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REVIEW ARTICLE

The young fruit of *Citrus aurantium* L. or *Citrus sinensis* Osbeck as a natural health food: A deep insight into the scientific evidence of its health benefits

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Abstract Fruits are consumed as foods or medicines to supply people with nutrition or treat diseases. Zhishi, the dried young fruit of *Citrus aurantium* L. or *Citrus sinensis* Osbeck, is one of the most representative health food from the fruit of the *Citrus* genus. It is widely used in flavorings, canned food, beverages, and medicines because of its outstanding curative effects. The bidirectional regulating effect of Zhishi on the gastrointestinal tract for treating food stagnation or diarrhea has been confirmed. Its active ingredients, including synephrine and *N*-methyltyramine, have been used clinically as blood pressure boosting and anti-shock drugs. Flavonoids and alkaloids of Zhishi also make it potential weight loss and beauty products due to their definite effectiveness and safety. This paper intends to review the different therapeutic applications of Zhishi and the phytochemicals associated with its medicinal values. Besides, up-to-date information on its botany and analytical methods for the quality control of the medicine is supplied. To conclude, numerous independent research on Zhishi have been conducted in the past decades, but most of them are not deep enough in elucidating its scientific evidence of its health benefits. Further studies may unveil additional pharmacological activities and is beneficial to the mankind.

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1. Introduction

Fruit, one of the most common foods, is loved by people all over the world for its good taste and rich nutrition. Some are also used as medicines because of their therapeutic effect on specific diseases. Herbal material used for both food and Traditional Chinese Medicine (TCM) is also known as dietary herbal medicine or health food (Shan et al., 2015). Dietary herbal medicine can be directly sold and used as food casually but uses of health food in products for healthcare purposes require the approval of the regulatory authority.

With a plantation area of 9 million hectares and a fruit production of 122.3 million tons worldwide in 2009, the *Citrus* genus became the largest productive fruit crop (Xu et al., 2018). The *Citrus* genus originates from Southeast Asia, and China has a history of growing them for more than 2,400 years. Among 78 fruit medicines recorded in the Chinese Pharmacopoeia (ChP, 2020 edition) (Chinese Pharmacopoeia Commission, 2020a), 8 originated from the *Citrus* genus, which makes it the most abundant botanical source for fruit-derived medicines.

Zhishi (ZS), the dried young fruit of *C. aurantium* and its cultivars (known as Suancheng Zhishi, SCZS) or *C. sinensis* (known as Tiancheng Zhishi, TCZS) gathered between May to June, is one of the most important Qi-regulating medicine in the clinical practice of TCM system. It is primarily used for the auxiliary treatment of distension, abdominal pain, chest pain, phlegm, severe diarrhea, and organ prolapse induced by Qi stagnation. It possesses broad pharmacological actions such as effects on gastrointestinal and cardiovascular systems. More than 121 compounds, including flavonoids, coumarins, alkaloids, limonoids, and other compounds, along with some minor ingredients in significance such as polysaccharides and organic acids, have been isolated and identified from ZS. Synephrine significantly increases blood pressure without any side effects (Stohs, 2017), which is used as the marker for quality control, according to ChP (Chinese Pharmacopoeia Commission, 2020b).

However, the plant resource of ZS has changed from *Poncirus trifoliata* (L.) Raf to *C. aurantium*, and the planting area has also changed from north of the Yangtze River to Jiangxi, Sichuan, and Hunan Province. A variety of adulterations emerged with the historical changes, which led to the impossibility of guaranteeing the safety and effectiveness of ZS in clinic practice (Cai et al, 1999; Li, 2002). Besides, the pharmacological mechanism of Qi-regulating effects of ZS in the TCM theory system remains unclear. To further exploit the therapeutic potentials and supply scientific basis for its development and utilization of ZS, its application in TCM or health food, phytochemistry, quality control, pharmacological activity, toxicology, and clinical use are summarized in this paper.

2. Fruits used in health food or dietary herbal medicine

2.1. Fruits in TCM

Among 590 crude drugs documented in the latest ChP (Chinese Pharmacopoeia Commission, 2020a), 130 were derived from seed or fruit (Fig. 1), accounting for 25 % of the total, only less than root and rhizome, which account for 30 %. They were used for treating a variety of diseases due to their various efficacy in the TCM system. Besides, different parts of the fruit, such as pericarps, clusters, etc., can also be used separately as TCMs (Table 1). For instance, Lajiao (fruit of *Capsicum annuum* L.) was considered to have therapeutic effects on stomachache, emesis and chilblain (Yan et al., 2018). Goji (fruit of *Lycium barbarum* L.) had the ability to maintain the function of the eyes and strengthen the activity of the liver, kidneys, and lungs (Cheng et al., 2014). Dazao (fruit of *Ziziphus jujuba* Mill.) was believed to reinforce the spleen and stomach and was commonly used for the treatment of anorexia, fatigue, and loose stools related to deficiency syndromes of the spleen (Li et al., 2018).

Furthermore, they have therapeutic effects not only when used alone but also used in combination with other drugs. Zhishi Xiebai Guizhi decoction, one of the classical prescriptions, could improve chest, impediment, and heart pains, which are the symptoms of coronary heart disease and myocardial infarction in modern medicine. In this prescription, Trichosanthis Fructus and Allii Macrostemonis Bulbus work as the chief medicine to treat the main cause of the disease. ZS and Magnoliae Officinalis Cortex act as the deputy medicine to enhance the curative effect of chief medicine or treat concomitant symptoms due to the effect of Qi-regulating and phlegm-eliminating. Cinnamomi Ramulus plays an auxiliary effect as an assistant drug (Sang et al., 2021). Zhishi Daozhi pill was used for the treatment of bloating and constipation, in which ZS is used as the deputy medicine for producing a Qi-regulating effect to promote the purgation effect of Rhei Radix et Rhizoma of chief medicine. (Liu and Shen, 2010). Zhishi Xiaopi pill was used primarily for the treatment of dyspepsia to nourish the spleen and stomach with ZS as the chief medicine owing to its Qi-regulating, phlegm-eliminating, and digestion-eliminating effects (Lin et al., 1998).

2.2. Fruits in the diet

According to the National Health Commission of the People's Republic of China (NHCPRC), 21 fruit-derived medicines in the ChP used for both medicine and food (Chinese Pharmacopoeia Commission, 2020a), including Bajiaohuixiang, Xiaohuixiang, et al., were listed as dietary herbal medicine based on their health benefits, safety evaluation, and especially a time-honored history of applications (Table 1).

However, some fruits in daily life, although they are not included in the list, were still used as dietary herbal medicine or health food in the folk, such as Ningmeng (fruit of *Citrus limon* (L.) Burm. f.) (Elena et al., 2008), Lizhi (fruit of *Litchi chinensis* Sonn.) (Zhao et al., 2020), Yingtao (fruit of *Cerasus pseudocerasus* (Lindl.) G. Don) (Jing et al., 2018) and Putao (fruit of *Vitis vinifera* L.) (Impei et al., 2015). In addition, Yueju (fruit of *Vaccinium vitis-idaea* L.) is consumed as food in raw or cooked in lingonberry jam, compote, juice, or syrup (Kowalska, 2021). Huaishi (fruit of *Sophora japonica* L.) is treated as one of the fat-reducing diets. Suanjiao (fruit of *Tamarindus indica* L.) is widely used as food flavorings and fruit drinks in Southeast Asia (Dai et al., 2015). These three health products are not recorded in ChP (Chinese Pharmacopoeia Commission, 2020a). In summary, as an essential part of the TCM system, fruit protects people's health in daily life and plays a crucial role in treating diseases.

3. ZS used in the TCM or health food

3.1. ZS in the diet

The fruit of *Citrus* genus is one of the top four consumed fruits in the world. The juice content of the fruit of *Citrus* genus is up to 37.48 %∼52.46 % (Gao et al, 2022). It contains high content of amino acid and vitamin C (Hasan et al., 2022). However, ZS tastes sour and bitter, and as such it is not eaten

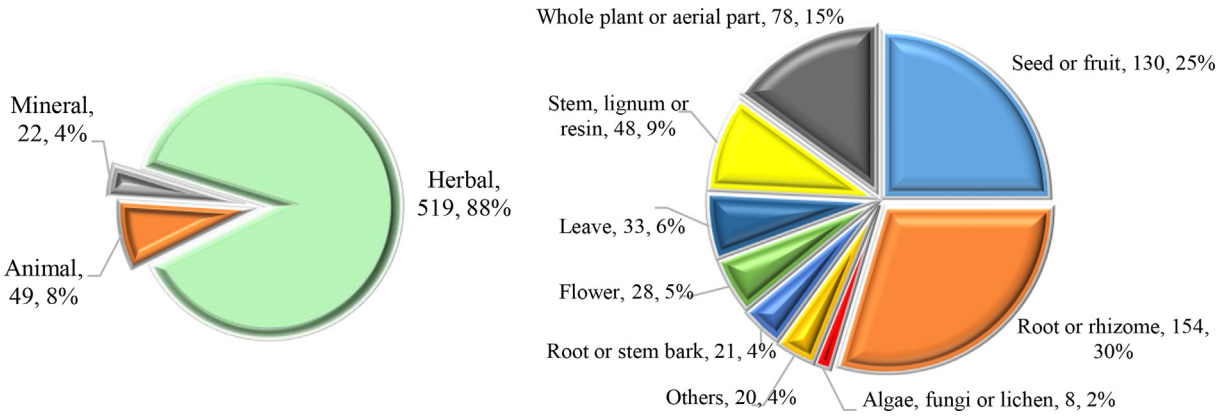

Fig. 1 Sources of crude drugs recorded in ChP (2020 edition).

fresh, so the most of them are processed into concentrated juice (Lv et al., 2015). According to the Food and Agricultural Organization of the United Nations, the fruit of *C. aurantium* is consumed mainly as fresh or raw materials for juice in the world-leading fruit-producing countries such as Brazil, America, India, Mexico, and Spain (Lv et al., 2015). The fruit of *C. sinensis* is widely distributed in the Mediterranean basin (such as Southern Italy and Spain) and America, becoming an essential element of the Sicilian kitchen (Barreca et al., 2015).

ZS is commonly used as a health food product in China for the benefits of relaxing the bowels and protecting against gastric mucosa damage. The candied fruit of *C. aurantium* has become a specialty in China's Hunan Province. According to the data of the State Administration for Market Regulation (National Health Commission of the People's Republic of China, 2002), there are 48 types of domestic health food containing ZS extract in China and one health product (Baoxianpai JuJu Zhishi pills) imported from Denmark. Daidaihua, flower buds of its varieties *Citrus aurantium* L. *var. amara* Engl., were also recorded in the list of dietary herbal medicine, which is frequently used to make tea due to its positive effects on improving appearance and losing weight (Wang et al., 2009; Shen et al., 2019).

3.2. ZS used in TCM

3.2.1. History of ZS used in medicine

ZS has a long history of medicinal use. It was recorded as a medicine in the *ShenNongBenCaoJing* (the earliest book on TCM in China) in the Han Dynasty for the first time (202 BCE to 220 CE) (Wang, 1985; Li, 2002; Tsai, 2013). It was bitter in taste and cold in nature and was used to treat pruritus, dysentery, and skin disease formed by the combination of pathogenic heat/pathogenic cold and phlegm/blood stasis. Zhiqiao (ZQ), the dried immature fruit of *C. aurantium* harvested a month later than ZS, was used separately from ZS until the Tang dynasty (618–907 CE) due to their differences in therapeutic effects (Zhu and Li, 2013; Zhao et al., 2020). Officially they were separately recorded in *KaiBaoBencao* (the first official-revised Materia Medica in the Song dynasty) in 974 CE (Yu et al., 2004; Zhu and Li, 2013; Li et al., 2015). According to *BenCaoGangMu* (known as the great classic of Oriental Pharmacy), published in 1578 CE of the Ming Dynasty, ZS was bitter, sour, and slightly cold in the medicinal property and had functions of promoting Qi, reliving asthma, removing phlegm, relieving pain, and treating dysentery (Xu et al., 2012). It had been recorded in ChP since 1963 (Chinese Pharmacopoeia Commission, 1963; Tsai, 2013). The history of ZS used in medicine is summarized in Fig. 2.

3.2.2. Changes in plant origin of ZS

The earliest ZS before the Song Dynasty was the fruit of *P. trifoliata*, which is known as Lvyi ZS nowadays in Fujian (Cai et al., 1998; Hu et al., 2019; Zhao et al., 2020). *BenCaoTuJing* (the earliest botanical atlas of medicinal herbs in China) included the first botanical picture of ZS in 1061 CE, which also confirmed that the fruit of *P. trifoliata* cannot be used as ZS (Xie, 1991; Cai et al., 1998; Xu et al., 2012; Zhao et al., 2020). In the Song Dynasty, the fruit of *C. aurantium* was gradually used as the authentic ZS (Cai et al., 1998; Xu et al., 2012). At that time, *BenCaoGangMu* made it clear that the fruit of *P. trifoliata* was the adulterant of ZS in the market (Xie, 1991; Xu et al., 2012; Hu et al., 2019; Zhao et al., 2020).

ChP recorded ZS for the first time in 1963, and the plant sources were *C. aurantium* and *Citrus wilsonii* Tanaka (Chinese Pharmacopoeia Commission, 1963). In the 1977 edition of the ChP, *Citrus wilsonii* Tanaka was removed (Chinese Pharmacopoeia Commission, 1977). While in the 1985 edition of the ChP, the plant source of ZS was changed to *C. aurantium* and its varieties, considering that the fruit of some varieties has a long history of being used as ZS (Chinese Pharmacopoeia Commission, 1985). Fruit thinning is usually conducted to ensure the quality of the fruit. For economic purposes, the young fruit of *C. sinensis* obtained by fruit thinning was gradually used as ZS in the market. It was first recorded as the source of ZS in the 1985 edition of ChP (Chinese Pharmacopoeia Commission, 1985; Xie, 1991; Zhou, 2014) (Fig. 2).

3.2.3. ZS and its common adulterations

C. aurantium and *C. sinensis* are distributed in the south of the Qinling Mountains. Most are artificially cultivated, while some are semi-wild (Fig. 3) (Wu, 2004). Jiangxi of China is the genuine producing area of SCZS and one of the famous products called "Eyan ZS" (Hu et al., 2019). While TCZS was mainly produced in Sichuan and Guizhou (Fig. 4). There are five cultivars of *C. aurantium* according to ChP which can be used for ZS (Chinese Pharmacopoeia Commission, 2020b; Xie, 1991)

Table 1 All fruit-originated medicines in ChP (2020 edition).

No.	Chinese name	English name	Species	Used parts	Harvesting seasons	Applications
1	Bajiaohuixiang*	Anisi Stellati Fructus	*Illicium verum* Hook. f.	Mature fruits	Autumn and winter	Vomiting, stomach ache, inflammation, insomnia, and rheumatic pain
2	Dazaojiao	Gleditsiae Sinensis Fructus	*Gleditsia sinensis* Lam.	Mature fruits	Autumn	Apoplexy, expectorant, and pesticide
3	Dazao*	Jujubae Fructus	*Ziziphus jujuba* Mill.	Mature fruits	Autumn	Digestive disorders, skin infections, urinary trouble, and cardiovascular diseases
4	Dafupi	Arecae Pericarpium	*Areca catechu* L.	Pericarps	Winter to the following spring	Parasitic diseases, dyspepsia, diarrhea, edema, and jaundice
5	Shanzhuyu#	Corni Fructus	*Cornus officinalis* Sieb. et Zucc.	Sarcocarp	Late autumn and early winter	Spontaneous sweating, spermatorrhea, and enuresis
6	Shanzha*	Crataegi Fructus	*Crataegus pinnatifida* Bge. var. major N. E. Br. *Crataegus pinnatifida* Bge.	Mature fruits	Autumn	Hypertension and hyperlipidaemia
7	Chuanlianzi	Toosendan Fructus	*Melia toosendan* Sieb. et Zucc.	Mature fruits	Winter	Irregular menstruation, hyperplasia of mammary glands, and breast-cancer
8	Guangzao	Choerospondiatis Fructus	*Choerospondias axillaris* (Roxb.) Burtt et Hill	Mature fruits	Autumn	Cardiovascular diseases
9	Nüzhenzi#	Ligustri Lucidi Fructus	*Ligustrum lucidum* Ait.	Mature fruits	Winter	Osteoporotic bone pain and rheumatic bone
10	Xiaoyelian	Sinopodophylli Fructus	*Sinopodophyllum hexandrum* (Royle) Ying	Mature fruits	Autumn	Irregular menstruation, hyperplasia of mammary glands, and breast-cancer
11	Xiaohuixiang*	Foeniculi Fructus	*Foeniculum vulgare* Mill.	Mature fruits	Autumn	Hepatoprotective and remediation of liver toxicity
12	Mugua*	Chaenomelis Fructus	*Chaenomeles speciosa* (Sweet) Nakai	Nearly mature fruits	Summer and autumn	Weakness of muscles and bones, muscle pain, and arthritis
13	Wuweizi#	Schisandare Chinensis Fructus	*Schisandra chinensis* (Turcz.) Baill.	Mature fruits	Autumn	Dysphoria and palpitation, insomnia, and dreaminess
14	Niubangzi#	Arctii Fructus	*Arctium lappa* L.	Mature fruits	Autumn	Throat pain and swelling, and detoxification
15	Maohezi	Terminaliae Belliricae Fructus	*Terminalia bellirica* (Gaertn.) Roxb.	Mature fruits	Winter	Diabetes, hypertension, and rheumatism
16	Huajuhong	Citri Grandis Exocarpium	*Citrus grandis* 'Tomentosa' *Citrus grandis* (L.) Osbeck	Immature or nearly mature epicarps	Summer	Cough, copious phlegm, indigestion, hyperglycemia, and hyperlipemia
17	Wumei*	Mume Fructus	*Prunus mume* (Sieb.) Sieb. et Zucc.	Nearly mature fruits	Summer	Chronic cough and expectoration
18	Huomaren*	Cannabis Fructus	*Cannabis sativa* L.	Mature fruits	Autumn	Anti-inflammatory and antioxidant
19	Badou	Crotonis Fructus	*Croton tiglium* L.	Mature fruits	Autumn	Constipation, visceral pain, and intestinal inflammation
20	Shuifeiji	Silybi Fructus	*Silybum marianum* (L.) Gaertn.	Mature fruits	Autumn	Hepatitis, cirrhosis, toxic liver damage, and jaundice
21	Shuihonghuazi	Polygoni Orientalis Fructus	*Polygonum orientate* L.	Mature fruits	Autumn	Swelling, indigestion, hypertension, cardiomyopathy, and chronic hepatitis
22	Shiliupi	Granati Pericarpium	*Punica granatum* L.	Pericarps	Autumn	Diarrhoea, haemostatic and insect repellent
23	Gualou	Trichosanthis Fructus	*Trichosanthes kirilowii* Maxim. *Trichosanthes rosthornii* Harms	Mature fruits	Autumn	Cardiovascular disease and cerebral ischaemic diseases
24	Gualoupi	Trichosanthis Pericarpium	*Trichosanthes kirilowii* Maxim. *Trichosanthes rosthornii* Harms	Pericarps	Autumn	Qi Stagnation, regulate lipid metabolism, and atherosclerosis

Table 1 (*continued*)

No.	Chinese name	English name	Species	Used parts	Harvesting seasons	Applications
25	Dongguapi	Benincasae Exocarpium	*Benincasa hispida* (Thunb.) Cogn	Epicarps		Gastrointestinal disease, respiratory disease, and diabetes
26	Dongkuiguo	Malvae Fructus	*Malva verticillata* L.	Mature fruits	Summer and autumn	Constipation, diuresis, and galactagogue
27	Mudingxiang	Caryophylli Fructus	*Eugenia caryophyllata* Thunb.	Nearly mature fruits		Invigorate blood circulation, cold pain of heart and abdomen, and galactagogue
28	Difuzi	Kochiae Fructus	*Kochia scoparia* (L.) Schrad.	Mature fruits	Autumn	Antibacterial, inflammation, gastric ulcer, hypoglycemic, and immunodepression
29	Xiqingguo	Chebulae Fructus Immaturus	*Terminalia chebula* Retz.	Young fruits		Fevers, diarrhea, asthma, rheumatism, and dysentery
30	Hongdoukou	Galangae Fructus	*Alpinia galanga* Willd.	Mature fruits	Autumn	Emesis, diarrhea, and indigestion
31	Huajiao*	Zanthoxyli Pericarpium	*Zanthoxylum schinifolium* Sieb. et Zucc. *Zanthoxylum bungeanum Maxim.*	Mature pericarps	Autumn	Gastric diseases, indigestion, diarrhea, and toothache
32	Cang'erzi	Xanthii Fructus	*Xanthium sibiricum* Patr.	Mature fruits with involucre	Autumn	Allergic rhinitis and other nasal disease
33	Doukou[#]	Amomi Fructus Rotundus	*Amomum kravanh* Pierre ex Gagnep. *Amomum compactum* Soland ex Maton	Mature fruits		"Humidness evil" eliminating and qi promoting, stomach cold, vomit, and indigestion
34	Lianqiao	Forsythiae Fructus	*Forsythia suspensa* (Thunb.) Vahl	Fruits	Autumn	Hepatoprotective, neuroprotective, and cardiovascular protective
35	Wuzhuyu[#]	Euodiae Fructus	*Euodia rutaecarpa* (Juss.) Benth. *Euodia rutaecarpa* (Juss.) Benth. var. *officinalis* (Dode) Huang *Euodia rutaecarpa* (Juss.) Benth. var. bodinieri (Dode) Huang	Nearly mature fruits	August to November	Bacterial infection and inflammation
36	Foshou*	Citri Sarcodactylis Fructus	*Citrus medica* L. var. *sarcodactylis* Swingle	Fruits	Autumn	Indigestion, hepatic stagnation, "humidness evil" eliminating and copious phlegm
37	Yuganzi*	Phyllanthi Fructus	*Phyllanthus emblica* L.	Mature fruits	Winter to the following spring	Anti-tumor, anti-inflammatory, anti-bacterial, and anti-viral activities
38	Shaji*	Hippophae Fructus	*Hippophae rhamnoides* L.	Mature fruits	Autumn and winter	Indigestion, cough, copious phlegm, and blood stasis syndrome
39	Hezi[#]	Chebulae Fructus	*Terminalia chebula* Retz. *Terminalia chebula* Retz. var. *tomentella* Kurt.	Mature fruits	Autumn and winter	Cancer, diabetic, mutagenic, hepatoprotective, and cardio-protective
40	Buguzhi[#]	Psoraleae Fructus	*Psoralea corylifolia* L.	Mature fruits	Autumn	Leucoderma, cardiovascular diseases, nephritis, bone fracture and osteoporosis
41	Chenpi	Citri Reticulatae Pericarpium	*Citrus reticulata* Blanco	Mature pericarps		Qi stagnation, chest and hypochondriac region pain, and hernia-like pain.
42	Qingpi[#]	Citri Reticulatae Pericarpium Viride	*Citrus reticulata* Blanco	Pericarps of young or immature fruit	May to August	Liver Qi stagnation, disperse stagnation
43	Qingguo*	Canarii Fructus	*Canarium album* Raeusch.	Mature fruits	Autumn	Sore throat, cough and sputum viscosity
44	Luohanguo*	Siraitiae Fructus	Siraitia grosvenorii (Swingle) C. Jeffrey ex A. M. Lu et Z. Y. Zhang	Fruits	Autumn	Immuno-regulation, anti-oxidation, anti-cancer and anti-obesity
45	Shijunzi	Quisqualis	*Quisqualis indica* L.	Mature fruits	Autumn	Deworming

