Lonicerae Japonicae Flos has been used as a tea and medicine for more than 1,500 years. It has the functions of clearing heat, detoxification, and is often used to treat carbuncle, furuncle, throat arthralgia, erysipelas, heat-toxic blood dysentery, febrile fever. This paper summarizes the botany, ethnopharmacology, chemical composition and pharmacological action of Lonicerae Japonicae Flos from 1986 to 2022, and looks forward to the future research direction of Lonicerae Japonicae Flos. At present, the components isolated from Lonicerae Japonicae Flos include essential oils, organic acids, flavonoids, iridoids, saponins and other compounds. It has the effects of anti-inflammation, anti-virus, anti-bacteria, anti-oxidation, anti-tumor, protect liver and galltesticles, hypotensive, hypolipidemic, anti-thrombosis, anti-allergy, immune regulation and so on. It is often used in clinical treatment of diarrhea, hematochezia, febrile disease, exogenous wind-heat, and cold, swelling and toxin of carbuncle, sore throat and so on. The comprehensive evaluation of the quality of Lonicerae Japonicae Flos and the understanding of multi-target network pharmacology also need to be studied. As a kind of health food with high value, LJF is worthy of further promotion and development.

KEYWORDS
Lonicerae Japonicae Flos, botany, ethnopharmacology, phytochemistry, pharmacology, toxicology

Introduction

Lonicerae Japonicae Flos (LJF) is the dried bud or flower with initial blooming of Lonicera japonica Thunb.(Caprifoliaceae) (Hou and Jiang, 2013), it is used as food by Chinese people. LJF is also a commonly used traditional Chinese medicine with a long history, which is first listed in "Ming Yi Bie Lu" (名医别录) (A.D. 220-450) and listed as the top grade. LJF first appeared in Li Shizhen’s "Compendium of Materia Medica" and has been included in the Chinese Pharmacopoeia (Chinese Pharmacopoeia Commission, 2020). It tastes sweet and cold. Return to the meridians of the lung, heart and stomach. It has the functions of clearing away heat and detoxification, dispersing wind-heat and other functions, and is often used to treat carbuncle, furuncle, throat arthralgia, erysipelas, heat-
toxic blood dysentery, wind-heat cold, febrile fever and other diseases. It is mainly distributed in Shandong, Henan and other places (Zhang et al., 2014).

Phytochemical studies show that the components isolated from LJF include essential oils, organic acids, flavonoids, iridoids, saponins and so on (Peng et al., 2006; Wang Y. et al., 2008; Guan et al., 2014; Wang L. et al., 2016; Ge et al., 2019). Pharmacological studies show that LJF has the effects of anti-oxidation, anti-tumor, anti-bacterial, anti-virus, anti-inflammation, anti-allergy, heat-clearing and detoxification, protecting liver and gallbladder, hypolipidemic, hypoglycemic, immune regulation and so on (Li, 2004; Li, 2006; Guo and Shi, 2009; Sun et al., 2010; Han et al., 2016; Wang et al., 2017; Bang et al., 2019; Fan et al., 2019; Wang et al., 2019).

LJF can be eaten raw or cooked with porridge or peach blossoms, which can boost the body’s immune system. More people take it as a tea drink, you can add mint, chrysanthemum, herbs and de-stemmed Chinese wolfberry, you can also use it to make compound preparations, such as Xiao bai huang, which can boost the body’s immune system. More people like to take it as a tea drink, you can also add mint, chrysanthemum, and de-stemmed Chinese wolfberry, you can also make compound preparations, such as Xiao bai huang, which can boost the body’s immune system.

2016; Wang et al., 2017; Bang et al., 2019; Fan et al., 2019; Wang et al., 2019).

According to the Chinese Pharmacopoeia (Edition 2020), Lonicerae Japonicae Flos (LJF) is the dried bud or flower with the initial blooming of Lonicera japonica Thunb. This plant enjoys a warm and humid climate, and enjoys sufficient sunshine, cold resistance, drought resistance and waterlogging resistance. It is suitable for growth at 20°C-30°C, with loose soil requirements and salt tolerance. It is suitable for cultivation in humus soil with deep and loose soil layers. It is mainly produced in Sichuan, Guangdong, Guangxi, Hunan, Guizhou, Yunnan and other places. The dried buds of Lonicera japonica Thunb. are long rod-shaped, thick at the top and thin at the bottom, slightly curved, 2-3 cm in length, 3 mm in diameter in the upper part and 1.5 mm in the lower part. The surface is yellowish-white or green-white (dark over time), covered with pubescent and glandular hairs. The base has a small green calyx, 5-lobed, triangular lobes, and glabrous. When the bud is cut open, there are 5 stamens and 1 pistil. The corolla is lip-shaped, and the androgens and pistils protrude like whiskers. The breath is fragrant, the taste is light and bitter. It is better for those whose flowers are not blooming, yellow and white and fat. From May to June, on a sunny morning, the buds are picked when the dew is dry, dried in the sun or in the shade on the stalk, and pay attention to the rotation, otherwise it is easy to black. It should be protected from the hot sun. It should be kept in a highly dry and ventilated place to prevent insects and discoloration. (Wang et al., 2010; Kang et al., 2014). The pictures of Lonicera japonica Thunb. And Lonicerae Japonicae Flos are showed in Figure 1.
of food." "Dian nan ben cao" (滇南本草) (A.D. 1476) records: "LJF is cold in nature and tastes bitter. It can clear heat, remove various sores, carbuncle and carbuncle from the hair and back."

"Sheng cao yao xing bei yao" (生草药性备要) (A.D. 1711) records: "LJF can eliminate carbuncle, gangrene and furuncle, stop dysentery, wash malnutrition sore, skin blood heat."

"Ben cao bei yao" (本草备要) (A.D. 1694) records: "LJF can nourish blood to quench thirst to treat scabies."

"Chong qing tang sui bi" (重庆堂随笔) (A.D. 1808) records: "LJF can clear heat and promote diuresis, relieve the epidemic and the liver and gallbladder, and treat spasm, convulsion, epilepsy and other diseases."

"Chang yong zhong cao yao shou ce" (常用中草药手册) (1969) records: "LJF is capable of clearing heat and detoxicating, and treating exogenous fever, cough, enteritis, bacillary dysentery, septicemia, sore, furuncle and swelling toxin, appendicitis, traumatic infection, and infantile miliaria toxin. It can be made into herbal tea for prevent heatstroke, common cold and intestinal infectious diseases."

Common compatibility and application

In clinical application, LJF is often used in combination with other drugs. LJF compatible with Forsythiae Fructus, Arctii Fructus, Menthae Haplocalycis Herba, Schizonepetae Herba, used for surface antipyretic. LJF compatible with Scutellariae Radix, Captidis Rhizoma, Paeoniae Radix Alba, Portulacae Herba, used for diarrhoea and stool bleeding. LJF compatible with Rehmanni glutinosae(Gaetn.) Libosch. exFisch. et Mey., Scrophulariae Radix, Forsythiae Fructus, Lophatheri Herba, used to relieve heat. LJF combined with Scutellariae Radix, Angelicae Sinensis Radix, Paeonie Radix Alba and Glycyrrhiza Radix Et Rhizoma is used for suppressing toxin, clearing heat and eliminating carbuncle. LJF combined with Violae Herba, Chrysanthemi Indici Flos, Taraxaci Herba, used for detoxification and treatment of sores.

The commonly used clinical compound preparations include Yinqiao San, Rendong San, Huichuang Jinyinhua San, Rendong Tang, Yinhuu Tang, Shuanghuanglidan Koufuye and Lianhua Qingwen Jiaonang (Table 1). Among them, Shuanghuanglidan Koufuye and Lianhua Qingwen Jiaonang are the most widely used in clinic. They have strong effects on fever, cough, runny nose, headache, dry eye, sore throat, and muscle soreness caused by exogenous wind-fever and influenza. Other compound preparations also have the functions of clearing heat and detoxification, dispersing lung qi and dissipation phlegm, relieving pain, tonifying kidney and spleen, promoting diuresis and detumesence, calming nerves and relieving palpitation, nourishing blood and moistening skin, purging the lungs, relieving diarrhea and soothing the liver. The dosage forms involved include: water decoction, oral liquid preparation, syrup, tablet, capsule, granule, pill, spray, liniment, powder, paste, mixture and so on.

