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Ziziphus jujuba Mill., a plant used as medicinal food: a review of its phytochemistry, pharmacology, quality control and future research

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Abstract Jujubae Fructus (*ZJF*) [called Dazao (大枣) in Chinese], the fruit of *Ziziphus jujuba* Mill. (*ZJ*), is utilized as a food and traditional medicine in China. In TCM use, *ZJF* is traditionally used to treat and nourish the stomach, tonify the spleen, and nourish the blood, as well as for overall nourishing and strength. According to the available literature from 1974 to March 2019, more than 278 compounds have been isolated and identified from *ZJ*. Local books, papers and dissertations were also searched. The aim of this review was to examine this plant's traditional uses, botany, phytochemistry, pharmacological effects, toxicity, pharmacokinetics, quality control and economically important uses. In vivo and in vitro scientific investigations have initially confirmed its pharmacological potential by showing anti-inflammatory, antioxidant, antimicrobial, gastrointestinal protective, cardiovascular, neuroprotective, anticancer, anti-HIV, sedative-hypnotic and anxiolytic effects. Bioactive metabolites belonging to different classes are responsible for these activities, including triterpenoid acids, saponins, cyclopeptide alkaloids, flavonoids and neo-lignans, which are considered the characteristic and active components of *ZJ*. The TCM use of *ZJF*, including tonifying and replenishing the middle Qi and nourishing the blood to tranquilize, is based on its gastrointestinal protective, cardiovascular, neuroprotective, sedative-hypnotic and anxiolytic properties. Its detoxification effects are attributed to its anti-inflammatory, antiviral, anticancer and antibacterial activities. Moreover,

Qi: In terms of acupuncture, "Qi" is the "life force". It provides the circulation of nourishment in the bloodstream and maintains body temperature (Wang et al. 2018c). Chinese heat-clearing herbs are considered to be antipyretic in TCM. They are mostly cold in nature and can clear away heat and toxic materials (Liu et al. 2018c).

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the TCM characteristics of *ZJF* (sweet flavour; warm nature; and spleen, stomach, and heart meridian effects) support its traditional uses and pharmacological effects. We encourage more studies to further clarify the relationship between modern applications and traditional uses in the future. Furthermore, no one has studied *ZJ* blossoms, and researchers should allocate more time to the study of *ZJ* blossoms. Additionally, unsolved problems include the scientific principle of the Chinese material medica processing [CMMP (中药炮制) in Chinese] of *ZJF*, the molecular mechanisms of the biological activity of *ZJ* and its other medicinal parts, the overall pharmacokinetics rather than single molecule pharmacokinetics, the efficacy and the toxicology. All of the unsolved problems noted above require further study.

Keywords *Ziziphus jujuba* Mill. · Traditional uses · Phytochemistry · Pharmacology · Quality control · Biological effects

Abbreviations

ABTS	2,2′-azino-bis-3-ethylbenzo-thiazoline-6-sulfonic acid
AD	Alzheimer's disease
AMPK	AMP-activated protein kinase
BAL	Bronchoalveolar lavage
BHA	Butylated hydroxyl anisole
BHT	Butylated hydroxyl toluene
CAIA	Collagen antibody-induced arthritis
$CHCl_3$-F	Chloroform fraction
CI	Confidence interval
CMMP	Chinese material medica processing
CSIETP	College Students' Innovative Entrepreneurial Training Programme
DPPH	2,2-diphenyl-1-picrylhydrazyl
DW	Dry weight
FRAP	Ferric-reducing antioxidant power
FW	Fresh weight
GAE	Gallic acid equivalents
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
HFWD	High-fat Western-style diet
IL	Interleukin
ISO	Isoproterenol
JPBP	The bond phenols from jujube peel
JPFP	The free phenols from jujube peel
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MIC	Minimum inhibitory concentration
NAFLD	Non-alcoholic fatty liver disease
NF	Neurofilament
NF-κB	Nuclear factor-kappa B
NFs	Neurofilaments
NGF	Nerve growth factor
NNSFC	National Natural Science Foundation of China

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PEDV	Porcine epidemic diarrhoea virus
ROS	Reactive oxygen species
SOD	Superoxide dismutase
SRB	Sulforhodamine B
TCM	Traditional Chinese medicine
TH2	T-helper type 2
TI	Therapeutic index
TNF	Tumour necrosis factor
ZJ	*Ziziphus jujuba* Mill.
ZJB	*Ziziphus jujuba* bark
ZJC	*Ziziphus jujuba* core
ZJF	*Ziziphus jujuba* Fructus (Jujubae Fructus)
ZJJ	*Ziziphus jujuba* cv. Jinsixiaozao
ZJL	*Ziziphus jujuba* leaves
ZJR	*Ziziphus jujuba* roots
ZJS	*Ziziphus jujuba* seeds
ZJRB	*Ziziphus jujuba* root bark
ZJSB	*Ziziphus jujuba* stem bark

Introduction

Ziziphus jujuba Mill. (*ZJ*) (Family Rhamnaceae) is a small tree, or less commonly, a shrub; the fruits of *ZJ* are notably used in TCM "Jujubae Fructus" (*ZJF*) (大枣/红枣 in Chinese). The characteristics of *ZJF* in TCM are summarized as sweet in flavour, with a warm nature and good spleen, stomach, and heart meridian distributions (Pharmacopoeia Commission of PRC 2015). According to Chen and Zhang (2014), these characteristics are similar to the characterization of anti-inflammatory agents in TCM. *ZJF* is used to nourish the stomach, fortify the spleen, and replenish blood, as well as for overall enriching and tonifying and to improve one's health (Editorial Board of Flora of China 1982). In Shennong's Classic of Materia Medica, *ZJF* is considered an effective drug for treating heart and abdominal pathogenic Qi, tonifying the spleen and stomach, as well as being beneficial for the twelve meridians, balancing stomach Qi, unblocking the nine orifices, tonifying a shortage of Qi and fluid-humour, tonifying an insufficiency of middle Qi, tranquilizing, heaviness of the limbs, and harmonizing the hundred medicinals. *ZJF* extracts are used to treat fullness in the chest and ribs or chronic hepatitis in Japan (Kubota et al. 2009). Five forms of *ZJ* are available, including *ZJF*, *Ziziphus jujuba* leaves (*ZJL*), *Ziziphus jujuba* core (*ZJC*), *Ziziphus jujuba* bark (*ZJB*) and *Ziziphus jujuba* roots (*ZJR*) (Fig. 1) (Wang 2014), although *ZJF* is most frequently used in TCM prescriptions (Liu et al. 2017d). The main production areas of *ZJF* are Hebei, Henan, Shandong, Shaanxi and other places in China [cultivated in Asia, Africa, Europe, and North and South America] (Editorial Board of Flora of China 2007). Sixty-six Chinese medicinal preparations containing *ZJF* are listed in the 2015 edition of the Chinese Pharmacopoeia, such as Anshen Bunao liquid (安神补脑液 in Chinese), in which the function of *ZJF* is to tonify Qi, nourish the blood and tranquilize; Xiangsha Yangwei pills (香砂养胃丸 in Chinese), in which the function of *ZJF* is to warm the middle to harmonize the stomach; Jianpi Shenxue tablets (健脾生血片 in Chinese), in which the function of *ZJF* is to fortify the spleen to harmonize the stomach and nourish the blood to tranquilize, etc. (Pharmacopoeia Commission of PRC 2015).

Modern studies have shown that *ZJF* has anti-inflammatory (Goyal et al. 2011), antioxidant (Ko et al. 2008), anticancer (Lee et al. 2003), and anti-HIV effects (Fujioka et al. 1994), in addition to serving as a sweetness inhibitor (Suttisri et al. 1995), and other functions. Although only *ZJF* is used in TCM, some studies have reported the pharmacological effects and phytochemistry of *Ziziphus jujuba* leaves (*ZJL*) (Yoshikawa et al. 1991, 1992), *Ziziphus jujuba* roots (*ZJR*) (Kang et al. 2015, 2016, 2017), *Ziziphus jujuba* stem bark (*ZJSB*) (Han et al. 1989) and *Ziziphus jujuba* seeds (*ZJS*) (Choi et al. 2011). Although approximately 278 components have been separated and identified from *ZJ*, the mechanisms and material basis of its efficacy are not still clear. Therefore, it is necessary for us to present a systematic overview of *ZJ* and discuss possible future research directions.

Traditional uses

While different from clinical studies, ethnopharmacological fieldwork is also focused on understanding the medical use of substances (Heinrich et al. 2018). In classical Chinese herbal medicine, *ZJF* is considered an effective drug to treat heart and abdominal pathogenic Qi; tonify the spleen and stomach; balance stomach Qi; tonify a shortage of Qi, fluid and humour; tonify

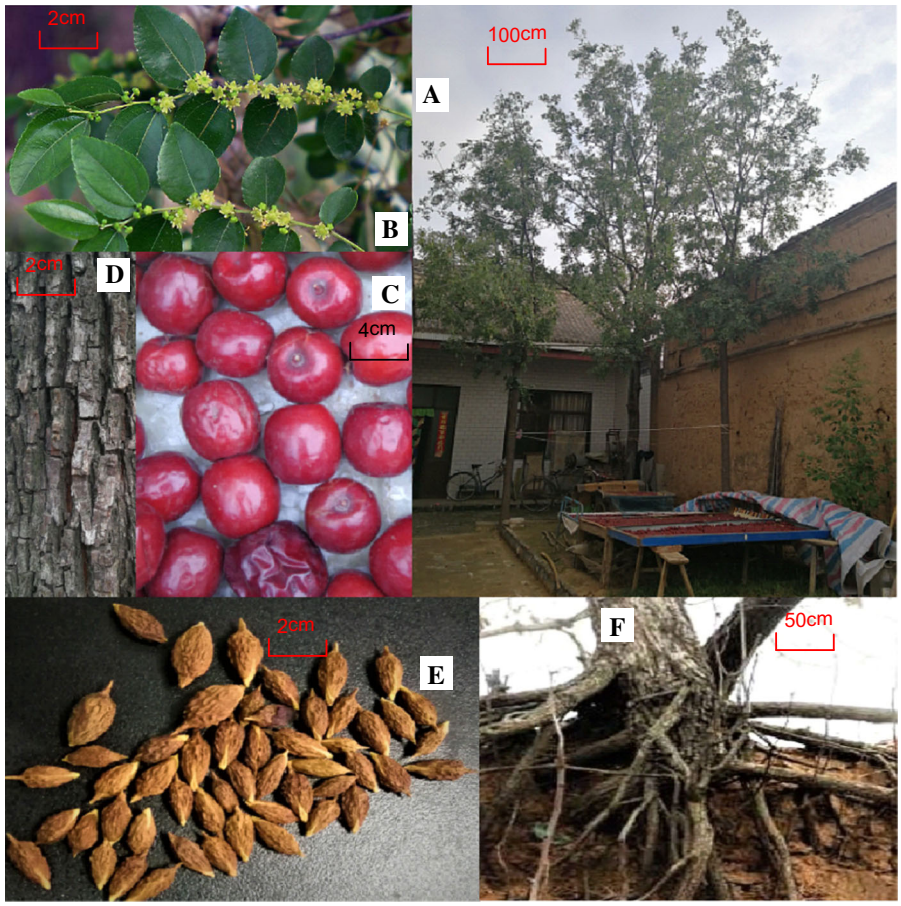


Fig. 1 Whole *ZJ* plant (A); the leaves and flowers of *ZJ* (B); the fruits of *ZJ* (C); the stem bark of *ZJ*(D); the cores of *ZJ* (E); the roots of *ZJ* (F)

insufficiency of middle Qi; tranquilize; harmonize the nature of medicinals (Shennong's Classic of Materia Medica); moisten the lungs and heart; suppress cough; tonify the five viscera; treat consumptive disease; eliminate intestinal and stomach pathogenic Qi (Rihuazi Materia Medica); tonify fluids and humour; nourish spleen Qi; strengthen will (Wupu Materia Medica; Dietetic Materia Medica), harmonize nutrients and defenses; soothe yin-blood; clear the twelve meridians; unblock the nine orifices (Shennong's Classic of Materia Medica); maintain beauty and youth (Wupu Materia Medica); warm and tonify the spleen and stomach (Compendium of Materia Medica); and reduce the toxicity of Caowu (Aconiti kusnezoffii radix), Fuzi (Aconiti lateralis radix praeparata), and Chuanwu (Aconiti radix) (Variorum of the Classic of Materia Medica). There are some differences in the records of traditional usage of *ZJF* in different classical works associated with herbal medicine that need to be further verified in clinical practice. According to many ancient books, *ZJF* has considerable effects for tonifying and replenishing the middle Qi and nourishing the blood to calm. Furthermore, *ZJF* has been used for spleen deficiency, decreased appetite, loose stool, fatigue and lack of strength, blood deficiency and sallow complexion, women's hysteria, and restlessness of mind and will (Huang 2002). In the Chinese Pharmacopoeia (Pharmacopoeia Commission of PRC 2015), preparations containing *ZJF* are mainly used for tonifying and replenishing the middle Qi and nourishing the blood to tranquilize. In traditional use, *ZJF* is directly eaten or combined with other drugs to prepare decoction for oral use.

In addition, *ZJL*, *ZJC*, *ZJB* and *ZJR* are also widely used in Chinese folk traditional medicine. *ZJL* is characterized as having a sweet flavour and a warm

nature. It is mainly used for detoxifying and heat-clearing. It is effective for treating fevers in children, sores and furuncles, hot prickly heat, athlete's foot, and burns and scalds (using a decoction with water for oral administration or douching). *ZJC* is characterized as being bitter in flavour with a flat nature and is useful for liver and kidney meridian distributions in TCM; it has also been described as useful in treatment for detoxifying and promoting wound healing. Additionally, it is suitable for the treatment of chancre sores and ulcerative gingivitis; *ZJC* may be used for external application after grinding it into powder after carbonizing it through burning. *ZJB* is bitter with an acerbic flavour and a warm nature; it is effective for lung and large intestine meridian distributions. It is used for astringing the intestines and improving diarrhoea, suppressing cough and stopping bleeding, and it has been noted to be suitable for diarrhoea, dysentery, cough, flooding and spotting; 6–9 g of the ground powder is decocted with water for oral administration or 1.5–3 g of powder are taken with water. For uses such as bleeding due to traumatic injury and burns, appropriate amounts should be used externally use through decocting with water for douching or grinding it into powder and applying it directly. *ZJR* is sweet in flavour with a warm nature and is effective for liver, spleen, and kidney meridian distributions. It is used for regulating menstruation to stop bleeding, dispelling wind to relieve pain, and tonifying the spleen to improve diarrhoea. It is suitable for menstrual irregularities, infertility, flooding and spotting, haematemesis, stomach pain, impediment pain, spleen deficiency and diarrhoea (by decocting 10–30 g with water for oral administration), rubella, and erysipelas (for external use with an appropriate amount. or by decocting with water for douching) (Wang 2014). In sum, all parts of *ZJ* are useful (Fig. 2), and the literature related to any portion of *ZJ* needs to be further organized and studied to provide a basis for clinical use and for inclusion in the Chinese Pharmacopoeia.

Different parts of *ZJ* have different effects, which is directly related to the contents of their different chemical components; both *ZJF* and *ZJR* fortify the spleen, both *ZJL* and *ZJC* have detoxicating effects, and both *ZJB* and *ZJR* are effective at stopping bleeding, which may be related to some chemical composition shared between them (Table S1).