(*continued on next page*)

Table 1 (*continued*)

No.	Chinese name	English name	Species	Used parts	Harvesting seasons	Applications
		Fructus				
46	Jinyingzi#	Rosae Laevigatae Fructus	*Rosa laevigata* Michx.	Mature fruits	October to November	Chronic diseases
47	Bibo#	Piperis Longi Fructus	*Piper longum* L.	Nearly mature or mature clusters		Jaundice and allergy
48	Bichengqie	Litseae Fructus	*Litsea cubeba* (Lour.) Pers.	Mature fruits	Autumn	Abdominal cold pain, cold hernia, and stomach hiccup
49	Caoguo#	Tsaoko Fructus	*Amomum tsao-ko* Crevost et Lemaire	Mature fruits	Autumn	Stomach disorders and throat infection
50	Chongweizi	Leonuri Fructus	*Leonurus japonicus* Houtt.	Mature fruits	Autumn	Blood stasis syndrome and edema
51	Hujiao*	Piperis Fructus	*Piper nigrum* L.	Nearly mature or mature fruits	Last autumn to following spring	Anti-oxidant, anti-depressant, anti-tumor, and anti-inflammatory
52	Nanwuweizi	Schisandrae Sphenantherae Fructus	*Schisandra sphenanthera* Rehd. et Wils.	Mature fruits	Autumn	Insomnia, lipid peroxidation in liver, and myocardial ischemia
53	Nanheshi	Carotae Fructus	*Daucus carota* L.	Mature fruits	Autumn	Parasite, hemorrhoid fistula, viral keratitis, and edema
54	Zhiqiao#	Aurantil Fructus	*Citrus aurantium* L.	Immature fruits	July	Acute lung injury, inflammation, obesity, and gastrointestinal dysfunctions
55	Zhishi#	Aurantil Fructus Immaturus	*Citrus aurantium* L. *Citrus sinensis* Osbeck	Young fruits	May to June	Copious phlegm, cancer, cardiovascular diseases, and gouty arthritis
56	Zhizi*	Gardeniae Fructus	*Gardenia jasminoides* Ellis	Mature fruits	September to November	Febrile diseases, jaundice, edema, and sprains
57	Gouqizi*	Lycii Fructus	*Lycium barbarum* L.	Mature fruits	Summer and autumn	Atherosclerosis, cancer, neurodegeneration, and diabetes
58	Sharen*	Amomi Fructus	*Amomum villosum* Lour. *Amomum villosum* Lour. var. *xanthioides* T. L. Wu et Senjen *Amomum longiligulare* T. L. Wu	Mature fruits	Summer and autumn	Digestive diseases, rheumatism, malaria, toothache, and promoting appetite
59	Yadanzi	Bruceae Fructus	*Brucea javanica* (L.) Merr.	Mature fruits	Autumn	Prostate, lung, and gastrointestinal cancer
60	Xiangyuan*	Citri Fructus	*Citrus medica* L. *Citrus wilsonii* Tanaka	Mature fruits	Autumn	Stomach ache, headache, edema, rheumatism, arthritis, and infectious hepatitis
61	Xiakucao	Prunellae Spica	*Prunella vulgaris* L.	Clusters	Summer	Liver inflammation, improve eyesight, mammary gland hyperplasia and swelling
62	Yizhi	Alpiniae Oxyphyllae Fructus	*Alpinia oxyphylla* Miq.	Mature fruits	Summer and autumn	Dementia
63	Yuzhizi	Akebiae Fructus	*Abebia quinata* (Thunb.) Decne. *Akebia trifoliata* (Thunb.) Koidz. *Akebia trifoliata* (Thunb.) Koidz. var. *australis* (Diels) Rehd.	Nearly mature fruits	Summer and autumn	Primary dysmenorrhea
64	Sangshen*	Mori Fructus	*Morus alba* L.	Clusters	April to June	Sore throats, anemia, and hypertension
65	Shechuangzi	Cnidii Fructus	*Cnidium monnieri* (L.) Cuss.	Mature fruits	Summer and autumn	Atopic dermatitis, asthma, psoriasis, urticaria, ringworm, and osteoporosis
66	Zhuyazao	Gleditsiae Fructus Abnormalis	*Gleditsia sinensis* Lam.	Infertility fruit	Autumn	Cerebral stroke sequelae
67	Chushizi	Broussonetiae	*Broussonetia papyrifera*	Mature fruits	Autumn	Alzheimer disease, neurons

Table 1 (*continued*)

No.	Chinese name	English name	Species	Used parts	Harvesting seasons	Applications
		Fructus	(L.) Vent.			protect
68	Zisuzi*	Periliae Fructus	*Perilla frutescens* (L.) Britt.	Mature fruits	Autumn	Cough and asthma with copious phlegm and stiffness in the chest
69	Jili	Tribuli Fructus	*Tribulus terrestris* L.	Mature fruits	Autumn	Eye trouble, cutaneous pruritus, edema, tracheitis, and blood stasis syndrome
70	Huaijiao	Sophorae Fructus	*Sophora japonica* L.	Mature fruits	Winter	Heart diseases, neoplasms, inflammation, and hyperlipidemia
71	Lulutong	Liquidambaris Fructus	*Liquidambar formosana* Hance	Infructescences	Winter	Ovarian cancer, prostatic cancer, and liver cancer
72	Manjingzi	Viticis Fructus	*Vitex trifolia* L. var. *simplicifolia* Cham. *Vitex trifolia* L.	Mature fruits	Autumn	Colds, head-ache, migraine, and eye pain
73	Yingsuqiao	Papaveris Pericarpium	*Papaver somniferum* L.	Shells	Autumn	Chronic cough, chronic lax, and cramp
74	Lajiao	Capsici Fructus	*Capsicum annuum* L.	Mature fruits	Summer and autumn	Stomachache, emesis, and chilblain
75	Ruiren	Prinsepiae Nux	*Prinsepia uniflora* Batal. *Prinsepia uniflora Batal. var. serrata Rehd.*	Kernels	Between summer and autumn	Respiratory infections in children
76	Heshi	Carpesii Fructus	*Carpesium abrotanoides* L.	Mature fruits	Autumn	Anti-diarrheal, anti-inflammatory, abirritatiye, and antibacterial
77	Juhong	Citri Exocarpium Rubrum	*Citrus reticulata* Blanco	Epicarps	Last autumn and early winter	Respiratory diseases
78	Fupenzi	Rubi Fructus	*Rubus chingii* Hu	Fruits	Summer	Enuresis, impotence, frequency of micturition, and spermatorrhea

*Dietary herbal medicine, #Health food.

(shown in Table 2). Interestingly, *C. sinensis* currently cultivated in various countries, are all introduced from Guangdong or Fujian of southern China (Laura et al., 2019).

The plant source of ZS has undergone a variety of changes in history. In addition, the fruits of many other *Citrus* plants share similar appearance, chemical constituents, and pharmacology with ZS. These reasons resulted in the phenomenon that the fruits of other *Citrus* plants were commonly used as adulterants of ZS in the market. Detailed adulterants information is shown in Table 2 and Fig. 5. The adulterants cannot be used as ZS due to the variations of their chemistry and efficacy (Li et al., 2016; Zeng et al., 1997; Zhong et al., 2021; Zhu and Pan, 2005; Li, 2002).

3.2.4. Ethnopharmacology

3.2.4.1. Discussion on the medicinal property of ZS. In the TCM theory system, the properties of TCM, also known as the "Yao Xin", include cold, hot, warm, and cool, which are summarized based on the reactions of medicines acting on the body. ZS was identified as "bitter, pungent, sour, and warm in nature" in both 1995 and 2000 editions of ChP (Chinese Pharmacopoeia Commission, 1995, 2000). The reasons are as follows (Liu and Zhou, 1988, 1993; Guo et al., 2001): (1) All Qi-moving drugs derived from the *Citrus* genus are warm in nature; (2) ZS is able to stimulate the sympathetic nerve and adrenal system, which belongs to the property of warm medicine; (3) ZS is often used in combination with warm-hot medicines to treat the cold syndrome.

In fact, ZS is actually used to treat the hot syndrome but not the cold syndrome. According to *ShenNongBenCaoJing*, ZS is bitter in taste and cold in nature. Among the 108 prescriptions containing ZS, 49 were used for the hot syndrome, accounting for about 45.4 % of the total. Forty-six were used for the cold and hot mixed or inconspicuous syndrome, and only 13 were used for the cold syndrome (Wu et al., 2008). Besides, in the 2020 edition of ChP (Chinese Pharmacopoeia Commission, 2020b), ZS is recorded as bitter, pungent, sour, and slightly cold. Therefore, the medicinal properties of ZS are either sightly cold or flat, rather than warm. However, the discussion still needs further experimental verification.

3.2.4.2. Application of ZS. Traditionally, it is believed that ZS used alone can improve stagnation of dyspepsia and gastrointestinal function, reduce chest pain and cure organ prolapse. Using alone or in combination with other herbs, the medicinal effect of ZS is severer than ZQ, which is named as "Po Qi" (Bai et al., 2018). ZS is used for gastrointestinal accumulation, while ZQ is used for the stagnation of Qi in the lungs or stomach.

Among the 100 classical prescriptions published by National Administration of Traditional Chinese Medicine in 2018, five contained ZS (Table 3). According to the database (https://db.yaozh.com/), there are 766 classic prescriptions containing ZS. So far, quality standards of 186 prescriptions containing ZS have been recorded by the NHCPRC. Among them, 40 were recorded in the ChP (Chinese Pharmacopoeia

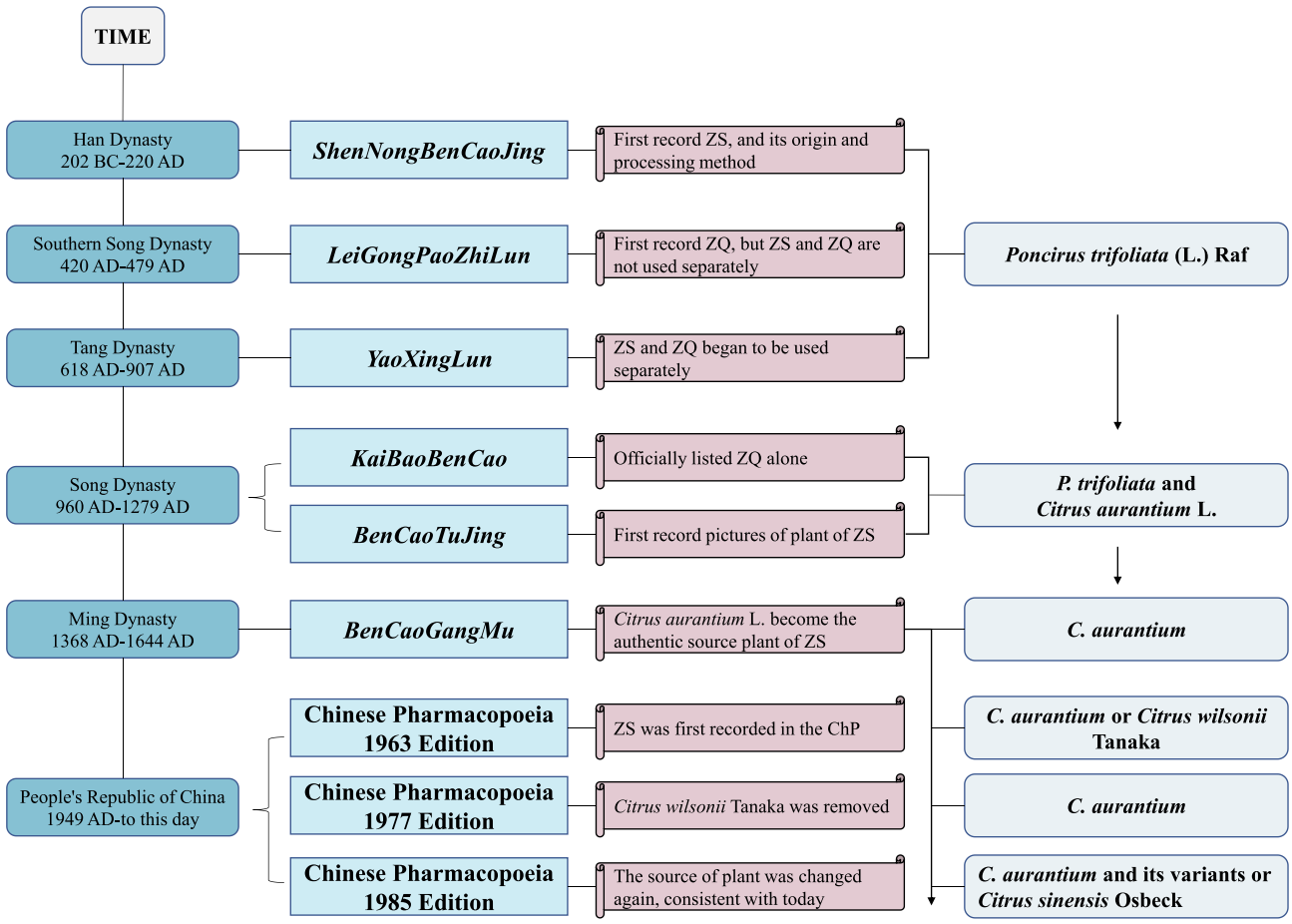

Fig. 2 The history of ZS used in medicine and the changes in plant origin of ZS.

Commission, 2020b). However, only 3 Chinese patent medicines (Zhishi Daozhi pills, Zhishi Xiaopi pills, and Fufang Zhishi pills) are available on the market. Therefore, there is a great potential for the development and use of prescriptions of ZS.

3.3. Phytochemistry

A variety of methods have been used for the extraction, separation, and identification of chemical constituents of ZS. Currently, a total of 121 compounds have been isolated and identified from ZS, predominantly flavonoids, coumarins, alkaloids, limonoids, and other phenolic compounds.

3.3.1. Flavonoids

Flavonoids in ZS are mainly divided into four types: flavones, polymethoxy flavonoids, flavonols, and flavanones based on their differences in skeleton and substituents (Fig. 6).

3.3.1.1. Flavones. Flavones are 2-phenyl chromone derivatives without substituent at the C-3 position. Both C-5 and C-7 positions of its A ring are substituted by hydroxyl groups, while the C-4′ and C-3′ positions of its B ring are often substituted by hydroxyl groups or methoxy groups. Most of the flavones isolated from ZS are glycosides, including *O*-glycosides (**1**–**7**) and *C*-glycosides (**8**–**15**). As shown in Table 4 and Fig. 6, *O*-glycosides are mostly substituted in the C-7 position, while *C*-glycosides are mainly substituted in the C-8 position.

3.3.1.2. Polymethoxy flavonoids. Polymethoxy flavonoids, unique flavonoids in *Citrus* plants, refer to a class of natural products containing four or more methoxy groups on the molecular skeleton at the C-5, C-8, C-3′, and C-5′ positions, or more at the C-7 and/or C-4′ positions (**16**–**26**). A total of 11 polymethoxy flavonoids (**16**–**26**) were isolated from ZS (Table 4).

3.3.1.3. Flavonols. Hydroxyl groups or other oxygen-containing groups are attached to the C-3 position of the skeleton of flavonoids. But flavonols with hydroxyl or methoxy groups in other positions were also isolated from ZS (**27**–**39**) (Table 5 and Fig. 6).

3.3.1.4. Flavanones. Flavanones in ZS are present in the forms of glycoside or aglycone. Among the aglycones, naringenin (**40**) and hesperetin (**41**) are the most important due to their broad pharmacological activity. Apart from glucosides (**42**–**44**), there are other two types of flavanones, including rutinosides (**45**–**51**) and neohesperidosides (**53**–**56**) (Table 6 and Fig. 6).

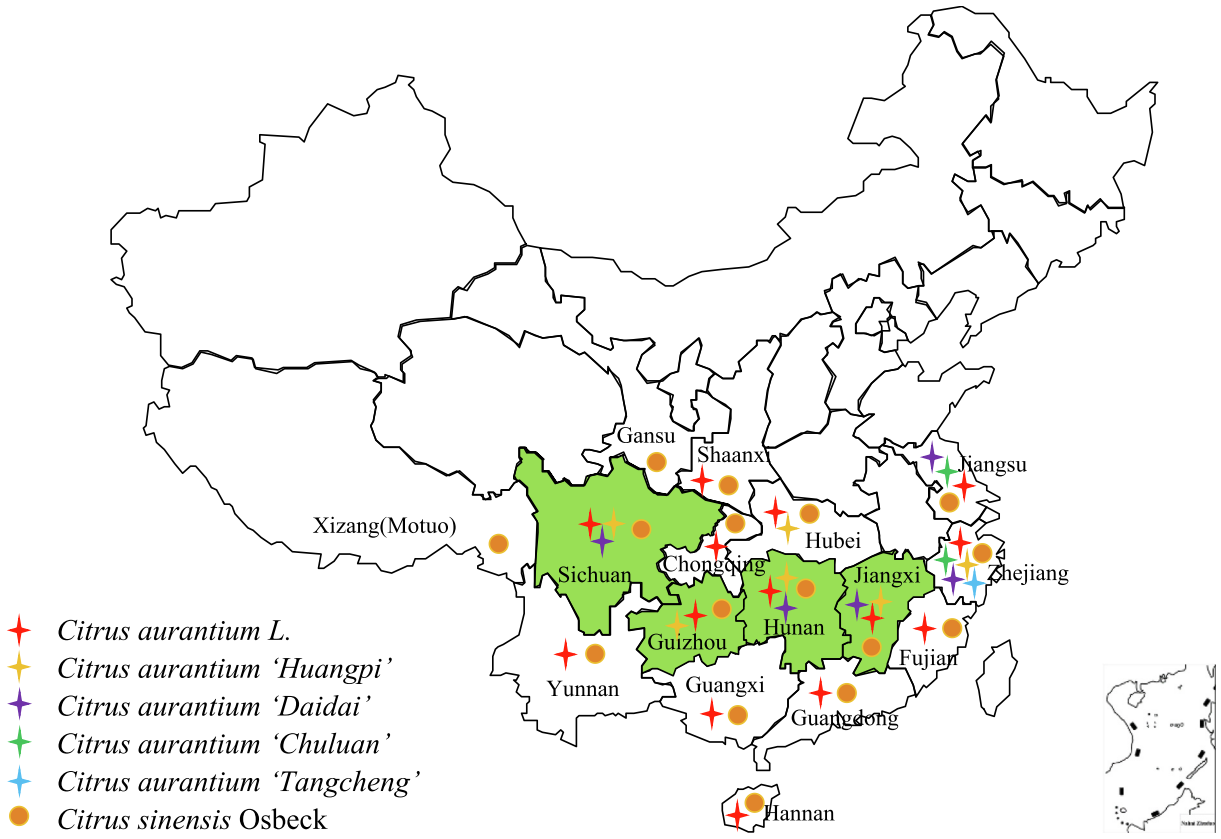

Fig. 3 Climatic and ecological adaptability distribution of ZS in China.

Fig. 4 (A) Eyan ZS; (B) SCZS; (C) TCZS.

3.3.2. Coumarins

Coumarins are a class of natural compounds with a benzo-α-pyrone, which are divided into furanocoumarins and pyranocoumarins. They are also another major biologically active compound found in the *Citrus* genus. They were three types of coumarins in ZS, including typical coumarins (**61**–**69**), isocoumarins (**70**–**72**) and furanocoumarins (**73**–**77**) (Table 7 and Fig. 7). However, the isolation of pyranocoumarins from ZS has not been reported.

3.3.3. Alkaloids

The alkaloids in ZS possess the effects of blood pressure elevating, contraction of uterine smooth muscle promoting, cardiotonic, and anti-obesity. The intravenous injection of ZS has a significant effect on raising blood pressure. Synephrine (**78**) and *N*-methyltyramine (**79**) were identified from the elevating blood pressure components of ZS (Hu'Nan Medicine Industry Research Institute, 1976). Zhang used silica gel column chromatography, Sephadex LH-20 column chromatography, preparative high-performance liquid chromatography (HPLC), and other methods for the separation and purification of the four alkaloids (**81**–**84**) (Zhang et al., 2015). Peng also extracted and separated 4 alkaloids (**78**–**80** and **86**) from the ethanol extract of ZS to obtain (Peng et al., 2001). In addition, some other alkaloids (**85**, **87** and **88**) with multiple nitrogen atoms were also isolated (Table 8 and Fig. 8) (Zhang et al., 2005; Deng et al., 2018).

Table 2 Comparison of botanical appearance between ZS and its adulterants.