In addition, LJF is also used in the fields of animal husbandry, food, health products, daily necessities and cosmetics and applies for several patents. Such as moxa pig feed and preparation method (CN201911004525.1), preparation method and application of Chinese herbal medicine preparation for treating live pig viral enteritis (CN201910867827.5), nutritious hot pot seasoning and preparation method (CN201910862216.1), LJF flavored apple canned (CN201810679783.9), a herbal tea whose main ingredients are Hordeum vulgare Linn. var. nudum Hook.f., Eleocharis dulcis (Burm. f.) Trin. and LJF. (CN201911234063.2), a preparation method of LJF ginseng health herbal tea (CN20191172448.0), a preparation method of bagged asparagus LJF substitute meal solution (CN201911203081.4), a Chinese herbal medicine children’s toothpaste (CN201810649037.5), a Humei LJF facial mask (CN201930421728.5), an anti-aging and anti-wrinkle essence solution (CN201910895717.X), etc.
| Preparation name          | Dosage forms | Main compositions                                                                 | Traditional and clinical uses                      | References                  |
|---------------------------|--------------|-----------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------|
| Yinqiao San               | Powder       | LJF, Forsythiae Fructus, Bitter Plantcodeon Grandiflorum, Menthae Haplocalycis Herba, Lophatheri Herba, Glycyrrhizae Radix Et Rhizoma, Schizonepetae Spica, Sojae Semen Preparatum, Arctii Fructus | Cold fever Wen Bing Tiao Bian (溫病條辨)             |                             |
| Rendong San               | Powder       | LJF                                                                               | Treat dysentery Hui Zhi Tang Jing Yan Fang (傷寒筆談) |                             |
| Huichuang Jinyinhua San   | Decoction    | LJF, Atragral Radix, Glycyrrhizae Radix Et Rhizoma                                | Treat sores and ulcers Hua Fa Ji Yao (活法機要)     |                             |
| Guihua Tang               | Decoction    | LJF, Angelicae Sinensis Radix                                                     | Treatment of carbuncle Dong Tian Ao Zhi (洞天奧旨) |                             |
| Rendong Tang              | Decoction    | LJF, Glycyrrhizae Radix Et Rhizoma                                                 | Treatment of carbuncle Yi Xue Xin Wu (醫學心悟)     |                             |
| Qingchong Tang            | Decoction    | LJF, Angelicae Sinensis Radix, Sanguisorbae Radix, Ophiopogonis Radix, Pterae Herba, Glycyrrhizae Radix Et Rhizoma, Coix Seed, Astragali Radix | Treatment of large intestine carbuncle Dong Tian Ao Zhi (洞天奧旨) |                             |
| Yinshua Tang              | Decoction    | LJF, Atragral Radix, Angelicae Sinensis Radix, Glycyrrhizae Radix Et Rhizoma, Trifoliate-Orange Immature Fruit Leaves | Treat sores and ulcers Zhu Lin Nv Ke (竹林女科)     |                             |
| Rendong Tang              | Decoction    | LJF, Glycyrrhizae Radix Et Rhizoma, Glycinemax(L.) merr, Smalacis Glabratae Rhizoma | Reduce the toxicity Wai Ke Shi Fa (外科十法)         |                             |
| Xiaoer Feire Kejuan Koufuye| Liquid preparation | Ephedrae Herba, Armeniacae Semen Amaranum, Gypsum Fibrosum, Glycyrrhizae Radix Et Rhizoma, LJF, Forsythiae Fructus, Anemarrhenae Rhizoma, Scutellariae Radix, Isatisidis Radix, Ophiopogonis Radix, Hoututtuinae Herba | Clearing heat and detoxification, expelling lungs and resolving phlegm Chinese Pharmacopoeia |                             |
| Xiaoer Yanbian Keli       | Granules     | LJF, Belamcandae Rhizoma, Tinosperae Radix, Platycodonis Radix, Pterae Herba, Ophiopogonis Radix, Bovis Calculus Artificatus, Borneesium | Clearing heat and promoting pharynx, detoxifying and relieving pain Chinese Pharmacopoeia |                             |
| Xiaoer Tuire Heji Keli    | Mixture      | Isatisidis Folium, LJF, Gardeniae Fructus, Scutellariae Radix, Pteretim, Bupleuri Radix, Isatisidis Radix, Forsythiae Fructus, Moutan Cortex, Lophatheri Herba, Paridis Rhizoma, Cynanchi Atrati Radix Et Rhizoma | Detoxification and pharynx Chinese Pharmacopoeia |                             |
| Xiaoer Tuire Koufuye      | Liquid preparation | Granules | | Chinese Pharmacopoeia |                             |
| Xiaoer Tuire Keli         | Granules     | Isatisidis Folium, LJF, Gardeniae Fructus, Scutellariae Radix, Pteretim, Bupleuri Radix, Isatisidis Radix, Forsythiae Fructus, Moutan Cortex, Lophatheri Herba, Paridis Rhizoma, Cynanchi Atrati Radix Et Rhizoma | Detoxification and pharynx Chinese Pharmacopoeia |                             |
| Xiaoer Resuing Koufuye    | Liquid preparation | Bupleuri Radix, Isatisidis Radix, LJF, Forsythiae Fructus, Scutellariae Radix, Puerariae Lobatae Radix, Bubali Cornu, Rhei Radix Et Rhizoma | Clearing heat and detoxification, purging fire and promoting pharynx Chinese Pharmacopoeia |                             |
| Xiaoer Resuing Keli       | Granules     | Bupleuri Radix, Isatisidis Radix, LJF, Forsythiae Fructus, Scutellariae Radix, Puerariae Lobatae Radix, Bubali Cornu, Rhei Radix Et Rhizoma | Clearing heat and detoxification, purging fire and promoting pharynx Chinese Pharmacopoeia |                             |
| Xiaoer Resuing Tangiang   | Syrup        | Bupleuri Radix, Isatisidis Radix, LJF, Forsythiae Fructus, Scutellariae Radix, Puerariae Lobatae Radix, Bubali Cornu, Rhei Radix Et Rhizoma | Clearing heat and detoxification, purging fire and promoting pharynx Chinese Pharmacopoeia |                             |
| Xiaoer Gammaoing Tangiang | Syrup        | Menthae Haploclaycis Herba, Armeniacae Semen Amaranum, Scutellariae Radix, Peucedani Radix, Gardeniae Fructus, Massa Medicata Fermentata, Phragmites Rhizoma, Schizonepetae Spica, Arctii Fructus, Platycodonis Radix, Angelicae Dahuricae Radix, Crapeagi Fructus, Hordei Fructus Germinatus, LJF, Forsythiae Fructus | Reduce fever and cough Chinese Pharmacopoeia |                             |
| Xiaoer Jaebiao Keli       | Granules     | LJF, Forsythiae Fructus, Arctii Fructus, Taraxaci Herba, Scutellariae Radix, Saposhnikoviae Radix, Perillae Folium, Schizonepetae Spica, Puerariae Lobatae Radix, Bovis Calculus Artificatus | Relieving the lung and relieving the surface, clearing heat and detoxification Chinese Pharmacopoeia |                             |
| Niuhuang Huadu Pian       | Tablet       | Arisaematis Rhizoma Preparatum, LJF, Glycyrrhizae Radix Et Rhizoma, Myrrha, Forsythiae Fructus, Angelicae Dahuricae Radix, Olbanum, Bovis Calculus Artificatus | Detoxification, detumescence and Relieve pain Chinese Pharmacopoeia |                             |
| Niuhuang Jingnao Pian      | Tablet       | Bovis Calculus Artificatus, Forsythiae Fructus, Coptidis Rhizoma, Taraxaci Herba, Cinnabaris, Calcin Magneti, Pige’ S Bile, Realgar, Trichosanthis Radix, Rehmanniae Radix, Scrophulariae Radix, Rhei | Clearing heat and detoxification Chinese Pharmacopoeia |                             |

(Continued on following page)
| Preparation name | Dosage forms | Main compositions | Traditional and clinical uses | References |
|------------------|-------------|-------------------|-------------------------------|------------|
| Niuhuang Qinggong Wan | Pill | Bovis Calculus Artificatus, Scutellariae Radix, Trichosanthis Radix, Rhei Radix Et Rhizoma, Gehrigiadis Radix, Gardeniae Fructus, Forsythiae Fructus, Curcumae Radix | Clearing heat and detoxification | Chinese Pharmacopoeia |
| Niuhuang Qinggan Jiaonang | Capsule | Scutellariae Radix, LJF, Forsythiae Fructus, Bovis Calculus Artificatus, Margaritifera Concha | Clearing heat and detoxification | Chinese Pharmacopoeia |
| Shuanghu Qinggan Keli | Granules | LJF, Polygono Cuspidati Rhizoma | Clearing heat, resolving phlegm and activating blood circulation | Chinese Pharmacopoeia |
| Shuanghuanglian Koufuye | Liquid preparation | LJF, Scutellariae Radix, Forsythiae Fructus | Clearing heat and detoxification | Chinese Pharmacopoeia |
| Qidong Yixin Koufuye | Liquid preparation | Scutellariae Radix, Ophiopogonis Radix, Ginseng Radix Et Rhizoma, Porta, Rehmanniae Radix, Testudinis Carapax Et Plastrum, Fluorite, Cinnamonomum Ramulus, Epimedi Foliun, LJF, Salviae Miltiorrhizae Radix Et Rhizoma, Curcumae Radix, Aurantrici Fructus | Soothe the nerves | Chinese Pharmacopoeia |
| Kegan Liyuan Koufuye | Liquid preparation | LJF, Scutellariae Radix, Schizonepetae Spica, Gardeniae Fructus, Forsythiae Fructus, Scrophulariae Radix, Bombyx Batrytis, Rehmanniae Radix, Belamcandae Rhizoma, Platycodonis Radix, Menthae Haplocalycis Herba, Cicadae Periostracum, Saposhnikoviae Radix, Glycyrrhizae Radix Et Rhizoma | Detoxification | Chinese Pharmacopoeia |
| Liyan Jiedu Keli | Granules | Isatidis Radix, LJF, Forsythiae Fructus, Menthæe Haplocalycis Herba, Arctii Fructus, Crataegi Fructus, Chrysanthemi Indici Flos, Violæ Herba, Pinelliae Rhizoma, Preparedatum, Aurantrici Fructus Immaturus, Glycyrrhizae Radix Et Rhizoma | Protect lungs and throat | Chinese Pharmacopoeia |

