output and raising the total peripheral vascular resistance (Rossato et al. 2011). But the side effects derived from synephrine (**54**) ingestion, such as increased resting heart rate and blood pressure, are generally minimal, especially in comparison to more active substances like caffeine (Bush et al. 2018). Considering the scarce toxicological data available and the many confounding factors in case reports, it was difficult to attribute toxic manifestations to only one compound of the combinations frequently found in weight-loss products (Stohs et al. 2012). And it turned out experimentally that after ten healthy adult had taken Advantra Z (single doses of *C. aurantium* L., containing 46.9 mg synephrine (**54**)) and Xenadrine EFX (multi-component formulation, containing 5.5 mg synephrine (**54**)) for 1 week, Xenadrine EFX but not Advantra Z increased systolic and diastolic blood pressure and heart rate (Haller et al. 2005). This indicated that the cardiovascular stimulant actions of ephedra-free weight loss supplements are not likely caused by *C. aurantium* L. alone, because an eightfold

higher dose of synephrine (**54**) (Advantra Z) had no obvious adverse effect on blood pressure, but may be attributable to other stimulants in the multi-component formulation. Stohs also believed that although synephrine (**54**) and ephedrine have some structural similarity, synephrine (**54**) has poor binding to adrenergic receptors, and thus the effects produced by ephedrine cannot be extrapolated to synephrine (**54**) (Stohs and Ray 2020).

There have been a lot of studies on the safety and toxicity of synephrine (**54**) (Stohs 2017; Arbo et al. 2008, 2009), but additional studies are still required to determine at what dosage levels adverse effects might be expected to occur.

Conclusion

In this review, we systematically summarize knowledge on botany, ethnopharmacology, phytochemistry, pharmacological activity, clinical use, quality control and toxicology of ZQ. Although there are many reports, gaps still exist in the scientific studies on ZQ. Therefore, we provide several topics which should have priority for further detailed investigation.

Firstly, ZQ is the dried unripe fruit and young fruit of *C. aurantium* L. or its cultivated variety, and have been well documented in the China *Pharmacopeia* as drugs to regulate Qi flow in clinical applications and to strengthen the spleen and stomach. Modern pharmacological researches have proved that ZQ improves functional dyspepsia and cures depression at the same time via brain–gut axis, a bi-directional connection of the brain and the gastrointestinal system (Julio-Pieper et al. 2013), such as regulating 5-HT and dopamine in vivo. And other traditional uses of ZQ such as curative effects on chest pain, bloating and indigestion also have been gradually substantiated by modern pharmacological studies except the application of organ prolapse treatment. In terms of TCM theory, ZQ can be used to treat uterine prolapse, anus prolapse, gastroptosis and other diseases based on its function of Qi regulating. However, at present, there is no detailed pharmacological experiment or chemical component research data could be used to prove its effect on Qi regulating. In further, studies focused on regulation of Qi effect by evaluating body surface signs, hemodynamics and hemorheology indexes, muscle tissue movement of animals are preferred.

Secondly, in 2015 Edition ChP, ZQ contains 5 sources of plants. But there are many other plant sources of ZQ currently in circulation on the market. Some of them are approved by local standards, while others are circulated as fake ZQ, which brings great deficiency to the quality control and clinical application of ZQ. For a better-quality control, in addition to measuring the content of only two markers of naringin (**1**) and neohesperidin (**6**), it is possible to determine the ratio of the contents of several main ingredients. It is also possible to establish a character or microscopic identification criterion for each variety. What's more, another Chinese medicine variety that is often confused with ZQ is called ZS. ZS is the dried young fruits of *C. aurantium* L.. Its harvest time is from May to June every year, earlier than that of ZQ, and it looks smaller than ZQ. Since the Northern and Southern Dynasties, ancient Chinese people have distinguished ZQ and ZS in clinical use. From the view of TCM, the medicine property of ZS is more violent than ZQ. ZS is commonly used to dissipate stagnant qi, eliminate sputum, disperse painful abdominal mass, cure food retention syndromes, relive chest impediment and epigastric stuffiness. Phytochemistry studies show that the composition of ZQ and ZS is similar, but the content is different, especially ZS flavonoids content is significantly higher than that of ZQ (Li et al. 2016; Tian et al. 2020). However, the difference between the two drugs still needs further study.

Finally, as a traditional health medicine, the economic value of ZQ can be further developed. Such as *C.* sinensis Osbeck cv. Newhall is the major navel orange cultivar planted in east Ganzhou, China's Jiangxi province where total planting areas of navel orange had reached around 103.2 thousand hectares by the end of 2017. However, the consumption of pulps has caused a lot of waste of peels, which account for about 30% weight of the whole fruits. In some other countries, the peel of *C. aurantium* L. is often used in marmalade, and dried peel is used in bouquet garni and for flavoring a Belgian beer called Orange Muscat. Hence, we can also make full use of various parts of the original plants such as the flowers, steams, roots, leaves, etc. to develop their economical values.

In conclusion, it is necessary to accelerate the phytochemistry and pharmacological studies of ZQ, and figure out its difference and similarity with various plant sources more in-depth. Future direction of research should pay attention to accurate and rapid

authentication of varieties of ZQ, because it is crucial to ensure the safety and function of medicinal or edible herbs as well as their preparations. Additionally, more efforts deserve to gain insights into the toxicological actions of ZQ and efficacy of ZQ in prescriptions.

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