Botany

ZJ (syn. *Z. Mauritania*) is a common species in the genus *Ziziphus* of Dicotyledoneae of Angiospermae that belongs to the plant family Rhamnaceae (Rodríguez Villanueva and Rodríguez Villanueva 2017). There are approximately 170 species of genus

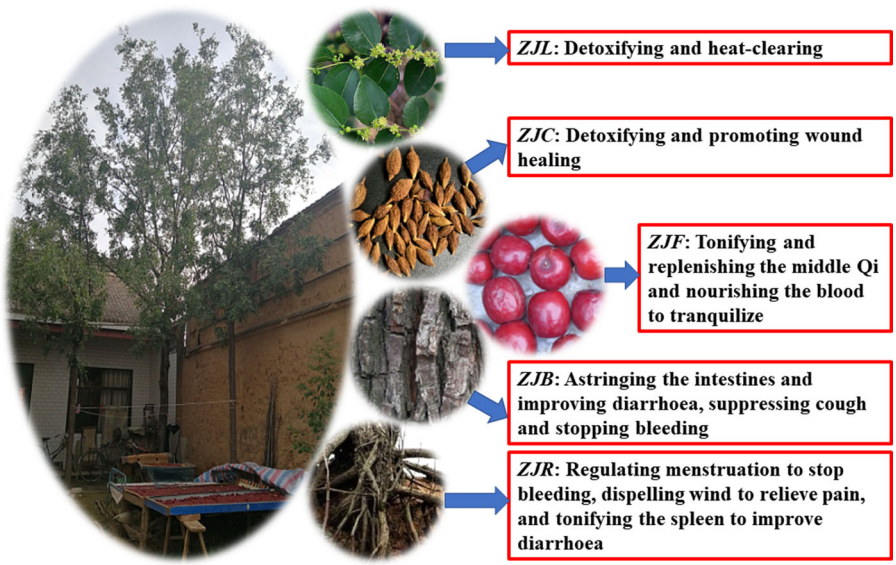


Fig. 2 Traditional uses of different parts of *ZJ*

Ziziphus in the world, and 12 species of genus *Ziziphus* are cultivated for their important economic and medicinal value (Li 2015). At present, there are more than 750 varieties of *ZJ* in China (Liu 2008).

Ziziphus jujuba Mill. (*ZJ*) is a deciduous tree native to China that grows approximately 10 metres high (Fig. 1). It has brown or grey-brown bark, and its branchlets can have 2 stipular spines; the spines are long, erect, and stout, whereas the short spines recurved. The stipular spines are slender and caducous. The petioles are glabrous or sparsely puberulent. The leaf blades are abaxially pale green, adaxially dark green, ovate, and papery. The flowers are yellow-green, bisexual, 5-merous, and glabrous with a 2–3 mm pedicel. The sepals are ovate-triangular, oblong or narrowly ovoid and are drupe red at maturity before turning red–purple; the petals are obovate, the disk is orbicular, and the seeds are compressed-orbicular (Editorial Board of Flora of China 2007).

ZJ grows on high mountains, hills, clear and dry slopes and plains and is also widely planted below 1700 m above sea level. *ZJF* is the fruit of *ZJ* (Fig. 1); it is collected when it matures in autumn, washed, and dried in the sun (Pharmacopoeia Commission of PRC 2015).

Phytochemistry

There are approximately 170 species of genus *Ziziphus* in the world. The main components of genus *Ziziphus* are triterpenoid acids, alkaloids, saponins, flavonoids and their glycosides (Che and Zhang 2011).

Triterpenoid acids, saponins, alkaloids, flavonoids and simple phenols are the dominant pharmacologically active compounds of *ZJ*. *ZJF* is also a good source of medium-chain fatty acids and β-carotene (Guil-Guerrero et al. 2004), and the chemical composition of *ZJF* varies between varieties, different cultivation areas and different water and fertilizer management (Jiao and Liu 2018).

According to the available literature, approximately 278 compounds have been isolated from *ZJ*, including 55 triterpenoid acids (**1–55**) (Fig. 3), 26 saponins (**56–81**) (Fig. 4), 37 alkaloids (**82–118**) (Fig. 5), 37 flavonoids (**119–155**) (Fig. 6), 11 sterols (**156–166**) (Fig. 7), 14 simple phenols (**167–180**) (Fig. 8), 10 glycosides (**181–190**) (Fig. 9), 9 nucleosides and nucleobases (**191–199**) (Fig. 10), 29 amino acids (**200–228**) (Fig. S1), 7 vitamins (**229–235**) (Fig. S2), 2 amides (**236–237**) (Fig. S3), 28 fatty acid derivatives (**238–265**) (Fig. S4), 5 saccharides (**266–270**) (Fig. S5), and 8 other compounds (**271–278**) (Fig. S6). While there have been no components isolated from *ZJ* flowers, 69 components (**23**, **25**, **28**, **56–81**, **119–121**, **124–126**, **128**, **133**, **144**, **148**, **151**, **153**, **156–157**, **160–165**, **167**, **169**, **173**, **179**, **189**, **240–243**, **245**, **251–255**, **260–261**, and **277–278**) were isolated from *ZJL*, 73 constituents (**1**, **7**, **134**, **137–143**, **145–147**, **149**, **156–157**, **160–161**, **163–174**, **186–188**, **200–210**, **212–221**, **223–225**, **227**, **240–245**, **250**, **252–254**, and **262–266**) were isolated from *ZJS*, and 42 components (**1**, **2**, **4**, **11–16**, **25–27**, **29–49**, **83**, **90**, **92** and **96–101**) were isolated from *ZJR*. Moreover, 30 components were isolated from *ZJB*, including 8 (**1**, **8**, **23**, **25**, **27**, **105, 108**, and **118**) from the root bark and 22 (**83–91**, **93–95**, **102–107**, **109–111**, and **155**) from the stem bark. Furthermore, 150 components (**1–6**, **9–10**, **17–28**, **50–55**, **65**, **82**, **112–117**, **119**, **121–127**, **129–132**, **135–136**, **148**, **150–152**, **154**, **156–159**, **167–185**, **190–249**, **255–259**, **267–274**, and **276**) were isolated from *ZJF*. Confusingly, there are multiple terms used for the alkaloids isolated. For example, Daechuine-S1 (**104**) is also called Frangufoline, Daechuine-S2 (**105**) is also known as Frangulanine, and Daechuine-S4 (**106**) is also named Franganine, and so on. The corresponding names, pharmaceutical effects, parts of the plant, quantity (total), and place of origin of the compounds from *ZJ* are systematically listed in Table S1. The Table S1 also includes data concerning the source of the respective compounds, their concentrations, etc. The contents of polysaccharides, flavonoids and nucleotides in *ZJF* could be affected by its drying process and maturity (Chen et al. 2013). In addition, the amount of bioactive substances and antioxidant capacities vary among different *ZJ* cultivars (Kou et al. 2015). The contents of the chemical components (fatty acids, phenols, α-tocopherols and β-carotene composition) also differed between different parts (fruit and leaves) of *ZJ* (San and Yildirim 2010).

Fig. 3 The triterpenoid acids isolated from *ZJ*

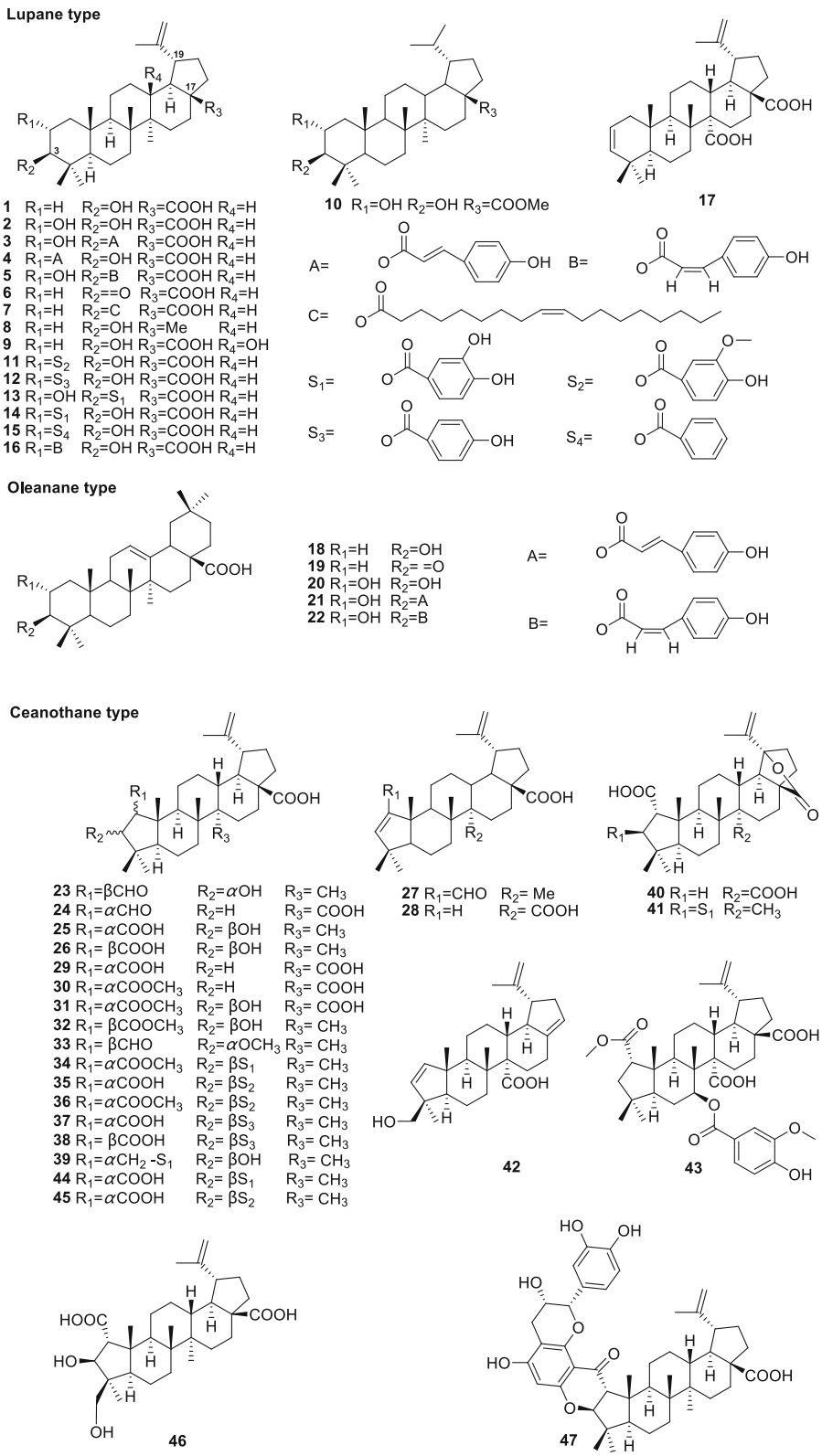
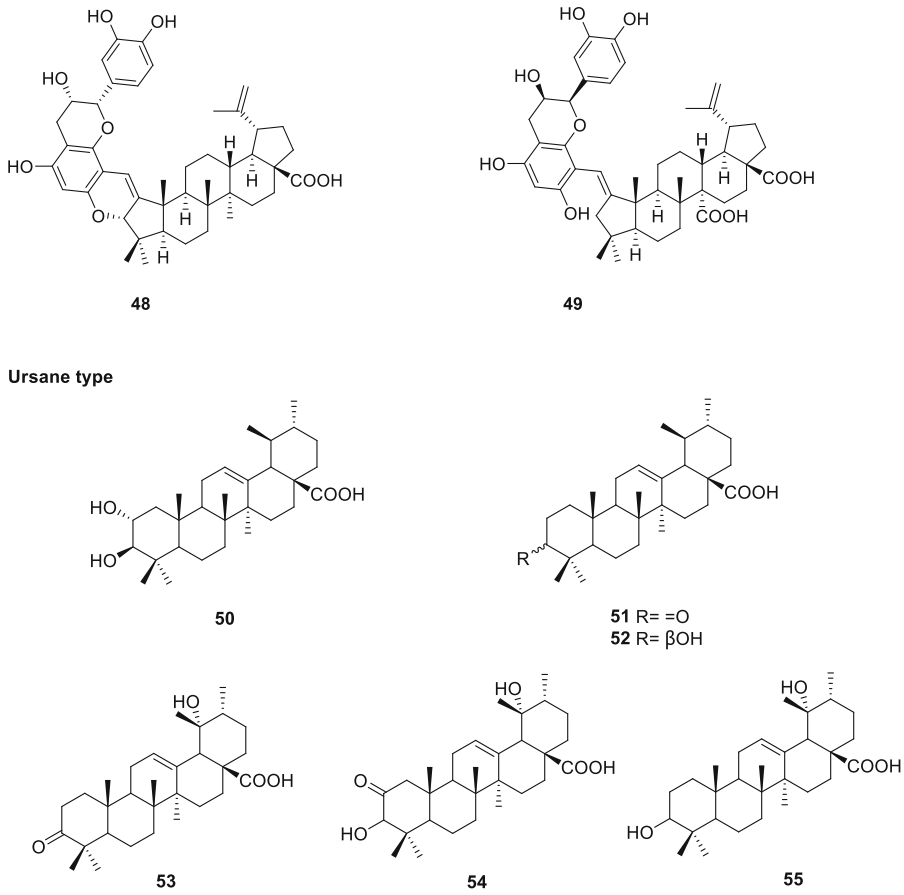


Fig. 3 continued



Triterpenoid acids

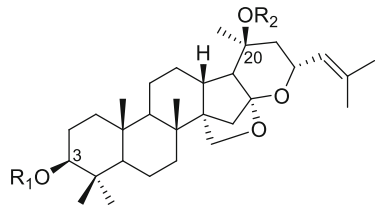
Fifty-five triterpenoid acids (**1**–**55**) (Fig. 3) were isolated and identified from *ZJ* (Yagi et al. 1978a, b; Kundu et al. 1989; Bai et al. 1992; Su et al. 2002; Lee et al. 2003, 2004; Mishra et al. 2007; Niu 2008; Guo 2009; Guo et al. 2009b, c; Fujiwara et al. 2011; Guo et al. 2011a, b; Bai et al. 2016; Kang et al. 2016, 2017; Masullo et al. 2019), some of which were reported to exhibit anticancer and anti-HIV properties. The mechanisms of action of the triterpenoids against cancer (Qiao et al. 2014) and HIV are worthy of further investigation. To date, 17 lupane-type triterpenoid acids (**1**–**17**), 5 oleanane-type triterpenoid acids (**18**–**22**), 27 ceanothane-type triterpenoid acids (**23**–**49**) and 6 ursane-type triterpenoid acids (**50**–**55**) have been isolated. These triterpenoid acids are pentacyclic triterpenoids, and among the triterpenoid acids, compounds **1**–**6**, **9**–**10**, **17**–**28**, and **50**–**55** were isolated from *ZJF*; compounds **1**, **2**, **4**, **11**–**16**, **25**–**27**, and **29**–**49** were isolated from *ZJR*; compounds **1**, **8**, **23**, **25**, and **27** were isolated from *ZJ* root bark; and compounds **1**, **7**, **23**, **25**, and **28** were isolated from the *ZJ* leaves and seeds.