Herbal name	Plant	Diameter (cm)	Ladybug pouch	Number of chambers (pcs)	Mesocarp thickness (cm)	Exocarp	Mesocarp	Transverse section	Carpopodium	Reference
ZS	*Citrus aurantium* L.	0.5–2.5	Sepia	7–12	0.3–1.2	Dark green or brownish-brown	Yellowish white or yellowish brown	Smooth and slightly bulging	Disk remnants or fruiting pedicel abscission scars	
	C. aurantium 'Huangpi'	1.5–2.5	Light brown	8–10	0.5–0.9	Brown or greenish-yellow	Yellowish brown	Slightly curled or flat	Slightly protruding from the peel	(Li et al., 2007)
	C. aurantium 'Daidai'	1.7–2.5	Light brown	9–11	0.5–0.7	Tan or grey-brown	Yellowish brown	Slightly outward	Disc from the peel with slightly radiate ridge	(Liu et al., 2019)
	C. aurantium 'Chuluan'	0.75–1	Pale yellow	10–12	0.6–1.1	Brownish green or greenish black	Off-white	Thick and bulging	Dented into the peel, radial wrinkles all around	(Chen, 1998)
	C. aurantium 'Tangcheng'	*	*	*	*	Surface coarse	Yellowish white	Poor thickness	Protruding from the peel	(Wang et al., 2009)
	Citrus sinensis Osbeck	1–2.5	Dark yellow to deep red	8–12	0.2–0.4	Dark brown	Off-white color	Flat	Disc	
QP	*Citrus reticulata Blanco*	0.5–2	Light brown	8–10	0.1–0.2	Grey-green or black-green	Yellowish brown or light yellowish brown	Poor thickness	Disc	(He et al., 2021)
ZQ	*Citrus aurantium* L.	3–5	Brown or tan	7–12	0.4–1.3	Tan to brown	Yellowish white	Smooth and slightly outward	Dented into the peel	(Gao et al., 2020)
Juyuan	*Citrus medica* L.	4–10	Yellowish white	10–17	1–3	Yellow or chartreuse	Yellowish white or light yellowish brown	Transverse section with undulating margins	*	(Mondal et al., 2021)
Xiangyuan	*Citrus wilsonii* Tanaka	1.5–2.5	Brown or light reddish brown	9–11	0.4–0.8	Blackish green or yellowish brown	Light reddish brown	Extremely outward	Disc	(Yan et al., 2021)
Lvyi ZS	*Poncirus trifoliata* (L.) Raf	0.6–1.6	Yellowish white	5–7	0.3–0.6	Greenish-brown	Off-white color	Flat	Disc with slightly radiate ridge	(Jang et al., 2018)
Honghecheng	*Citrus hongheensis* Ye et al	3–5.5	Brown	10–12	1–1.3	Yellowish brown	Outer edges green, inner dark brown	Flat or inward	Longitudinal ribs or persistent calyx	(Zhang et al., 2020)
You	*Citrus grandis* (L.) Osbeck	1.5–3	Light brown	10–18	0.5–1.5	Tan and grey-brown	Light yellowish brown	Inward	Disc	(Anmol et al., 2021)
Xiecheng	*Citrus.junos Sieb. ex* Tanaka	2.5–4	Pale yellowish white	9–11	0.3–0.5	Turquoise	Pale red	Slightly outward	Coarse with radiate ridge	(Song et al., 2019)
Yichangcheng	*Citrus.ichangensis* Swingle	2.5–4	Yellowish white	5–7	0.2–0.4	Greyish green or light yellowish brown	Pale yellowish white	Flat	Protruding from the peel	(Ding et al., 2012)

Table 2 (*continued*)

Herbal name	Plant	Diameter (cm)	Ladybug pouch	Number of chambers (pcs)	Mesocarp thickness (cm)	Exocarp	Mesocarp	Transverse section	Carpopodium	Reference
Xiangcheng	*Citrus aurantium* 'Xiangcheng'	0.5–2.5	Sepia	9–12	0.6–1.1	Brownish green or greenish black	Yellowish white	Outward and roll	Radiate ridge	(Luo et al., 2008)
Xiucheng	*Citrus aurantium* 'Xiucheng'	0.5–2.5	Browness	9–12	0.7–1.2	Grey-green or yellowish brown	Yellowish white	Slightly bulging and outward	Not obvious	(Ding and Lu, 1986)
Zhicheng	*Poncirus trifoliata* × *C. aurantium*	3.6–6	Milky white or milky yellow	6–8	0.3–0.6	Scarlet	Milky yellowish white	Flat	Slightly dented into the peel with a ring	(Lu, 2015)

3.3.4. Limonoids

Limonoids are a group of highly oxygenated tetracyclic triterpenoids, which are also present in the form of aglycones and glycosides. Deepak used water-based polystyrene adsorption resin to extract and purify deacetyl nomilin (**89**), limonin (**90**), and deacetyl nomilin acid glucoside (**95**) (Dandekar et al., 2008). In screening constituents of improving gastrointestinal motility from the 70 % ethanol–water extract, isoobacunoicacid (**91**) was obtained (Zhang et al., 2019). Jayaprakasha isolated isolimonoic acid (**94**) and ichanexic acid (**96**) from ZS (Jayaprakasha et al., 2008). In addition, Zhao and Bai used UHPLC-Q-TOF-MS to determine nomilin (**92**) and obacunone (**93**) (Zhao et al., 2017; Bai et al., 2018) (Table 8 and Fig. 9).

3.3.5. Other phenolic compounds

Other phenolic compounds of ZS have also been reported (Table 8 and Fig. 10). Phlorin (**101**) was first obtained from ZS in 2005 (Zhang et al., 2005). The new compound (**104**) was isolated later in 2006 (Zhang et al., 2006). Two other new compounds (**103** and **105**) were isolated 11 years later (Zhang et al., 2017). Zhang obtained a new phenolic compound (**106**) and four known compounds (**99**–**100** and **103**–**104**) (Zhang et al., 2019). Deng used silica gel column chromatography, HW-40F gel column chromatography, ODS reversed-phase column chromatography, and preparative HPLC to separate phenolic compounds from ZS, leading to the isolation of a new compound (**102**) and two firstly reported compounds (**97** and **98**) in ZS (Deng et al., 2020).

3.3.6. Other compounds

Phenyl compounds and phenyl glycosides were also present in ZS (Table 8 and Fig. 11). Besides, ZS is rich in the nutrients necessary for human life. For example, 4 cyclic peptides (Matsubara et al., 1991), 5 amino acids (Deng et al., 2018), and 4 polysaccharides were obtained from ZS (Wang et al., 2014).

3.4. Quality control

Quality control of TCMs has received much attention in recent years. Thin-layer chromatography (TLC) and HPLC are the main techniques used for quality control in pharmacopeias in China and around the world. According to ChP (Chinese Pharmacopoeia Commission, 2020b) and Taiwan Traditional Chinese Medicine Dictionary (the third edition), synephrine (**78**) was used as an indicator component, whose content in ZS should be no < 0.3 %. The fourth issue of Hong Kong Chinese Materia Medica discriminated SCZS from TCZS based on their appearance, micrograph, and HPLC chromatogram. Besides, hesperidin (**49**) and naringin (**53**) were used for the quality control of ZS, and the contents of naringin (**53**) and synephrine (**78**) should be no < 0.66 % and 0.3 %, respectively. In 2021, The Japanese Pharmacopoeia (the 18th edition) prescribed a color reaction method for the identification of ZS. According to Food and Drug Administration (FDA), the content of synephrine (**78**) in dried fruit of *C. aurantium* ranged from 0.012 % to 0.25 % (Correll, 2015).

Different countries or regions have various requirements for quality control standards of herbal medicines. Determina-

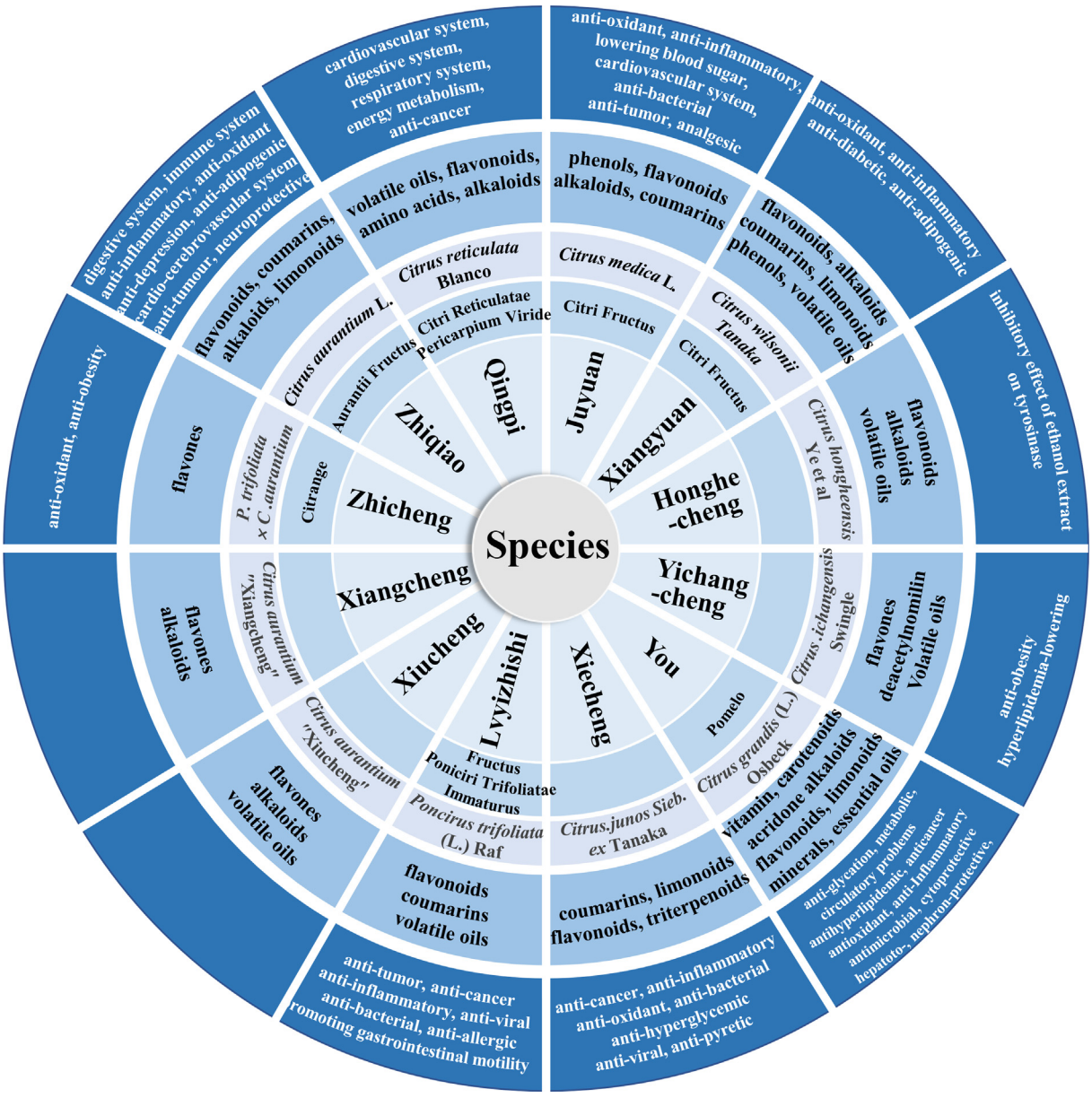

Fig. 5 The adulterants of ZS.

tion of multi-components and application of multi-instruments are the trends of the times for quality control. The literature data for quality control from 1984 to 2022 were summarized. As shown in Fig. 12, synephrine (**78**), the most representative constituent in ZS, was investigated as a single-marker for quality control of ZS in 22 papers from 1994 to 2022. The results also suggested naringin (**53**), hesperidin (**49**), neohesperidin (**56**), and synephrine (**78**) were the most investigated compounds in TLC, HPLC, and other technical research.

3.4.1. TLC

TLC is a major force in the quality control of TCM, which is more suitable for the detection of the components without UV absorption compared with HPLC (Deng et al., 2019). Yuan compared the TLC methods of ZS, ZQ, Qingpi (QP, the young fruit or peel of *Citrus* reticulata Blanco), and Chengpi (CP, the mature peel of *Citrus* reticulata Blanco) in various pharmacopeias and literature and found the method of ZQ in ChP (Chinese Pharmacopoeia Commission, 2020b) is the best one, which allowed discrimination of the four medicines (Yuan et al., 2021). In addition, the contents of total flavonoid (Wang and Luo, 1989) and alkaloid (Wang et al., 1994) were determined by TLC-Scanning. Bagatela established a more robust high-performance TLC (HPTLC) method coupled with desorption electrospray ionization mass spectrometry (DESI-MS) for the analysis of more compounds (Bagatela et al., 2015). Tao described a new approach that applies artificial neural networks (ANN) to raw HPTLC images for the discrimination of ZS, ZQ, QP, and CP (Li et al., 2019).

3.4.2. HPLC/UHPLC

The contents of alkaloids and flavonoids were different among ZS and its adulterants, and no alkaloids was detected in Honghecheng using HPLC method (Chen et al., 2022; Wu et al.,

Table 3 Application of ZS in classical prescriptions of TCM.

Prescription name	Main herbs	Traditional use	References	Dynasty
Xiaochengqi Decoction	Rhei Radix et Rhizoma, Magnoliae Officinalis Cortex, Aurantii Fructus Immaturus	Reliving chronic constipation and food stagnation	*ShangHanLun*	Han (B.C.202-A.D.220)
Zhishi Xiebai Guizhi Decoction	Aurantii Fructus Immaturus, Magnoliae Officinalis Cortex, Allii Macrostemonis Bulbus, Cinnamomi Ramulus	Reducing heart and chest pain, expectorant	*JinGuiYaoLue*	Han (B.C.202-A.D.220)
Houpo Qiwu Decoction	Magnoliae Officinalis Cortex, Glycyrrhizae Radix et Rhizoma, Rhei Radix et Rhizoma, Jujubae Fructus, Aurantii Fructus Immaturus, Cinnamomi Ramulus, Zingiberis Rhizoma Recens	Dissipating cold and painful abdominal Mass	*JinGuiYaoLue*	Han (B.C.202-A.D.220)
Wendan Decoction	Pinelliae Rhizoma, Bambusae Caulis in Taenias, Aurantii Fructus Immaturus, peel of *Citrus reticulata* Blanco, Zingiberis Rhizoma Recens, Glycyrrhizae Radix et Rhizoma	Dissipating stagnant qi and eliminating sputum in gallbladder	*BeiJiQianJinYaoFang*	Tang (A.D.618–907)
Sanhua Decoction	Magnoliae Officinalis Cortex, Rhei Radix et Rhizoma, Aurantii Fructus Immaturus, Notopterygii Rhizoma et Radix	Treating stroke	*SuWenBingJiQiYiBaoMing Ji*	Jin (CE1115–1234)

2022; Zeng et al., 1997; Zhu and Pan, 2005). Naringin (**53**) and neohesperidin (**56**) were not detected in Zhizhu pills containing TCZS, but they did in those containing SCZS (Song et al., 2016). Shi compared the level of limonin (**90**) of ZS in different origins, and those from Hunan were the highest in the content (Shi and Liu, 2011). Chuang established a HPLC method coupled with an algorithm to discriminate ZS, ZQ, Gouju (fruit of *P. trifoliata*), and Xiangyuan (fruit of *Citrus wilsonii* Tanaka) (Chuang et al., 2007). Furthermore, solid-phase extraction column coated with Strata-X (Zeng et al., 2016) and rapid resolution LC (Wang et al., 2009) were also used for the determination of phenolic compounds and flavonoids. Mid-June proved to be the best harvest time of ZS by UHPLC analysis because the content of total chemical compounds was highest at that time (Deng et al., 2017). Additionally, the chemical differences between peel and pulp of ZS were discovered by UHPLC (Shi et al., 2021).

Fingerprints can provide a comprehensive description and evaluation of the quality of TCMs. The fingerprints of the SCZS and TCZS were established separately, and 17 peaks were identified by comparing retention time and UV spectroscopy with the standard. The mark compounds, naringin (**53**) and neohesperidin (**56**), were discovered based on their variable important value, which did not exist in TCZS, and thus can be used for discrimination of these two herbal materials (Zeng et al., 2016). Synephrine (**78**) was used for fingerprint analysis for the first time in 2011, and this method was then recorded in the Hong Kong Chinese Materia Medica in 2012 (Zhang et al., 2011). However, naringin (**53**) was detected in TCZS by this method, which was inconsistent with the results of most reported studies (Lu et al., 2022). It may be caused by inaccurate identification of the plant origins of the samples. Gao established a method for simultaneous determination of nine components by using quantitative analysis of multi-components by single-marker (QAMS) (Gao et al., 2020). Qi used chemical pattern recognition technology such as similarity evaluation, cluster analysis (CA), principal component analysis (PCA), and orthogonal partial least square discriminant analysis (OPLS-DA) for the data analysis and quality evaluation of ZS (Qi et al., 2021). Notably, the fingerprint of standard decoction of ZS should be studied separately due to the chemical differences between SCZS and TCZS (Shi et al., 2019).

The content of naringin (**53**) heightened along with the increase of the diameter of ZS slices (Huang et al., 2008; Lin et al., 2022). With the prolonging of storage time, the content of naringin (**53**) was increased, while the content of neohesperidin (**56**) and synephrine (**78**) decreased (Zhou and Gui, 1997; Xu et al., 2020). In addition, the level of synephrine (**78**) and flavonoids varied among the different processed products of ZS. For example, the vinegar-fried ZS was the highest in its content, and the alcohol-fried one was the lowest (Cai et al., 2022; Ouyang, 2005). HPLC analyses of the formula granule and decoction of ZS suggested they showed high similarity in chemistry (Zhang et al., 2007). Granules from different manufacturers showed significant variations according to UHPLC analysis results (Chen et al., 2010).

3.4.3. Lc-MS/GC–MS

Currently, high-resolution quadrupole time-of-flight tandem mass spectrometry (QTOF-MS/MS) becomes a powerful technology for the identification and determination of herbal materials chemical constituents. In 2020, a total of 295 metabolites were screened using this method, and 89 phytochemicals were identified in the flowers, fruits, roots, leaves, and branches of *C. aurantium* 'Daidai'. Among them, sixty-nine were reported for the first time (Yu et al., 2020). Wu developed a simultaneous qualitative and quantitative analysis method for 10 bioactive flavonoids in ZS (Wu et al, 2022). There were 19 different components between raw material and bran-fried product of ZS, which provided a deep insight into the processing mechanism of ZS (Peng et al., 2020). QTOF-MS/MS coupled with genetic algorithm optimized support vector machines (GA-SVM) was successfully employed to discriminate of the fruit of seven *Citrus* herbs (Duan et al., 2014). Tong developed an online extraction strategy, which eliminated sample pretreat-

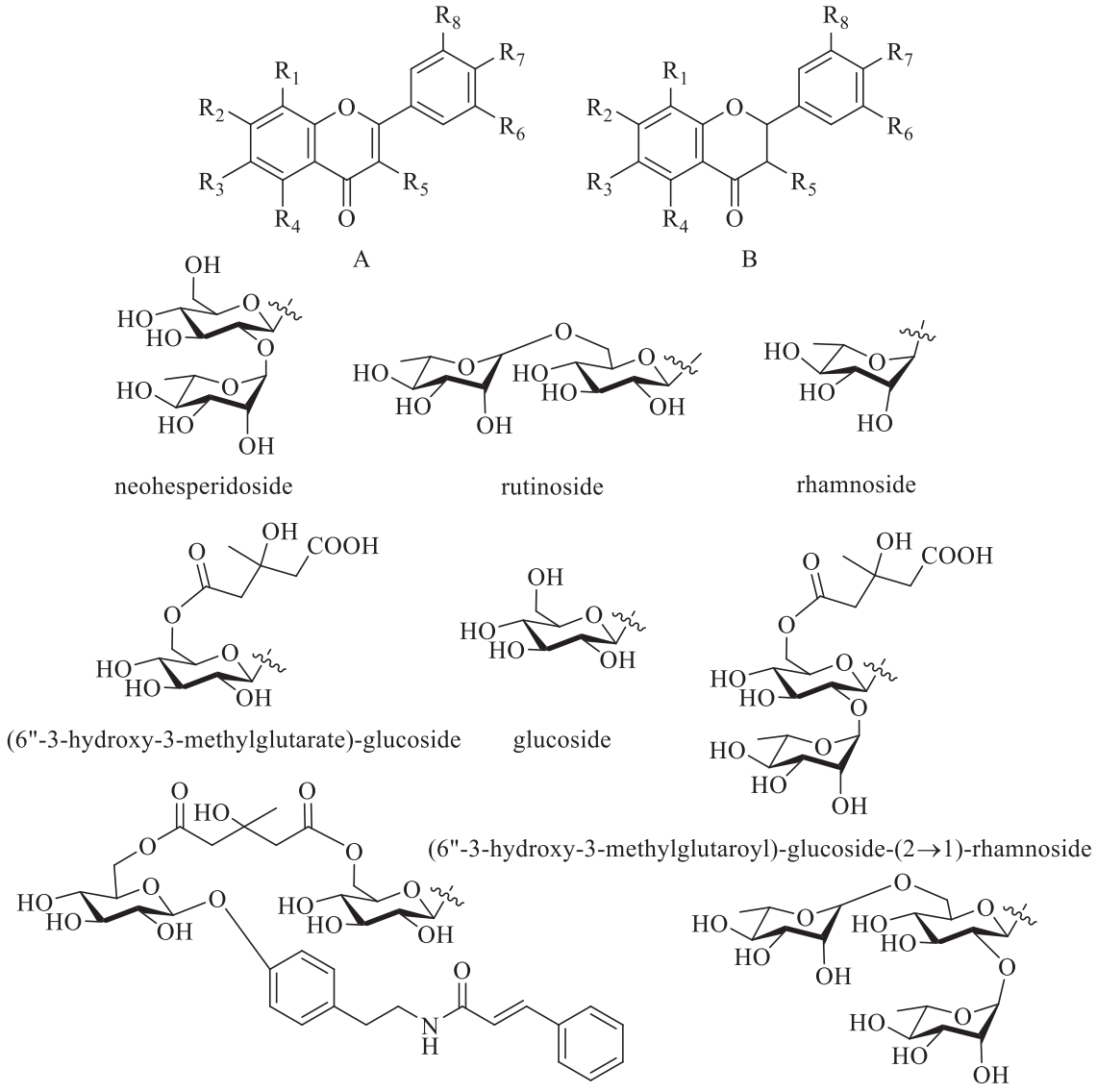

Fig. 6 The skeleton of flavonoids and their substituent moieties in ZS.

ment steps and increased extraction efficiency (Tong et al., 2018). In addition, an UHPLC coupled with linear ion trap-Orbitrap tandem mass spectrometry (UHPLC-LTQ-Orbitrap-MS/MS) method was developed to detect the chemical composition of ZS, and a total of 27 compounds were detected, including 14 flavonoids, 7 coumarins, 5 limonoids, and 1 alkaloid (Yu et al., 2016).

GC–MS was applied in the identification of *Citrus* genus (Dong et al. 2022). The volatile composition of ZS from China was different from those from Korea (the fruit of *P. trifoliate* and *C. aurantium*) according to GC–MS analysis results (Liu et al., 2003). Twenty-nine and thirty-eight constitutes were identified from SCZS and TCZS, respectively. Among them, twenty-four are common in these two herbal materials (Liu et al., 2011). He established HS-GC-IMS-fingerprint for the identification of SCZS and TCZS (He et al., 2022). Sixty-five compounds, including 57 different from SCZS, were identified from Xiangyuan (Yang et al., 2010). Differences in harvesting periods resulted in variations in the levels of volatile components of ZS, and limonene content increased along with fruit growth (Deng et al., 2019). Compared with raw material, bran, honey and bran, or honey and chaff fried ZS caused the generation of 52, 26, and 28 derivatives, respectively (Yu et al., 2015). In addition, Deng established a method for the determination of limonene, gamma terpene, linalool, and 4-terpineol of ZS (Deng et al., 2020).