(Continued on following page)
| Preparation name            | Dosage forms | Main compositions                                                                 | Traditional and clinical uses                                                                 | References           |
|-----------------------------|--------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------|
| Lidan Pian                  | Tablet       | Scrophulariae Radix, Scutellariae Radix, Rhenanniae Radix, Trichosanthis Radix, Rhei Radix Et Rhizoma, Fritillariae Thunbergii Bulbus, Ophiopogonis Radix | Protect the liver and relieve pain                                                                 | Chinese Pharmacopoeia|
| Qingguo Wan                | Pill         | Canarii Fructus, LJF, Scutellariae Radix, Menispermi Rhizoma, Ophiopogonis Radix, Scrophulariae Radix, Paonae Radix Alba, Platycodonis Radix | Reduce swelling and relieve pain                                                                  | Chinese Pharmacopoeia|
| Badao                       | Ointment     | LJF, Forsythiae Fructus, Rhei Radix Et Rhizoma, Platycodonis Radix, Paeoniae Radix Alba, Scrophulariae Radix | Clearing heat and detoxification, Promoting blood circulation and detumescence                   | Chinese Pharmacopoeia|
| Shenyanshu Pian             | Tablet       | Atractylodis Rhizoma, Poria, Lalong Grass Rhizome, Stephaniae Tetrandrae Radix, Ginseng Radix Et Rhizoma, Polygynati Rhizoma, Cuscutae Semen, Lycii Fructus, LJF, Taraxaci Herba | Tonifying the kidney and invigorating the spleen, Diuresis and detumescence                     | Chinese Pharmacopoeia|
| Jinbei Tiankeqing Keli      | Granules     | Fritillariae Thunbergii Bulbus, LJF, Peucedana Radix, Arumamicae Semen Amarum, Mori Cortex, Platycodonis Radix, Belamcandae Rhizoma, Ephedrae Herba, Chuanxiong Rhizoma, Glycyrrhizae Radix Et Rhizoma | Tonifying lung and kidney                                                                         | Chinese Pharmacopoeia|
| Jinqi Jiangtang Pian        | Tablet       | Coptidis Rhizoma, Astragali Radix, LJF                                           | Clear heat                                                                                      | Chinese Pharmacopoeia|
| Jinyinhuai Lu               | Spray        | LJF                                                                               | Clearing heat and detoxification, reducing swelling and relieving pain, Resolving phlegm        | Chinese Pharmacopoeia|
| Jinpingu Jiaoneng           | Capsule      | Bovis Calculus Artifactus, LJF, Scopendera, Manis Squama, Bufonis Venenum, Taraxaci Herba, Scutellariae Barbatae Herba, Cremastrae Pseudobulbus Pleiones Pseudobulbus, Cucumae Rhizoma, Herdritis Diffusa, Sophorae Flavescentis Radix, Solanum Nigrum, Margarita, Rhei Radix Et Rhizoma, Aipotato Mot Rhizome, Olibanum, Myrrha, Corydalis Rhizoma, Carthami Flos, Pinelliae Rhizoma Praeparatum Cum Zingiberi Et Alumine, Codonopsis Radix, Astragali Radix, Acanthopanacis Senticosi Radix Et Rhizoma Sea Caulis, Amomum Fructus | Clearing heat and detoxification, reducing swelling and relieving pain, Resolving phlegm        | Chinese Pharmacopoeia|
| Jinsang Kaiyin Wan          | Pill         | LJF, Forsythiae Fructus, Scrophulariae Radix, Isatidis Radix, Paonae Radix Rubra, Scutellariae Radix, Mori Follifm, Chrysanthemi Flos, Peucedani Radix, Armeniacae Semen Amarum, Arcii Fructus, Alismatis Rhizoma, Scolopariae Lychnophorae Semen, Bombyx Batryticatus, Cicadae Periostracum, Oroxyli Semen | Clearing heat and detoxification, and promoting pharynx                                          | Chinese Pharmacopoeia|
| Zhizi Jinhuai Wan           | Pill         | Gardeniae Fructus, Coptidis Rhizoma, Scutellariae Radix, Rhei Radix Et Rhizoma, LJF, Anemarrhenae Rhizoma, Trichosanthis Radix | Clearing heat and detoxification                                                                | Chinese Pharmacopoeia|
| Fufang Daqingye He Ji       | Mixture      | Isatidis Foli, LJF, Notopterygi Rhizoma Et Radix, Bistortaie Rhizoma, Rhei Radix Et Rhizoma | Clearing heat, detoxification, chologagic and detumescence                                      | Chinese Pharmacopoeia|
| Fufang Qinlan Koufaye       | Liquid preparation | LJF, Scutellariae Radix, Forsythiae Fructus, Isatidis Radix                  | Clearing heat and detoxification                                                               | Chinese Pharmacopoeia|

(Continued on following page)
To date, LJF has been used in a variety of ethnic pharmaceutical formulations and foods. There are more than one hundred prescriptions involving LJF, among which there are a large number of prescriptions with LJF as the monarch drug. Among them, 62 proprietary Chinese patent medicines are sold in the medicine market. With this long history and these varied applications, LJF actually has a good curative effect on diseases. However, undiscovered active ingredient and molecular mechanism, uniform quality of LJF, which all prevent LJF from being widely used in modern clinic. We summarize the identified components and pharmacological studies of LJF in the following sections, hope to provide a material basis for further development and utilization of LJF.

**Phytochemistry**

LJF contains essential oils, organic acids, flavonoids, iridoids, saponins, trace elements and so on. In this paper, the chemical constituents of LJF are summarized. The structure of the main chemical components of LJF is shown in Figures 2–6.
FIGURE 2
The structures of organic acids from LJF.
FIGURE 3
The structures of flavonoids from LJF.
FIGURE 3
(Continued)
FIGURE 4
The structures of triterpenes and triterpenoid saponins from LJF.
Organic acids

Organic acids are the main components of LJF. The 2020 edition of Chinese Pharmacopoeia takes chlorogenic acid as the index component to control the quality of LJF, and stipulates that the content of chlorogenic acid in LJF should not be less than 1.5%. So far, about 44 kinds of organic acids have been isolated from LJF (Iwahashi et al., 1986; Choi et al., 2007; Qi et al., 2009; Song et al., 2014; Chen et al., 2015; Yang et al., 2016; Liu et al., 2018; Tan et al., 2018; Wu et al., 2019; Yang, 2019), which can be used as antioxidation, anticancer, liver protection, immune regulation, bacteriostasis, anti-virus, relieving cough and asthma and so on. The structures of organic acids are shown in Figure 2.

Flavonoids

Flavonoids are one of the main active components of LJF. According to the 2020 edition of Chinese Pharmacopoeia, the flavonoids in LJF should not be less than 0.050%. At present, there are about 62 kinds of flavonoids found in LJF (Table 3) (Son et al., 1992; Lee et al., 1995; Ren et al., 2008; Song et al., 2014; Chen et al., 2015; Liu et al., 2018; Tan et al., 2018; Wu et al., 2019; Yang, 2019), which have antibacterial, antiviral, anti-tumor, anti-oxidation, anti-inflammatory and analgesic activities, protecting liver and gallbladder, hypolipidemic, immune regulation, antitussive and expectorant, allergy and so on. The structures of flavonoids are shown in Figure 3.

Triterpenes and triterpenoid saponins

Triterpenes and triterpenoid saponins are more active components in LJF. So far, more than 35 species of triterpenoids have been isolated from LJF (Table 4) (Chen et al., 2015; Liu et al., 2018; Wu et al., 2019; Yang, 2019). It has anti-inflammatory, anti-tumorous, antibacterial, antiviral and anti-fertility activities. The structures of triterpenes and triterpenoid saponins are shown in Figure 4.