Triterpenoid acids are one of the most important components of *ZJ* and are expected to be the main active compounds responsible for the pharmacologic activity of *ZJ* activities in its various applications. The triterpenoids oleanolic acid and betulinic acid are the main active ingredients in *ZJF*, and they have therefore been selected as markers for evaluating the quality of *ZJF* and its related preparations (Pharmacopoeia Commission of PRC 2015).

Saponins

Twenty-six saponins (**56**–**81**) (Fig. 4) were isolated from fresh *ZJL* (Yoshikawa et al. 1991, 1992) and dry *ZJ* leaves (Masullo et al. 2019), and jujuboside B (**65**) was also isolated from *ZJF* (Niu 2008). These

Fig. 4 The saponins isolated from *ZJ*



56 R_1= —ara(2→)rha R_2= —rha

57 R_1= —ara(2→)rha R_2= —rha(2→)Ac

58 R_1= —ara(2→)rha R_2= —rha(3→)Ac

62 R_1= —ara(3→)glc, ara(2→)6-deoxy-talose R_2=H

63 R_1= —ara(3→)glc, ara(2→)rha R_2=H

64 R_1= —ara(3→)glc(2→)xyl, ara(2→)6-deoxy-talose R_2=H

65 R_1= —ara(3→)glc(2→)xyl, ara(2→)rha R_2=H

66 R_1= —ara(4→)rha R_2= —rha(2→)Ac, rha(3→)Ac

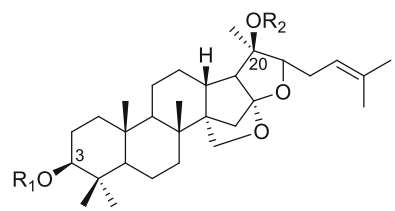
67 R_1= —ara(2→)rha, ara(3→)glc(2→)glc, glc(6→)glc R_2=H

68 R_1= —ara(2→)fuc, fuc(3→)glc(2→)xyl, glc(6→)glc R_2=H

69 R_1= —ara(2→)fuc, fuc(3→)glc(2→)xyl R_2=H

70 R_1= —ara(2→)rha, rha(3→)glc R_2=H

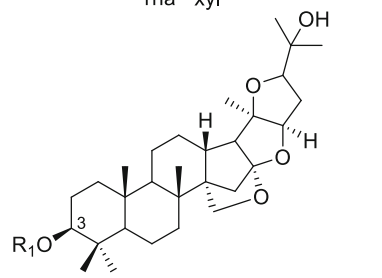
71 R_1= —ara(2→)glc, glc(3→)rha R_2=H



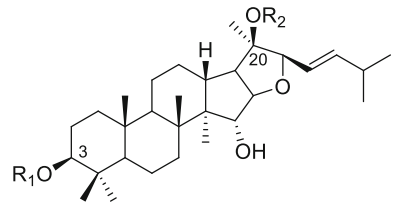
59 R_1= —gal(3→)glc, gal(2→)rha R_2= H

60 R_1= —glc(3→)glc, glc(2→)rha R_2= H

72 R_1= —xyl(3→)glc, glc(2→)rha, glc(2→)xyl R_2= H



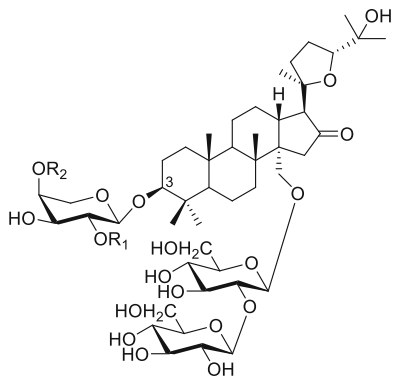
61 R_1= —gal(2→)rha



73 R_1= —gal(3→)glc, gal(2→)rha R_2= H

74 R_1= —glc(3→)glc, glc(2→)rha R_2= H

75 R_1= —glc(2→)rha, rha(4→)rha R_2= H



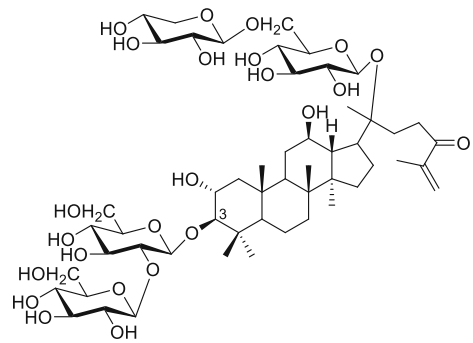
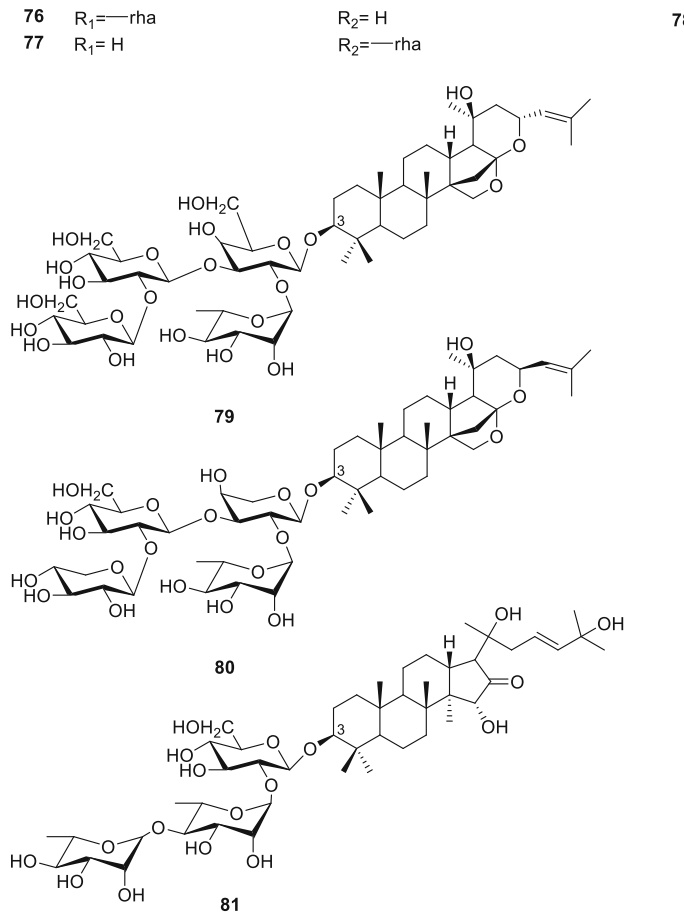


Fig. 4 continued



saponins are mainly dammarane type triterpene saponins, and their mother structures can generally be divided into three main types, all of which include a glycosyl unit linked to C-3 and C-20. These glycosyl units are mainly D-glucose, D-galactose, L-6-deoxy-talose, L-rhamnose, L-arabinose, D-xylose and acetyl rhamnose (Guo 2009). Compounds **56–66** showed sweet-reducing activities (Yoshikawa et al. 1991, 1992) and can be used as raw materials for sweetness inhibitor products (Liu et al. 2015).

Alkaloids

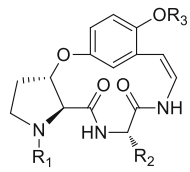
Thirty-seven alkaloids (**82–118**) (Fig. 5) have isolated from *ZJ* (Otsuka et al. 1974; Tschesche et al. 1976; Han et al. 1987, 1989; Khokhar et al. 1994; Tripathi et al. 2001; Kang et al. 2015; Bai et al. 2016), mostly composed of cyclopeptides and aporphine alkaloids and mainly distributed in the root and stem bark. Since the 1980s, thirteen- and fourteen-membered ring type cyclopeptide alkaloid skeletons have been found in *ZJ*. Alkaloids (**82–118**) can also be used as chemical taxonomic representatives and markers for the genus *Ziziphus* (Che and Zhang 2011).

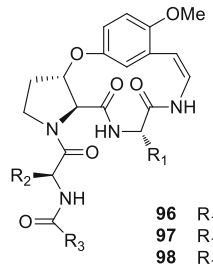
Flavonoids

To date, 37 flavonoids (**119–155**) (Fig. 6) have been isolated and identified from *ZJ*. Twelve of these flavonols (**119**, **121–127**, and **129–132**) have been isolated from *ZJ* fruit (Niu 2008; Guo 2009; Guo et al. 2009c; Pawlowska et al. 2009; Wang et al. 2010; Choi et al. 2011, 2012; Gao et al. 2012a, b; Bai et al. 2016; Elaloui et al. 2016; Cui et al. 2017; Pu et al. 2018), while 9 flavonols (**119–121**, **124–126**, **128**, and **132–133**) are present in *ZJL* (Cui et al. 2017; Masullo et al. 2019) and one (**117**) is present in *ZJS* (Alam et al. 2017). Two flavanones (**135–136**) were first isolated from *ZJF* in 1981 (Okamura et al. 1981). Eleven flavones (**137–143**, **145–147**, and **149**) have

Fig. 5 The alkaloids isolated from *ZJ*

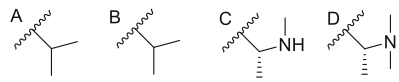
Cyclopetides alkaloids

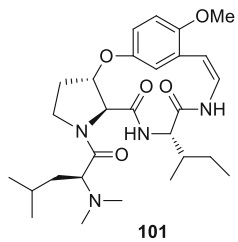




82 R_1=N(Me)$_2$Phe- R_2=C_3H_6(Me)- R_3=H
83 R_1=N(Me)$_2$Il1e-Il1e- R_2=C_3H_6(Me)- R_3=Me
84 R_1=N(Me)$_2$Phe- R_2=C_3H_6(Me)- R_3=Me
85 R_1=N(Me)$_2$Leu- R_2=$(CH_3)_2CHCH_2$- R_3=Me
86 R_1=N(Me)$_2$Leu-Leu- R_2=$(CH_3)_2CHCH_2$- R_3=Me
87 R_1=N(Me)$_2$Phe-Leu- R_2=C_3H_6(Me)- R_3=Me
88 R_1=N(Me)$_2$Thr- R_2=C_3H_6(Me)- R_3=Me
89 R_1=N(Me)$_2$Phe- R_2=C_3H_6(Me)- R_3=H
90 R_1=NHMeA1a-Va1- R_2=Benzyl- R_3=Me
91 R_1=NHMePhe-Leu- R_2=C_3H_6(Me)- R_3=Me
92 R_1=N(Me)$_2$Phe-Pro- R_2=C_3H_6(Me)- R_3=Me
93 R_1=N(Me)$_2$Phe-Phe- R_2=C_3H_6(Me)- R_3=Me
94 R_1=N(Me)$_2$Phe-Phe- R_2=Benzyl- R_3=Me
95 R_1=N(Me)$_2$A1a-Va1- R_2=Benzyl- R_3=Me

96 R_1=A R_1=A R_1=C
97 R_1=A R_1=B R_1=C
98 R_1=B R_1=B R_1=C
99 R_1=B R_1=A R_1=D
100 R_1=B R_1=B R_1=D





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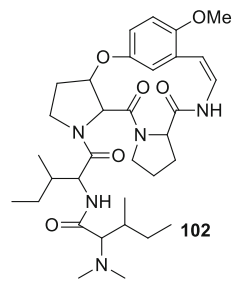

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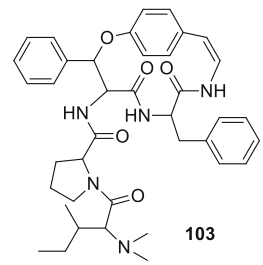

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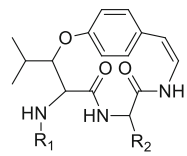
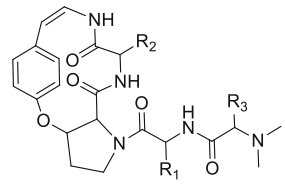
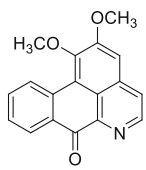


104 R_1=N(Me)$_2$Phe- R_2=$(CH_3)_2CHCH_2$-
105 R_1=N(Me)$_2$Il1e- R_2=$(CH_3)_2CHCH_2$ -
106 R_1=N(Me)$_2$Leu- R_2=$(CH_3)_2CHCH_2$-
107 R_1=N(Me)$_2$Va1- R_2=$(CH_3)_2CHCH_2$ -
108 R_1=N(Me)$_2$Leu- R_2=C_3H_6(Me) -
109 R_1=N(Me)$_2$Il1e- R_2=Benzyl-

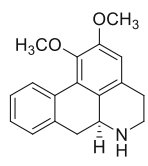


110 R_1=$CH(CH_3)_2$ R_2=$CH_2C_6H_5$ R_3=CH_3
111 R_1=$CH(CH_3)_2$ R_2=$CH_2C_6H_5$ R_3=$CH(CH_3)C_2H_5$

Aporphine alkaloids



112



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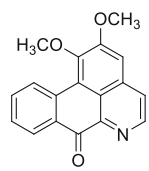

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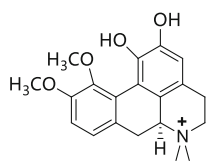

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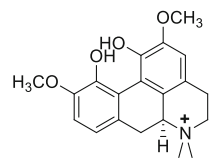
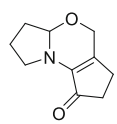


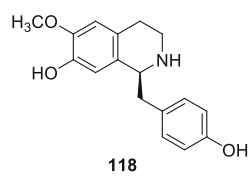
116

Pyrrolidine alkaloid



117

Tetrahydroisoquinoline alkaloid



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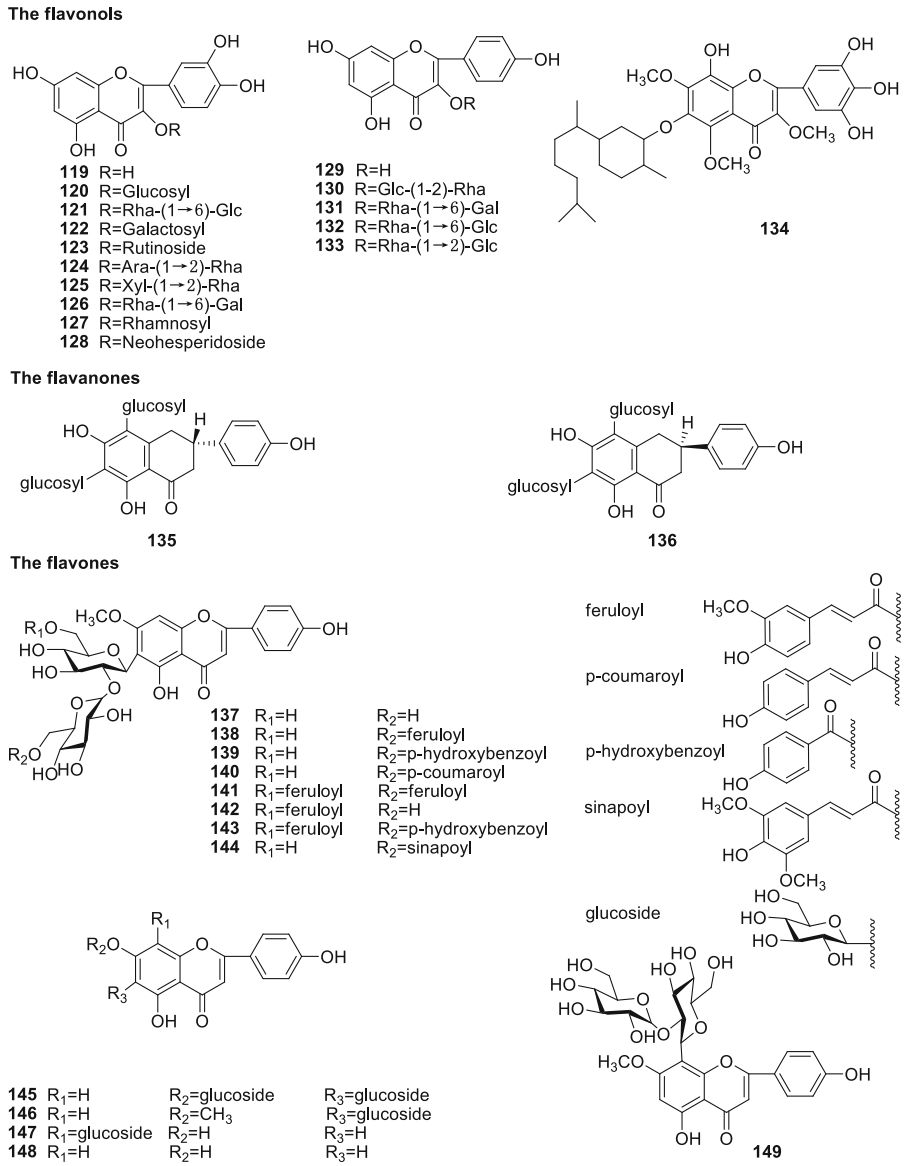