3.4.4. DNA molecular techniques.

DNA molecular marker and DNA barcode were used for species identification and genetic characteristics research based on PCR amplification technology. The origin and evolution of *Citrus* genus were studied by analyzing their whole-genome sequences. Both *C. aurantium* and *C. sinensis* come from the hybridization of pomelo and mandarin (Wu et al., 2014; Wu et al., 2018). The differences of genetic relationship among *C. aurantium*, *C. sinensis*, and other cultivars were revealed

Table 4 Flavones and polymethoxy flavonoids in ZS.

No.	Compound name	Skeleton	R1	R2	*R*3	R4	R5	R6	R7	R8	Reference
1	Rhoifolin	A	H	*O*-neohesperidoside	H	OH	H	H	OH	H	(Mencherini et al., 2013)
2	Rhoifolin-4′-glucoside	A	H	*O*-neohesperidoside	H	OH	H	H	*O*-glucoside	H	(Mencherini et al., 2013)
3	Luteolin-7-*O*-neohesperidoside	A	H	*O*-neohesperidoside	H	OH	H	OH	OH	H	(Mencherini et al., 2013)
4	Neodiosmin	A	H	*O*-neohesperidoside	H	OH	H	OH	OCH_3	H	(Mencherini et al., 2013)
5	Chrysoeriol-7-*O*-neohesperidoside*	A	H	*O*-neohesperidoside	H	OH	H	H	OH	OCH_3	(Barreca et al., 2015)
6	Diosmin*	A	H	*O*-rutinoside	H	OH	H	OH	OCH_3	H	(Bai et al., 2018)
7	6-*C*-*β*-glucosyldiosmin	A	H	OH	*O*-glucoside	OH	H	OH	OCH_3	H	(Zhang et al., 2019)
8	Lucenin-2*	A	glucoside	OH	glucoside	OH	H	H	OH	OH	(Barreca et al., 2015)
9	Apigenin-6,8-di-*C*-glucoside	A	glucoside	OH	glucoside	OH	H	H	OH	H	(Mencherini et al., 2013; Barreca et al., 2015)
10	Diosmetin-6,8-di-*C*-glucoside	A	glucoside	OH	glucoside	OH	H	OH	OCH_3	H	(Mencherini et al., 2013)
11	Chysoeriol-6,8-di-*C*-glucoside*	A	glucoside	OH	glucoside	OH	H	H	OH	OCH_3	(Barreca et al., 2015; Tong et al., 2018)
12	Scoparin*	A	glucoside	OH	H	OH	H	H	OH	OCH_3	(Barreca et al., 2015)
13	3,8-di-*C*-glucosylapigenin	A	glucoside	OH	H	OH	glucoside	H	OH	H	(Matsubara and Sawabe, 1994)
14	3,8-di-*C*-glucosyldiosmetin	A	glucoside	OH	H	OH	glucoside	H	OCH_3	OH	(Matsubara and Sawabe, 1994)
15	Quercetin-3-hydroxy-3-methylglutaryl-glycoside*	A	H	OH	H	OH	(6″-3-hydroxy-3-methylglutarate)-glucoside	H	OH	OH	(Barreca et al., 2015)
16	Tangeretin	A	OCH_3	OCH_3	OCH_3	OCH_3	H	H	OCH_3	H	(Han et al., 2010)
17	Nobiletin	A	OCH_3	OCH_3	OCH_3	OCH_3	H	H	OCH_3	OCH_3	(Han et al., 2010)
18	5-demethyl nobiletin	A	OCH_3	OCH_3	OCH_3	OH	H	H	OCH_3	OCH_3	(Zhang et al., 2015)
19	5-hydroxy-6,7,8,4′-tetramethoxyflavone	A	OCH_3	OCH_3	OCH_3	OH	H	H	OCH_3	H	(Jiang et al., 2016)
20	Isosinensetin*	A	OCH_3	OCH_3	H	OCH_3	H	H	OCH_3	OCH_3	(Bai et al., 2018; Tong et al., 2018)
21	Tetramethyl-*O*-isoscutellarein*	A	OCH_3	OCH_3	H	OCH_3	H	H	OCH_3	H	(Tong et al., 2018)
22	5,7,8,4′-tetramethoxyflavone	A	OCH_3	OCH_3	H	OCH_3	H	H	OCH_3	H	(Han et al., 2010)
23	7,8,3′,4′-tetramethoxyflavone*	A	OCH_3	OCH_3	H	H	H	OCH_3	OCH_3	H	(Bai et al., 2018)
24	Sinensetin	A	H	OCH_3	OCH_3	OH	H	H	OCH_3	OCH_3	(Jiang et al., 2016)
25	5-hydroxy-6,7,3′,4′-tetramethoxyflavone	A	H	OCH_3	OCH_3	OCH_3	H	H	OCH_3	OCH_3	(Jiang et al., 2016)
26	5,6,7,4′-tetramethoxyflavone*	A	H	OCH_3	OCH_3	OCH_3	H	H	OCH_3	H	(Bai et al., 2018)

*Detected by HPLC or LC-MS.

Table 5 Flavonols in ZS.

No.	Compound name	Skeleton	R1	R2	*R*3	R4	R5	R6	R7	R8	Reference
27	Natsudaidai	A	OCH_3	OCH_3	OCH_3	OCH_3	OH	H	OCH_3	OCH_3	(Jiang et al., 2016)
28	3,5,6,7,3′,4′-hexamethoxy flavone*	A	H	OCH_3	OCH_3	OCH_3	OCH_3	H	OCH_3	OCH_3	(Tong et al., 2018)
29	3-methoxynobiletin*	A	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	H	(Bai et al., 2018)
30	Natsudaidain-3-*O*-glucoside*	A	OCH_3	OCH_3	OCH_3	OCH_3	*O*-glucoside	H	OCH_3	OCH_3	(Tong et al., 2018)
31	Quercetin-3-*O*-glycoside*	A	H	OH	H	OH	*O*-glucoside	H	OH	OH	(Barreca et al., 2015)
32	Rutin*	A	H	OH	H	OH	*O*-rutinoside	OH	OH	H	(Bai et al., 2018)
33	Nicotiflorin	A	H	OH	H	OH	*O*-rutinoside	H	OH	H	(Bai et al., 2018)
34	Narcissoside	A	H	OH	H	OH	*O*-rutinoside	OCH_3	OH	H	(Bai et al., 2018)
35	Quercetin-3-*O*-(2-rhamnosyl)-rutinoside*	A	H	OH	H	OH	*O*-(2-rhamnosyl)-rutinoside	H	OH	OH	(Barreca et al., 2015)
36	Natsudaidain-3-*O*-(3-hydroxy-3-methylglutarate)-glucoside*	A	OCH_3	OCH_3	OCH_3	OCH_3	*O*-(6″-3-hydroxy-3-methylglutarate)-glucoside	H	OCH_3	OCH_3	(Tong et al., 2018)
37	Limocitrin-3-*O*-(3-hydroxy-3- methylglutarate)-glucoside*	A	OCH_3	OH	H	OH	*O*-(6″-3-hydroxy-3-methylglutarate)-glucoside	H	OH	OCH_3	(Tong et al., 2018)
38	5,7,4′-trihydroxy-8,3′-dimethoxyflavone-3-*O*-6″-(3-hydroxyl-3-methylglutaroyl)-*β*-D-glucopyranoside	A	OCH_3	OH	H	OH	*O*-(6″-3-hydroxy-3-methylglutaroyl)-glucoside-(2 → 1)-rhamnoside	H	OH	OCH_3	(Deng et al., 2020)
39	Citrusauranosides A	A	OCH_3	OH	H	OH	*O*-(cinnamoyltyramine-1-glucoside-6–3-hydroxy-3-methyl-pentanedioic-6)-glucoside	OCH_3	OH	H	(Zhang et al., 2019)

*Detected by HPLC or LC-MS.

Table 6 Flavanones and flavanonols in ZS.

No.	Compound name	Skeleton	R1	R2	*R*3	R4	R5	R6	R7	R8	Reference
40	Naringenin	B	H	OH	H	OH	H	H	OH	H	(Liu et al., 2016)
41	Hesperetin	B	H	OH	H	OH	H	OH	OCH_3	H	(Liu et al., 2016)
42	Hesperetin-7-*O*-*β*-D-glucoside	B	H	*O*-glucoside	H	OH	H	H	OCH_3	OH	(Zhang et al., 2005; Feng et al., 2012)
43	Isosakuranin	B	H	*O*-glucoside	H	OH	H	H	OCH_3	H	(Feng et al., 2012)
44	Hesperetin-7-*O*-*β*-D-glucopyranoside	B	H	*O*-glucoside	H	OH	H	H	OCH_3	OH	(Jiang et al., 2017)
45	Narirutin	B	H	*O*-rutinoside	H	OH	H	H	OH	H	(Deng et al., 2020)
46	Eriocitrin	B	H	*O*-rutinoside	H	OH	H	H	OH	OH	(Deng et al., 2020)
47	Didymin*	B	H	*O*-rutinoside	H	OH	H	H	OCH_3	H	(Tong et al., 2018)
48	Isosakuranetin-7-rutinoside*	B	H	*O*-rutinoside	H	OH	H	H	OCH_3	H	(Sommella et al., 2017)
49	Hesperidin	B	H	*O*-rutinoside	H	OH	H	H	OCH_3	OH	(Liu et al., 2016)
50	Methyl hesperidin	B	H	*O*-rutinoside	H	OH	H	H	OCH_3	OCH_3	(Yang, 2007)
51	Narirutin-4′-*O*-glucoside*	B	H	*O*-rutinoside	H	OH	H	H	*O*-glucoside	H	(Barreca et al., 2015; Tong et al., 2018)
52	Eriodictin	B	H	*O*-rhamnoside	H	OH	H	H	OH	OH	(Feng et al., 2012)
53	Naringin	B	H	*O*-neohesperidoside	H	OH	H	H	OH	H	(Liu et al., 2016)
54	Neoeriocitrin	B	H	*O*-neohesperidoside	H	OH	H	OH	OH	H	(Mencherini et al., 2013)
55	Poncirin	B	H	*O*-neohesperidoside	H	OH	H	H	OCH_3	H	(Feng et al., 2012)
56	Neohesperidin	B	H	*O*-neohesperidoside	H	OH	H	OH	OCH_3	H	(Liu et al., 2016)
57	Melitidin	B	H	*O*-(6″-3-hydroxy-3-methylglutaroyl)-glucoside-(2 → 1)-rhamnoside	H	OH	H	H	OH	H	(Mencherini et al., 2013)
58	Brutieridin	B	H	*O*-(6″-3-Hydroxy-3-methylglutaroyl)-glucoside-(2 → 1)-rhamnoside	H	OH	H	OH	OCH_3	H	(Mencherini et al., 2013)
Flavanonols											
59	Aromadendrin-7-*O*-*β*-D-glucopyranside	B	H	*O*-glucoside	H	OH	OH	H	OH	H	(Deng et al., 2020)

*Detected by HPLC or LC-MS.

Table 7 Coumarins in ZS.

Type	No.	Compound name	Skeleton	R1	R2	*R*3	R4	Reference
Simple coumarins	**60**	Meranzin hydrate-*β*-D-glucoside	A	H	H	OCH_3	8,3′-*β*-glucosyloxy-2′-hydroxy-3′-methylbutyl-7-	(Deng et al., 2018)
	61	Meranzin hydrate	A	H	H	OCH_3	7-methoxy-8-(2′,3′-dihydroxy-isopentyl)-	(Mencherini et al., 2013)
	62	Isomeranzin	A	H	H	OCH_3	7-methoxy-8-(2-oxo-3-methylbutyl)-	(Zhang et al., 2015)
	63	Auraptene	A	H	H	7-[(3,7-dimethyl-2,6-octadienyl)oxy]-(E)-	H	(Satoh et al., 1995)
	64	Marmin	A	H	H	7-(6′,7′-dihydroxygeranyloxy)	H	(Satoh et al., 1995)
	65	Praealtin D	A	H	H	7-[(2,6,7-trihydroxy-7-methyl-3-methyleneoctyl)oxy]-	H	(Xiong et al., 2016)
	66	Umbelliferone	A	H	H	OH	H	(Deng et al., 2018)
	67	Scopoletin	A	H	OCH_3	OH	H	(Feng et al., 2012)
	68	5,7-dihydroxylcoumarin	A	OH	H	OH	H	(Feng et al., 2012)
	69	5,7-dihydroxylcoumarin-5-*O*-*β*-D-glucopyranoside	A	*O*-glucoside	H	OH	H	(Zhang et al., 2005)
Isocoumarin	**70**	5,7-dihydroxychromone	B	H	OH	H	OH	(Zhang et al., 2015)
	71	5,7-dihydroxy-chromone-7-neohesperidoside	B	H	*O*-neohesperidoside	H	OH	(Zhang et al., 2019)
	72	5,7-dihydroxy-8-methoxychromone	B	OCH_3	OH	H	OH	(Jiang et al., 2016)
Furanocoumarins	**73**	Xanthotoxol	C	H	OH			(Feng et al., 2012)
	74	Bergapten	C	H	OCH_3			(Xiong et al., 2016)
	75	Citraurancoumarin A	C	OH	6,7-dihydroxy-3,7-dimethyloct-1-en-3-yl-			(Xiong et al., 2016)
	76	5[(6′,7′-*dihydroxy*-3′,7′-*dimethyl*-2-*octenyl*) *oxy*]-psoralen	C	5-[(6′,7′-dihydroxy-3′,7′-dimethyl-2-octenyl)oxy]	H			(Satoh et al., 1995)
	77	Citraurancoumarin B	C	7-[(2,6,7-trihydroxy-7-methyl-3-methyleneoctyl)oxy]-	H			(Xiong et al., 2016)

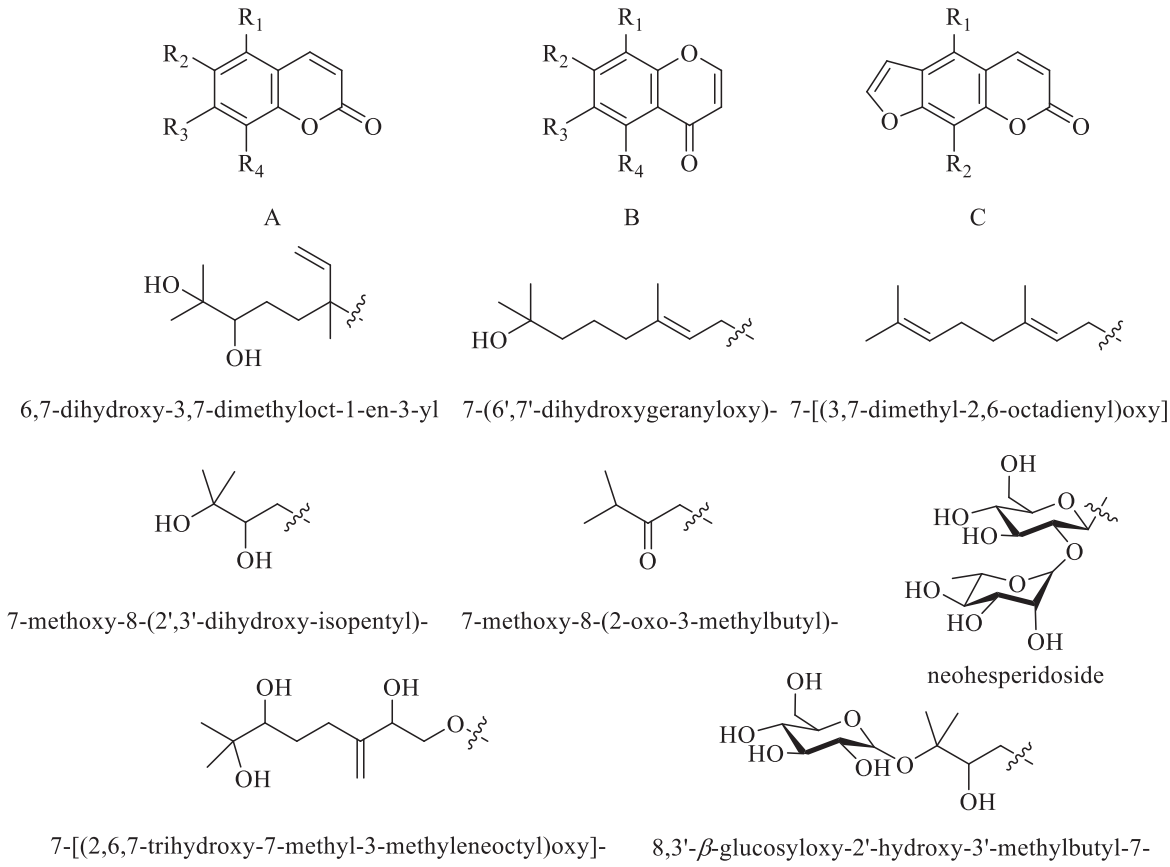

Fig. 7 The skeleton of coumarins and their substituent moieties in ZS.

by Simple Sequence Repeats (SSR), Inter-SSR (ISSR), Sequence-Related Amplified Polymorphism (SRAP), and Random Amplified Polymorphism DNA (RAPD) technologies (Goh et al., 2022; Liu et al., 2005; Luo et al., 2007; Polat et al., 2012; Sun et al., 2012; Zuo et al., 2005). The *trnH-psbA* and ITS2 were screened out as promising DNA barcode for the identification of *Citrus* genus plants (Luo et al., 2010; Mahadani and Ghosh, 2014). In addition, the laser-induced fluorescence spectroscopy technology was also used for the identification of *C. sinensis* (Kubota et al., 2017; Magalhães et al., 2021).

3.4.5. Other methods

Other technologies, such as flow-injection with ultraviolet spectroscopic (UV) detection and proton nuclear magnetic resonance (Zhang et al., 2016), flow-injection mass spectrometric metabolic fingerprinting (Zhao et al., 2015), paper spray-mass spectrometry (Liu et al., 2017), and electronic tongue technology (Wu et al., 2012), were used to differentiate ZS and its adulteration. Headspace solid-phase microextraction coupled with electronic nose based on mass spectrometry was developed for the discrimination of geographical origins (Italy, South Africa, and Spain) of the fruit of *C. sinensis* (Centonze et al., 2019). Zhang used the mass constant method to evaluate the quality of ZS (Zhang et al., 2019).

Infrared spectroscopy (IR) could distinguish the different origins of ZS (Song et al., 2009; Huyi et al., 2013), and determine the content of synephrine (Lei et al., 2015). Total alkaloids, volatile oils, and flavonoids were determined by UV (Tang, 2008; Xu et al., 2016). Green chromatography using aqueous solutions of room temperature ionic liquids (Tang et al., 2006) and packed-column supercritical fluid chromatography could determine the content of alkaloids (Lu et al., 2006). Capillary electrophoresis with electrochemical detection and capillary GC were used to determine the active ingredient and organochlorine pesticide residues, respectively (Hui and Wang, 2004; Peng and Ye, 2007). Zhao developed a sensitive and practical indirect competitive enzyme-linked immunosorbent assay based on anti-monoclonal antibodies to determine the content of naringenin (**40**), the critical biological active compound of ZS (Zhao et al., 2021).

3.5. Biological activities

ZS exhibits anti-depressant and anti-adipogenic activities, which are closely related to the treatment of digestive and cardiovascular systems diseases. Besides, ZS show significant anti-inflammatory and antioxidant activities for being rich in polyphenols.

3.5.1. Effect on the digestive system

3.5.1.1. Gastrointestinal motility regulating. ZS and its ingredients play an important role in exciting gastrointestinal smooth muscle and promoting gastrointestinal movement. Currently, the research on the promotion of gastrointestinal motility of ZS mainly focuses on slow transit constipation (STC), migrat-

Table 8 The name of compound **78**–**121** in ZS.

Type	No.	Compound name	Reference
Alkaloids	**78**	Synephrine	(Hu'Nan Medicine Industry Research Institute, 1976)
	79	*N*-methyltyramine	
	80	*N*-acetyloctopamine	(Peng et al., 2001)
	81	*N*-benzoyl tyramine	(Zhang et al., 2015)
	82	*N*-benzoyl tyramine methyl ether	(Zhang et al., 2015)
	83	2-hydroxybenzoic acid N-2-(4-hydroxyphenyl) ethylamide	(Zhang et al., 2015)
	84	N-[2-(4-hydroxyphenyl) ethyl]-3-methylbut-2-enamide	(Zhang et al., 2015)
	85	Uracil	(Deng et al., 2018)
	86	GABA	(Peng et al., 2001)
	87	Thymidine	(Deng et al., 2018)
	88	Adenosine	(Zhang et al., 2005)
Limonoids	**89**	Deacetyl nomilin	(Dandekar et al., 2008)
	90	Limonin	(Dandekar et al., 2008)
	91	Isoobacunoicacid	(Zhang et al., 2019)
	92	Nomilin	(Zhao et al., 2017)
	93	Obacunone*	(Bai et al., 2018)
	94	Isolimonoic acid	(Jayaprakasha et al., 2008)
	95	Deacetyl nomilinic acid glucoside	(Dandekar et al., 2008)
	96	Ichanexic acid	(Jayaprakasha et al., 2008)
Phenols	**97**	Phloroglucinol	(Deng et al., 2020)
	98	Methyl 3-(2′,4′-dihydroxy phenyl) propanoate	(Deng et al., 2020)
	99	*Trans*-ferulic acid	(Zhang et al., 2019)
	100	(3R)-Thunberginol C	(Zhang et al., 2019)
	101	Phlorin	(Zhang et al., 2005)
	102	6′-*O*-*trans*-cinnamoyl-3,5-dihydroxyphenyl-*β*-D-glucopyranoside	(Deng et al., 2020)
	103	Citrusauranosides C	(Zhang et al., 2017)
	104	Aurantiside A	(Zhang et al., 2006)
	105	1-*O*-3,5-dihydroxyphenyl-(6-*O*-4-hydroxybenzoyl)-*β*-D-glucopyranoside	(Zhang et al., 2017)
	106	Citrusauranosides B	(Zhang et al., 2019)
Others	**107**	Cymol	(Zhang et al., 2019)
	108	Benzoic acid	(Xiong et al., 2016)
	109	Cinnamic acid	(Zhang et al., 2019)
	110	Rimboxo	(Deng et al., 2018)
	111	Quinic acid*	(Bai et al., 2018)
	112	Citrauranoside A	(Xiong et al., 2016)
	113	6′-(*β*-D-apiosyl)-*β*-D-glucosyl-columbianetin	(Zhang et al., 2019)
	114	Linaloyl glucoside	(Deng et al., 2018)
	115	Picraquassioside A	(Zhang et al., 2019)
	116	Citrusin C	(Matsubara and Sawabe, 1994)
	117	Coniferin	(Sawabe et al., 1986)
	118	Syrigin	(Sawabe et al., 1986)
	119	Dehydrodiconiferyl alcohol-4-*β*-D-glucoside	(Matsubara and Sawabe, 1994)
	120	Citrusin A	(Matsubara and Sawabe, 1994)
	121	Citrusin B	(Matsubara and Sawabe, 1994)

*Detected by HPLC or LC-MS.

ing myoelectric complex (MMC), and functional dyspepsia (FD) (Table 9 and Fig. 13).