Iridoids

Iridoids have basic cores such as cyclic allyl ethers and alcoholic hydroxyl groups. Since alcoholic hydroxyl groups are hemiacetal hydroxyl groups and have active properties, such compounds mostly exist in the form of iridoid glycosides. The iridoids in LJF include common iridoid glycosides, iridoid glycosides, 4-position unsubstituted iridoid glycosides and so on. It has the pharmacological effects of protecting liver and gallbladder, anti-inflammation and analgesia, relieving pain, anti-tumor, anti-oxidation, antibacterial and so on. At present, about 66 iridoids have been isolated from LJF, which are shown in Table 5 (Song et al., 2014; Chen et al., 2015; Liu et al., 2018; Tan et al., 2018; Wu et al., 2019). The structures of iridoids are shown in Figure 5.
Essential oils

Essential oils are a kind of aromatic oily liquids in plants that can be distilled with steam. They mainly contain aliphatic compounds, aromatic compounds, sulfur-containing nitrogen compounds, terpenes and oxygen-containing derivatives. Most of them have the functions of expectorant and antitussive, invigorating stomach, antipyretic and analgesic, antibacterial

FIGURE 6
The main structures of essential oils from LJF.
and anti-inflammatory. At present, more than 279 essential oils have been isolated and identified from LJF, as shown in Table 6 (Wang et al., 1992; Wang Y. et al., 2008; Xia et al., 2012; Xiao et al., 2013; Chen et al., 2015; Wang, 2015; Li et al., 2017; Xia et al., 2017; Liu et al., 2018). The main structures of essential oils are shown in Figure 6.

| NO. | Components | References |
|-----|------------|------------|
| 1   | Ferulic acid | Chen et al. (2015) |
| 2   | 4-ferulic acid | Liu et al. (2018) |
| 3   | 5-ferulic acid | Liu et al. (2018) |
| 4   | Benzoic acid | Wu et al. (2019) |
| 5   | 1,2,4-pyrogallol | Yang (2019) |
| 6   | Caffeic acid | Choi et al. (2007) |
| 7   | Ethyl caffeate | Wu et al. (2019) |
| 8   | 5-O-caffeoylquinic acid methyl ester | Wu et al. (2019) |
| 9   | P-hydroxyphenol | Chen et al. (2015) |
| 10  | P-hydroxybenzoic acid | Wu et al. (2019) |
| 11  | Myristic acid | Song et al. (2014) |
| 12  | 1, 3-dihydroquinic acid | Liu et al. (2018) |
| 13  | 1, 5-dihydroquinic acid | Chen et al. (2015) |
| 14  | 3, 4-dihydroxyphenylproponic acid | Tan et al. (2018) |
| 15  | Isochlorogenic acid A | Iwahashi et al. (1986) |
| 16  | Isochlorogenic Acid B | Iwahashi et al. (1986) |
| 17  | Isochlorogenic Acid C | Iwahashi et al. (1986) |
| 18  | 3, 5-dio-O-caffeinoquinic acid methyl ester | Chen et al. (2015) |
| 19  | 3, 4-dio-O-caffeinoquinic acid methyl ester | Chen et al. (2015) |
| 20  | 4, 5-dio-O-caffeinoquinic acid methyl ester | Chen et al. (2015) |
| 21  | 3, 5-dio-O-caffeoxinilulate ethyl ester | Chen et al. (2015) |
| 22  | 3, 4-dio-O-caffeoxinilulate ethyl ester | Chen et al. (2015) |
| 23  | 3, 5-dio-O-baris-quinililate | Chen et al. (2015) |
| 24  | 4-Hydroxycinnamic acid | Chen et al. (2015) |
| 25  | 5-O caffeoquinic acid | Qi et al. (2009) |
| 26  | 4-O caffeoquinic acid | Qi et al. (2009) |
| 27  | 1-O caffeoquinic acid | Tan et al. (2018) |
| 28  | 3-O caffeoquinic acid methyl ester | Chen et al. (2015) |
| 29  | 5-O caffeoyl quinic acid butyl ester | Chen et al. (2015) |
| 30  | Succinic acid | Chen et al. (2015) |
| 31  | Chlorogenic acid | Yang et al. (2016) |
| 32  | Chlorogenic acid butyl ester | Chen et al. (2015) |
| 33  | Bis -(2- methyl propyl) phthalate | Tan et al. (2018) |
| 34  | Lonfuranacid A | Wu et al. (2019) |
| 35  | Lonfuranacid B | Wu et al. (2019) |
| 36  | 4 - hydroxy cinnamic acid | Chen et al. (2015) |
| 37  | 4 - hydroxy cinnamic acid methyl ester | Chen et al. (2015) |
| 38  | Cinnamic acid | Chen et al. (2015) |
| 39  | Ethyl laurate | Tan et al. (2018) |
| 40  | Tetrapedicacid B | Wu et al. (2019) |
| 41  | Vanillic acid | Wu et al. (2019) |
| 42  | 4-O- vanilic acid -D-6-O- benzoilpyranosyl group | Song et al. (2014) |
| 43  | 2(E) -3-ethoxy acrylic acid | Liu et al. (2018) |
| 44  | Palmitic acid | Liu et al. (2018) |
TABLE 3 Flavonoids in LJF.

| NO. | Components                        | References                  |
|-----|-----------------------------------|-----------------------------|
| 1   | Chrysin                           | Chen et al. (2015)          |
| 2   | 5,3′-Dimethoxyluetolin            | Liu et al. (2018)           |
| 3   | Prunetin                          | Chen et al. (2015)          |
| 4   | Flavonoidininb                    | Song et al. (2014)          |
| 5   | Hydnocarpin                       | Soo et al. (1992)           |
| 6   | Yellow Queretoside B              | Chen et al. (2015)          |
| 7   | Quercetin                         | Yang (2019)                 |
| 8   | Isoqueretin                       | Liu et al. (2018)           |
| 9   | Quercetin - 3-O-a-L-Pyran Rhamnoside | Wu et al. (2019)          |
| 10  | Quercetin-8-0-β-D-Gluconopyranosyl| Chen et al. (2015)          |
| 11  | 5′-Hydroxymethoxyhydracarpin      | Wu et al. (2019)            |
| 12  | 3′-O-Methylflavilflavone          | Chen et al. (2015)          |
| 13  | Madreselvin A                     | Song et al. (2014)          |
| 14  | Madreselvin B                     | Song et al. (2014)          |
| 15  | Luteolin                          | Yang (2019)                 |
| 16  | Luteolin - 7-0-β-D-Glucoside      | Liu et al. (2018)           |
| 17  | Luteolin - 7-0-β-D - Glucose      | Liu et al. (2018)           |
| 18  | Luteolin - 7-0-β-D - Galactoside  | Liu et al. (2018)           |
| 19  | Luteolin - 5-0-β-D - Glucose      | Liu et al. (2018)           |
| 20  | Luteolin - 7-O- Neohesperidoside  | Chen et al. (2015)          |
| 21  | 5′-Hydroxy-6, 7, 8, 4′-Tetramethoxy Flavone | Wu et al. (2019)         |
| 22  | 5′-Hydroxy-7, 4′-Dimethoxyflavone  | Chen et al. (2015)          |
| 23  | 5′-Hydroxy-7, 3′, 4′-Trimethoxy Flavones | Tan et al. (2018)        |
| 24  | 5′-Hydroxy-7, 3′,4′,5′- Tetramethoxy Flavone | Chen et al. (2015)         |
| 25  | Apigenin-7-O-a-L-Rhamnoside       | Wu et al. (2019)            |
| 26  | Apigenin-7-O-β-D-Glucoside        | Chen et al. (2015)          |
| 27  | Apigenin-5-O-β-D-Glucoside        | Chen et al. (2015)          |
| 28  | Rhoifolin                         | Song et al. (2014)          |
| 29  | Lonicerin                         | Lee et al. (1995)           |
| 30  | Kaempferol-3-O-Rutinoside         | Tan et al. (2018)           |
| 31  | Kaempferol-3-0-β-D-Glucopyranosyl | Wu et al. (2019)            |
| 32  | Kaempferol-3-0-β-D-Glucopyranosyl | Wu et al. (2019)            |
| 33  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 34  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 35  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 36  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 37  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 38  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 39  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 40  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 41  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 42  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 43  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 44  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 45  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 46  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 47  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 48  | 5,3′,4′-Tetrahydroxyflavonol-3-O-β-D-Glucoside | Chen et al. (2015)       |
| 49  | Alfalfa                           | Liu et al. (2018)           |
| 50  | Tricin                            | Chen et al. (2015)          |
| 51  | Alfalfa-7-O-β-D-Glucoside         | Chen et al. (2015)          |
| 52  | Geraniin-7-0-β-D-Glucoside        | Chen et al. (2015)          |
| 53  | Diosmetin                         | Chen et al. (2015)          |
| 54  | Diosmin                           | Chen et al. (2015)          |
| 55  | Isohamnetin                       | Wu et al. (2019)            |
| 56  | Isohamnetin-3-O-Rutinoside        | Chen et al. (2015)          |
| 57  | Isohamnetin-7-O-β-D-Glucoside     | Chen et al. (2015)          |
| 58  | Isohamnetin-3-0-β-D-Glucoside     | Chen et al. (2015)          |
| 59  | Apigenin                          | Tan et al. (2018)           |
| 60  | Ethylshikonin Dimethyl Acetol     | Wu et al. (2019)            |
| 61  | Astragalin                        | Tan et al. (2018)           |
| 62  | Apigenin-7-O-L-Rhamnoside         | Chen et al. (2015)          |

(Continued in next column)

**Glycoside**

LJF contains a variety of glycosides, such as (+)-(e)-3,5-dimethoxyphenylpropene (+)-southern candle resin; 9-0-β-d-glucopyranoside-4-o-β-d-(6-o-benzoyl)-glucopyranoside; (-)-southern candle wood resin phenol 9-0-β-d-glucopyranoside; (-)-2-hydroxy-5-methoxybenzoic acid-2-o-β-d-(6-o-benzoyl)-glucopyranoside; (-)-4-hydroxy-3,5-dimethoxybenzoic acid-4-o-β-d-(6-o-benzoyl)-glucopyranoside; (-)-(7s,8r)-4-hydroxy-3-methoxyphenylglycerin; 9-0-β-d-[6-o-(e)-4-hydroxy-3,5-dimethoxyphenylacryloyl]-glucopyranoside and so on (Chen et al., 2015).