Fig. 6 The flavonoids isolated from *ZJ*

been isolated from *ZJS* (Fu et al. 2016; Choi et al. 2011) and 2 flavones (**144** and **148**) have been found in *ZJL* and *ZJF* (Elaloui et al. 2016; Masullo et al. 2019). Four flavan-3-ols (**150**–**152** and **154**) have been isolated from *ZJF* (Choi et al. 2011, 2012; Gao et al. 2012a, b; Pu et al. 2018), and 3 flavan-3-ols (**151**, **153** and **155**) are present in *ZJL* (Cui et al. 2017) and *ZJB* (Malik et al. 2002). Cheng et al. reported the presence of sedating flavonoids such as spinosin (**137**) and swertish (**146**) (Cheng et al. 2000). Flavonoids can be isolated from most natural plants and therefore cannot be used as chemical markers for the genus *Ziziphus*.

Sterols

Eleven sterols (**156**–**166**) (Fig. 7) have been reported in *ZJ*. Two compounds (**156**–**157**) were isolated from *ZJ* fruit, leaves and seeds (Guo 2009; Guo et al. 2009c; Aloui et al. 2012; Liu et al. 2015; Elaloui et al.

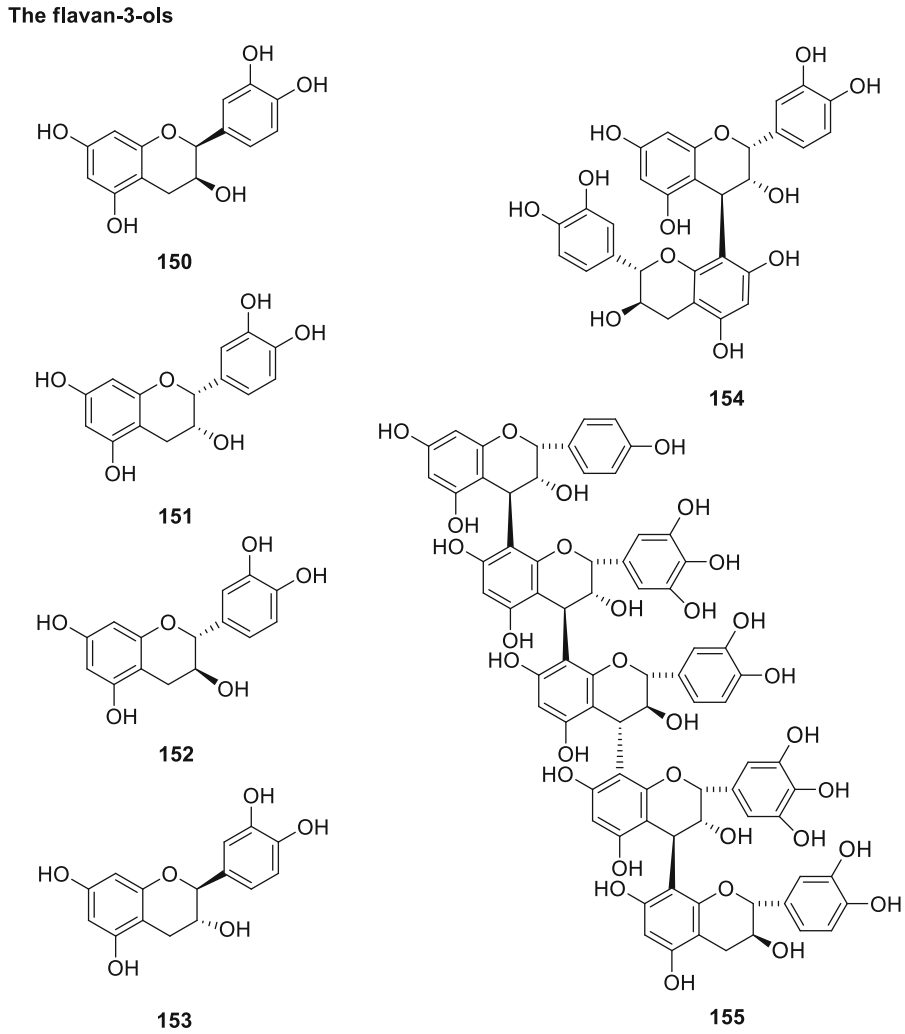


Fig. 6 continued

2016). β-daucosterol (**158**) and 3β, 6β-stigmast-4-en-3,6-diol (**159**) were isolated from *ZJF* in 2008 and 2009 (Niu 2008; Guo 2009; Guo et al. 2009c). Five compounds (**160–161** and **163–165**) have been isolated from *ZJL* and *ZJS* (Aloui et al. 2012; Elaloui et al. 2016), while stigmastanol (**162**) and cholesterol (**166**) were only isolated from *ZJL* (Elaloui et al. 2016) and *ZJS* (Aloui et al. 2012), respectively.

Simple phenols

Fourteen simple phenols (**167–180**) (Fig. 8) have been isolated from *ZJ* and identified (Niu 2008; Wang et al. 2010; Zhang, et al. 2010; Wang et al. 2011; Gao et al. 2012a, b; Bai et al. 2016; Cui et al. 2017; Pu, et al. 2018), including 5 hydroxycinnamic acids (**167–171**), 6 benzoic acids (**172–177**), 2 benzaldehydes (**178–179**) and 1 trihydroxybenzene (**180**). Among the simple phenols, compounds **167–180** were isolated from *ZJ* fruit, compounds **167–174** were isolated from *ZJ* seeds, and compounds **167**, **169**, **173**, and **179** were isolated from *ZJ* leaves.

ZJF's antioxidant capacity is closely related the concentration of efficient oxygen- free radical scavengers, such as vitamin C and phenolic compounds (Jiao and Liu 2018), which vary by the variety of *ZJF* and the source of the fresh *ZJF*. Vitamin C content is generally higher than 200 mg/100 g FW, with most

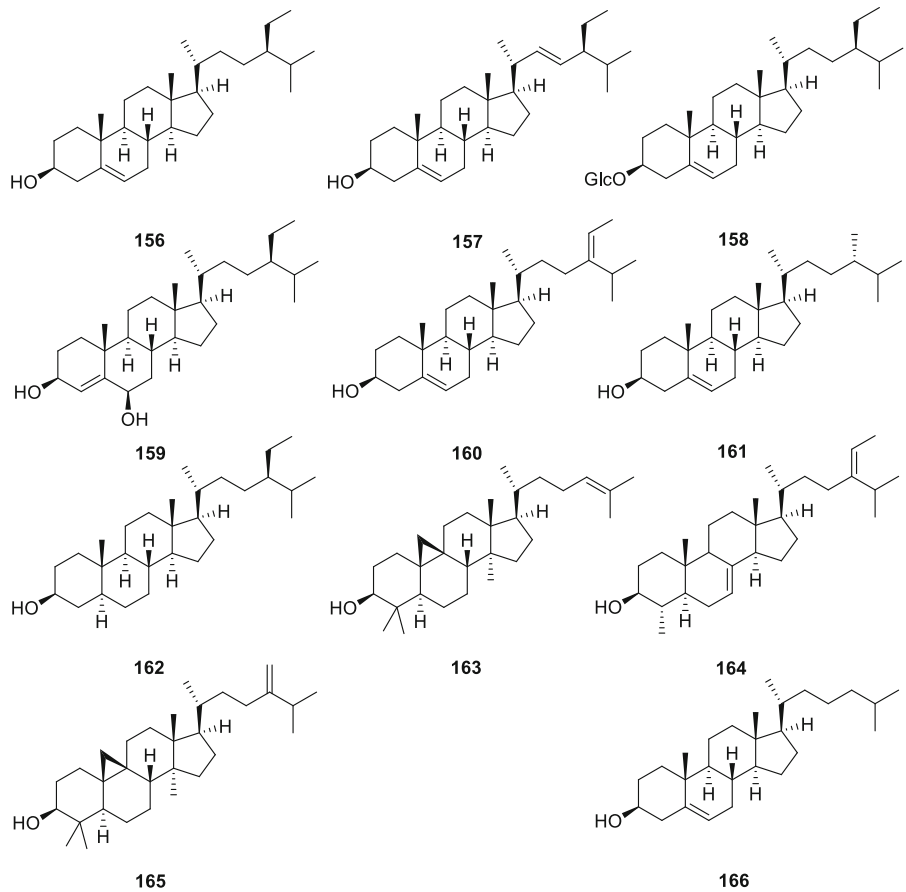


Fig. 7 The sterols isolated from *ZJ*

samples containing between 300 and 500 mg/100 g FW; the highest level of vitamin C found has been 600 mg/100 g FW. The total phenol content ranges between 0.558 and 2.520 mg GAE/g FW, and while these compounds provide the material basis for the antioxidant effects of *ZJF*, both vitamin C and phenol concentrations are decreased after *ZJF* is dried (Jiao and Liu 2018).

Glycosides

Ten glycosides (**181–190**) (Fig. 9) were separated and identified from *ZJ* (Okamura et al. 1981; Niu 2008; Alam et al. 2017; Cui et al. 2017; Pu et al. 2018), including 6 compounds (**181–185** and **190**) isolated from *ZJ* fruit, 3 compounds (**186–188**) isolated from *ZJ* seeds, and compound **189**, which was isolated from *ZJ* leaves.

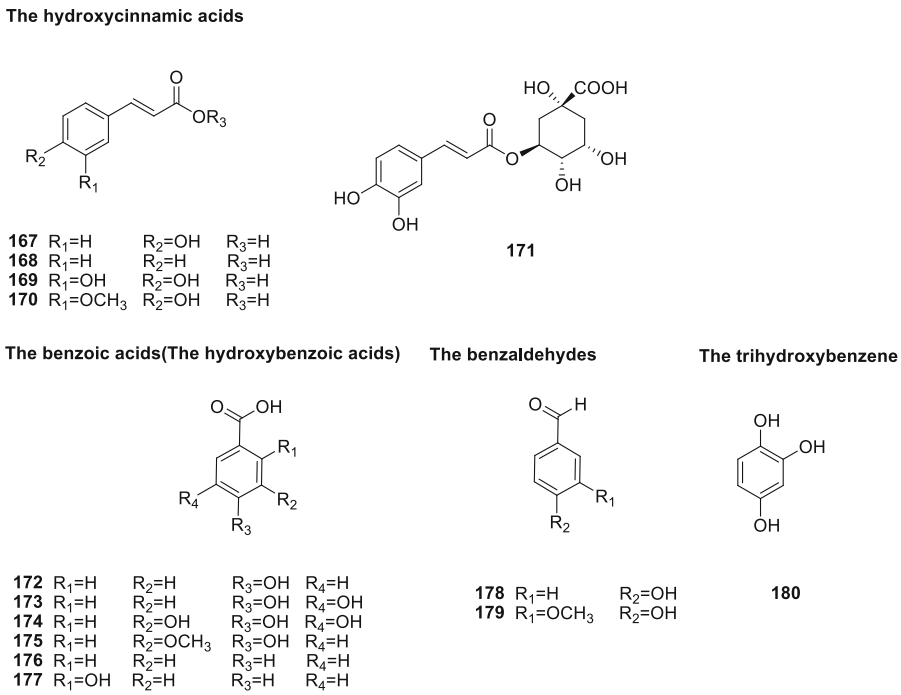
Nucleosides and nucleobases

Nine nucleosides and nucleobases (**191–199**) (Fig. 10) were isolated and identified from *ZJ* (Guo et al. 2010b), all of which were from the *ZJ* fruit. The cAMP contents were much higher in the mature flesh of *ZJ* (38.05 nmol/g fw) than in the other tested materials from 14 types of horticultural plants and was the highest among the higher plant fruits. The highest cAMP content found in the test was 302.50 nmol/g fw. from Muzao of Shanxi, which was also the highest among the higher plants (Liu and Wang 1991).

Amino acids

Twenty-nine amino acids (**200–228**) (Fig. S1) were isolated and identified from *ZJ* (Choi et al. 2011, 2012; Pu et al. 2018). All of the compounds were found in the *ZJ* fruit, and 25 compounds (**200–210**, **212–221**, **223–225** and **227**) were isolated from

Fig. 8 The simple phenols isolated from *ZJ*



ZJ seeds. These amino acids include eight amino acids that are essential for the human body, including arginine and histidine, which cannot be synthesized by children.

Vitamins

All of the compounds (**229**–**235**) (Fig. S2) were isolated from *ZJ* fruit (Gao et al. 2012a, b; Liu et al. 2015). *ZJF* is known as a "natural vitamin pill" and is rich in vitamins A, B, and C. For example, concentrations of vitamin C in fresh jujube fruit are up to 400–600 mg/100 g (Jiao and Liu 2018), which is 70–80 times that of an apple (Liu et al. 2015).

Amides

Two compounds (**236**–**237**) (Fig. S3) were isolated from *ZJ* fruit (Guo 2009; Guo et al. 2009c).

Fatty acid derivatives

Twenty-eight fatty acid derivatives (**238**–**265**) (Fig. S4) were isolated and identified from *ZJ* (Bai et al. 1992; Su et al. 2002; Guo 2009; Guo et al. 2009c, 2011a; Aloui et al. 2012; Liu et al. 2015; Bai et al. 2016; Elaloui et al. 2016; Cui et al. 2017), including 17 compounds (**238**–**249** and **255**–**259**) that were separated from *ZJ* fruit, 14 compounds (**240**–**245**, **250**, **252**–**254**, and **262**–**265**) isolated from *ZJ* seeds, and 12 compounds (**240**–**243**, **245**, **251**–**255**, **260**–**261**) isolated from *ZJ* leaves.

Saccharides

Five compounds (**266**–**270**) (Fig. S5) were isolated from *ZJ* (Guo 2009; Guo et al. 2009c; Gao et al. 2012a, b; Alam et al. 2017; Pu et al. 2018), including 1 compound (**266**) that was isolated from *ZJ* seeds and 4 compounds (**267**–**270**) isolated from *ZJ* fruit.