STC is a condition of prolonged bowel cycles and difficult defecation caused by dysfunction of the large intestine and abnormal conduction. The medicinal serum (Liu et al., 2010), volatile oil (He et al., 2013), and decoction of ZS (Zhang and He, 2010) improved STC by increasing the content of substance P and vasoactive intestinal peptide (VIP) (Tao, 2011), and promoting the expression of neurofilament-H and 5-HTR4 (Wang et al., 2015).

MMC was divided into four phases, including the stationary, intermittent contractions, strong contractions, and the transition phases. MMC symptoms of dogs and sheep (Kuang, 1997) were improved by affecting the period, frequency, and intensity of phases I–III after treatment with lemon terpene (Yang et al., 1995) and ZS decoction (Bi et al., 1991). ZS stimulated the electro-reactivity of small intestines by improving the content of cholecystokinin and substance P (Wang et al., 2001) and reducing the content of somatostatin (Song et al., 2006). The therapeutic effect of ZS may be related to M and H_1 receptors (Liu et al., 2001), as well as intracellular Ca^{2+} fluorescence intensity (Li et al., 2015), but not to β receptors and H_2 receptors (Huang et al., 1996; Yang et al., 1996).

FD is the most common gastrointestinal motility disorder in gastroenterology. The interstitial cells of Cajal (ICC) are

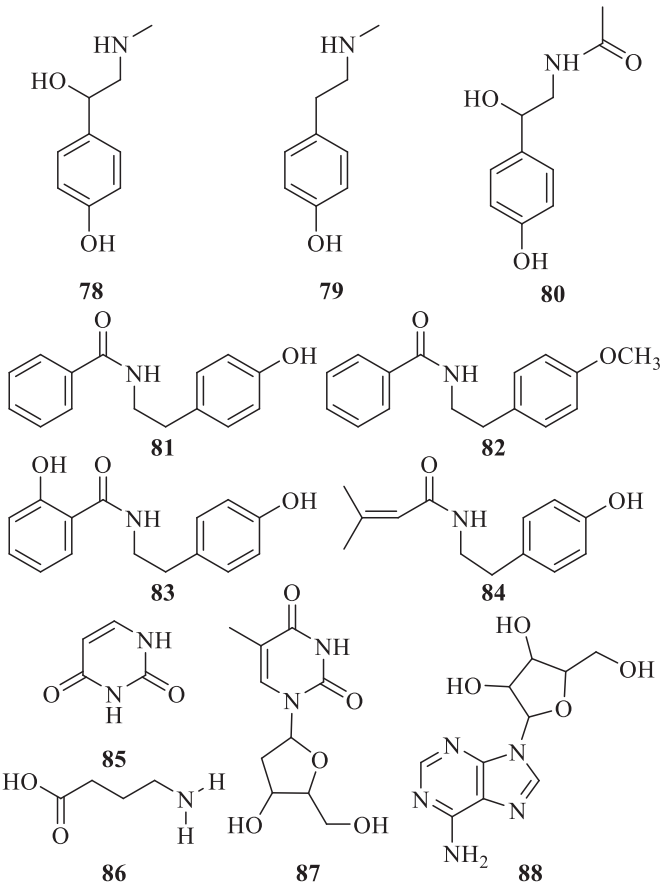

Fig. 8 Chemical structures of alkaloids in ZS.

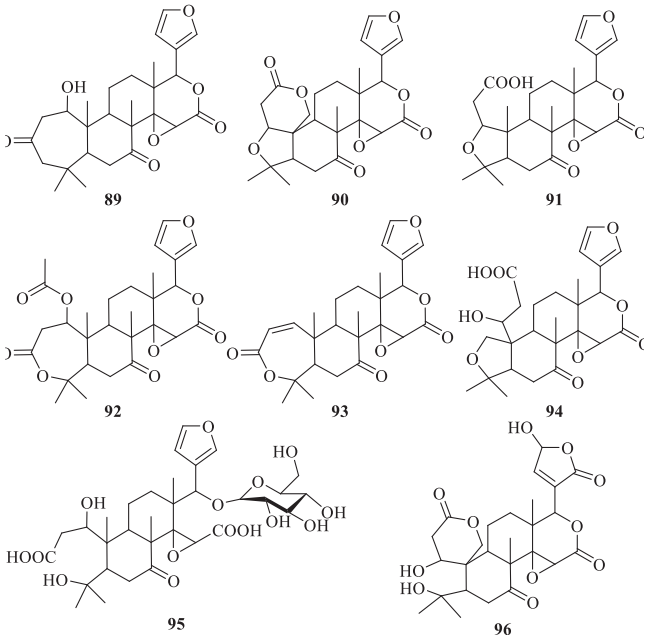

Fig. 9 Chemical structures of limonoids in ZS.

pacemakers and regulators of gastrointestinal activity, which participate in the transmission of gastrointestinal neurotransmitters. Compounds **40**, **49**, **56**, and **78** promoted gastric emptying by increasing the content of substance P, motilin, and stem cell factor (SCF) and reducing the content of VIP and interleukin (IL)-6 (Zhu et al., 2005; Huang et al., 2012; Hu et al., 2017; Zhang and Li, 2018; Lin et al., 2020). ZS promoted the proliferation of ICC by starting SCF/c-Kit (gastric sinus tissue) signaling pathways (Deng et al., 2018) and increasing the expression of X-linked apoptosis inhibitory protein and proliferating cell nuclear antigen (PCNA) protein (Teng et al., 2020). Besides, ZS protected against endoplasmic reticulum stress injury of ICCs (Wang et al., 2018). Flavonoid of ZS could improve reduced proximal gastric adaptability (Wu et al., 2016) and visceral hypersensitivity (Li et al., 2016). The absorption and the elimination processes of compounds **40** and **41** increased in model mice compared with normal mice (Xu et al., 2019).

However, ZS has proven to possess bi-directional regulation effects on the gastrointestinal tract. The extracts (Hu et al., 1992; Hu et al., 1994), pure compounds including **16**–**17**, **22**, **24**, **28**, **39**–**40**, and **64** (Takase et al., 1994; He et al., 2018; Zhang et al., 2019), and decoction of ZS (Chen et al., 1981; Cho et al., 1996; Zhang et al., 2006) showed significant inhibitory effects on the contraction of gastrointestinal tract (Yang et al., 1998; Xie et al., 2001). The inhibitory effect of naringenin (**40**) could be completely antagonized by L-NAME and indomethacin (He et al., 2018), and those of ZS extract could be partly antagonized by phentolamine (Yang et al., 1998; Xie et al., 2001). However, the inhibition of ZS volatile oil could not be antagonized by phentolamine. In addi-

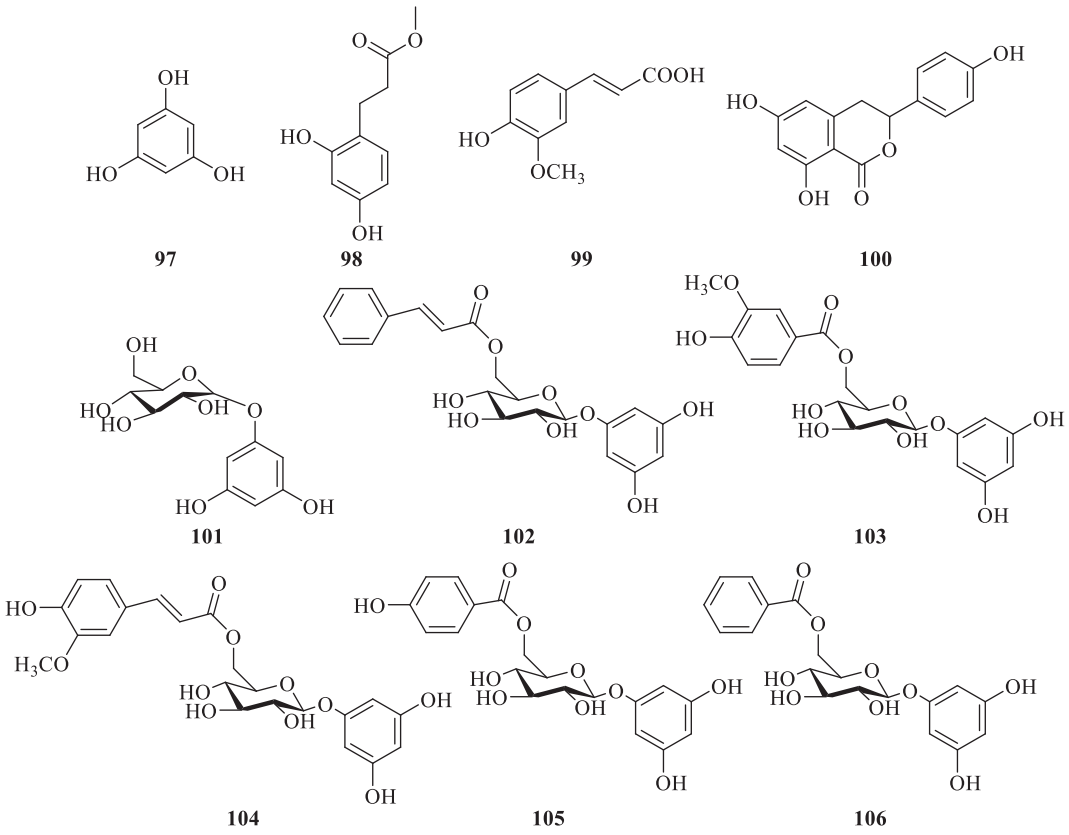

Fig. 10 Chemical structures of phenols in ZS.

tion, it could also inhibit intestinal propulsion *in vivo* (Hu et al., 1992). Furthermore, the inhibitory effect of ZS was not related to *N*-receptor, *β*-receptor, prostaglandin, and NO (Yang et al., 1998; Xie et al., 2001). The smooth muscle relaxes after promoting Ca^{2+} outflux and inhibiting Ca^{2+} influx. ZS, similar to verapamil, could inhibit the contraction of smooth muscle by inhibiting Ca^{2+} influx (Huang et al., 1993; Sheng et al., 1994). Epoxyauraptene, isolated from bran-fried ZS (Lin et al., 2012), could inhibit the contractility of gastrointestinal smooth muscle by inhibiting the function of smooth muscle myosin (Xu et al., 2012). Besides, ZS flavonoid have a therapeutic effect on irritable bowel syndrome (IBS) (Liang et al., 2014) Detailed information and possible mechanisms of bi-directional regulation effects of ZS on the gastrointestinal tract are shown in Table 10 and Fig. 13.

It is found that promoting and inhibiting effects of ZS on the gastrointestinal tract were mainly investigated *in vivo* and *in vitro*, respectively. There was also direct experimental evidence to verify the bi-directional regulation effect of ZS (Table 10) (Hu et al., 1994; Kim, 2013; Xiong et al., 2014; Chen et al., 2019). In addition, when in combination with Baizhu (rhizome of *Atractylodes macrocephala* Koidz.), ZS showed the inhibiting effect while Baizhu used separately had an enhancing effect on the contractile activity of isolated gastric muscular strips *in vitro* (Zheng et al., 1998).

3.5.1.2. Anti-gastric ulcer effect. The hot water extract of ZS significantly inhibited gastric ulcers and hemorrhagic lesions (Takase et al., 1994) caused by ethanol and aspirin. Interestedly, marmin (**64**) and nobiletin (**17**) showed a stronger anti-gastric ulcer effect than aluminum thioglycolate (Hiroyuki, 1997). Volatile oils of ZS could prevent the formation of pyloric ligation ulcers and reduce the secretion of gastric juice and pepsin activity (Hu et al., 1992). Epoxyauraptene was decreased injury index on ulcerative colitis. Flavonoids of ZS reduced the expression of PCNA and C-erbB-2 protein to protect gastric mucosa (Zhang et al., 2020). ZS had a protective effect on gastric mucosa injury after cerebral infarction (Tang et al., 2014) by regulating the expression of the motilin and VIP (An et al., 2015) (Table 11).

3.5.1.3. Hepatoprotection. Ethanol extract of ZS could improve liver cell damage and reduce cell edema and cell vacuoles of diabetic rats (Jiao et al., 2007). ZS protected against acetaminophen-induced liver necrosis by inhibiting the p53 up-regulated apoptosis regulator and reversing disorder of liver lipid metabolism (Shu et al., 2020). Ethanol extract of ZS possessed a protective effect on the restoration of intestinal microbiota composition and reshaped barrier integrity of liver-gut axis, which prevented the translocation of microbiota endotoxin product from the intestine to the liver (Liu et al., 2020). Moreover, the ethanol extract of ZS combined with methotrexate which was the disease-modifying agent for the treatment of rheumatoid arthritis significantly ameliorated methotrexate-induced chronic hepatic injury (He et al., 2018). Si Ni San, a prescription containing ZS, could significantly reduce the hepatocyte damage induced by CCl_4 and 2–4-6-trinitrochlorobenzene (Jiang and Xu, 2004) and promote hepatic stem cell differentiation via Wnt/β-catenin signaling pathway (Xu et al., 2022) (Table 11).

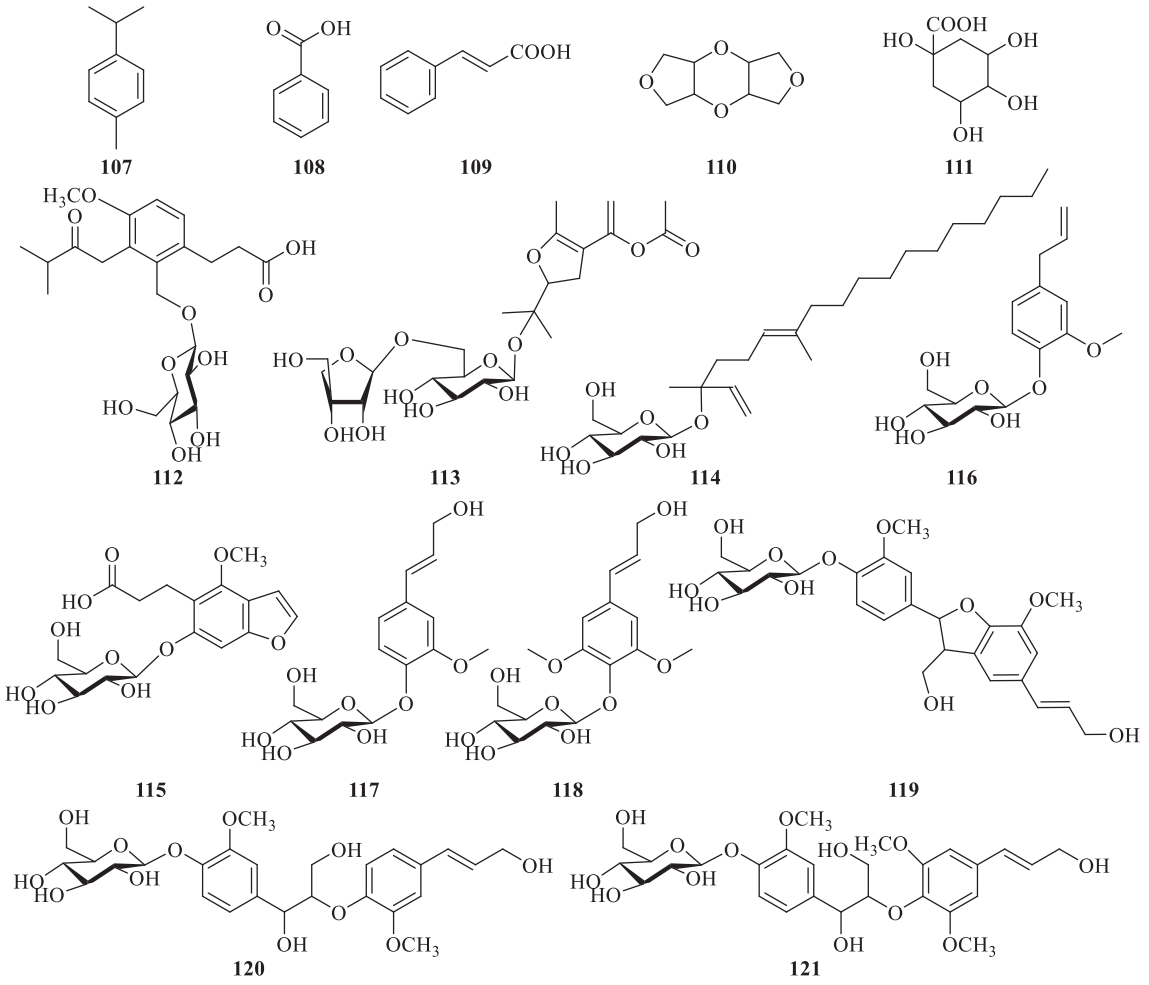

Fig. 11 Chemical structures of other compounds isolated from ZS.

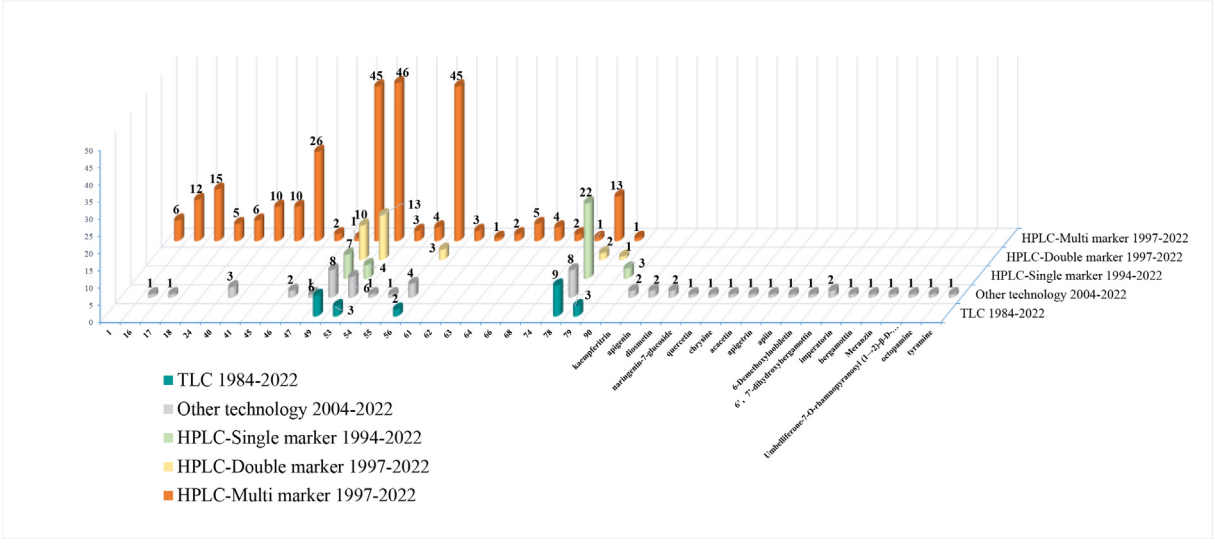

Fig. 12 The hotspot compounds in TLC, HPLC, and other technical research for quality control of ZS.

3.5.2. Anti-depression activity

The severe depressive disorder has a close and bidirectional association with FD (Koloski et al., 2014). Consequently, ZS has become the research hotspot because it can promote gastrointestinal motility while exerting anti-depressant effects. Volatile oil (Hu et al., 1994) or essential oil from the peel of

Table 9 Gastrointestinal motility promoting effect of ZS.