**Other compounds**

In addition to the above ingredients, LJF also contains ginkgo alcohol, phenylalanine, stigmasterol, trans cinnamic acid, β-sitosterol-3-β-glucopyranoside-6-ethyl palmitate, daucosterol, valine, (+)-n-(3-methylbutyryl-β-d-glucosyl) nicotinic acid internal salt, (+)-n-(3-methylbutyryl-β-d-glucosyl) nicotinic acid internal salt, 2-methyllethy-o-methyladenosine, 5-methyluracil, 5-methylol adenosine, arginine, lonijaposides A1, A2, A3, A4, B1, B2, tyrosine, guanosine, guanosine, guanosine (3-hydroxybenzaldehyde)-adenosine monophosphate, 4-hydroxybenzaldehyde, 6-hydroxyethyl-3-hydroxypropidine, bisresistin, asbacisic acid, ursolic acid, adenine, isoleucine, syringin, sucrose and other compounds as well as B, Ba, Ca, Cu, Co, Cr, Fe, K, Li, Mn, Mg, Mo, Ni, Pb, Sr, Ti, V, Zn and other microelement (Shang et al., 2011; Li et al., 2020).

Researchers are currently focusing on determining the organic acids, iridoids, and flavonoids in LJF. Coumarins, steroids, and...
polysaccharides have been studied relatively little, possibly due to their low content and complex component, which are difficult to separate and purify. LJF has a wide range of medicinal values, and its annual use is particularly large, so the annual production of LJF is in short supply. Studies have shown that the flavonoid content in the leaves of LJF is two times that in the flowers, and the polysaccharide content in the stems is 1.5 times that in the flowers. On the other hand, a large number of LJF stems and leaves were discarded, which caused both resource waste and environmental pollution. Polysaccharides in LJF have been shown to have

| NO. | Components | References |
|-----|------------|------------|
| 1   | 3-O-β-D glucopyranosyl (1 → 4) - β-D-glucopyranosyl (1 → 3) - α-L-rhamnopyranosyl (1 → 2) - α-L-arabinose-Changchun saponin-28-O-β-D-glucopyranosyl (1 → 6) - β-D-glucopyranosyl ester | Liu et al. (2018) |
| 2   | 3-O-a-L-Rhamnopyranosyl (1 → 2) - α-L-arabinopyranosyl-vinchun-saponin-28-O-β-D-xlyopyranose (1 → 6) - β-D-glucopyranosyl ester | Liu et al. (2018) |
| 3   | 3-O-a-L-Rhamnopyranosyl (1 → 2) - α-L-arabinopyranosyl-Changchun-saponin-28-O-β-D-glucopyranosyl (1 → 6) - β-D-glucopyranosyl ester | Liu et al. (2018) |
| 4   | 3-O-a-L-Rhamnopyranosyl (1 → 2) - α-L-arabinopyranosyl-Changchun-saponin-28-O-a-L- (1 → 2) - β-D-xlyopyranose (1 → 6) - β-D-glucopyranosyl ester | Chen et al. (2015) |
| 5   | 3-O-a-L-Rhamnopyranosyl (1 → 2) - α-L-arabinopyranosyl-Changchun-saponin-28-O-a-L-Rhamnopyranosyl (1 → 2) - β-D-xlyopyranose (1 → 6) - β-D-glucopyranosyl ester | Liu et al. (2018) |
| 6   | 3-O-β-D-glucopyranosyl (1 → 3) - α-L-rhamnopyranosyl (1 → 2) - α-L-arabinopyranosyl-Changchun-saponin-28-O-β-D-glucopyranosyl (1 → 6) - β-D-glucopyranosyl ester | Liu et al. (2018) |
| 7   | 3-O-a-L-arabinopyranosyl-Changchun saponin-28-O-a-L-rhamnopyranosyl (1 → 2) - β-D-xlyopyranose (6) - β-D-glucopyranosyl ester | Chen et al. (2015) |
| 8   | 3-O-a-L-Rhamnopy (1 → 2) - α-L-arabinopyranosyl-vinchun-saponin-28-O-6-acetoxy-β-D-glucopyranosyl (1 → 6) - β-D-glucopyranoside | Chen et al. (2015) |
| 9   | 3-O-a-L-arabinose-oleanolic acid-28-O-β-D-glucopyranosyl (1 → 6) - β-D-glucopyranosyl ester | Chen et al. (2015) |
| 10  | 3-O-a-L-Rhamnopyranosyl (1 → 2) - α-L-arabinopyranosyl-oleanolic acid | Chen et al. (2015) |
| 11  | 3-O-β-D-glucopyranosyl-Changchun saponin-28-O-β-D-glucopyranosyl (1 → 2) - β-D-xlyopyranose (1 → 6) - β-D-glucopyranoside | Chen et al. (2015) |
| 12  | 3-O-a-L-arabinopyranosyl-oleanolic acid-28-O-β-D-glucopyranosyl (1 → 6) - β-D-glucopyranoside | Chen et al. (2015) |
| 13  | 3-O-a-L-Rhamnopyglycins (1 → 2) - α-L-arabinyl arabinosyl-oleanolic acid-28-O-β-D-glucopyranosyl (1 → 6) - β-D-glucopyranoside | Chen et al. (2015) |
| 14  | Dipsacose B | Wu et al. (2019) |
| 15  | Changchun saponin-3-O-a-L-rhamnopyranosyl (1 → 2) - α-L-arabinopyranoside | Liu et al. (2018) |
| 16  | Hederagenin | Wu et al. (2019) |
| 17  | Macranthoid A | Wu et al. (2019) |
| 18  | Macranthoid B | Wu et al. (2019) |
| 19  | Kalepanax saponin H | Wu et al. (2019) |
| 20  | Macranthoid C | Wu et al. (2019) |
| 21  | Japonicaside | Wu et al. (2019) |
| 22  | Leontoside A | Chen et al. (2015) |
| 23  | Limonin | Chen et al. (2015) |
| 24  | Akebia saponin D | Wu et al. (2019) |
| 25  | Xyloside F | Chen et al. (2015) |
| 26  | Oleanic acid | Yang (2019) |
| 27  | Oleanolic acid-28-O-a-L-rhamnopyranosyl (1 → 2) - β-D-xlyopyranosyl (1 → 6) - β-D-glucopyranoside | Chen et al. (2015) |
| 28  | Loncin A | Chen et al. (2015) |
| 29  | Loncin B | Chen et al. (2015) |
| 30  | Loncin C | Chen et al. (2015) |
| 31  | Loncin D | Chen et al. (2015) |
| 32  | Loncin E | Chen et al. (2015) |
| 33  | Ursolic acid | Yang (2019) |
| 34  | Cauloside C | Chen et al. (2015) |
| 35  | Ursolic acid | Chen et al. (2015) |
| No. | Components                                                                 | References                  |
|-----|--------------------------------------------------------------------------|-----------------------------|
| 1   | (E)aldosecologanin                                                       | Tan et al. (2018)           |
| 2   | Adinoside A                                                              | Chen et al. (2015)          |
| 3   | 7-epimacin                                                               | Liu et al. (2018)           |
| 4   | 7-epiproside                                                             | Chen et al. (2015)          |
| 5   | 7-epilog                                                                | Liu et al. (2018)           |
| 6   | 8-epimacin                                                               | Liu et al. (2018)           |
| 7   | 8-epimalic acid                                                          | Tan et al. (2018)           |
| 8   | 8-epiproside                                                             | Tan et al. (2018)           |
| 9   | 8-epigenin                                                               | Chen et al. (2015)          |
| 10  | 8-Epipanic acid                                                          | Tan et al. (2018)           |
| 11  | L-phenylalaninosecologanin B                                             | Liu et al. (2018)           |
| 12  | L-phenylalaninosecologanin C                                             | Liu et al. (2018)           |
| 13  | Dioxocetin dibutyl acetal                                                | Chen et al. (2015)          |
| 14  | Dimethyl secologanoside                                                  | Song et al. (2014)          |
| 15  | Demethylsecologanol-7-O-arabinoside                                      | Wu et al. (2019)            |
| 16  | Dehydromorronisi                                                         | Liu et al. (2018)           |
| 17  | 7-o-butyl cyclosporine                                                  | Chen et al. (2015)          |
| 18  | Sveroside                                                                | Tan et al. (2018)           |
| 19  | Dimethoxy-clavulzone                                                    | Liu et al. (2018)           |
| 20  | 7-epi-vogeloside                                                        | Tan et al. (2018)           |
| 21  | 7-O-ethyl sweroside-7-methyl ester                                       | Song et al. (2014)          |
| 22  | Grandifloroside                                                          | Chen et al. (2015)          |
| 23  | 7-O-(4-β-D-glucopyranosylxy-3-methoxy benzoyl) secologanolic acid        | Chen et al. (2015)          |
| 24  | 6′-O-(7α-hydroxyswerosyloxyl)loganin                                     | Chen et al. (2015)          |
| 25  | Japonicaside E                                                          | Wu et al. (2019)            |
| 26  | Aglycin                                                                  | Chen et al. (2015)          |
| 27  | Honeyuckle A-W                                                           | Liu et al. (2018)           |
| 28  | Split ring mackinin                                                     | Liu et al. (2018)           |
| 29  | Clef cyclic maleic acid                                                  | Chen et al. (2015)          |
| 30  | Cyclosporin                                                              | Liu et al. (2018)           |
| 31  | Split epoxide                                                            | Liu et al. (2018)           |
| 32  | Cyclosporin dimethyl acetal                                              | Chen et al. (2015)          |
| 33  | 7-epi-schizolide hemiacetal lactone                                      | Chen et al. (2015)          |
| 34  | 7-ethyl-epi-schitolid hemiacetal lactone                                 | Chen et al. (2015)          |
| 35  | Lonjaponpioside A                                                        | Wu et al. (2019)            |
| 36  | Lonjaponpioside B                                                        | Wu et al. (2019)            |
| 37  | Lonjaponpioside C                                                        | Chen et al. (2015)          |
| 38  | Lonjaponpioside D                                                        | Chen et al. (2015)          |
| 39  | Lonuphenyruvirusidose-D                                                  | Chen et al. (2015)          |
| 40  | Lonjaposide A ~ W                                                        | Chen et al. (2015)          |
| 41  | Malic acid                                                               | Tan et al. (2018)           |
| 42  | Loganin                                                                  | Tan et al. (2018)           |
| 43  | Macassin-7-one                                                           | Tan et al. (2018)           |
| 44  | Dehydromononoside                                                        | Song et al. (2014)          |
| 45  | 7α-Monoside                                                              | Tan et al. (2018)           |
| 46  | 7β-Monoside                                                              | Tan et al. (2018)           |
| 47  | L-phenylalaninosecologanin                                               | Chen et al. (2015)          |
| 48  | Deoxypropioninoxyloganin A                                               | Liu et al. (2018)           |
immunomodulatory and antiviral properties in pharmacological studies. Compared with LJF buds, the collection of stems and leaves was easier and the price was lower. These leaves and leaves, especially the leaves of LJF, should be fully utilized.