Others

Eight other compounds (**271**–**278**) (Fig. S6) were also isolated and identified (Okamura et al. 1981; Fukuyama et al. 1986; Heo et al. 2003; Niu 2008; Guo 2009; Guo et al. 2009b; Gao et al. 2012b; Elaloui et al. 2016; Pu et al. 2018; Masullo et al. 2019).

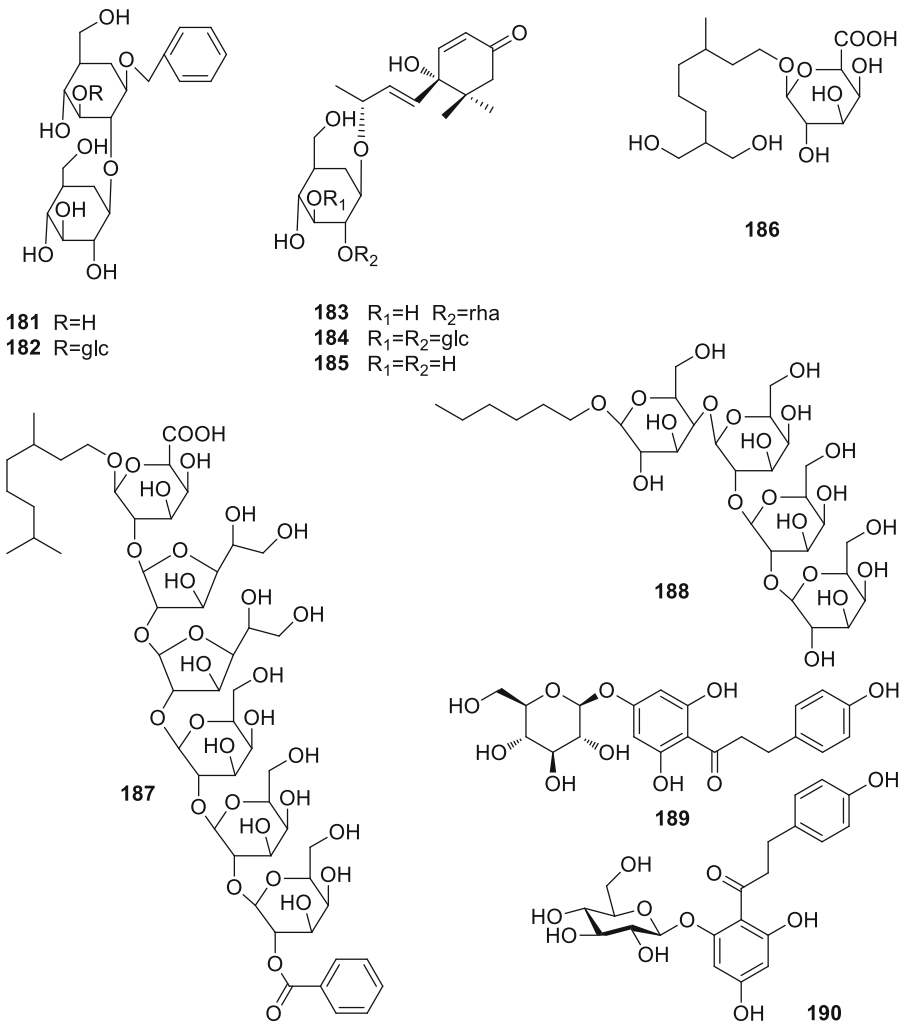


Fig. 9 The glycosides isolated from *ZJ*

Pharmacological effects

The biological activities of *ZJ* and its components have long been studied in vitro and using animal models (in vivo) (Huang et al. 2007; Vahedi et al. 2008; Li et al. 2011c; Gao et al. 2013; Ding et al. 2016; Rodríguez Villanueva and Rodríguez Villanueva 2017), but there is no evidence from human interventional and epidemiological studies. In these two respects, more research should be performed. Multiple pharmacological effects have been associated with *ZJ* and compounds isolated from *ZJ* in animals and cells, as described below.

Anti-inflammatory activity

The control of inflammation is very important to improving health and vitality, as inflammation can aggravate arthritis, diabetes, etc. (Ignat et al. 2011).

ZJF potentially plays a protective role by attenuating NOS activity in anti-acute and chronic inflammation in Wistar albino rats. In one study, one of three doses (100, 200 and 400 mg/kg) of 60% ethanol extract of *ZJF* or indomethacin (10 mg/kg) were administered orally one hour before an injection of carrageenan (Goyal et al. 2011). Pretreatment with *ZJF* extract showed marked dose-dependent attenuation in oedema compared to control in the acute study, and *ZJF* extract significantly decreased granuloma tissue formation compared to control in the

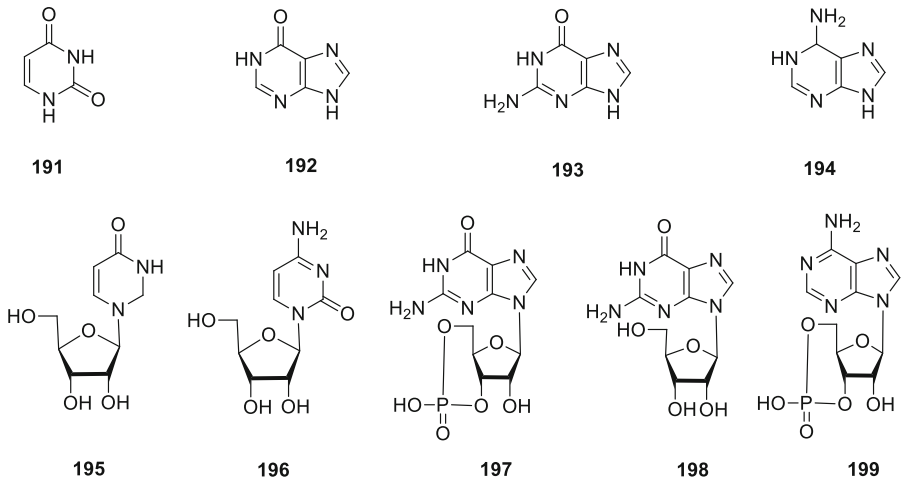


Fig. 10 The nucleosides and nucleobases isolated from *ZJ*

chronic study. This study therefore provides the ethnopharmacological basis for the use of *ZJF* as an anti-inflammatory agent.

In *Shizao Tang* (*Euphorbia kansui*, *Euphorbia fischeriana*, *Daphne genkwa*, ***ZJF***) from *Shanghanlun* (*Treatise on Cold Damage Diseases*), *ZJF* is used in traditional Chinese formulas as an antidote to relieve the drastic inflammatory response due to *Euphorbia* species. Yu et al. determined that the triterpene acid fraction was the most active part of *ZJF* through the inhibition of inflammatory cells activated by *Euphorbia kansui* and a phorbol ester (prostratin) isolated from *Euphorbia fischeriana* (Yu et al. 2012). The triterpene acid fraction of *ZJF* might be helpful in attenuating the irritant action of *Euphorbiaceae* plants and protecting the gastrointestinal tissue from potent inflammatory injury, further confirming the rationality of the medicines (*Euphorbia kansui*, *Euphorbia fischeriana*, *Daphne genkwa*, ***ZJF***) of *Shizao Tang*.

Table 1 Inhibitory effects of compounds **137–138, 140–143, 149** against COX-1 and COX-2

Compound	Inhibition rate (%), 50 μM	
	COX-1	COX-2
137	18.2	21.3
138	42.1	37.2
140	24.9	21.7
141	38.4	39.1
142	32.6	38.4
143	28.2	33.7
149	18.7	19.2

SC560 and NS398 were used as positive control for COX-1 (IC_{50} 0.02 μM) and COX-2 (IC_{50} 0.22 μM), respectively

The presence of a ketone at the C-3 of oleanonic acid (**19**) implies an increase in inhibition of in vivo inflammatory processes and models related to 5-lipoxygenase activity. Oleanonic acid (**19**), with an IC_{50} of 17 μM, reduced leukotriene B4 production from rat peritoneal leukocytes and was more active against in vitro leukotriene formation and dermatitis due to TPA (Giner-Larza et al. 2001). Its efficacy and effectiveness in inflammatory cells, however, requires further study.

Maslinic acid (**20**) (purity: 94.7%) was orally administered to CAIA mice daily at a dose of 200 mg/kg of body weight for 11 days starting on day 1, and the daily intake of maslinic acid for 12 weeks prevented and alleviated arthritis. The preventive effects of **20** on arthritis are attributed to the promotion of tissue formation and inhibition of synovium inflammation through toll-like receptor signal inactivation and downregulation of leukotrienes by the glucocorticoid receptor (Shimazu et al. 2018). Further studies, such as the use of localized cells for time-course analyses, will provide more detailed insights into the indirect and direct antiarthritis effects of **20**.

Compounds **137–138**, **140–143**, and **149** showed moderate inhibitory activities against COX-1 and COX-2 enzymes (Table 1). SC560 and NS398 were used as positive controls for COX-1 (IC_{50} 0.02 μM) and COX-2 (IC_{50} 0.22 μM), although no COX-2

selectivity was evident for any of the active compounds (Fu et al. 2016).

Antioxidant activity

Ko et al. reported full and detailed descriptions of 70 antioxidant Korean medicinal plants using three oxidation reactions [luminol/Fenton reagent, 2,7-dichlorodihydro- fluorescein (DCHF)/Fenton reagent and DCHF/peroxynitrite] (Ko et al. 2008) and confirmed the in vitro antioxidant activity of *ZJF*. The antioxidant activity of *ZJF* was lower compared to other plants, and while this study is not suitable to evaluate the antioxidant activity of *ZJF* through pure redox-chemical experiments, it can serve as a reference.

Scientists have found that the antioxidant ability (scavenging effect on the DPPH radical) of *ZJF* was related to the variety of *ZJF* (Li et al. 2005). It was also found that the peel from all the varieties had the highest antioxidant capacity using the DPPH and FRAP assays, which was reflected by the high total concentrations of phenols (protocatechuic, caffeic, chlorogenic and gallic acids), flavonoids, and anthocyanins in their peels (Zhang et al. 2010). The free, esterified, glycosylated, and insoluble binding forms of 8 phenolic acids found in the peel, pulp, and seed of *ZJF* were studied using HPLC-ECD. The glycoside and insoluble-binding phenolic acid fractions in the *ZJF* pulp displayed the highest total phenolic contents and the strongest antioxidant effects determined by DPPH and FRAP assays (Wang et al. 2011).

Traumatic acid (**255**) shows stimulatory and antioxidant effects on collagen biosynthesis and can be used to treat many skin diseases associated with oxidative stress and collagen biosynthesis disorders (Jabłońska-Trypuć et al. 2016), which corresponds with the traditional use of *ZJF* for maintaining beauty and youth and confirming the Chinese proverb, "three jujubes a day, youth never grows old" due to the link between antioxidation and anti-aging (Sohal and Orr 2012; Koltover 2017). However, the molecular mechanisms of the collagen content changes in the cells remains unclear and requires further study.

ZJF and *ZJF* extract are potential sources of natural antioxidants in the food industry, though the basic metabolic functions of ROS should be investigated. In fact, removal of excess ROS can disrupt cellular signalling pathways and increase the risk for chronic diseases (Finley et al. 2011), highlighting the need for further scientific research.

One neutral polysaccharide fraction and three acidic polysaccharide fractions were separated from a hot water extraction of *ZJF* by Chang et al., and the average molecular weight of the fractions ranged from 40,566 to 129,518 Da. Four polysaccharide fractions (12.33–19.30 μM) were found to be more effective in scavenging superoxide anions than hydroxyl radicals, while the chelating effect of acidic polysaccharides on ferrous ion was more pronounced. Data on the antioxidant activity of different polysaccharide fractions from *ZJF* are significantly different at $P < 0.05$ (Chang et al. 2010).

Antioxidant effects of solvent extracts from the pulp, leaf, and seed of *ZJ* via sonication were investigated by Kim and Son. For ABTS radical scavenging activity analysis at a concentration of 1 mg/mL, 70% ethanol *ZJS* (94.76 ± 0.23%) and 80% methanol *ZJL* (95.46 ± 0.14%) extracts were observed to have higher activity than the controls, such as vitamin C (89.27 ± 0.12%), vitamin E (88.53 ± 0.12%), BHA (89.60 ± 0.00%), and BHT (84.07 ± 0.50%). Pulp and *ZJS* extracts at concentrations of 0.1–1 mg/mL showed SOD-like activity of 24.46–34.84%, and the 80% methanol *ZJL* extract demonstrated the highest activity (43.66 ± 0.37%) among the samples. The results showed that *ZJ* pulp and *ZJS* have excellent antioxidants activity, and the antioxidant effects of *ZJL* were found to be even higher than those of vitamins E and C (Kim and Son 2011), which provides a basis for the development of *ZJL*-related products.

However, it is important to note that pure redox-chemistry studies have no pharmacological relevance (Gafner 2018). In animal or human studies, there is little evidence that antioxidant activity observed in vitro has an impact on health. Pure redox-chemistry tests that prove the in vitro antioxidant effects of compounds isolated from *ZJ* and the different medicinal uses of *ZJ* are insufficient, but they can be used as a pre-test to provide some references or directions for further study of the antioxidant activity of *ZJ*.

Antimicrobial activity

ZJR ethanol extracts (1 and 2 mg/mL) had obvious inhibitory effects on fungi, including *Candida*

tropicalis, C. albicans, *Malassezia furfur* (strains 1374 and 1765), *Aspergillus niger*, and *A. flavus* when compared with nystatin as the standard. (Sarfaraz et al. 2002). It is not clear, however, which components of *ZJR* play an antimicrobial role. Additionally, *ZJRB* extracts demonstrated antibacterial effects against 20 different bacteria (Elmahi et al. 1997). Ceanothic acid (**25**) showed growth inhibitory activities against *Streptococcus mutans, Prevotella intermedia, Porphyromonas gingivalis* and *Actinomyces viscosus*, with MICs of 513.68, 127.39, 127.39 and 86.30 μM, respectively (Li et al. 1997). However, the MIC values of the positive control sanguinarine were 45.13, 6.02, 6.02 and 45.13 μM, respectively. The efficacy of compound **25** is lower than that of positive drugs, and it has little potential to become a lead antimicrobial compound.

According to microdilution antifungal susceptibility testing, magnoflorine (**116**) demonstrated high growth inhibitory effects when tested with *Candida strains*, with a MIC of 146.02 μM. Cytotoxicity testing demonstrated that it has no toxicity to HaCaT cells, even at treatments doses of 584.08 μM. Therefore, **116** is a good candidate lead compound for new antifungal agents (Kim et al. 2018).

Gastrointestinal protective activity

In hamster models, *ZJF* extracts (771 g kg^{-1} of water-soluble carbohydrate concentrates at 5.0 and 15 g kg^{-1} of diet), including hemicellulose, pectin polysaccharide, glucose, and fructose were observed to be effective in maintaining intestinal health by reducing intestinal mucosal exposure to toxic ammonia and other harmful substances (Huang et al. 2008). *ZJ* polysaccharides have also been shown to improve intestinal oxidative damage induced by ischaemia–reperfusion in rabbits. *ZJ* polysaccharides [fructose (21.6%), glucose (23%), mannose (12.9%) and xylose (31.3%)] have antioxidant activities that may contribute to this observed activity (Wang 2011), which is consistent with the traditional usage of *ZJF* for the role of tonifying the spleen and stomach.