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose	*p* value	References
STC	Accelerate the frequency of extracorporeal colonic muscle strips	*Vitro* (Wister rat)	The medicinal serum of ZS		$p < 0.05$	(Liu et al., 2010)
	Decrease the amplitude of colon slow waves and coefficient variation while increase the frequency	*Vivo* ((SPF) SD rat)	ZS volatile oil	2.7 g/kg for 30 d	$p < 0.05$ vs model control	(He et al., 2013)
	Increase impelling rate of small intestine, shorten the time and add the number of dark stools	*Vivo* (ICR mice)	ZS decoction	1 g/kg and 2 g/kg	$n = 10$, $p < 0.01$ or 0.05 vs model control	(Zhang and He, 2010)
	Increase SP and VIP in intestinal tissues	*Vivo* (Wister rat)	ZS decoction	4 and 8 g/kg/d, i.g for 3 months	$n = 10$, $p < 0.01$ or 0.05 vs model control	(Tao, 2011)
	Improve the intestinal motility	*Vivo* (Male SD rat)	ZS decoction	4 g/kg/d, i.g for 2 weeks	$n = 14$, $p < 0.01$ or 0.05 vs model control	(Wang et al., 2015)
MMC	Affect time course and peak potentials of phase I–II	*Vivo* (Dog)	Lemon Terpene	98 %, 0.1 mL/kg, i.g	$p < 0.01$	(Yang et al., 1995)
		Vivo (Female dog)	ZS decoction	100 %, 1 mL/kg, i.g	$n = 14$, $p < 0.01$	(Bi et al., 1991)
	Short the time duration of phase II and increase slow-wave load peaks, and intensity of peaks in phase III	*Vivo* (Female sheep)	ZS decoction	25 g, p.o	$n = 2$, $p < 0.01$, $p < 0.05$, respectively	(Kuang, 1997)
	Stimulate the electro-reactivity of small intestines by improving CCK and reducing SS in hypothamus	*Vivo* (SD rat)	ZS decoction	100 %, 8 mL/kg, i.g for 7 d	$p < 0.01$ vs control	(Song et al., 2006)
	Increase the ratio of A/T and SP in the myenteric nerve plexu	*Vivo* (SD rat)	ZS decoction	1 g/mL, 8 mL/kg, i.g for 5 d	$p < 0.05$	(Wang et al., 2001)
	H_1-receptor	*Vivo* (KM mice)	Carbon-ZS decoction	0.1 g/mL, 0.3 mL, i.g	$n = 12$, $p < 0.01$ vs model control	(Liu et al., 2001)

Table 9 (*continued*)

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose	*p* value	References
	Enhance the electrical activity in the small intestine	*Vivo* (Dog)	ZS decoction vs atropine	100 %, 1 mL/kg vs 0.5 mg	$n = 13$, $p < 0.01$ vs control	(Huang et al., 1996)
		Vivo (Dog)	ZS decoction vs propranolol	100 %, 1 mL/kg vs 0.5 mg/mL		(Yang et al., 1996)
	Promote intestinal transit	*Vivo* (SPF mice)	Wall-broken spore power of ZS	1.5 g/kg/d, 2 mL/10 g/each, i.g for 7 d	$n = 10$, $p < 0.05$	(Lin et al., 2012)
	Promote antral smooth muscle cell contraction and improve the intracellular Ca^{2+} fluorescence intensity	*Vitro* ((SPF) SD rat)	The medicinal serum of ZS	10 %, 20 %, 50 %	$p < 0.05$	(Li et al., 2015)
	Promote secretion of gastric acid and gastrointestinal motility and decrease the GAS and MTL	*Vivo* (Wister rat)	Suspension prepared with water	0.11 g/mL/d, 2 mL/each, i.g for 4 d,	$n = 8$, $p < 0.05$	(Tang et al., 2015)
FD	Promote gastric emptying by increasing SP and MTL and reducing VIP	*Vivo* (SD rat)	Suspension prepared with water	0.11 g/mL, 2 mL/d, i.g for 14 d	$n = 40$, $p < 0.05$ vs control	(Zhang and Li, 2018)
		Vivo (Wister rat)	ZS decoction	250 g/L, 10 mL/kg, i.g for 4 weeks	$n = 10$, $p < 0.05$ vs model control	(Zhu et al., 2005)
	Improve the small bowel propulsion and gastric emptying and **49** increase MTL	*Vivo* (Wister rat)	Compounds **40, 49, 56**	100 mg/kg/d, i.g for 2 weeks	$p < 0.05$ vs model control	(Huang et al., 2012)
	Promote gastrointestinal motility of model rats with spleen deficiency by affecting GAS, Ach, MTL, SP and VIP	*Vivo* (SD rat)	ZS decoction Compounds **53**, **56**, **78**	0.104, 0.208, 0.416 g/mL **53**: 3.267, 6.535, 13.070 mg/mL **56**: 3.865, 7.730, 15.460 mg/mL **78**: 0.252, 0.504, 1.008 mg/mL	10 mL/kg/d, i.g for 1 week	$n = 10$, $p < 0.05$ or 0.01 vs model control, except **78** had no effect on the GAS	(Hu et al., 2017)
	Increase SCF and MTL by reducing IL-6 in serum	*Vivo* (SD rat)	ZS decoction	1.0 g/mL and 2.0 g/mL, 1.5 mL/100 g, 2 times/d, i.g for 4 weeks	$n = 8$, $p < 0.05$ vs model control	(Lin et al., 2020)
	Promote the proliferation and differentiation of ICCs by starting SCF/c-Kit signaling pathways	*Vivo* (SD rat)	ZS decoction	0.5, 1.0 and 2.0 g/mL, 1.5 mL/100 g, 2 times/d, i.g for 4 weeks	$n = 8$, $p < 0.05$ vs domperidone group	(Deng et al., 2018)

(*continued on next page*)

Table 9 (*continued*)

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose	*p* value	References
	Reduce the ERS injury of ICCs by decreasing expression of GRP78 and ATF6	*Vitro* ((SPF) SD rat)	The medicinal serum of ZS	20 %	$p < 0.05$ vs control	(Wang et al., 2018)
	Promote ICC proliferation by increasing XIAP and PCNA protein	*Vitro* ((SPF) SD rat)	The medicinal serum of ZS	10 %	$n = 6$, $p < 0.01$ or 0.05	(Teng et al., 2020)
	Improve the ramp phase and the tonic phase	*Vivo* (Male SD rat)	ZS flavonoid	10 and 15 mg/mL, 1 mL/100 g, 1 time/d, i.g for 4 weeks	$n = 14$, $p < 0.05$ vs model control	(Wu et al., 2016)
	Improve gastric accommodation and decreased mRNA expression of 5-HT and c-fos	*Vivo* (Male (SPF) SD rat)	ZS flavonoid	100 mg/kg/d, i.g for 2 weeks	$n = 8$, $p < 0.05$ vs model control	(Li et al., 2016)
	Increase SP and MTL and reduce VIP	*Vivo* (SD rat)	ZS decoction vs bran-fried ZS with bran decoction	1 g/mL/d, 0.7 mL/100 g, i.g for 6 d	$n = 10$, $p < 0.05$	(Lin et al., 2012)

SP: substance P; VIP: vasoactive intestinal peptide; CCK: content of cholecystokinin; SS: somatostatin; A/T: the active phase to the circle; GAS: gastrin; MTL: motilin; Ach: acetylcholine; SCF: stem cell factor; IL: interleukin; c-Kit: gastric sinus tissue; GRP78: glucose regulatory protein; ATF6: activating transcription factor; XIAP: X-linked apoptosis inhibitory protein; PCNA: proliferating cell nuclear antigen.

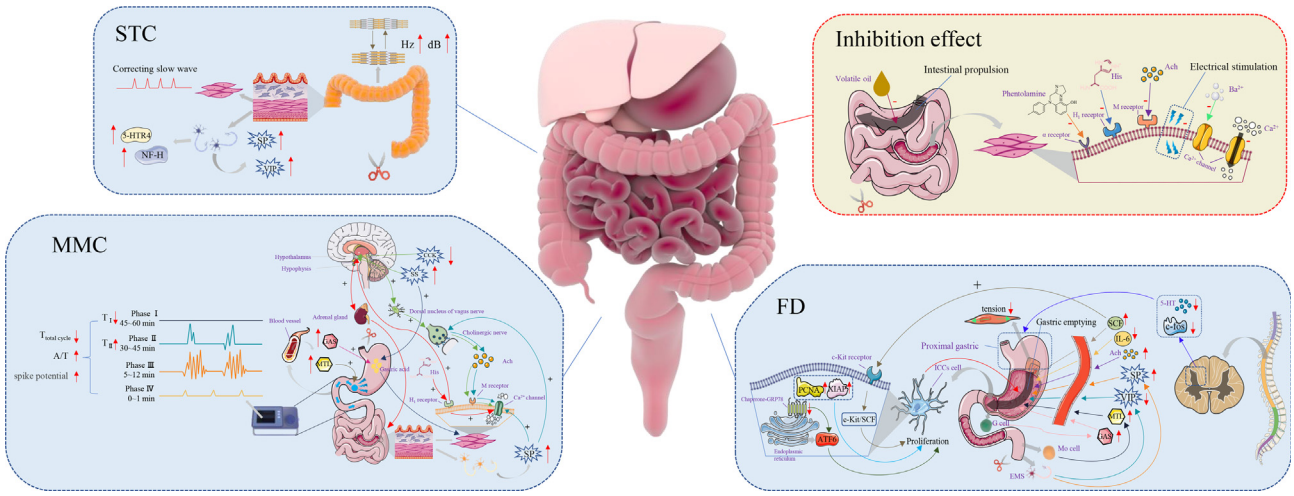

Fig. 13 Possible mechanisms of bi-directional regulation effects on the gastrointestinal tract.

ZS (Carvalho-Freitas and Costa, 2002) was able to treat depression and could increase the latency period of convulsing mice (Pultrini et al., 2005). However, the essential oil was not active in the forced swim test (Costa et al., 2013). Meranzin hydrate (**61**) elicited antidepressant effects and restored reward circuitry (Liu et al., 2021). ZS flavonoid increased the rearing score of IBS rats in open box horizontal movement (Liang et al., 2014) (Table 11).

In a clinical trial of cocaine withdrawal, essential oil from the peel of ZS provided an acute anxiolytic effect on the patients exposed to simulated public speaking (n = 17) (Neto et al., 2017). Si Ni San was also used to treat depression in clinical practice (Cong et al., 2021).

3.5.3. *Effect on the cardiovascular system*

3.5.3.1. Blood pressure elevating. The blood pressure of rats or dogs was significantly increased after intravenous injection of fluid extract (Yan, 1995), alkaloid aqueous solution (Hu et al., 1994), or injection (Chen et al., 1981) of ZS. Synephrine (**78**) and *N*-methyltyramine (**79**) with the blood pressure regulating effect were obtained by bio-guided isolation, and *N*-methyltyramine (**79**) significantly increased coronary and renal blood flow and decreased vascular resistance and myocardial oxygen consumption. The combination of compounds **79** and **78** (3:1, v/v) could resist the decrease of blood pressure caused by reserpine. Synephrine (**78**) affected adrenergic receptors directly, while *N*-methyltyramine (**79**) worked mainly through the indirect mechanism of catecholamine release (Guo, 1978). The blood pressure regulating effect of SCZS was severer than TCZS, probably due to the chemical variations (Cui et al., 2010). Furthermore, the raw material of ZS showed a stronger effect on raising blood pressure than its processed products (Yi et al., 2011) (Table 12).

3.5.3.2. Cardiotonic effect. ZS extract showed the function of enhancing cardiac contractility and increasing coronary flow in various experimental models, including cat (Jia et al., 1980), toad (Yan, 1995), guinea pig (XiangYa School Of Medicine, 1978), dog (Zhao et al., 1989), and rabbit (Li et al., 2001). Synephrine (**78**) and *N*-methyltyramine (**79**) showed significant cardiotonic effect that could be blocked by phentolamine, verapamil, and incubation with Ca^{2+}-free Krebs solution. It suggested this effect may be related to the activation of adrenergic α receptors, cholinergic M receptors, and verapamil-sensitive Ca^{2+} channels on the smooth muscle cell membrane (Chen et al., 1980; Li et al., 2001; Fang et al., 2003; Fang et al., 2004). In addition, hesperidin (**49**) and neohesperidin (**56**) possessed a cardioprotective effect (Wang et al., 2013) (Table 12).

3.5.3.3. Anti-atherosclerotic activity. ZS extract, as well as hesperidin (**49**) and neohesperidin (**56**), had a significant inhibitory effect on intercellular adhesion of human umbilical vein endothelial cells line (HUVEC) (Luo et al., 2012). In addition, hesperidin (**49**) inhibited the secretion of cyclic strain-induced HUVEC endothelin (ET)-1 secretion (Chiou et al., 2008). ZS injection (Ham et al., 2007) and neohesperidin (**56**) (Jia et al., 2015) significantly decreased the levels of triglycerides (TG), total cholesterol (TCH), and LDL-cholesterol in diabetic mice or hyperlipidemia rats. The 70 % ethanol extract of ZS was able to decrease blood glucose (Jiao et al., 2009). Hesperidin (**49**) significantly reduced endothelial dysfunction in rats (Kumar et al., 2017) (Table 12).

3.5.3.4. Antithrombotic activity. ZS decoction and its residue after removing ether-soluble ingredients had a significant inhibitory effect on thrombosis *in vitro*, indicating that the antithrombotic components of ZS are highly water-soluble substances (Ou et al., 1989). The effects of ZS decoction on inhibitory aggregation of platelet and red blood cell in both healthy and blood stasis rats was prior to those of aspirin and had a dose–effect relationship (Ji et al., 2003). Ethanol extract of ZS significantly decreased the platelet count in collagen-induced arthritis rats (He et al., 2018). Hesperidin (**49**) reduced serum homocysteine and serum cholesterol of L-methionine-treated rats (Kumar et al., 2017) (Table 12).

3.5.4. *anti-adipogenic activity*

Obesity has been considered as major global health challenge in modern society. Synephrine (**78**), an analog of ephedrine, has been suggested as a safe dietary supplement to reduce obesity without the toxic and side effects of ephedrine analogs

Table 10 Gastrointestinal motility inhibiting and directly experimental evidence in bi-directional effect.

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose		*p* value		References
Gastrointestinal motility inhibiting	Relax isolated intestinal smooth muscle	*Vitro* (Rabbit)	ZS injection	2×10^{-3}–4×10^{-3}				(Chen et al., 1981)
	Decrease the frequency and amplitude of jejunal contraction	*Vitro* (Wister rat)	Volatile oils	3 μL/mL, 10 μL/mL				(Hu et al., 1992)
	Inhibit the contraction of isolated intestinal smooth muscle	*Vitro* (Wister rat)	ZS flavonoid	20 mg/mL				(Hu et al., 1994)
	Counteract the spastic contraction induced by $BaCl_2$, Ach and His in ileum	*Vitro* (guinea pig)	ZS flavonoid	20 mg/mL		$n = 4$		
	Inhibit the isometric contraction of ileum smooth muscle	*Vivo* (SD rat)	The water extract of ZS	$IC_{50} = 11.8 \times 10^{-2}$ g/L				(Cho et al., 1996)
	Inhibit contraction tension of isolated intestine tissue	*Vitro* (Male KM mice)	Compounds **16**, **17**, **22**, **24**, **28**, **39**, **64**	100 μM		$n = 6$, $p < 0.05$ vs control		(Zhang et al., 2019)
	Inhibit gastric motor activity	*Vivo* (Male Wistar rats)	Compound **17**	10–50 mg/kg	$ED_{50} = 17.2$ mg/kg	$n = 4$, $p < 0.05$ vs control		(Takase et al., 1994)
			Compound **64**		$ED_{50} = 8.0$ mg/kg			
	Exhibit relaxations of contractions in isolated ileum	*Vitro* (Male guinea pigs)	Compound **17**	Ach: $IC_{50} = 3.73 \times 10^{-4}$ g/mL transmural electrical stimulation: $IC_{50} = 4.05 \times 10^{-4}$ g/mL His: $IC_{50} = 1.48 \times 10^{-4}$ g/mL				
			Compound **64**	Ach: $IC_{50} = 2.56 \times 10^{-4}$ g/mL transmural electrical stimulation: $IC_{50} = 8.12 \times 10^{-4}$ g/mL His: $IC_{50} = 3.73 \times 10^{-4}$ g/mL				
	Inhibit the active tension on spontaneous contractions of intestine smooth muscle	*Vivo* (Male SD rat)	Raw medicinal materials	125–500 mg/kg, p.o		$n = 8$, $p < 0.001$, $p < 0.01$ vs control		(He et al., 2018)
	Decrease contractile amplitude and frequency of isolated colonic muscle strips and small intestinal longitudinal strips	*Vitro* (Wister rat)	ZS decoction	10^{-3} g/mL		$n = 12$, $p < 0.001$ vs control		(Xie et al., 2001)
		Vitro (Wister rat)	ZS decoction	0.1 g/mL		$n = 12$, $p < 0.001$ vs control		(Yang et al., 1998)
	Reduce contraction amplitude, frequency and tone in isolated intestinal smooth muscle	*Vitro* (Rabbit)	ZS decoction	1.2 mg/mL		$n = 6$, $p < 0.01$ vs control and model control		(Zhang et al., 2006)
	Antagonize the contraction of Ach and His on the smooth muscle of isolated small intestine	*Vitro* (KM mice)	ZS decoction	Ach group: 0.1 and 0.2 g/mL		Ach: $n = 4$, $p < 0.01$	vs control	(Huang et al., 1993)
				His group: 0.1 g/mL		His: $n = 4$, $p < 0.05$		
	Shift the dose–response curve of			$BaCl_2$ group: 0.1 g/mL		$BaCl_2$: $n = 5$, $p < 0.05$		

Table 10 (*continued*)

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose		*p* value	References
	$BaCl_2$ in parallel to the right						
	Inhibit the isolated intestine contraction induced by Ca^{2+} after high-K^+ depolarization	*Vitro* (KM mice)	ZS decoction	0.1 g/mL		$n = 4$	(Sheng et al., 1994)
	Relax the smooth muscle, relieve spasm and inhibit peristalsis of intestinal by increasing NO in the serum and decreasing MC of colon and ileum	*Vivo* (SD rat)	ZS flavonoid	3 g/kg, 1 time/d for 7 d		$n = 8$, $p < 0.05$ vs model control	(Liang et al., 2014)
	Reduce the resting tension of isolated gastric smooth muscle	*Vitro* (Male SD rat)	ZS flavonoid	6000–10000 μg/mL		$n = 7$, $p < 0.05$ vs control	(Wu et al., 2016)
Direct experimental evidence	Stimulate and inhibit the contractility of isolated jejunal segments in all 6 different low/high contractile states	*Vitro* (SD rat)	Compound **17**	2.5 μM			(Xiong et al., 2014)
	Stimulate and inhibit jejunal contractility	*Vitro* (SD rat)	Compound **17**	EC_{50} = 4.0 μM IC_{50} = 30.0 μM			
	Relax in the fundic circular muscle pre-contracted by U46619	*Vitro* (Male SD rat)	AIM, AIW and AIC	AIM = 100 μg/mL, AIW = 100 μg/mL, AIC = 10 μg/mL		$n = 4$–6	(Kim, 2013)
	Relax both fundic circular and longitudinal smooth muscle		Compound **41**	**41** = 10^{-4} M			
	Diphasic effects in the longitudinal smooth muscle contracted by U46619	*Vitro* (Male SD rat)	AIM, AIW	AIM = 100 μg/mL, AIW = 100 μg/mL		$n = 4$–6, $p < 0.05$ vs another group	
	Diastole in isolated pyloric circular smooth muscle strip in different Ca^{2+} environment	*Vitro* (Male SD rat)	ZS flavonoid	3000–10000 μg/mL		$n = 10$, $p < 0.01$ or 0.05 vs control	(Wu et al., 2016)
	Increase the contraction of isolated intestinal strips, decrease after 1–1.5 min	*Vitro* (Wister rat)	Volatile oil ZS flavonoid	10 μL/mL 20 mg/mL			(Hu et al., 1994)
	The high doge of aroma significantly reduced small intestinal propulsion and increased gastric residual rate, while the high doge of bitter and low doge of sour all promote.	*Vivo* (KM mice)	Aroma components of ZS bitter components of ZS sour components of ZS	0.06–0.3 g/kg 0.82–4.1 g/kg 0.25–1.25 g/kg	1 time/d for 3d	$n = 10$, $p < 0.01$ or 0.05 vs control	(Chen et al., 2019)
	Aroma on jejunum and ileum, bitter on duodenum, sour on ileum is bi-directionally regulated effect	*Vitro* (KM mice)	Aroma components of ZS bitter components of ZS sour components of ZS	2.5×10^{-4}–4×10^{-3} g/mL 4.015×10^{-3}–6.425×10^{-2} g/mL 3.125×10^{-3}–5×10^{-2} g/mL		$n = 8$	

His: histamine; AIM: Methanol extracts; AIW: water-fractions; AIC: chloroform-fractions; NO: nitric oxide; MC: mast cells.

Table 11 anti-gastric ulcer activity, hepatoprotection effects and anti-depression activity.

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose	*p* value	References
Anti-gastric ulcer	Caused by ethanol and aspirin	*Vivo*	Hot water extract of ZS	250 mg/kg, p.o	ethanol: 69.7–69.9 % aspirin: 37.3–46.8 %	(Hiroyuki, 1997)
		Vivo	Compound **64** Compound **17**	25 mg/kg, p.o	67.6 % 70 %	
	Inhibit ethanol-induced gastric hemorrhagic lesions	*Vivo* (Male wister rat)	Compound **64** Compound **17**	10–50 mg/kg, p.o	ED_{50} = 17.2 mg/kg ED_{50} = 8.0 mg/kg	(Takase et al., 1994)
	Prevent the formation of pyloric ligation ulcers, and reduce the secretion of gastric juice and pepsin activity	*Vivo* (Wister rat)	Volatile oil	20 %, 1.0 mL/100 g, i.p for 48 h	$n = 8$, $p < 0.01$ vs control	(Hu et al., 1992)
	Protect gastric mucosa by reduced the expression of PCNA and C-erbB-2	*Vivo* (Male (SPF) SD rat)	ZS flavonoid	150 mg/kg/d, i.g for 14 d	$n = 20$, $p < 0.05$ vs model control	(Zhang et al., 2020)
	Protect gastric mucosa injury appeared after cerebral infarction by regulated the expression of the MTL and VIP	*Vivo* (Male wister rat)	Suspension prepared with water	2 mL/d, i.g for 4 d	$n = 8$, $p < 0.01$ vs model control or control	(Tang et al., 2014; An et al., 2015)
	Decrease injury index on ulcerative colitis.	*Vivo* (BALB/C mice)	Compound epoxyauraptene	160 and 320 μmol/L	$n = 10$, $p < 0.05$ vs model control	(Lin et al., 2015)
Hepatoprotection	Improve liver cell damage, reduce cell edema, and degeneration of vacuoles	*Vivo* (KM mice)	70 % ethanol ZS extract	9.59 g/kg/d, i.g for 4 weeks	$p < 0.01$ or 0.05 vs model control	(Jiao et al., 2007)
	Against APAP-induced liver necrosis by inhibited the PUMA and reversing disorder of liver lipid metabolism	*Vivo* (Male SD rat)	Ethanol ZS extract	6 g/kg/d, i.g for 7 d	$n = 10$, $p < 0.01$ or 0.001 vs model control	(Shu et al., 2020)
	Protect the restoration of intestinal microbiota composition, reshaped barrier integrity	*Vivo* (Male C57BL6 mice)	Ethanol extract	8.7 g/kg/d, p.o for 4 weeks	$n = 10$, $p < 0.05$ or 0.01 vs model control	(Liu et al., 2020)
Anti-depression	Reduce the number of spontaneous activities	*Vivo* (Wister mice)	Volatile oil	(10 %, 20 %), 10 mL/kg/d, p.o for 3 d	$n = 12$, $p < 0.05$ vs control	(Hu et al., 1994)
	Increase the latency period of tonic seizures, increase the sleeping time and the time spent in the open arms of the elevated plus maze	*Vivo* (Male Swiss mice)	Essential oil	0.5 or 1.0 g/kg, p.o	$n = 9$, $p < 0.05$ vs model control	(Carvalho-Freitas and Costa, 2002)
		Vivo	Hexanic and dichloromethanic fractions from 70 % hydroethanolic extract	1.0 g/kg, p.o	$n = 9$, $p < 0.05$ vs model control	

Table 11 (*continued*)

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose	*p* value			References
	Light-dark box and the marble-burying test mediated by 5-HT_{1A} receptors	*Vivo* (Male Swiss mice)	Essential oil	0.5 or 1.0 g/kg, p.o 30 min (single dose) or once a day for 15 d (repeated doses)	Light-dark box	Single: $n = 8$ Repeated: $n = 7, 5$	$p < 0.05$ vs control.	(Pultrini et al., 2005)
					Marble-burying test	Single: $n = 6, 9$ Repeated: $n = 8, 7$	$p < 0.05$ vs control	
	Light/dark box procedure	*Vivo* (Male Swiss mice)	Essential oil	acute (5 mg/kg) or repeated 1 mg/kg/d for 14 d	$p < 0.01$ or 0.05 vs model control			(Costa et al., 2013)
	Restores reward circuitry	*Vivo* (Male Wister rat)	Compound **61**	10 mg/kg/d, i.g for 1 week	$n = 6$, $p < 0.001$, 0.01 or 0.05 vs model control			(Liu et al., 2021)
	Increase in open box horizontal movement	*Vivo* ((SPF) SD rat)	ZS flavonoid	3000 mg/kg/d i.g for 1 week	$n = 8$, $p < 0.01$ vs control, $p < 0.05$ vs model control			(Liang et al., 2014)

APAP: Acetaminophen; PUMA: p53 up-regulated apoptosis regulator.