Pharmacological effects

Antipyretic effect

LJF has the function of clearing heat and detoxicating since ancient times, and its heat-clearing mechanism has been extensively studied in modern pharmacology. Duan Hongyan et al. found that the antipyretic, anti-free radical injury and immune enhancement of LJF on febrile rats were related to the increase of nitric oxide (NO) and interleukin-6 (IL-6) content in vivo (Duan and Cheng, 2009). However, the study lacked a positive drug group. Song Jianhua et al. studied the antipyretic and anti-inflammatory effects of LJF on yeast-induced fever model mice and xylene-induced inflammatory model mice. It was found that all dose groups of LJF had obvious antipyretic and anti-inflammatory effects in a dose-dependent manner ($p < 0.05$) (Song, 2011). Wang Yaqiong et al. studied the antipyretic mechanism of LJF. The results showed that the antipyretic and detoxifying effect of LJF was related to the inhibition of tricarboxylic acid cycle metabolic pathway in rats and the decrease of succinic acid, α-ketoglutaric acid and malic acid. It is related to the increase of tricarboxylic acid intermediates such as 3- hydroxybutyric acid, leucine and isoleucine (Wang Y. et al., 2016). Li Xingping et al. studied the antipyretic effects of chlorogenic acid and luteolin on animal febrile models induced by 2Magna 4-dinitrophenol, yeast and endotoxin. The results showed that different doses of LJF extract had good antipyretic effect on the above-mentioned febrile model, but chlorogenic acid and luteolin had no obvious antipyretic effect (Li et al., 2012).

Peng sha et al. established a system dynamics model and found that the efficacy of LJF in heat-clearing and detoxicating was related to the inhibition of the expressions of interleukin-1 (IL-1) and Jun N-terminal kinase (JNK) in IL-1 signaling pathway and the expression of IL-6 and C-reactive protein (CRP) in IL-6 signaling pathway. At the same time, it was further found that chlorogenic acid and linalool were involved in the regulation of IL-1 signaling pathway, while chlorogenic acid and luteolin were involved in the regulation of IL-6 signaling pathway (Peng et al., 2020). This study provided the basis for the active components and action mechanism of heat-clearing and detoxicating of LJF. However, computer simulation alone cannot improve enough clinical basis, so it is recommended that the further experiments should be verified in vivo and in vitro.

LJF has antipyretic and analgesic effects in a dose-dependent manner in vivo. Such effects may be related to the regulation of the expressions of IL-1, Jun, IL-6 and CRP, and the regulation of tricarboxylic acid cycle pathway, IL-1 signaling pathway and IL-6 signaling pathway. However, these experiments have only studied the efficacy or detected the expression of only a few proteins in the pathway, and the research is not in-depth. These conclusions are not enough to prove the entire mechanism of LJF antipyresis.

---

**TABLE 5 (Continued) Iridoids in LJF.**

| No. | Components                                      | References                  |
|-----|-------------------------------------------------|-----------------------------|
| 49  | (1S, 6R)-8-hydroxyabscisic acid-β-D-glucoside   | Chen et al. (2015)          |
| 50  | Lonicoside                                      | Chen et al. (2015)          |
| 51  | Loniceracetalide A                              | Chen et al. (2015)          |
| 52  | Loniceracetalide B                              | Chen et al. (2015)          |
| 53  | Secoxyloganin 7-butylester                     | Chen et al. (2015)          |
| 54  | Secosesquiside-7-methylster                     | Chen et al. (2015)          |
| 55  | Secosesquiside                                 | Wu et al. (2019)            |
| 56  | Secologanic acid                               | Tan et al. (2018)           |
| 57  | Styrosinose                                     | Chen et al. (2015)          |
| 58  | Abscisic acid                                  | Chen et al. (2015)          |
| 59  | Urceolide                                       | Chen et al. (2015)          |
| 60  | Vogeloside                                      | Tan et al. (2018)           |
| 61  | Vagnin                                          | Liu et al. (2018)           |
| 62  | Spiroside A                                    | Liu et al. (2018)           |
| 63  | 7-O-ethyl swertian                              | Chen et al. (2015)          |
| 64  | 6′-O-Acetyl abutin hemiacetal lactone           | Wu et al. (2019)            |
| 65  | 6′-O-Acetyl Split-epoxidized Macanin            | Wu et al. (2019)            |
| 66  | 7- O-ethoxysymononoside                         | Tan et al. (2018)           |
| No. | Components                                      | References          |
|-----|------------------------------------------------|---------------------|
| 1   | Beta-cineol                                     | Xia et al. (2012)   |
| 2   | Patchouli alcohol                              | Wang et al. (2008b) |
| 3   | Methyl anthranilate                            | Wang et al. (2008b) |
| 4   | 1,8-eucalyptol                                 | Xia et al. (2012)   |
| 5   | 2-cyclohexyl acrylate                         | Wang et al. (1992)  |
| 6   | Alpha-cedrol                                    | Xia et al. (2012)   |
| 7   | Alpha-cadinene                                 | Xiao et al. (2013)  |
| 8   | Beta-cadinene                                  | Wang et al. (1992)  |
| 9   | Delta-cadinene                                 | Xia et al. (2012)   |
| 10  | Benzaldehyde                                   | Xiao et al. (2013)  |
| 11  | Benzyl benzoate                                | Wang et al. (1992)  |
| 12  | Ethyl benzoate                                 | Wang et al. (1992)  |
| 13  | Hexyl benzoate                                 | Wang et al. (2008b) |
| 14  | (Z) -benzoic acid-3-hexene-1-ol ester          | Wang et al. (2008b) |
| 15  | 2- (benzyldene) octanol                        | Wang et al. (2008b) |
| 16  | Phenethyl alcohol                              | Wang (2015)         |
| 17  | Phenylacetaldehyde                             | Wang et al. (2008b) |
| 18  | 2-phenyl-2,4-octadienol                        | Wang et al. (2008b) |
| 19  | Alpha calacorene                               | Wang et al. (2008b) |
| 20  | Sesquiphellandrene                             | Xia et al. (2012)   |
| 21  | Menthol                                        | Xia et al. (2012)   |
| 22  | [1ar- (1aA, 4A, 4aB, 7bA)] -Octahydro-1,1,4,7-Tetramethyl-Cyclopropane E Pyazine | Wang et al. (2008b) |
| 23  | 1a, 2,3,3a, 4,5,6,7b-Octahydro-1,1,3a, 7-Tetramethyl-1-Hydro-Cyclopropane [A] Naphthalene | Wang et al. (2008b) |
| 24  | [1ar- (1aA, 7A, 7aA, 7bA)]-1a, 2,3,5,6,7,7a, 7b-Hydrogen -1,1,7,7a-Tetramethyl-1-hydro-Cyclopropane Naphthalene | Wang et al. (2008b) |
| 25  | [1R- (1A, 3aB, 4A, 7B)]-1,2,3a, 4,5,6,7,8-Octahydro-1,4-Dimethyl-7- (1-Methylethylene Ki) O | Wang et al. (2008b) |
| 26  | [1s- (1a, 4a, 7a)]-1,2,3,4,5,6,7,8-octahydro-1,4-dimethyl-7- (1-methylethylene) o | Wang et al. (2008b) |
| 27  | (+)-Longifolene                                | Xia et al. (2012)   |
| 28  | Citral                                         | Xia et al. (2012)   |
| 29  | Nerol                                          | Xia et al. (2012)   |
| 30  | Nerol ethyl ester                              | Xia et al. (2012)   |
| 31  | Nerolidol                                      | Xia et al. (2012)   |
| 32  | Guaiol                                         | Xia et al. (2012)   |
| 33  | Atractyloidin                                  | Xia et al. (2012)   |
| 34  | (Z)-beta-damascone                             | Wang et al. (2008b) |
| 35  | Eugenol                                        | Wang et al. (1992)  |
| 36  | Beta-clovene                                   | Xia et al. (2012)   |
| 37  | Beta-carotene oxygenase                        | Xia et al. (2012)   |
| 38  | P-xylene                                       | Liu et al. (2018)   |
| 39  | Delta- cedrene                                 | Xiao et al. (2013)  |
| 40  | Anthracene                                     | Wang et al. (2008b) |
| 41  | 3,3'-dimethylbiphenyl                          | Wang et al. (2008b) |
| 42  | Dibenzothiophene                               | Wang et al. (2008b) |
| 43  | 1,3-dimethylnapthalene                         | Wang et al. (2008b) |
| 44  | 1,4-dimethylnapthalene                         | Wang et al. (2008b) |
| 45  | 1,6-dimethylnapthalene                         | Wang et al. (2008b) |
| 46  | 1- (1,4-dimethyl-3-cyclohexen-1-yl) ethanone    | Wang et al. (2008b) |
| 47  | 1,6-Dimethyl-4- (1-Methylpentyl)-1,2,3,4,4a, 7-hexahydronaphthalene | Wang et al. (2008b) |
| 48  | 2,7-dimethylnapthalene                         | Wang et al. (2008b) |