Maslinic acid (**20**) (21.16 and 211.55 μM, inhibits H^+ and K-ATPase activity) and ursolic acid (**52**) (218.98 μM, favours the gastric mucus barrier) demonstrate gastroprotective activity via different mechanisms of action (Da Rosa et al. 2017), which is consistent with the traditional Chinese medicine theory that *ZJF* can be used for gastric diseases. Maslinic acid (**20**) inhibits H^+, K^+-ATPase activity, whereas ursolic acid (**52**) affects the gastric mucus barrier. Maslinic acid (**20**) was absorbed with a peak plasmatic concentration at 30 min and oral bioavailability of 6.25% (Juan and Planas 2016). The bioavailability of ursolic acid (**52**) by oral administration is low since it is absorbed by the intestine through passive diffusion, although ursolic acid (**52**) dispersion preparations can increase the solubility and bioavailability (Zhang and Shen 2018). The components of *ZJF* involved in gastrointestinal protection are not limited to maslinic acid and ursolic acid, as other components may improve their bioavailability through solubilization or other mechanisms to allow them to deposit in their intact form to play an active role in vivo (Yin et al. 2012).

Cardiovascular activity

Betulinic acid (**1**) (at 10 μM) can upregulate endothelial NO synthase (eNOS) expression and downregulate NADPH oxidase expression in human endothelial cells, and thus has therapeutic potential in cardiovascular disease (Steinkamp-Fenske et al. 2007); betulinic acid (**1**) has also been shown to act as a TGR5 agonist (Genet et al. 2010; Lo et al. 2016).

NF-κB is an attractive target for cardiac hypertrophy. In abdominal aortic constriction rats, oleanonic acid (**19**) (15 or 45 mg/kg/day, oral gavage) markedly reduced left ventricular wall thickness and heart size in a dose-dependent manner. Further studies have shown that **19** can effectively improve cardiac hypertrophy by inhibiting the PKCζ-NF-κB signalling pathway (Gao et al. 2018). However, whether **19** inhibits the activation of the PKCζ-NF-κB pathway by reducing the activity of 5-lipoxygenase requires further study.

Beginning 1 day after surgery (sham surgery or aortic banding), all of the C57 mice were administered maslinic acid (**20**) (20 mg/kg) or vehicle orally for the following 4 weeks, and **20** was found to protect against pressure overload-induced cardiac fibrosis and cardiac hypertrophy. Further studies have shown that **20** can inhibit the activation of the ERK and AKT signalling pathways and reduce cardiomyocyte hypertrophy in vitro, making it a potential treatment option for cardiac hypertrophy (Liu et al. 2018e). However, the differences between the ERK

and AKT signalling pathways in cardiac myocyte function and survival require further elucidation.

The prevention of foam cell formation is considered one of the main mechanisms of preventing atherosclerosis. Triterpenoids such as oleanonic acid (**19**) and pomonic acid (**53**) from *ZJF*, which contain a carboxylic acid at C-28, play an important role in inhibiting foam cell formation in human macrophages. Therefore, triterpenoids may be useful for preventing atherosclerosis (Fujiwara et al. 2011).

Jujuboside B (**65**) (IC_{50}=92.1 μM) inhibited collagen (2 mg/mL)-induced platelet aggregation (aspirin as control, IC_{50}=130.5 μM). Furthermore, **65** (IC_{50}=201.5 μM) dose-dependently inhibited thrombin (0.4 U/mL)-induced platelet aggregation (aspirin as control, IC_{50}=1810.5 μM). Additionally, treatment with **65** (100 mg/kg) increased protection against acute thromboembolism in mice (~63% protection) (aspirin as control, 50 mg/kg) when **65** and aspirin were orally administered to mice. Effective inhibition of platelet aggregation has also been demonstrated by **65** both in vivo and in vitro, and **65** is therefore considered effective for the treatment and prevention of cardiovascular diseases connected to platelet hyperaggregation (Seo et al. 2012). Further research is needed to determine the appropriate systemic concentrations of **65** in order to minimize its side effects (extension of bleeding time) and maximize its protective effects (protection against thrombosis).

A neo-lignan (**278**) isolated from *ZJL* has been shown to increase the release of endogenous prostaglandin I_2 from the rat aorta by up to 25.3% at 7.76 μM (Fukuyama et al. 1986), and it too could be considered for use in the treatment of cardiovascular diseases (Zhang 2008a).

To study the enhancing effect of *ZJF* on haematopoietic function in cultured Hep3B human hepatocellular carcinoma cells, Chen et al. studied its effects on the expression of erythropoietin. Application of chemically standardized *ZJF* water extract (0.75–3.0 mg/mL) stimulated the expression of erythropoietin in a dose- dependent manner, with the highest response found to be an ~100% increase (Chen et al. 2014b). These results confirmed the haematopoietic function of *ZJF* in the regulation of the expression of erythropoietin in liver cells. In addition, a study by Cheng et al. showed that gavage with the bond phenols from jujube peel (*JPBP*) or the free phenols from jujube peel (*JPFP*) [(approximately 2 mL, equal to 300 mg/kg rat)/d] could reduce aluminium toxicity and prevent ISO-induced myocardial injury in rats (Cheng et al. 2012). While it would have been better if the phytochemical analyses of the chemically standardized *ZJF* water extract, *JPFP* and *JPBP* were evaluated in the above studies, the relationship between the structure of the active components and the pharmacological activities of *ZJF* have also not been investigated.

The research results discussed above are consistent with the effects of *ZJF* as having a sweet flavour and a warm nature, and the traditional use of *ZJF* for blood-nourishing and detoxification functions.

Neuroprotective effects

As for *ZJF* water extract, the treatment of 72 h at several different concentrations (0.75, 1.5, and 3.0 mg/mL) induced the expressions of NF200, NF160, and NF68, with the highest induction by 100, 150, and ~150%, respectively [GAPDH served as loading control; NGF (50 ng/mL) served as the positive control]. The expressions of NFs in *ZJF*-treated cultures demonstrated a dose-dependent increase. The results support the use of *ZJF* as a food supplement for the prevention of neurodegenerative diseases in which neurotrophin deficiency is involved (Chen et al. 2014c). However, the mechanism of neuroprotective effects of aqueous extracts of *ZJF* needs further study. In addition, *ZJF* has been proved to play a role in antioxidant enzymes in cultured astrocytes and regulating expressions of neurotrophic factors (Chen et al. 2014d), which are consistent with the traditional use of *ZJF* to calm the nerves.

Qian et al. employed a time window study with intracerebroventricular (i.c.v.) administration of maslinic acid (**20**) to investigate its synergistic effects. The presence of **20** prolonged the therapeutic time window for MK-801 from one to 3 h. Compared with the single treatment group or the vehicle, when **20** (0.85 μM) was given 15 min before middle cerebral artery occlusion followed by MK-801 (0.25 mg/kg) administration 1 h after the artery occlusion the combination therapy demonstrated synergistic effects on infarct volume. The synergistic effect of co-treatment with **20** and MK-801 on neuroprotection might be related to the improvement

in glial function, particularly the increased GLT-1 expression. The combination of **20** and MK-801 may prove to be a potential treatment strategy for acute ischaemic stroke (Qian et al. 2016), although **20** alone had minimal effects on glial function under normal physiological conditions.

Vitexin (**147**), which helps to increase neuroprotective factors and pathways and counteract targets that induce neurodegeneration, such as neuroinflammation (30–60 mg/kg vitexin was administered intraperitoneally to young rats); motor impairment (10–100 μM vitexin was administered in Parkinson disease simulation models); reduced cognition (5, 15, or 30 μM vitexin was added to the RAW 264.7 cell line), and redox imbalances and/or abnormal protein aggregation. These results provide strong support for the scientific exploration of vitexin for these pathologies (Lima et al. 2018).

Sedative-hypnotic and anxiolytic effects

The leaves and seeds from many *Ziziphus* species have been shown to promote sleep and depress the activity of the central nervous system, but these functions were not related to muscle relaxant or anticonvulsant activities (Peng et al. 2000). Lin et al. reported the anti-anxiety effects of multi-herbal medicines containing *ZJS* extract in mice (Lin et al. 2003).

Spinosin (**137**) and swertish (**146**) have significant sedative effects. Compared with the control group, oral administration of **137** (0.04 mmol/kg) and **146** (0.04 mmol/kg) prolonged sleeping time by 29 ± 31% compared to that induced by pentobarbital. The sedative effects of **146** have also been studied following the acid hydrolysis of **137** (Cheng et al. 2000).

Yang et al. studied the sedative and hypnotic activities of oleamide (**276**) in mice, and found that it dose-dependently inhibited motion activity in mice in doses ranging from 43.7 to 175.0 mg/kg by intraperitoneal injection. The positive control in this study was 2.5 mg/kg diazepam. Moreover, **276** promoted the hypnotic effects induced by sodium pentobarbital; these results provide further evidence for the sedative and hypnotic activities of **276** (Yang et al. 1999) and are consistent with the sedative effects targeted in the traditional usage of *ZJF*.

Unfortunately, few studies have focused on the material basis of the sedative effects of *ZJF*, and it is therefore necessary to strengthen the research in this respect in the future.

Hepatoprotective activity

Ent-epicatechinoceanothic acid A (**47**) showed antiproliferative effects towards the rat hepatic stellate cell line HSC-T6 with an IC_{50} value of 43.5 μM (95% CI 28.6–66.2 μM), while (-)-epigallocatechin gallate, which was used as the positive control, exhibited an IC_{50} value of 31.6 μM (95% CI 24.1–41.4 μM) (Kang et al. 2017). This finding indicates that **47** exhibited hepatoprotective effects in vitro, although the mechanism of these effects has not yet been elucidated.

Table 2 Cytotoxicity of compounds **1**, **3**, **5** and **6** isolated from *ZJF* against tumour cell lines[a]

Tumour cell	ED_{50} μM				
	1[b]	**3**	**5**	**6**	**AD**[c]
A549	14 ± 2.2	12 ± 1.7	4.7 ± 1.8	8.9 ± 2.1	0.67 ± 0.21
B16(F-10)	14 ± 0.2	7.3 ± 2.0	10.2 ± 0.2	> 20	0.06 ± 0.10
K562	13 ± 1.3	9.4 ± 1.0	10.7 ± 0.1	13.4 ± 1.5	0.09 ± 0.03
LOX-IMVI	9.2 ± 0.3	4.3 ± 1.3	5.5 ± 0.4	16 ± 0.6	0.38 ± 0.33
PC-3	15 ± 0.5	4.0 ± 0.4	7.3 ± 0.2	19 ± 0.8	0.83 ± 0.18
SK-MEL-2	7.2 ± 0.6	6.9 ± 0.9	8.9 ± 1.4	> 20	0.09 ± 0.03

[a] ED_{50} is defined as the concentration which resulted in a 50% decrease in cell number

[b] Results are means ± SD of 3–5 independent replicates

[c] Adriamycin as positive control

ZJF has been shown to effectively prevent liver injury, mainly through downregulation of inflammatory responses and oxidative stress (Shen et al. 2009). Treatment with polysaccharides from *ZJF* (*PZJF*) (400 mg/kg, i.g.) significantly ($P < 0.01$) reduced the activities of CCl_4-elevated aspartate aminotransferase (AST), lactic dehydrogenase (LDH) and alanine aminotransferase (ALT) in serum and hepatic malondialdehyde (MDA) levels in mice. The results are indicators of hepatic injury induced in the mice by CCl_4, as shown in the significant increase in serum activities of ALT and AST from 26.0±7.7 to 25.0±6.5 IU/L in the untreated normal group to 46.6±9.0 and 59.3±11.9 IU/L in the CCl_4 group ($P < 0.01$), respectively. The CCl_4-induced hepatic injury was further confirmed by the increased in LDH from 166.0±46.5 U/L to 265.6±44.4 U/L ($P < 0.01$). At a dosage of 400 mg/kg BW, the AST, LDH and ALT decreased to 36.9±9.6 IU/L, 183.2±20.3 U/L, and 30.2±5.6 IU/L, respectively, which were close to the levels obtained by the positive agent, biphenyldicarboxylate pills (BP) (400 mg/kg BW), with which the values were 25.0±6.1 IU/L, 157.2±49.2 U/L and 26.8±6.2 IU/L, respectively. A prominent elevation in the MDA level and a significant reduction in the glutathione peroxidase (GSH-P*x*) and superoxide dismutase (SOD) levels in the CCl_4-intoxicated group were clearly observed in comparison with the untreated normal group ($P < 0.01$). Interestingly, after the administration of *PZJF* at a dose of 400 mg/kg BW, there were significant increases in GSH-P*x* and SOD levels and a conspicuous reduction in MDA content from 251.6±84.9 U/gprot, 66.1±10.4 U/mgprot and 49.4±5.4 nmol/mgprot in the CCl_4-intoxicated group to 532.2±150.6 U/gprot, 192.5±33.2 U/mgprot and 39.4±4.2 nmol/mgprot ($P < 0.01$), respectively. These findings were very close to the 581.7±116.6 U/gprot, 203.7±33.2 U/mgprot and 37.6±3.7 nmol/mgprot of the normal group ($P > 0.05$) and the 581.7±116.6 U/gprot, 203.7±33.2 U/mgprot and 37.6±3.7 nmol/mgprot values of the positive drug BP (400 mg/kg BW, $P > 0.05$), respectively. Mice treated with *PZJF* exhibited a better antioxidant system profile and hepatosomatic index, with normal GSH-P*x* and SOD activities in the liver (Wang et al. 2012), which suggested that *ZJF* exerts hepatoprotective effects in vivo.

Wang et al. found that maslinic acid (**20**) (12.5, 25, 50 mg/kg, i.p.) dose- dependently increased the expression of HO-1 and Nrf2 and contributes to the protection against LPS/D-gal-induced liver injury by inhibiting the NF-κB and activating the Nrf2 signalling pathways (Wang et al. 2018b).

Anticancer and cytotoxic pro-apoptotic effects

Anticancer effect

The antitumour mechanisms of Jujuboside B (**65**) in vivo and in vitro have been investigated by Xu et al. HCT 116 cells were subcutaneously implanted into the right flank of each nude mouse. When the tumour size reached 60 mm^3, the mice were treated intraperitoneally with **65** (40 mg/kg) three times per week for 5 weeks. Compared with the control group, the group treated with **65** showed tumour growth inhibition of approximately 60% ($^*P < 0.05$ vs the untreated control group). No obvious change in body weight or toxicity were observed during the experimental period, and these results showed that **65** suppressed tumour growth in vivo. Further in vitro and other experimental results demonstrated that **65** induced protective autophagy to delay extrinsic pathway-mediated apoptosis (Xu et al. 2014).

Kangsamaksin et al. studied the effects of lupeol (**8**) and stigmasterol (**157**) on tumour and their anticancer activities in vivo and endothelial cells in vitro. In vivo, single or combined use of **8** (10 mg/kg) and **157** (10 mg/kg) via oral gavage disrupted tumour angiogenesis and reduced the growth of cholangiocarcinoma tumour xenografts in mice. Further in vitro and other experimental results have demonstrated that **8** and **157** are attractive candidates for anticancer treatment focused on cholangiocarcinoma tumours by targeting tumour endothelial cells and exerting anti-inflammatory activity (Kangsamaksin et al. 2017), although these findings require further verification in clinical trials.