(Haaz et al., 2006). As a non-stimulatory thermogenic agent, synephrine tended to bind with β-3 receptor, thus promoted lipolysis, and had no effect on the CNS and cardiovascular system (Ribeiro et al., 2019; Rossato et al., 2011; Stohs et al., 2011a, 2011b; Stohs and Badmaev, 2016; Stohs, 2017). Synephrine (Guo et al., 2019), flavonoid (Kim et al., 2012), and menthol extract of ZS (Raciti et al., 2018) reduced the viability of 3 T3-L1 cells and inhibited its differentiation, they could also promote lipolysis and reduce lipid accumulation. Synephrine and *N*-methyltyramine (**79**) could so stimulate lipolysis in both rats and human adipocytes (Mercader et al., 2011) (Table 13). The association of hypertension with cardiovascular risk in the short- and long-term was unequivocally established (Landsberg et al., 2013). As one of the main components of blood pressure elevating, synephrine and *N*-methyltyramine were easy to be destroyed by alkaline intestinal fluid after oral administration. Therefore, it elevates blood pressure only by injection (Xu, 2019).

Dietary supplementation of 0.2 % ploymethoxy flavonoids of ZS with high-fat diet (w/w) markedly reduced body weight gain of obese mice and elevated their thermogenesis in the cold tolerance test (4℃) (Kou et al., 2020). Neohesperidin (**56**) also inhibited lipid accumulation in the liver and decreased the size of epididymal adipocytes of KK-A^y mice (Jia et al., 2015).

3.5.5. *anti-inflammatory activity*

The constituents (Bi et al., 2016; He et al., 2018), extracts (Zhao et al., 2018), and preparations of ZS (Kim and Park, 2010; Liu et al., 2017; Wang et al., 2019) could reduce the expression of nuclear factor-kappa B (NF-κB), tumor necrosis factor-alpha (TNF-α), IL-1β, IL-6, NO, cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), and myeloperoxidase (MPO) of RAW 264.7 cells through mitogen-activated protein kinases signaling pathway. ZS flavonoids possessed similar effects on lipopolysaccharide-induced L6 skeletal muscle cells (Kim et al., 2012). Epoxyaurapten (Lin et al., 2015) up-regulated IL-10 and down-regulated TNF-α to treat ulcerative colitis. ZS exhibited higher inhibition on xanthine oxidase (Wang et al., 2019), which could induce gouty arthritis by increasing uric acid, than the mature fruit of *Citrus medica* L. and *Citrus medica* L. var. *sarcodactylis* Swingle, QP, and CP). Besides, the ethyl acetate extract showed the strongest inhibition than others (Liu et al., 2016).

ZS extract significantly inhibited inflammatory swelling of joints of rats induced by histamine, dextran (Mencherini et al., 2013), formaldehyde, and egg white (Zhang and Wang, 2004). The carbonized product of ZS significantly reduced the paw pressure score and volume, as well as ankle diameter of gouty arthritis rats (Wang et al., 2019). ZS reduced inflammatory cell infiltration and decreased the level of the inflammatory factor of trinitrobenzene sulfonic acid-induced inflammatory bowel disease rats (He et al., 2018). ZS flavonoid alleviated inflammation by decreased the levels of IL-6, IL-1β and TNF-α in DSS-induced colitis mice (Chen et al., 2022). Combination therapy of ethanol extract of ZS and MTX effectively reduced the inflammatory symptoms (ankle joint, bone destruction) and joint damage by inhibiting the NF-κB pathway (He et al., 2018) (Table 13).

3.5.6. *Anti-oxidant activity*

Flavonoids (Chiou et al., 2008; Jiao et al., 2008; Barreca et al., 2014), polysaccharides (CLB 1–4) (Wang et al., 2014), and extracts of ZS (Jiao et al., 2008; Kim and Park, 2010) showed scavenging activity on ·OH, $\cdot O_2^-$, DPPH·, and $ABTS^+$ radicals. The scavenging capacity of ·OH, $\cdot O_2^-$, and DPPH· of 70 % ethanol extract of ZS was 2.02–17.81 times higher than naringin (**53**) (Jiao et al., 2008). The antioxidant effect of ethanol extract and extract after purified by macroporous resin column chromatography had no significant difference, suggesting that polysaccharides and proteins of ZS may highly contribute to the activity (Xie et al., 2009). ZS harvested from June 11 to July 7 possessed the highest antioxidant capacity on H_2O_2-induced RIN-m5F cells (Tang et al., 2021).

Nobiletin (**17**) (Bi et al., 2016) and polysaccharides (Wang et al., 2014) exerted antioxidant effect by increasing concentrations of glutathione (GSH) PX, GSH, Catalase (CAT) and superoxide dismutase (SOD), and reducing the level of malondialdehyde and NO of isoflurane induced cognitive impairment rats and D-galactose-induced aging mice. Pretreatment with 80 % ethanol extract of ZS ameliorated all biochemical parameters of lung-damaged rats caused by chromium (Soudani et al., 2013). The extract of ZS could effectively enhance the kidney antioxidant function of diabetic rats (Jiao et al., 2009) (Table 13).

3.5.7. *Anti-tumour activity*

ZS had a good inhibitory effect on a variety of cancer cells, including colon cancer (Jayaprakasha et al., 2008), hepatocellular carcinoma (Ma et al., 2013), breast adenocarcinoma (Wang, 2008), gastric cancer (Dong et al., 2011), leukemia (Han et al., 2012), and hepatoblastoma (Lee et al., 2015) by arresting G2/M phase. ZS extract significantly enhanced the cytolytic activity of natural killer cells and the expression of natural killer cell-activating receptors, especially NKp30 and NKp46 (Park et al, 2022). Compounds **17**, **18**, and **22** play a great role in inhibiting angiogenesis, and the compounds with methoxy in C8 position were better than the others in inhibiting vascular growth (Yang, 2007). ZS flavonoid could inhibit the growth of tumor induced by HepG2 cells (Lee et al., 2015). Nobiletin (**17**) significantly inhibited the growth of H22 transplantable tumors (Ma et al., 2013) (Table 14).

3.5.8. *Anti-bacterial activity*

Limonin (**90**), glycosides of its analogues, and ZS flavonoids had sound inhibitory effects on *Escherichia coli* and *Staphylococcus aureus* (Liu et al., 2009). ZS flavonoids also could reduce the diversity and abundance of the intestinal microbiota in DSS-induced colitis mice (Chen et al., 2022). Currently, the antibacterial research of ZS mainly focuses on its essential oil. It showed a dose-dependent inhibition on mycelium growth and aflatoxin B1 genesis of *Aspergillus flavus* at 0.5–2 % (v/v). The effect varied among essential oils from different fruits of the *Citrus* genus (Restuccia et al., 2019). In addition, it showed inhibition on *Fusarium oxysporum*, *Fusarium solani*, *Botrytis cinerea*, *Bipolaris sorokiniana*, and *Fusarium avenaceum* with the inhibitory rate of 38.49 %–68.47 % at 2 μL/mL and 76.13 %–84 % at 4 μL/mL (Metoui et al., 2015).

Table 12 Effect on the cardiovascular system.

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose	*p* value	References
Blood pressure elevating	Elevate blood pressure	*Vivo* (Rat)	ZS injection	0.5 mL, iv drop		(Chen et al., 1981)
		Vivo (Wister rat)	Alkaloid aqueous solution	5 and 10 g/kg	$n = 5$, $p < 0.01$	(Hu et al., 1994)
		Vivo (Male SD (Ⅲ) rat)	70 % ethanol SCZS extract	2.1 and 4.2 g/kg, 0.84 mL/100 g duodenal administration	$n = 10$, $p < 0.05$ and 0.01 vs control	(Cui et al., 2010)
		Vivo	70 % ethanol TCZS extract	2.1 and 4.2 g/kg, 0.84 mL/100 g duodenal administration	$n = 10$, $p < 0.05$ and 0.01 vs SCZS group	
		Vivo (Rat)	ZS decoction	2 mg/kg/d, i.g for 5 weeks	$n = 10$, $p < 0.05$ vs control	(Yi et al., 2011)
		Vivo	Fried-ZS with bran decoction	2 mg/kg/d, i.g for 5 weeks	$n = 10$, $p < 0.05$ vs control	
		Vivo (Dog)	ZS injection	3 mL, iv drop		(Chen et al., 1981)
		Vivo (Dog)	ZS fliud extract	100 %, 3 mL, iv drop	$n = 6$, $p < 0.05$	(Yan, 1995)
	Increase coronary flow	*Vivo* (Dog)	Compound **79**	0.1 mg/kg/min, iv drop	0.2 mg/kg, $p < 0.05$	(Guo, 1978)
	Increase renal blood flow	*Vivo* (Dog)	Compound **79**	0.1 and 0.2 mg/kg/min, iv drop		
Cardiotonic effect	Enhance the contractility of the papillary muscles	*Vitro* (Cat)	ZS injection Compound **78** Compound **79**	12.5, 6.25 mg/mL 17.5, 8.75 μg/mL 12.5, 6.25 μg/mL	high dose: $n = 9$, $p < 0.01$ low dose: $n = 8$, $p < 0.05$ or 0.01 (**78***p* greater than 0.05)	(Jia et al., 1980)
	Induce autorhythmic contractions of the papillary muscles	*Vitro* (Cat)	ZS injection Compound **78** Compound **79**	6.25 mg/mL 8.75 μg/mL 6.25 μg/mL	$n = 17$, only **78***p* < 0.01	
	Increase the contractility and amplitude of the isolated heart	*Vitro* (Toad)	ZS fliud extract	10 %, 0.05 mL 50 %, 0.1 mL	$n = 6$	(Yan, 1995)
	Increase coronary flow and cardiac contractility in isolated heart	*Vitro* (Guinea pig)	ZS injection	0.1–0.2 g		(XiangYa School Of Medicine, 1978)
	Enhance systolic force, slow heart rate and output per minute in heart and lung preparations	*Vitro* (Guinea pig)	Perfusion of perfusate	6 mg/mL		
	Increase the cardiac output, accelerate the blood stream in bulbar conjunctiva	*Vivo* (Dog)	ZS injection	8 g/kg/h, iv drop	$n = 4$, $p < 0.05$ vs control	(Zhao et al., 1989)
		Vivo	Compounds **78**, **79**	4 g/kg/h, iv drop	$n = 5$, $p < 0.01$ vs control	
	Increased the tension of aortic strip	*Vitro* (Rabbit)	ZS decoction	1 %–200 %	r = 0.82, $n = 12$, $p < 0.001$	(Li et al., 2001)
	Increase the $I_{Ca\text{-}L}$ current in ventricular myocytes and promote the opening of calcium channel	*Vitro* (Guinea pig)	ZS extract	4×10^{-3}–1×10^{-1} g/mL	$n = 10$, $p < 0.05$ or 0.01 vs control	(Fang et al., 2003)
		Vitro (Guinea pig)	Compounds **78**, **79**	10–100 mmol/L	$n = 10$, $p < 0.05$ or 0.01 vs control	(Fang et al., 2004)

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Table 12 (*continued*)

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose	*p* value	References
	Enhance the cardiac function, the peak dp/dt and the percentage in dp/dt /GPIP	*Vivo* (Dog)	ZS injection	0.5 g/kg, iv drop	236 %, $n = 6$, $p < 0.01$ vs 111 %, control $p < 0.01$	(Chen et al., 1980)
			Compound **78**	1 mg/kg, iv drop	86 %/68 %, $n = 6$, $p < 0.05$ vs control	
			Compound **79**	0.25 mg/kg, iv drop	94 %, $n = 6$, $p < 0.01$ vs 111 %, control $p < 0.05$	
Anti-atherosclerotic activity	Inhibit the ICAM-1 expression of HUVEC induced by ox-LDL	*Vitro* (HUVEC cell)	70 % ethanol extract of ZS Compound **49** Compound **56**	1.0 and 2.0 mg/mL 15.625 μg/mL 0.25 mg/mL	$n = 4$, $p < 0.01$ or 0.05 vs model control	(Luo et al., 2012)
	Inhibit cyclic strain-induced HUVEC ET-1 secretion	*Vitro* (HUVEC cell)	Compound **49**	10 and 100 mmol/L	$n = 6$, $p < 0.05$ vs control	(Chiou et al., 2008)
	Reduce TG, TCH and LDL-cholesterol in the hyperlipidemia rats	*Vivo* (SD rat)	ZS injection	50, 200 mg/kg, ip drop	$p < 0.01$ or 0.05 vs control	(Ham et al., 2007)
	Decrease the blood glucose	*Vivo* (Male KM mice)	70 % ethanol extract of ZS	5.07 mg/kg/d, i.g for 4 weeks	$n = 10$, $p < 0.05$ vs model control	(Jiao et al., 2009)
	Reduce ED, and increase serum nitrite and vascular NO bioavailability	*Vivo* (Male Wistar rat)	Compound **49**	100 mg/kg/d, p.o for 2 weeks	$n = 10$, $p < 0.001$	(Kumar et al., 2017)
	Decrease the TG and TCH in the diabetic mice by abolishing the effect of L-methionine on Ach	*Vivo* (Male KK-Ay mice and C57BL/6 mice)	Compound **56**	50 mg/kg, BW i.g for 6 weeks	$n = 10$, $p < 0.001$ or 0.01 vs model control	(Jia et al., 2015)
Antithrombotic activity	Anti-thrombosis	*Vitro* (Rabbit)	ZS decoction	0.1 g/mL	$n = 5$	(Ou et al., 1989)
	Inhibit PLT and RBC aggregation	*Vivo* (Male Wister rat)	ZS decoction	1, 2.5 g/kg/d, i.g for 10 d	$n = 11$, $p < 0.001$ vs model control	(Ji et al., 2003)
	Decrease PLT number in CIA rat	*Vivo* (Male SD rat)	Ethanol extract	3.6 g/d, i.g for 9 weeks	$n = 8$, $p < 0.01$ vs model control	(He et al., 2018)
	Reduce serum Hcy and cholesterol in L-methionine-treated rats	*Vivo* (Male Wistar rat)	Compound **49**	100 mg/kg/d, p.o for 2 weeks (22.37 ± 0.30 vs 11.01 ± 1.01 mg/mL) and (182.7 ± 2.15 vs 101.5 ± 2.76 mg/mL), respectively	$n = 10$, $p < 0.001$	(Kumar et al., 2017)

ICa-L: L-type calcium; dp/dt: first derivative of the left ventricular pressure; GPIP: common peak isovolumetric pressure; ICAM-1: intercellular adhesion molecule-1; HUVEC: human umbilical vein endothelial cells line; ox-LDL: oxidized low-density lipoprotein; ET-1: endothelin; TG: triglycerides; TCH: total cholesterol; ED: endothelial dysfunction; PLT: platelet; RBC: red blood cell; CIA: collagen-induced arthritis; Hcy: homocysteine.

Table 13 anti-adipogenic, anti-inflammatory and anti-oxidant activity.

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose		*p* value	References
Anti-adipogenic	Suppress adipogenesis, adipocytes differentiation and lipid accumulation by inhibited expression of C/EBPα and PPARγ, the PKB/Akt pathway and GSK3β activity	*Vitro* (3 T3-L1 cell)	Compound **78**	1, 10 μM for 6 d		$P < 0.01$ vs control	(Guo et al., 2019)
		Vitro (3 T3-L1 cell)	ZS flavonoid	10, 50 μg/ml for 4 or 6 d		$p < 0.01$ or 0.05 vs control	(Kim et al., 2012)
	Reduce 10 % viability of cell	*Vitro* (3 T3-L1 cell)	Menthol extract of ZS	1000 μg/ml		$p < 0.001$ vs control	(Raciti et al., 2018)
	Stimulate the lipolysis	*Vitro* (Wistar rat)	Compound **78**	0.1–1000 μg/ml, 80 % of the maximal response		$p < 0.001$ vs model control	(Mercader et al., 2011)
		Vitro (Human WAT cells)	Compounds **78**	0.1–1000 μg/ml	33 % of the maximal response	$p < 0.001$ or 0.01 vs control	
			Compound **79**		20 % of the maximal response		
	Increase the activity of BAT and induce the browning of iWAT by activating AMPK-PGC1α pathway	*Vivo* (Male C57BL/6J mice)	Polymethoxy flavonoids	0.2 % (w/w) p.o for 12 weeks		$n = 10$, $p < 0.01$ vs model control	(Kou et al., 2020)
	Inhibit expression of SCD-1 and FAS. ACOX was induced by **56**	*Vivo* (Male KK-Ay mice and C57BL/6 mice)	Compound **56**	50 mg/kg, BW for 6 weeks		$n = 10$, $p < 0.05$, 0.01, or 0.001 vs control	(Jia et al., 2015)

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Table 13 (*continued*)

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose		*p* value	References
Anti-inflammatory	Reduce TNF-α, IL-1β and IL-6	*Vitro* (RAW 264.7 cell)	50 % methanol ZS extract	160 μg/mL		$p < 0.001$ vs model control	(Zhao et al., 2018)
			Compound **40**	160 μg/mL			
	Decrease the serum of IL-1β, IL-6 and TNF-α	*Vivo* (Male SD rat)	50 % methanol ZS extract	250 mg/kg, i.g		$n = 8$	
			Compound **40**	100 mg/kg, i.g			
	Reduce NF-κB, TNF-α, IL-1β and IL-6	*Vitro* (Male SD rat)	Compound **17**	10 and 25 mg/kg		$n = 20$, $p < 0.01$ or 0.05 vs control/model control	(Bi et al., 2016)
	Inhibit LPS-stimulated NO production by downregulating the protein expressions of TNF-α, NF-κB, COX-2, and iNOS	*Vitro* (RAW264.7 cell)	Compounds **17**, **40**, **41**	100 μM		$n = 6$, $p < 0.001$ vs model control	(He et al., 2018)
	Decrease IL-6, IL-1β and TNF-α in serum and colon tissue	*Vivo* (C57BL/6J mice)	ZS flavonoid	50, 100, 200 mg/kg p.o for 23 d.		$n = 10$, P < 0.001 vs model control	(Chen et al, 2022)
	Enhance IL-10 and reduce TNF-α in mice colon tissue	*Vivo* (BALB/C mice)	Compound epoxyaurapten	160 and 320 μmol/L, 0.01 mL/g, i.g for 10 d		$n = 10$, $p < 0.05$ vs model control	(Lin et al., 2015)
	Attenuate mRNA expression of COX-2	*Vitro* (RAW264.7 cell)	ZS pharmacopuncture	100, 50, 25, 12.5, 6.25 %			(Kim and Park, 2010)
	Inhibit both His and dextran-induced edema	*Vivo* (Male Wistar rat)	70 % EtOH extract of ZS	75–200 mg/kg, i.g for 2 weeks	IC_{50} = 119.6 mg/kg IC_{50} = 118.3 mg/kg	$n = 6$, $p < 0.05$	(Mencherini et al., 2013)
	Inhibit inflammatory swelling of ankle joints induced by formaldehyde and egg white	*Vitro* (Rat)	ZS extract	egg white: 15 g/kg formaldehyde: 20 g/kg first day, 10 g/kg/d later		$n = 5$, $p < 0.001$ vs control $n = 6$, $p < 0.05$ vs control	(Zhang and Wang, 2004)
	Decrease MPO and NO, and expressions of TNF-α, COX-2, iNOS and NF-κB	*Vivo* (Male SD rat)	Raw medicinal materials	125–500 mg/kg, p.o		$n = 8$, $p < 0.001$ vs model control	(He et al., 2018)

Table 13 (*continued*)

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose	*p* value	References
	Inhibit the LPS-induced production of NO, TNF-α, IL-6, IL-1β and PGE2 in macrophages and decrease the endotoxin level and TNF-α in RAW 264.7 cells	*Vitro* (Male Wistar rat)	ZS decoction, transformed ZS	0.5, 1.0 and 2.0 mg/mL	$n = 6$, $p < 0.01$ vs model control	(Liu et al., 2017)
	Reduce the paw pressure score and volume, ankle diameter by decreased IL-1β and TNF-α	*Vivo* (RAW 264.7 cell)	AFIC-CDs	2, 4 and 8 mg/kg	$n = 8$, $p < 0.05$ or 0.01	(Wang et al., 2019)
		Vitro		0.4, 0.8 and 1.6 mg/mL	$p < 0.05$ or 0.01 vs model control	
	Reduce XOD activity on serum and liver	*Vivo* (Male SD rat)	AFIC-CDs	2, 4 and 8 mg/kg		
		Vitro		2 mg/kg vs allopurinol 58.83 % 4 mg/kg 64.38 % 8 mg/kg 52.58 %		
	Decrease the production of iNOS, COX-2, IL-6 and TNF-α induced by LPS by suppressd NF-kB and MAPKs signal pathways	*Vitro* (L6 skeletal muscle cell)	ZS flavonoid	10, 50, 75 and 100 mg/mL	$p < 0.05$ vs model control/control	(Kim et al., 2012)

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Table 13 (*continued*)

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose	*p* value	References
Anti-oxidant	Increase GSH–PX, GSH, and SOD, and reduce MDA	*Vitro* (Male SD rat)	Compound **17**	10 and 25 mg/kg	$n = 20$, $p < 0.01$ or 0.05 vs control/model control	(Bi et al., 2016)
	Inhibit strain-induced ROS formation	*Vitro* (HUVEC cell)	Compound **49**	10 and 100 μmmol/L	$n = 6$, $p < 0.05$ vs control	(Chiou et al., 2008)
	Scavenging of ·OH, $\cdot O_2^-$and DPPH·	*Vitro*	Compound **53**	IC_{50} = 45.94 mg/mL SC_{50} = 10.16 mg/mL DC_{50} = 9.62 mg/mL		(Jiao et al., 2008)
			70 % ethanol ZS extract	IC_{50} = 2.71 mg/mL SC_{50} = 5.02 mg/mL DC_{50} = 0.54 mg/mL		
	Inhibit lipid peroxidation in mouse liver, kidney and heart tissue homogenates	*Vitro* (Male KM mice)	Compound **53**	9.87, 11.04, 10.40 mg/mL		
	Scavenging of ·OH, $\cdot O_2^-$, DPPH· and H_2O_2	*Vitro*	CLB 1–4	6.4 mg/mL > vitamin C (6.4 mg/mL)		(Wang et al., 2014)
	Enhance the enzyme activities of SOD, CAT, and GSH-Px in blood, heart, and liver	*Vivo* (Male C57BL/6N mice)	CALB	100 and 200 mg/kg		
	Reduce MDA formation in blood, heart, and liver		CALA	100 mg/kg		
	Scavenging of DPPH·, $ABTS^+$ and ·OH, FRAP	*Vitro*	Crude juice	DPPH: 14.39 ± 0.19 μM TE $ABTS^+$:14.30 μM TE (64 %) ·OH: 4.8 μM TE	$n = 4$	(Barreca et al., 2014)
			C- and *O*-glycosyl flavones	9.50 %		
			O-glycosyl flavanones	18.20 %		
			Flavonoid pool	DPPH·: 12.25 ± 0.70 μM TE (85.1 %) $ABTS^+$: 5.6 μM TE (25 %) ·OH: 32 %		

Table 13 (*continued*)

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose	*p* value	References
	Scavenging ·OH		FA3: contain flavonoids FA4: contain 9.96 % limonin	10–2000 mg/mL 2000 mg/mL		(Liu et al., 2009)
	Scavenging of DPPH· and SOD, against H_2O_2-induced cell injury and attenuate LPS-induced COX-2 mRNA expression	*Vitro* (RAW264.7 cell)	ZS pharmacopuncture	6.25 %–50 %		(Kim and Park, 2010)
	Ameliorate all biochemical parameters of lung damaged rats caused by chromium	*Vivo* (Female Wistar rat)	80 % ethanol ZS extract	100 and 300 mg/kg/d, p.o for 10 days	$n = 6$, $p < 0.001$ vs model control	(Soudani et al., 2013)
	Decrease the content of MDA, increase the content of NO, GSH and the activity of CAT	*Vivo* (Male KM mice)	70 % ethanol ZS extract	1.69, 3.37, 5.07 mg/kg, 1 time/d, i.g for 4 weeks,	$n = 10$, $p < 0.01$ or 0.05 vs model control	(Jiao et al., 2009)

C/EBPα: CCAAT/enhancer-binding protein α; PPARγ: peroxisome proliferator-activated receptor γ; PKB/Akt: protein kinase B; GSK3β: glycogen synthase kinase 3β; BAT: brown adipose tissues; iWAT: white adipose tissues; SCD-1: stearoyl-CoA desaturase 1; FAS: fatty acid synthase; ACOX: acylCoA oxidase; LPS: lipopolysaccharide; XOD: Xanthine oxidase; AFIC-CDs: ZS carbonisata-derived carbon dots; MDA: Malondialdehyde; ROS: reactive oxygen species; FRAP: Ferric reducing antioxidant power.