(Continued on following page)
### TABLE 6 (Continued) Essential oils components in LJF.

| No. | Components                                                                 | References                                     |
|-----|---------------------------------------------------------------------------|------------------------------------------------|
| 49  | 2,2-dimethylcyclohexanol                                                 | Wang et al. (1992)                             |
| 50  | 2,4-dimethylbenzaldehyde                                                 | Wang et al. (2008b)                            |
| 51  | 2,6-lutidine                                                             | Liu et al. (2018)                              |
| 52  | 2,6-dimethyl-5,7-octadien-2-ol                                           | Wang et al. (2008b)                            |
| 53  | 2,7-dimethyl-2,6-octadien-1-ol                                           | Wang et al. (2008b)                            |
| 54  | 3,7-dimethyl-1,6-octadienol                                              | Xia et al. (2012)                              |
| 55  | 3,7-dimethyl-6-octenol                                                   | Xia et al. (2012)                              |
| 56  | (Z) -3,7-dimethyl-2,6-octylene-1-ol                                       | Wang et al. (2008b)                            |
| 57  | 3,7-dimethyl-1,5,7-octatrien-3-ol                                        | Wang et al. (2008b)                            |
| 58  | 4,7-Dimethyl-1- (1-Methyl vinyl) -1,2,3,5,6,8a-Hexahydropnaphthalene      | Wang et al. (2008b)                            |
| 59  | 4a, 8-Dimethyl-2- (1-Methylvinyl) -1, 2, 3, 4, 4a, 5, 6, 8a-Octahydropnaphthalene | Wang et al. (2008b)                            |
| 60  | 4,8a -Dimethyl-6-Isopropenyl-1,2,3,5,6,7,8a-Octahydropnaphthalene-2-Ol    | Wang et al. (2008b)                            |
| 61  | (1s -cis) -4,7-dimethyl-1- (1-methylvinyl) -1,2,3,5,6,8-hexahydropnaphthalene | Wang et al. (2008b)                            |
| 62  | 6,10-dimethyl-2-undecane                                                 | Wang et al. (2008b)                            |
| 63  | 6,10-dimethyl-3,5,9-undecytrien-2-one                                    | Wang et al. (2008b)                            |
| 64  | Trans-2- (2-pentenyl) furan                                              | Wang et al. (1992)                             |
| 65  | 2,6-di-tert-butyl-4-methylphenol                                          | Chen et al. (2015)                             |
| 66  | Carveol                                                                   | Xia et al. (2012)                              |
| 67  | 2,3-dihydrofarnesol                                                      | Wang et al. (2008b)                            |
| 68  | Methyl arachidate                                                        | Xiao et al. (2013)                             |
| 69  | Methyl behenate                                                          | Chen et al. (2015)                             |
| 70  | Methyl tetracarbonate                                                    | Chen et al. (2015)                             |
| 71  | N-pentacosane                                                             | Xiao et al. (2013)                             |
| 72  | Hexacosane                                                                | Liu et al. (2018)                              |
| 73  | Linalool                                                                  | Xia et al. (2012)                              |
| 74  | Trans-2-methyl-2-vinyl-5- (α-hydroxyisopropyl) tetrahydrofuran            | Xia et al. (2012)                              |
| 75  | Trans-linalool oxide                                                     | Xia et al. (2012)                              |
| 76  | Trans-farnesene                                                          | Xia et al. (2012)                              |
| 77  | Trans-nerolidol                                                          | Wang et al. (2008b)                            |
| 78  | Phenanthrene                                                             | Wang et al. (2008b)                            |
| 79  | Decane                                                                    | Wang et al. (1992)                             |
| 80  | 1-decene                                                                 | Wang et al. (2008b)                            |
| 81  | (E) 2-decenal                                                             | Wang et al. (2008b)                            |
| 82  | (E, E) -2,4-decadienal                                                   | Wang et al. (2008b)                            |
| 83  | 2-heptanone                                                              | Liu et al. (2018)                              |
| 84  | Heptanoic acid                                                           | Wang et al. (2008b)                            |
| 85  | (Z) -2-heptenal                                                          | Wang et al. (2008b)                            |
| 86  | Trans-3-nonen-2-one                                                      | Wang et al. (2008b)                            |
| 87  | Germacrene-D                                                             | Xia et al. (2012)                              |
| 88  | Beta-rutene                                                              | Xia et al. (2012)                              |
| 89  | Cyclooctanol                                                             | Wang et al. (2008b)                            |
| 90  | Piperene                                                                  | Wang et al. (2008b)                            |
| 91  | Beta-bisabolene                                                          | Xiao et al. (2013)                             |
| 92  | Cyclopentyl methyl cyclohexane                                           | Chen et al. (2015)                             |
| 93  | Cyclohexyl methyl benzene                                                | Chen et al. (2015)                             |
| 94  | Cyclohexyl isobutyl oxalate                                              | Chen et al. (2015)                             |
| 95  | Cyclohexyl formate                                                       | Wang et al. (1992)                             |
| 96  | Hexanoic acid                                                            | Wang et al. (2008b)                            |

(Continued on following page)
### TABLE 6 (Continued) Essential oils components in LJF.

| No. | Components                                                                 | References                                      |
|-----|-----------------------------------------------------------------------------|-------------------------------------------------|
| 97  | (E) -2-hexenal                                                             | Wang et al. (2008b)                             |
| 98  | 3-hexenol                                                                  | Wang et al. (1992)                              |
| 99  | (Z) -3-hexene-1-ol                                                          | Wang et al. (2008b)                             |
| 100 | Jujutrienone                                                                | Wang et al. (2008b)                             |
| 101 | Alpha-curcumene                                                             | Xia et al. (2017)                               |
| 102 | Alpha-farnesene                                                             | Xia et al. (2012)                               |
| 103 | Farnesyl acetone                                                           | Wang (2015)                                    |
| 104 | Farnesol acetate                                                           | Xia et al. (2012)                               |
| 105 | 10-dodecatenal                                                             | Xia et al. (2012)                               |
| 106 | Farnesol                                                                   | Wang et al. (1992)                              |
| 107 | 1-methylphenanthrene                                                       | Wang et al. (2008b)                             |
| 108 | 1-methylthyl 4-methyl-3-cyclopentenol                                       | Wang et al. (2008b)                             |
| 109 | 1- (3-methylphenyl) ethaneone                                               | Wang et al. (2008b)                             |
| 110 | 1-methylnaphthalene                                                        | Wang et al. (2008b)                             |
| 111 | 1-methoxy-4- (1-propenyl) benzene                                          | Wang et al. (2008b)                             |
| 112 | 1-methylethyl-2-hydroxybenzoate                                             | Wang et al. (2008b)                             |
| 113 | 1- (1-Methylthyl) -4,7-Dimethyl-1,2,4,5,6,8a-Hexahydroxynaphthalene         | Wang et al. (2008b)                             |
| 114 | 1-methyl-5-methylene-8- [1,3-methylethyl] -1,6-cyclodecadiene               | Wang et al. (2008b)                             |
| 115 | 1-methyl-4- (benzoyl) benzene                                               | Wang et al. (2008b)                             |
| 116 | [(E, e)]-1-methyl-5-methylene-8- (1-methylethyl) -1,6 cyclodecadiene        | Xia et al. (2017)                               |
| 117 | 2- phenanthrene                                                            | Wang et al. (2008b)                             |
| 118 | 2-methyl-5-hepten-1-ol                                                      | Wang et al. (2008b)                             |
| 119 | 2-methylbenzaldehyde                                                       | Wang et al. (2008b)                             |
| 120 | 2-methoxy-4-vinylphenol                                                     | Wang et al. (2008b)                             |
| 121 | Methyl 2-formylbenzoate                                                    | Wang et al. (2008b)                             |
| 122 | 3-methyl-9h-fluorene                                                        | Wang et al. (2008b)                             |
| 123 | 3a-Methyl-6-Methyleneoctahydrocyclobutane [1,2, 3,4] Pyrrocyclopentene       | Wang et al. (2008b)                             |
| 124 | 4-methylphenanthrene                                                       | Wang et al. (2008b)                             |
| 125 | 4-methyl-3-cyclohexene-1-acetaldehyde                                      | Wang et al. (2008b)                             |
| 126 | 4-methyl-2- (2-methyl-1-propenyl) -tetrahydropyran                          | Wang et al. (2008b)                             |
| 127 | 5-methylfurural                                                            | Wang et al. (2008b)                             |
| 128 | 6-methyl-5-hepten-2-one                                                    | Xia et al. (2012)                               |
| 129 | Copaene                                                                    | Xia et al. (2017)                               |
| 130 | Ascorbyl palmitate                                                          | Xia et al. (2012)                               |
| 131 | Carane                                                                     | Xia et al. (2012)                               |
| 132 | 2-carene-4-ol                                                              | Xia et al. (2012)                               |
| 133 | Delta-3-carene                                                             | Xia et al. (2012)                               |
| 134 | Ledol                                                                      | Xia et al. (2012)                               |
| 135 | O-hydroxyphenylacetone                                                     | Wang et al. (2008b)                             |
| 136 | 1,2-butyl isobutyl phthalate                                               | Wang et al. (2008b)                             |
| 137 | Dibutyl phthalate                                                          | Wang et al. (2008b)                             |
| 138 | Lilac aldehyde c                                                           | Wang et al. (2008b)                             |
| 139 | elemol                                                                      | Xia et al. (2012)                               |
| 140 | Beta-elemolic acid                                                          | Xia et al. (2012)                               |
| 141 | Cinene                                                                      | Xia et al. (2012)                               |
| 142 | Naphthalene                                                                | Wang et al. (2008b)                             |
| 143 | Alpha-pinene                                                               | Xia et al. (2012)                               |
| 144 | Beta-pinene                                                                | Xia et al. (2012)                               |
TABLE 6 (Continued) Essential oils components in LJF.