Cytotoxic pro-apoptotic effect

The cytotoxicities of lupane-type triterpenoic acids (**1**, **3**, **5**, and **6**) against A549, B16(F-10), K562, LOX-IMVI, PC-3 and SK-MEL-2 cancer cell lines (Table 2) were studied in vitro using the sulforhodamine B (SRB) method with adriamycin serving as the positive control. These results showed that the coumaroyl moiety at the C-3 position in lupane-type

triterpenes may play an important role in enhancing the cytotoxic activity (Lee et al. 2003), although the mechanism of action of **3** and **5** requires further study.

A large amount of in vitro evidence shows that betulinic acid (**1**) is effective against cervical, ovarian, human melanoma, and non-small-cell and small-cell lung cancers as well as head and neck carcinomas (Eiznhamer and Xu 2004). Betulinic acid demonstrated selective toxicity against cultured human melanoma cells (Kim et al. 1998) and induced apoptosis (Kim et al. 1998; Liu et al. 2004) in sensitive cells in a CD95- and p53-independent fashion (Eiznhamer and Xu 2004).

The induction of apoptosis is one mechanism for the anticancer activities of *ZJF* extracts in different cell lines (Vahedi et al. 2008). Huang et al. found that the *ZJF* extracts decreased the activity of the human hepatoma cells (HepG2) (Huang et al. 2007). Triterpenic acids from *ZJ* have been shown to inhibit the growth of MCF-7 and SKBR3 breast cancer cell lines and induce their apoptosis (Plastina et al. 2012). Choi et al. found that *ZJF* extracts from eight growth stages (S1–8) had dose-dependent inhibitory effects on HeLa cervical cancer cells. However, the inhibitory effects on A549 lung cancer and Hel299 normal lung cells decreased with fruit maturation and were closely related to the flavonoid contents and fruit antioxidant activities (Choi et al. 2012). In vitro studies showed that deproteinized polysaccharides from *ZJF* inhibited melanoma cells at the G2/M phase of the cell cycle accompanied by the formation of apoptotic bodies and increases in caspase-9 and caspase-3 activities (Hung et al. 2012).

Four isomers of coumaroyl alphitolic acid (**3**, **4**, **5**, and **16**) showed strong apoptotic cell death-inducing activities in a concentration-dependent manner with IC_{50} values of approximately 9–12 μM in human cancer cell lines [IC_{50} values (μM) (A549: **3** (9.4 ± 1.2), **4** (12.0 ± 1.4), **5** (10.5 ± 1.6), and **16** (12.1 ± 1.8); MDA-MB-231: **3** (10.5 ± 1.1), **4** (11.4 ± 1.3), **5** (11.5 ± 1.8), and **16** (12.5 ± 2.2); and PC-3: **3** (10.1 ± 1.5), **4** (11.7 ± 1.7), **5** (10.9 ± 1.9), and **16** (12.1 ± 2.1)]. Compound **3** can induce apoptotic cell death in these cancer cells by increasing mitochondrial ROS production and the subsequent activation of p38 MAPK. These results provide a reasonable basis for using *Ziziphus* extracts to treat cancer in traditional oriental medicine (Shin et al. 2018). However, it is necessary to further clarify the exact mechanism by which **3** or other isomers of coumaroyl alphitolic acid increase the production of mitochondrial ROS in order to better understand the anticancer activities of the isomers of *p*-coumaroyl alphitolic acid from *ZJF*.

Pentacyclic triterpenes that possess a carboxylic acid functional group at C-28, including betulonic acid (**6**), oleanonic acid (**19**), ursonic acid (**51**), and ursolic acid (**52**), had significant cytotoxic effects against three human cancer cell lines (HT29 colorectal carcinoma cells, HONE-1 nasopharyngeal carcinoma, and KB oral epidermoid carcinoma) and resulted in IC_{50} values ranging from 4.0 to 8.8 μM (Chiang et al. 2005). However, the mechanism of action of this effect has not been clarified and requires further study.

2α-hydroxyursolic acid (**50**) at the concentrations of 15, 20, and 25 μM showed anticancer activities by inhibiting MDA-MB-231 human breast cancer cell proliferation in a dose-dependent manner ($P < 0.05$) and inducing apoptosis by regulating the p38/MAPK signalling pathway. The EC_{50} was 19.82 μM, suggesting a specific anti-proliferative activity of **50** towards MDA-MB-231 human breast cancer cells (Jiang et al. 2016).

The anticancer characteristics of three anticancer biomarkers (**8**, **52**, and **156**) were explored by Alam et al. in vitro against HepG2 and MCF-7 cell lines using the MTT assay, and an effective HPTLC method was developed for the simultaneous analysis of these three compounds [**8**, **52**, and **156** (7.47, 5.50 and 11.85 μg/mg, respectively)] in different species. The results also supported their strong anticancer effects (Alam et al. 2018). However, the anticancer effects and mechanisms of these compounds in vivo still require further study.

Sweetness inhibitors

Extracts from *ZJL* inhibited sweet taste sensations in flies, hamsters and rats. Anti-sweet substances separated from *ZJ* included jujubasaponin II (**57**), III (**58**), IV (**59**), V (**60**) and VI (**61**) from *ZJL*; jujuboside B (**65**) from *ZJL* and *ZJF*; and zizyphus saponins I-III (**62**–**64**) from dried *ZJL*. Compounds **57**, **58** and **66**, the only three compounds with acyl groups, were up to four times more active at inhibiting sucrose sweet tastes than the other anti-sweet components, which could be used to reduce obesity in overweight or

diabetic patients (Suttisri et al. 1995). Ziziphin (**66**) extracted from *ZJL* inhibited the sweetness induced by aspartame, D-glucose, D-fructose, glycine, naringin dihydrochalcone, sodium saccharin and steviosides (Kurihara et al. 1988). However, it did not inhibit hydrochloric acid-induced acidity or quinine-associated bitterness, suggesting that **66** has a strong specificity for sweetness (Kurihara. 1992). While **66** was also found to suppress human sweetness receptors (Smith and Halpern 1983), the mechanism of action of **66** is considered to be due to changing the taste. Anti-sweetness potencies of these compounds are expressed as relative anti-sweetness potencies on a molar comparison basis to gymnemic acid I, and their anti-sweetness potencies are 0.5 (**57**–**58**, **66**), 0.25 (**59**–**61**, **64**–**65**) and 0.125 (**62**–**63**), respectively (Suttisri et al. 1995).

Immunostimulant activity

ZJL might stimulate the intracellular killing capacity and chemotactic and phagocytic activities of human neutrophils at 0.005–0.050 mg/mL, although it did not show any significant effect at a concentration of 0.100 mg/mL (Ganachari et al. 2004). The *ZJL* water-alcohol extract stimulates the cell-mediated immune system by increasing the phagocytic functions of neutrophils. It is logical to suggest that this preparation may be useful as an adjuvant in several immunosuppressed clinical conditions, although further in-depth study is necessary to determine which components of *ZJL* play this role.

Zhao et al. found that crude *ZJJ* significantly increased the spleen and thymus indices in mice and enhanced the proliferation of peritoneal macrophages and spleen cells. Ju-B-2 pectic polysaccharides from *ZJJ* fruits had a dramatic ($P < 0.01$) effect in promoting splenocyte proliferation at a higher dose (> 0.030 mg/mL), while Ju-B-3 pectic polysaccharides from *ZJJ* fruits did not demonstrate any proliferation effects compared to the control group. Based on their structures, rhamnuronic acid and its side chains were considered to be the main factors causing stimulating immune responses (Zhao et al. 2006), although the structure–activity relationship of these polysaccharides needs further study.

Chen et al. investigated the roles of *ZJF* on the expressions of pro-inflammatory cytokines in cultured macrophages. Application of various chemically standardized concentrations of *ZJF* water extract (0–3.0 mg/mL) for 24 h stimulated the transcriptional expression of TNF-α, IL-1β, and IL-6 in cultured RAW 264.7 macrophages. In contrast, pretreatment with *ZJF* water extract suppressed the expression of IL-6 and IL-1β, but not TNF-α in LPS-stimulated macrophages. The IL-6 and IL-1β cytokines in LPS-induced macrophages were suppressed by *ZJF* water extract in both protein and mRNA levels. In parallel, the inhibition by *ZJF* water extract on the transcriptional activity of NF-κB was revealed in LPS-induced macrophages. These results confirmed that *ZJF* served bidirectional immune- modulatory roles by regulating the expressions of pro-inflammatory cytokines in macrophages (Chen et al. 2014a). However, which components in the aqueous extract of *ZJF* play a double regulatory role is an important direction for future research.

Lai et al. injected maslinic acid (**20**) i.p. at different doses (0, 8, 16 and 32 mg/kg) into leukaemia mice for 2 weeks. Monocyte (at 32 mg/kg treatment) and T cell (at 16 mg/kg treatment) markers were increased by **20**, but B-cell markers (at 8 mg/kg treatment) were reduced. Moreover, at the 32 mg/kg dose, **20** increased macrophage-induced phagocytosis by peripheral blood mononuclear cells in the peritoneal cavity and increased NK cell activities at a target cell: splenocyte ratio of 25:1; however, B-cell and T-cell proliferation were not affected, the detailed mechanism behind this has yet to be clarified. The results showed that **20** increased immune responses by enhancing NK cell effects and macrophage phagocytosis in leukaemic mice (Lai et al. 2019), which is consistent with the traditional use of *ZJF* for invigorating the spleen.

Wound-healing activity

In their book on herbal drugs, Ansari et al. mentioned *ZJR* use in wound healing (Ansari et al. 2006). Very recently, Chopda, M.Z. confirmed the wound healing activity of *ZJR* in an experimental rat model using a topical ointment form of 5 mg/mL and 10 mg/mL concentrations by topical application (Chopda 2009), which confirms the view of Ansari et al. (Ansari et al. 2006). Additionally, at the 1 μM dose, squalene (**275**) from *ZJL* can promote wound healing by promoting macrophage responses during inflammation, meaning **275** was useful at the resolution stage of wound

healing. These results are consistent with the traditional Chinese medicine treatment for traumatic haemorrhage. Compound **275** is currently only separated from *ZJ* leaves, not from *ZJ* root bark and bark, and its mechanism needs further study (Sánchez-Quesada et al. 2018).

Additionally, local application of adelmidrol + *trans*-traumatic acid (**255**) plays an important role in the closure and healing of diabetic wounds in a streptozotocin- induced diabetic mouse model (Siracusa et al. 2018), which is consistent with the traditional use of *ZJ* for wound healing. However, the relationship between the activity of *ZJ* on wound healing and compound **255** requires further research.

Lupeol (**8**) has many pharmacological effects, such as antioxidant, anti-inflammatory, anti-mutagenic, and anti-diabetic effects. Pereira Beserra et al. studied the effects of **8** (0.23, 2.34, 23.43, and 46.87 μM) in wound healing assays as well as its signal transduction mechanism in vitro in human neonatal prepuce keratinocytes and fibroblasts. The results demonstrated that **8** has therapeutic potential in promoting wound healing (Pereira Beserra et al. 2018), although further in vivo and clinical studies are needed to explore these effects and to develop **8** as a therapeutic agent for the treatment of skin wounds.

Chlorogenic acid (**171**) or PBS was applied directly to the wound area twice a day, and at 13 days post-infection, the wound healing rate of the **171**-treated groups reached 72.35% ± 2.86 (1/16MIC) or 83.85% ± 4.82 (1/2MIC), while the control group treated with PBS demonstrated wound closure of 53.53% ± 6.58. On the 5th and 7th days after infection, the high-dose-treated group had a significant decrease in bacterial number. In a mouse wound model, the wound healing speed of the **171**-treated groups was faster and the number of bacteria in the wound area was also reduced, suggesting that **171** has the potential to be used as a wound healing agent (Wang et al. 2018a) and is expected to be developed as a drug for wound healing.

Anti-HIV activity

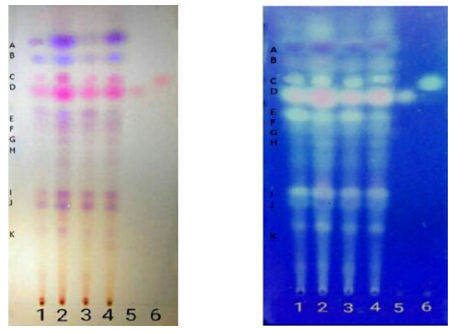
Betulinic acid (**1**) inhibited HIV replication in H9 lymphocytes with an EC_{50} value of 1.4 μM and inhibited the growth of uninfected H9 cells with an IC_{50} value of 13 μM. Betulinic acid has a lupane skeleton and was the first identified triterpene to show anti-HIV effects. Platanic acid and **1** are structurally interrelated, except that the isopropenyl group in **1** is replaced with an acetyl group in platanic acid. The C-19 substituents, the C-17 carboxylic acid group and the C-3 hydroxy group contribute to the enhanced anti-HIV effects (Fujioka et al. 1994). The mechanism of the anti-HIV activity of compound **1** requires further study.

PA-457 (as a positive control, IC_{50}: 15.2 μM) and epiceanothic acid (**26**) were detected in MT-4 cells acutely infected with HIV-1_{NL4-3}, and compound **26** showed only moderate anti-HIV effects with an IC_{50} value of 38.9 μM and a TI of 2.49 (Zhang et al. 2011). The mechanism of compound **26** against HIV and whether it can be used as an anti-HIV drug or lead compound needs further study.

An in silico wafer virtual screening method was used to identify lead compounds from a natural compound library or database to be used as an HIV-1 protease inhibitor. HIV-1 protease was examined using a virtual screening against the Indonesian Herbal Database with AutoDock. The results found that ursonic acid (**51**) had anti-HIV effects (Yanuar et al. 2014), although whether **51** truly exerts anti-HIV effects needs to be studied both in vivo and in vitro.

Anti-asthmatic activity

The anti-asthmatic activities of the ethanolic extracts of *ZJF* (*EZJF*) and Jujuboside B (**65**) were evaluated by various screening methods. The results showed that *EZJF* and **65** significantly inhibited milk-induced



Visible light **Ultraviolet light (365 nm)**

1. ZJF_1 2. ZJF_2 3. ZJF_3 4. ZJF_4
5.oleanolic acid 6. betulinic acid

Fig. 11 Thin layer chromatogram of *ZJF*

eosinophilia and leucocytosis, clonidine- induced catalepsy, passive paw anaphylaxis, and clonidine-induced mast cell degranulation. After **65** pretreatment (33, 66, and 132 mg/kg, p.o.) in mice, the number of inflammatory cells in BAL fluid was significantly reduced and the degree of pulmonary inflammation was alleviated. High TH2 cytokine expression levels were observed in lung homogenates and BAL fluid, whereas serum levels were markedly decreased. Therefore, *EZJF* and **65** displayed strong anti-asthmatic effects and have a potential role in the treatment of asthma (Ninave and Patil 2018). This finding is consistent with the traditional use of *ZJF* for its lung-moistening effects, although the results of this study were weakened because the two researchers (Ninave and Patil 2018) did not perform mass spectrometric analysis of Jujuboside B (**65**) to determine the exact molecular weight.

Others

The other pharmacological effects of *ZJF* can be found in the supplementary materials (Pharmacological effects S1-S13).