Table 14 anti-tumour activity and neuroprotective activity.

Bioactivity	Mechanism	*Method type*	Extracts/compounds	Active concentration/dose	*p* value	References
Anti-tumour	G2/M cell cycle arrest	*Vitro* (HT-29 cell)	Compounds **94**, **96**	1.25, 2.5, 5.0, and 10.0 μM		(Jayaprakasha et al., 2008)
	G2 cell cycle arrest, decrease the expression of Bcl-2 and COX-2 and increase Bax and caspase-3	*Vitro* (SMMC-7721 cell)	Compound **17**	IC_{50} = 26.51 mg/L		(Ma et al., 2013)
	Inhibit the growth of H22 transplantable tumor by decreased the expression of COX-2 and Bcl-2/Bax and increased Bax and caspase-3	*Vivo* (H22 cell)	Compound **17**	125, 250, and 500 mg/kg, i.g daily	$n = 10$, $p < 0.01$ or 0.05 vs model control	
	Inhibit angiogenesis	*Vivo* (Hatching egg)	Compounds **14**, **18**, **22**		$n = 15$, $p < 0.05$ vs control	(Yang, 2007)
		Vitro (SMMC-7721 cell and BcaP37 cell)	Compounds **16**, **17**, **22**	12.5, 25, 50, 100 μg/mL		(Wang, 2008)
	G2/M cell cycle arrest and apoptosis, upregulate p53 and p21 protein	*Vitro* (AGS cell)	Compound **24**	5, 10, 30, 60, 120 μmol/L	$p < 0.01$ or 0.05 vs control	(Dong et al., 2011)
	Inhibit the expression of XIAP and Bcl-xL and the activity of Akt	*Vitro* (U937 cell)	Crude methanol extracts of the ZS	10–100 μg/ml	$p < 0.05$ vs control	(Han et al., 2012)
	Increase the expressions of caspase 3, P-p38, Bax, and Bak, decrease Bcl-2, Bcl-xL, pAkt, and phosphoinositide-3-kinase/Akt pathway	*Vitro* (HepG2 cell, Thle2 cell)	ZS flavonoid	25, 50, 75, and 100 μg/ml IC_{50} = 75 μg/mL	$p < 0.05$ vs control	(Lee et al., 2015)
	Inhibit tumor induced by HepG2 cell growth in the xenograft model	*Vivo* (BALB/c mice)	ZS flavonoid	25 and 50 mg/kg	$n = 3$	
	Enhances natural killer cytolytic activity	*Vivo* (C57BL/6 mice)	ZS extract	200 mg/kg, p.o for 10 d	$p < 0.05$ or $p < 0.01$	(Park et al., 2022)
		Vitro (NK-92, K562 and Y AC-1 cells)		50, 100 μg/mL	$p < 0.05$ or $p < 0.01$	
Neuroprotective	Via modulation of Akt, Bax, p-CREB and BDNF in aging rats	*Vivo* (Male SD rat)	Compound **17**	10, 25 mg/kg/d, ip drop	$n = 20$, $p < 0.01$ or 0.05 vs model control	(Bi et al., 2016)
	Prevent rise in ELT and decrease TSTQ	*Vivo* (Male Wistar rat)	Compound **49**	50 and 100 mg/kg, p.o for 2 weeks.	$n = 10$, $p < 0.001$	(Kumar et al., 2017)
	Decrease the activity of AchE in the cortex and hippocampus and the expression of Bax and caspase–3 protein, increase the expression of Bcl–2 in the hippocampus	*Vivo* (Male c57Bl/6J mice)	ZS extract	50, 100 mg/kg, p.o for 4 weeks	$n = 8$, $p < 0.05$ vs model control	(Lee et al., 2019)
			Compound **17**	50 mg/kg, p.o for 4 weeks		
	Increase cerebral blood flow and decrease cerebral vascular resistance	*Vivo* (Dog)	ZS injection	1 g/kg, iv drop	$n = 5$, $p < 0.01$	(XiangYa School Of Medicine, 1978)
	The activities of SOD, CAT and GSH-Px were significantly enhanced against 6-OHDA-induced oxidative stress	*Vitro* (PC12 cell)	ZS flavonoid	3.75, 7.5, 15 μg/mL	$p < 0.05$	(Liang et al., 2021)

CREB: response element binding protein; BDNF: brain-derived neurotrophic factor; ELT: escape latency time; TSTQ: time spent in the target quadrant.

Table 15 Toxicity of ZS.

Extracts/compounds	*Vitro*/*vivo*		Active concentration/dose	Effect	Reference
Wall-broken spore power of ZS	*Vivo*	(SPF) KM mice	120 g/kg, 40 mL/kg, p.o for 7 d	n = 10, no cytotoxicity	(Lin et al., 2012)
70 % ethanol extract of ZS	*Vitro*	HUVEC cell	2 mg/mL	n = 4, survival rate greater than 80 %	(Luo et al., 2012)
Compound **49**			0.03125 mg/mL		
Compound **56**			0.25 mg/mL		
Ethanol extracts	*Vitro*	LS180 cell	20 mg/mL	No cytotoxicity	(Okada et al., 2017)
AFIC-CDs	*Vitro*	RAW 264.7 cell	5000 μg/mL	No cytotoxicity	(Wang et al., 2019)
C. aurantium extract	*Vivo*	Human	Containing 49 mg compound **78**, for 15 d	n = 16, no stimulant (cardiovascular) and adverse effects.	(Shara, Stohs and Smadi, 2018)
Synephrine, caffeine and green tea extract	*Vivo*	Human	13 mg synephrine + 176 mg caffeine + 55.5 mg green tea extract, for 24 h	n = 23, not increased cardiovascular stress	(Seifert et al., 2011)
ZS extract	*Vivo*	Male albino CF1 mice	400, 2000 or 4000 mg/kg, p.o for 28 d	n = 9–10, no cytotoxicity	(Arbo et al., 2009)
Compound **78**			30 or 300 mg/kg, p.o for 28 d		
Compound **78**	*Vivo*	Sprague-Dawley rats	50, 100 mg/mL	n = 7, not produce developmental toxicity	(Hansen et al., 2011)
6 % synephrine extract and caffeine			25 mg/ kg 6 % synephrine extract + 25 mg/ kg caffeine		
ZS extract (contain 7.5 % compound **78**)	*Vivo*	SD rat	1000 mg/kg/d, p.o for 90 d	n = 10, resulted in non-adverse effects	(Deshmukh et al., 2017)
Compound **78**	*Vitro*	3 T3-L1 cell	200 μM for1 or 6 d	No cytotoxicity	(Guo et al., 2019)
Compound **78**	*Vitro*	HepG2 cell	2, 20 and 200 μM	No cytotoxic, genotoxic, and mutagenic	(Ribeiro et al., 2019)
Compound **78**	*Vivo*	CF1 mice	300, 350, 400 mg/kg	Some nonspecific toxic effects	(Schmitt et al., 2012)
ZS flavonoid	*Vitro*	L6 skeletal muscle cell	150, 200 μg/mL	Affect viability	(Kim et al., 2012)
ZS extract	*Vivo* (Mice)		i.g for 3 d	n = 10, LD_{50} = 118.3 g/kg, maximum safe dose = 68.5 g/kg	(Zhang and Wang, 2004)
			i.h	LD_{50} = 58.4 g/kg, the maximum safe dose = 27.5 g/kg	
ZS injection	*Vivo* (Mice)		Tail vein injection	LD_{50} = 71.8 ± 6.5 g/kg	(XiangYa School Of Medicine, 1978)
			i.p	LD_{50} = 267 ± 37 g/kg	
	Vivo	Dog	21 g/kg, iv	No cytotoxicity	

3.5.9. Neuroprotective activity

ZS flavonoid significantly enhanced SOD, CAT, and GSH-Px activities of 6-hydroxydopamine-treated PC12 cells (Liang et al., 2021). Synephrine (**78**) was able to bind to the neuromedin U2 receptor of HEK293 cells with high efficacy and potency (Zheng et al., 2014). Synephrine (**78**) was synthesized in 1927 as a sympathomimetic drug and was included in Nordic Pharmacopoeia and Deutsches Apothekerbuch. ZS extract (Lee et al., 2019), nobiletin (**17**) (Bi et al., 2016), and hesperidin (**49**) (Kumar et al., 2017) effectively decreased the escape latency time, path length (length taken to reach the platform), and swim distance. They also increased the time spent in the target quadrant and the number of crossed the platform. Nobiletin (**17**) might ameliorate cognitive impairment of aging rats *via* modulation of Akt, B-cell lymphoma 2-associated X protein, p-cAMP response element binding protein, and brain-derived neurotrophic factor (Bi et al., 2016). Furthermore, it could also down-regulate the acetylcholinesterase activity and caspase 3 protein expression and up-regulate the Bcl 2 expression of the cortex and hippocampus (Lee et al., 2019). ZS injection could significantly increase cerebral blood flow and decrease cerebrovascular resistance of dogs (XiangYa School Of Medicine, 1978) (Table 14).

3.5.10. Immunomodulatory activity

ZS extract, hesperidin (**49**), and neohesperidin (**56**) can significantly increase the content of NO in the supernatant of HUVEC induced by ox-LDL. The extract and hesperidin can also increase NO content in the supernatant of normal HUVEC (Luo et al., 2012). Endothelial NO synthase (eNOS) activity and the phosphorylation of eNOS and Akt of HUVEC were enhanced after being treated with compound **49** (Chiou et al., 2008).

3.5.11. Effect on the reproductive system

ZS extracts, rich in synephrine (**78**) and *N*-methyltyramine (**79**), had the effect of stimulating isolated circular muscles of the vaginal (Tang, 2001) and uterus (n = 7, $p < 0.01$ or $p < 0.05$) (Zhang et al., 2007) of rabbit, which resulted in rhythmically compress activities of muscle or increase of the spontaneous muscle contract intension and frequency. This result was consistent with those conducted *in vivo* (Yan,

1995). The extract showed bidirectional regulation on the isolated mouse uterus. ZS, combined with Kushen (the root of *Sophora flavescens* Ait.) (2:1, v/v), showed stronger inhibitory activity in the circular muscle of the vaginal (Tang, 2001).

3.5.12. Adrenaline action

Synephrine (**78**) could promote lipolysis by binding with β-3 receptor (Ribeiro et al., 2019; Rossato et al., 2011; Stohs et al., 2011a, 2011b; Stohs and Badmaev, 2016; Stohs, 2017). A novel cell-based functional assay suggested that the ZS are the possible agonists of β-2 adrenoceptor (Wang et al., 2009). *N*-methyltyramine (**79**) could treat gastrointestinal disorders *via* the regulation of adrenergic receptors, which may be related to the bio-transformation of compound **79** to epinephrine by serial synthase in nerve cells of the small intestine (Ni et al., 2019). ZS injection (1.5 g/kg) and compound **79** (0.1 and 0.2 mg/kg) significantly increased renal blood flow and urine output, and decreased renal vascular resistance of dogs (Guo, 1978).

3.5.13. Others

Hesperetin (**41**) and naringenin (**40**) displayed broad-spectrum inhibition against human glucuronosyltransferases (Liu et al., 2016). The methanol extracts of ZS showed obvious inhibitory effects on α-glucosidase and acetylcholinesterase. Flavanone glycosides of ZS were effective on α-glucosidase while polymethoxy flavonoids were effective on acetylcholinesterase (Guo et al., 2021). In addition, ethanol extract of ZS induced the expression of P-glycoprotein and cytochrome P450 3A4 of expression *via* upregulation of the pregnane X receptor in LS180 cells (Okada et al., 2017).

The volatile oil (Hu et al., 1994) and extract of ZS (10.8 g/kg) (Zhang and Wang, 2004) significantly reduced the incidence of acetic acid-induced torsional reactions in mice ($p < 0.05$, $p < 0.01$, respectively). ZS could improve the bioavailability of omeprazole in rats (Yu et al., 2013). Nomilin (**89**) and limonin (**90**) showed anti-obesity and anti-hyperglycemic effects *via* binding to Takeda G protein-coupled receptor 5, a bile acid receptor (Zohra et al., 2020). ZS can significantly increase the growth of *Ctenopharyngodon idella* (Ding et al., 2005) and *Litopenaeus vannamei* (Guo et al., 2005). Essential oil of ZS could reduce the survival rate of larvae of *Culex pipiens* (Michaelakis et al., 2009).

3.6. Toxicity

Safety is the most basic properties of health foods. Toxicity studies (Table 15) indicated ZS is safe for health food purposes. No obvious toxicity of ZS on mice was observed (Lin et al., 2012). Ethanol extract and pure compounds (**49** and **58**) had no toxicity on HUVEC (Luo et al., 2012), LS180 (Okada et al., 2017), and/or RAW 264.7 cells (Wang et al., 2019). Since 2004, ephedra products have been banned for weight loss by FDA due to their safety problems (Bent et al., 2004). The extracts of the fruit of *C. aurantium*, which contains synephrine (**78**) with a similar chemical structure and effect on weight loss, rapidly became its replacement due to its safety (Haaz et al., 2006). Clinical trials indicated that synephrine and *C. aurantium* extracts did not result in cardiovascular diseases and did not act as stimulants at commonly used doses compared to with more active substances like caffeine (Stohs, 2017). No adverse reactions were observed after sixteen healthy subjects treated with the extracts of *C. aurantium* for 15 days (Shara, Stohs and Smadi, 2018). The mixture containing synephrine, caffeine and green tea extract did not lead to increased cardiovascular stress (Seifert et al., 2011). Both commercial ZS extract (containing 7.5 % synephrine) and synephrine could reduce the body weight gain of the mice but had no significant effects on the relative weight of their organs and biochemical and hematological parameters (Arbo et al., 2009). Synephrine or combined with caffeine did not produce developmental toxicity in rats (Hansen et al., 2011). No adverse effect was observed in a 90-day subchronic safety/toxicity study (Deshmukh et al., 2017). Synephrine did not exhibit cytotoxicity on the 3 T3-L1 cells even at a high dose (Guo et al., 2019). Synephrine was not cytotoxic, genotoxic, and mutagenic towards human liver cells at specific concentrations (Ribeiro et al., 2019).

There were several clinical hazard reports containing extract of the fruit of *C. aurantium* (Stohs, 2010; Stohs and Ray, 2020). They all emphasized the similarities of the chemical structure and side effects between ephedrine and synephrine. However, ephedrine is a phenylpropanolamine derivative without a substituted hydroxy group, while synephrine is a phenylethanolamine derivatives with a *para*-substituted hydroxyl group, which led to the difference of their half-life (Stohs et al., 2011b; Stohs, 2017; Stohs et al., 2020a, 2020b). Ephedrine exhibited better effect for binding to α, β-1, and β-2 receptor, while synephrine bound to β-3 receptor (Costa et al., 2022; Stohs et al., 2011b; Stohs and Badmaev, 2016; Stohs et al., 2020). In addition, the para hydroxy group and the lack of the methyl group on the side-chain of synephrine greatly decreased its lipid solubility and the ability of crossing the blood–brain barrier, which resulted in no effect on the CNS and cardiovascular stimulation (Rossato et al., 2011; Stohs et al., 2011a, 2011b; Stohs, 2017).

As a trace amine, synephrine have been detected in human plasma and platelets (Costa et al., 2022; Rossato et al., 2011). On a daily basis, *C. aurantium* extract (Advantra Z®; synephrine)-containing products and a variety of orange juices were consumed by tens of millions of people worldwide without the report of serious incidents (Stohs et al., 2011a; Stohs, 2017). Under the specified dose, direct experimental evidence and numerous peer reviews have proved the safety of *C. aurantium* extract and synephrine from human, animal, and cell levels whenever used alone or combined with stimulants such as caffeine (Stohs, 2017) The clinical hazard reports containing *C. aurantium* extract and synephrine should consider other ingredients, adulteration problems, and the physical condition of patient (Costa et al., 2022; Hansen et al., 2011; Rossato et al., 2011; Stohs, 2017). As a consequence, the hazard of synephrine cannot be inferred through the current scientific assumptions.

However, studies also suggested that ZS could cause damage when used in high doses, which is one of the most important reasons why ZS can be used as a health food but not as dietary herbal medicine. According to ChP, the clinical administrations of ZS for adults are suggested to be 3–10 g daily (Chinese Pharmacopoeia Commission, 2020b). When the dose of synephrine reached to 400 mg/kg, no specific toxic side effects such as erection and salivation was observed in mice (Schmitt et al., 2012). ZS flavonoids could affect viability of L6 skeletal muscle (Kim et al., 2012). According to the

NHCPRC, the rat with an oral LD_{50} value is 5001–15000 mg/kg was listed as grade 2 (practically non-toxic). High LD_{50} values were also observed when the mice were intragastrically administered and intraperitoneally or intravenously injected (Zhang and Wang, 2004). A high dose of ZS caused high and fast elevation of blood pressure (over 180–200 mmHg), temporary ectopic rhythm, and anuria of anesthetized dogs (XiangYa School Of Medicine, 1978). The oral administration (23.42 g/kg/d) of ZhiZi HouPo Decoction containing ZS caused damage to the liver and kidneys, and that of the SCZS-containing group ($n = 5$) was more severe to the liver and kidneys of rats than the TCZS-containing group (Zhang and Feng, 2019).

3.7. Clinical research

Zhizhu pills containing SCZS ($n = 82$) exhibited superior effects on FD patients with spleen-deficiency and Qi-stagnation syndrome than those containing TCZS ($n = 78$) (Wu et al., 2011). The effective rate on FD patients ($n = 60$) after 4 weeks of treatment with Weikang pian (flavonoids extracted from ZS) was 94 %–96 %, and no adverse event occurred (Yan et al., 2019). In addition, ZS and its main constituents, including synephrine (**78**) and *N*-methyltyramine (**79**), had a therapeutic effect on septic shock children (Pediatric Septic Shock Research Cooperative Group, 1981; Zhao et al., 1989). Furthermore, ZS extraction could improve the symptoms of atopic dermatitis patients (Kim and Jung, 2014).

ZS capsules could increase the levels of HDL-C and NO and decrease the levels of ET-1, TC, TG, and LDL-C of hyperlipidemia patients ($p < 0.01$, $n = 40$). These effects of ZS capsules were significantly better than fluvastatin ($p < 0.01$) (Wu et al., 2012). ZS increased NO and reduced platelet aggregation, RBC aggregation, CD_{62p}, D-dimer, ET-l, and Ox-LDL of acute coronary syndrome patients ($p < 0.05$ or 0.01, $n = 34$) (Ji et al., 2008).

4. Discussion and conclusions

This article presents a systematic review of ZS as an example of the fruit used as both food and medicine. The plant origin of ZS has undergone a variety of changes in history, which caused the phenomenon of the fruit of other *Citrus* genus plants used as ZS to become quite common. In addition, the plant source of ZS used in the classical prescriptions of different periods needs to be further investigated for their development. It is unable to identify all the adulterants by the current quality control methods. Therefore, systematic research is needed for the authentification of ZS. The fruit of both *C. aurantium* and *C. sinensis* can be used as ZS according to ChP, but their difference in the chemical composition may result in variation in pharmacological effect, which should be the focus of later research (Shi et al., 2019; Song et al., 2016; Zeng et al., 2016; Zhang et al., 2011). The harvesting time is a significant factor causing the variations in chemistry and bioactivity, but these variations remain to be further clarified (Deng et al., 2017; Deng et al., 2019; Tang et al., 2021). Thus, it is important to use ZS samples harvested in the right season in clinic practice or academic research.

The discussion on the warm or cold medicinal properties of ZS requires more experimental and clinical evidence. Synephrine, the major compound of ZS, is safe at a specific dose, but long-term safety study should be conducted. Besides, more attention should be paid to other compounds, such as flavonoids, and their bioactivities in digestive and cardiovascular systems. ZS is able to eliminate the food stagnation, constipation, diarrhea, and phlegm caused by the Qi being blocked in the abdominal cavity due to its Qi-regulating effect which is closely related to the bi-directional regulation effects on gastrointestinal tract. For example, ZS stimulate or inhibit gastrointestinal smooth muscle when treating food stagnation or diarrhea, respectively. Whether its phlegm eliminating effect is related to bronchial smooth muscle stimulating activity is not clear. Stimulating smooth muscle is the pharmacological basis for its therapeutic effect on the prolapse of stomach, uterus, and anus.

In summary, as a health product and TCM, ZS possesses extensive health care and therapeutic effects, but more comprehensive studies on its quality control, pharmacology, and safety is necessary to reveal its scientific evidence of health benefits.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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