Some of these pharmacological studies prove the traditional usage of *ZJ*, and some are the development of the traditional usage of *ZJ*. These results can be considered conducive to the rational use of *ZJ* and the development of a local economy.

Toxicity

Thus far, no report has been published on the toxicity of *ZJF*. The recommended daily dose of *ZJF* is 6–15 g (Pharmacopoeia Commission of PRC 2015), and relevant reports have shown that the ethanolic extract from *Zizyphus sativa* Gaertn (Syn.=*Zizyphus jujuba* Mill.) fruit (prepared by extraction of *ZJF* along with the seeds with 95% ethanol) resulted in no acute or chronic toxicity in Swiss albino mice. In an acute toxicity test, animals that received three doses of 0.5 g/kg, 1 g/kg and 3 g/kg body weight (p.o.) were observed every 24 h and treated by chronic treatment and dose (100 mg/kg body weight extract) for 3 months. In addition to examining the effects on average body weight and the weight of important organs, external visceral toxicity, morphological changes, spermatogenic dysfunction, and haematological changes were also recorded. The crude drug had no obvious toxic effects (Shah et al. 1989). Administration of *ZJF* extract (prepared by extraction of *ZJF* with 60% ethanol using Soxhlet extraction) did not cause any behavioural changes, toxic symptoms or mortality, even at high doses (2 g/kg, p.o.) in Wistar albino rats. However, the toxicity of *ZJF* aqueous extracts has not yet been studied. Long-term traditional clinical experience shows that it is used with caution in cases of food stagnation or damp-phlegm because it can help induce distention in the middle energizer and the dampness can produce heat (Zhang 2008b). It is also used in some prescriptions to reduce the toxicity of various herbs and protect the stomach Qi. For example, Jingdaji (Euphorbiae pekinensis radix), Gansui (Kansui radix), and Yuanhua (Genkwa flos) in *Shizao Tang* from *Shanghanlun* (*Treatise on Cold Damage Diseases*) are used in conjunction with *ZJF* to alleviate toxicity and the violent effects associated with three herbs to protect the stomach Qi. Additionally, it is also compatible with Shengjiang (Zingiberis rhizoma recens) to enhance the coordination of the spleen and stomach (Zhang 2008b) and harmonize the nutrient and defence (Huang 2002).

Pharmacokinetics

The Chinese Pharmacopoeia controls the quality of *ZJF* using betulinic acid (**1**) and oleanolic acid (**18**). The pharmacokinetics of these two compounds have been well studied (Udeani et al. 1999; Cheng et al. 2003; Song et al. 2006; Jeong et al. 2007).

The extent of binding of **1** to plasma proteins in dog, mouse and rat plasma was determined by LC/MS. The results showed that in dog or rat plasma, **1** was 99.99% bound to serum proteins at 25 and 15 µg/mL and that **1** was also 99.97% bound at 5 µg/mL (Cheng et al. 2003).

Udeani et al. examined CD-1 rats at designated times after a single intraperitoneal (IP) dose of **1** at 250 or 500 mg/kg. The results demonstrated that after 500 and 250 mg/kg **1** IP, serum concentrations reached peaks at 0.23 and 0.15 h, respectively. The distribution of **1** in the tissues and organs of the mice was studied, and compound **1** was found to be mostly distributed in the perirenal fat and less in the heart and brain. After administering different doses,

although the elimination phase remained basically the same, the absorption rate was obviously different (Udeani et al. 1999).

Song et al. studied the pharmacokinetics of oleanolic acid (**18**) in 18 healthy male Chinese volunteers. The concentration–time curves in plasma following oral administration of 40 mg oleanolic acid (**18**) for most of the 18 subjects were consistent with the single compartment model. The mean values of C_{max}, T_{max}, $AUC_{0\text{-}48}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, CL/F, and V/F of **18** after p.o. administration of a single 40 mg dose were 12.12±6.84 ng/mL, 5.2±2.9 h, 114.34±74.87 ng h/mL, 124.29±106.77 ng h/mL, 8.73±6.11 h, 555.3±347.7 L/h, and 3371.1±1990.1 L, respectively. These results showed that V_d was 2.5 times larger than the average total plasma volume in a man, potentially because **18** was distributed to a great extent out of the blood or amassed in a specific tissue (Song et al. 2006).

Jeong et al. studied the absorption and metabolism of **18** by using a Caco-2 cell permeation and rat liver microsome model and found that **18** underwent transmembrane transport mediated by passive transport. The osmotic coefficient showed that its intestinal absorption was poor, and **18** could be metabolized by liver microsomes but was not stable. The rats were administered different doses (0.5, 1 and 2 mg/kg doses) of **18**, and the pharmacokinetic parameters of **18** showed good linear-dose pharmacokinetics as evidenced by the unaltered *CL* (28.6–33.0 mL/min/kg), V_{ss} (437–583 mL/kg), dose-normalized *AUC* (16.0–17.9 mg min/mL based on 1 mg/kg) and $t_{1/2}$ (41.9–52.7 min), but the oral bioavailability of **18** was very low, which may be closely related to its poor intestinal absorption and extensive metabolic clearance in the liver (Jeong et al. 2007).

Many studies have shown that the lipid solubility of **18** is strong and that its water solubility is very low because of the specific parent nucleus present in soap. The structure of pentacyclic triterpenoid saponins distributes these compounds widely in lipophilic tissues, but their bioavailability is low; thus, the clinical applications of existing preparations are greatly limited (Cheng and Xiong 2008).

Unfortunately, pharmacokinetic studies of whole *ZJF* plants and some compounds have not been reported; thus, this is an important research direction for future studies.

Quality control

To control the quality of *ZJF*, the Chinese Pharmacopoeia suggests examining the plant origin and performing morphological, microscopic and TLC identification in addition to determining the total ash and aflatoxin. Qualified *ZJF* samples should contain betulinic acid (**1**) and oleanolic acid (**18**) (Pharmacopoeia Commission of PRC 2015) (Fig. 11), although the presence of **1** and **18** alone seems insufficient to assess the quality of *ZJF*. Recently, various bioactive components in *ZJF* were examined using TLC, HPLC–DAD, HPLC-ELSD-MS, RP-HPLC, UPLCDAD-MS, HPLC, MS and NMR methods, such as betulinic acid (**1**), alphitolic acid (**2**), oleanolic acid (**18**), zizyberanalic acid(colubrinic acid) (**23**), zizyberanal acid (**24**), ceanothic acid (**25**), epiceanothic acid (**26**), zizyberenalic acid (**27**), ceanothenic acid (**28**), ursonic acid (**51**), ursolic acid (**52**), zizyberanone (**271**), nucleosides, nucleobases, etc. (Lee et al. 2004; Guo et al. 2009a, b, 2010a, b). Although scholars at home and abroad have performed much research on its chemical constituents, the water-soluble components with high polarity (Ji et al. 2017) require relatively highly technical experimental conditions for separation and purification, and the current research is not yet sufficiently detailed.

To date, the research on pharmacological activities and quality control of the water-soluble components of *ZJF* is relatively weak, and the research in this area should therefore be further strengthened. At present, betulinic acid (**1**) and oleanolic acid (**18**) are used for *ZJF* quality control (Pharmacopoeia Commission of PRC 2015) in the current Pharmacopoeia. It is not sufficient for comprehensive quality control of *ZJF* with betulinic acid (**1**) and oleanolic acid (**18**) because betulinic acid (**1**) and oleanolic acid (**18**) are insoluble in water, while *ZJF* is mostly used as a decoction (water extract) in clinical treatment.

Therefore, it is necessary to find other effective components and establish quality control standards corresponding to their efficacy. If necessary, further study of the *ZJF* fingerprint will provide stronger quality assurance for *ZJF* quality control (Liu et al. 2015).

Economically important use

The diversity of plant usages provides opportunities for the development of new food and/or pharmaceutical products (Yao et al. 2018). *Zizyphus jujuba* has medicinal value throughout the body. Its fruit is rich in nutrients and chemical components and has a wide range of pharmacological effects. Its important dietary and therapeutic ingredients are at the top of the list. The saccharides are the most concentrated of the nutrients in *ZJF*, as the content of soluble saccharides can reach approximately 30% in mature fresh *ZJF*, and the content of the dry *ZJF* can reach 60–70% or even higher, which is much higher than that of other fruits. The vitamin C in fresh *ZJF* can reach more than 600 mg/100 g FW (Jiao and Liu 2018), and either fresh or dried fruits can be used. In addition to being a common fruit, it is also an important festival product, TCM, and food product that can be deep-processed into products and functional foods, such as jujube formula granules (Liu et al. 2017a), dietary fibre biscuits (Liu et al. 2017f), jujube polysaccharide capsules (Liu et al. 2016a), edible red pigments (Liu et al. 2016b), jujube brown sugar ginger tea (Liu et al. 2018a), jujube yogurt (Liu et al. 2018b), etc. The jujube core can be converted into furfural (Liu et al. 2017b), activated carbon (Liu et al. 2017c), and other products. Jujube leaves can be used to produce sweetener inhibitors (Liu et al. 2017e) and chlorophyll (Liu et al. 2017g). Li et al. closely studied the nutritional composition of five cultivars of Chinese jujube (Li et al. 2007) and polysaccharides from *ZJF* (Li et al. 2011a, b, 2013), which laid the foundation for the further development of functional foods from *ZJF*. Siriamornpun et al. offered practical information about how best to use the bioactive compounds and health implications of the green *ZJF* and ripe *ZJF* as potential sources of nutritive and functional applications (Siriamornpun et al. 2015). *ZJ* is the main cash crop of farmers in Xinjiang, Shaanxi, Shanxi, Henan and other provinces. At present, China has 99% of the world's jujube resources and accounts for nearly 100% of the international trade in jujube products. The total annual output value of the jujube industry is more than 20 billion Yuan. In many key jujube producing counties, the income of the jujube industry accounts for 40% of farmers' income, reaching as high as 80% in some counties (Liu 2008). This is also a way for farmers to escape poverty and become rich. It is worth noting that *ZJ* is an entomophilic plant pollinated by flies, ants, bees, and other insects, and the unabi fly in particular is a pest of the culture fruits (Gusakova et al. 1999). More research is necessary to determine how to optimize the relationship between the yield of *ZJF* and these insects to maximize the benefits to fruit farmers.

Conclusions and future prospects

ZJ is a well-known plant worldwide, and its fruit (*ZJF*) is listed in the Chinese Pharmacopoeia. *ZJF* plays an important role in both the food industry and health care. *ZJF* includes more triterpenoid acids, cyclopeptide alkaloids and flavonoids than the other plant parts, which may explain why *ZJF* is more frequently used in TCM prescriptions than other plant parts. Currently, according to the available literature, approximately 278 compounds have been isolated and identified from *ZJ*. It mainly contains triterpenoid acids, saponins, alkaloids, flavonoids and simple phenols, which provide the material basis for *ZJ* to have obvious antioxidation, anti-inflammation, antibacterial, anti-anxiety, anticancer, sweet inhibitor, anti-HIV and other pharmacological effects. Pharmacological studies in vitro and in vivo have increasingly confirmed the traditional uses of *ZJF* as tonifying and replenishing the middle Qi and nourishing the blood to tranquilize.

We showed preliminary evidence of a relationship between modern pharmaceutical studies and traditional uses. The strong gastrointestinal protective, cardiovascular, neuroprotective, sedative-hypnotic and anxiolytic effects correspond to *ZJF*'s TCM characteristics (sweet flavour, warm nature and spleen, and stomach and heart meridians). Moreover, the remarkable sedative-hypnotic, anxiolytic, antioxidant and anti-inflammatory capacities of *ZJF* contribute to its neuroprotective and anticancer activities. However, in studies, some experiments lacked controlled clinical trials, so it is impossible to draw unequivocal conclusions about the effects of these compounds in humans.

Not all the available information contributes to traditional evidence-based usages, and there is not even enough evidence to make it a registered evidence-based drug because of lack of the best basis

for in vivo experiments and clinical research. If *ZJF* is to become an evidence-based drug, in vivo experiments and clinical studies should be conducted.

In future studies, we encourage more clinical studies and in vivo experiments to further clarify the relationship between modern applications and traditional uses of this plant.

Nevertheless, there are still some questions that have not been clarified and that require further study by researchers to promote further scientific and clinical research.

First, the traditional actions of *ZJF* to tonify and replenish the middle Qi and nourish the blood to tranquilize require more modern pharmacological studies to elucidate their intrinsic mechanisms.

Second, previously reported pharmacological studies mostly focus on a limited number of ingredients, and only a few studies have focused on holistic pharmacodynamics. Therefore, we need to answer whether these identified compounds can achieve the equivalent effect of *ZJF*, and, if not, to what extent. Otherwise, more bioactive ingredients, especially Qi-enriching, spleen-invigorating, blood-nourishing and sedative substances should be identified through chemical standardization and bioactivity-guided separation strategies for bioactive compounds, and their mechanism of action is still unclear and needs further study.

Third, no recent studies have investigated the clinical differences between *ZJF*, *ZJB*, *ZJC*, *ZJL*, and *ZJR*. These should be one of the main research directions for future studies.

Fourth, though the fruit has been traditionally used as a TCM, some researchers have studied the phytochemicals of other plant parts (seeds, barks, and leaves, but not in flowers) and revealed their pharmacological effects. Therefore, it is necessary to compare the chemical constituents from different parts and their corresponding pharmacological effects. Furthermore, no one has studied *ZJ* blossoms, and exploratory research should therefore focus on *ZJ* blossoms.

Fifth, *ZJF* is commonly combined with other TCMs [such as Gancao (Glycyrrhizae radix et rhizoma), Ejiao (Asini corii colla), Tinglizi (Descurainiae semen lepidii semen), and Danggui (Angelicae sinensis radix)] in conventional therapies. The interactions between *ZJF* and other TCMs as well as their underlying mechanisms need further study (Gao and Zhong 2006).

Sixth, there are currently no reports focused on *ZJF* toxicity. However, we are encouraged by the evaluation of side effects or toxicity associated with *ZJB*, *ZJC*, *ZJL*, and *ZJR* in in vitro, in vivo and clinical studies.

Seventh, *ZJF* has been stir-baked to yield yellow, brown, and charcoal colours; steamed; and stir-fried with wine, vinegar, etc. during its traditional processing methods (Liu et al. 2018d). The scientific principles and mechanisms of CMMP associated with these changes are not clear, and therefore require further study.

Eighth, in terms of the number and depth of research of papers published at home and abroad, there are still very few works focused on *ZJF* storage, preservation and processing, which is a weakness in the *ZJF* scientific research.

Ninth, there are some differences in the records of traditional usage of *ZJF* in different classical works associated with herbal medicine that need to be further verified in clinical practice.

Tenth, the volatile components in *ZJF* are relatively complex. Different processing methods have greater impacts on the volatile components in *ZJF*, which may create changes in its efficacy, and this aspect requires further study (Lu et al. 2013; Wang et al. 2014).

We believe that if we can answer the above questions, we will be one step closer to understanding the roles and characteristics of *ZJ* and its components.

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Authors' contribution S-JL and Z-ST conceived and designed the review. S-JL, C-LC, H-BL, YZ, H-BX, D-BZ, Y-PL, H-HS, Z-XS, and S-MW were responsible for collecting the documents. S-JL, Z-ST and Y-PL analysed the data. S-JL and Z-ST wrote the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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