| N0. | Components                                      | References          |
|-----|------------------------------------------------|---------------------|
| 145 | Palmitic acid                                   | Xia et al. (2017)   |
| 146 | Methyl myristate                                | Wang et al. (2008b) |
| 147 | Myristic acid                                   | Wang et al. (2008b) |
| 148 | Nonane                                          | Wang et al. (2008b) |
| 149 | Nonanal                                         | Xiao et al. (2013)  |
| 150 | Nonanoic acid                                   | Wang et al. (2008b) |
| 151 | (E) -nonenal                                    | Wang et al. (2008b) |
| 152 | B-ginsengene                                    | Wang et al. (2008b) |
| 153 | 2,3,6-trimethylnapththalene                     | Wang et al. (2008b) |
| 154 | 1,6,7-trimethylnapththalene                     | Wang et al. (2008b) |
| 155 | 1,4,6-trimethylnapththalene                     | Wang et al. (2008b) |
| 156 | 1,4,5-trimethylnapththalene                     | Wang et al. (2008b) |
| 157 | 1,1,6-trimethyl-1,2,3,4-tetrahydronapthalene     | Wang et al. (2008b) |
| 158 | 1,1,6-trimethyl-1,2-dihydronapthalene           | Wang et al. (2008b) |
| 159 | 4- (2,6,6-trimethyl-1,3-cyclohexadienyl) -3-buten-2-one | Wang et al. (2008b) |
| 160 | 4- (2,6,6-trimethyl-1-cyclohexenyl) -3-buten-2-one | Wang et al. (2008b) |
| 161 | 6,10,14-trimethyl-5,9,13-pentadecatrien-2-one   | Wang et al. (2008b) |
| 162 | 6,10,14-trimethyl-2-pentadecanone               | Wang et al. (2008b) |
| 163 | (Z, e) -3,7,11-trimethyl-2,6,10-dodecatrien-1-ol | Xia et al. (2017)   |
| 164 | [1α- (1A, 4αb, 7A, 7α)]-Decahydro-1,1,7-Trimethylene-1-hydro-Cyclopropane [I] Pyrene | Wang et al. (2008b) |
| 165 | 6,7,10-trihydroxy-8-octadecenoic acid           | Wu et al. (2019)    |
| 166 | 3,3,7,11-tetramethyltricyclo [5.4.0.0 (4,11)] undec-1-ol | Wang et al. (2008b) |
| 167 | 3. 5-di-tert-butyl-4-hydroxybenzaldehyde        | Wang et al. (1992)  |
| 168 | Undecyl                                        | Wang et al. (2008b) |
| 169 | 2-dodecyl alcohol                               | Wang et al. (2008b) |
| 170 | 2-tridecane                                     | Wang et al. (2008b) |
| 171 | Pentadecanoic acid                              | Wang et al. (2008b) |
| 172 | Methyl pentadecanoate                           | Wang et al. (2008b) |
| 173 | Hexadecanoic acid                               | Wang (2015)         |
| 174 | Methyl hexadecanoate                            | Chen et al. (2015)  |
| 175 | Ethyl hexadecanoate                             | Chen et al. (2015)  |
| 176 | 2-heptadecane                                   | Xiao et al. (2013)  |
| 177 | Octadecaldehyde                                 | Wang et al. (2008b) |
| 178 | Octadecane                                      | Wang et al. (2008b) |
| 179 | Ethyl octadecadienoate                          | Chen et al. (2015)  |
| 180 | 9,12-octadecadiacarboxylic acid methyl ester    | Xiao et al. (2013)  |
| 181 | 9,12,15-octadecatetraenoic acid methyl ester    | Chen et al. (2015)  |
| 182 | 9,12,15-octadecanoic acid ethyl ester           | Xiao et al. (2013)  |
| 183 | Caryophyllene                                   | Wang et al. (2008b) |
| 184 | 2,5-bis (1,1-dimethyl)al -phenol                | Wang et al. (2008b) |
| 185 | Terpinene                                       | Xia et al. (2012)   |
| 186 | Umbelliferone                                   | Wang et al. (1992)  |
| 187 | Cis-2-methyl-2-vinyl-5- (α-hydroxisopropyl) tetrahydrofuran | Xia et al. (2012)   |
| 188 | Cis-3-octene-1-ol                               | Wang et al. (2008b) |
| 189 | Cis-linalool oxide                              | Xia et al. (2012)   |
| 190 | Cis-transfarnesol                               | Xia et al. (2012)   |
| 191 | Cis-jasmone                                     | Wang et al. (2008b) |
| 192 | Benzy1 salicylate                               | Wang et al. (2008b) |

(Continued on following page)
| No. | Components                           | References               |
|-----|--------------------------------------|--------------------------|
| 193 | Beta-terpinene                        | Wang et al. (1992)       |
| 194 | Beta-terpineol                        | Wang et al. (1992)       |
| 195 | 2-pentylfuran                         | Wang et al. (2008b)      |
| 196 | (+)-Aromadendrene                     | Xia et al. (2012)        |
| 197 | (-)-Alloaromadendrene                 | Liu et al. (2018)        |
| 198 | Geraniol                              | Xiao et al. (2013)       |
| 199 | Citronellol                           | Xia et al. (2012)        |
| 200 | Geranylacetone                        | Wang et al. (2008b)      |
| 201 | Cedarwood oil                         | Wang et al. (2008b)      |
| 202 | Octanal                               | Wang et al. (1992)       |
| 203 | Caprylic                              | Wang et al. (2008b)      |
| 204 | 1-octen-3-ol                          | Wang et al. (2008b)      |
| 205 | (E, e) -2,4-octadienal                | Wang et al. (2008b)      |
| 206 | 3-octanol                             | Wang et al. (2008b)      |
| 207 | 3,5 octadien-2-one                    | Wang et al. (2008b)      |
| 208 | Neolongene                            | Wang et al. (2008b)      |
| 209 | 2-vinyl alcohol                       | Wang et al. (1992)       |
| 210 | 2-ethylphenol                         | Wang et al. (2008b)      |
| 211 | 3-vinylpyridine                       | Wang et al. (2008b)      |
| 212 | 3-ethyl-2-methyl-1,3-hexadiene        | Wang et al. (2008b)      |
| 213 | 4-ethyl resorcinol                    | Wang et al. (2008b)      |
| 214 | 7-acetyl-8,9-dihydroxythymol          | Wu et al. (2019)         |
| 215 | Ethyl cyclohexane                     | Liu et al. (2018)        |
| 216 | 2-phenylethyl acetate                 | Wang et al. (2008b)      |
| 217 | Geranyl acetate                       | Wang et al. (1992)       |
| 218 | Linalyl acetate                       | Wang et al. (1992)       |
| 219 | Benzyl acetate                        | Wang et al. (1992)       |
| 220 | Terpine acetate                       | Wang et al. (1992)       |
| 221 | Isoeugenyl acetate                    | Wang et al. (1992)       |
| 222 | Ε-ylangene                            | Xia et al. (2017)        |
| 223 | F-ylangene                            | Xia et al. (2012)        |
| 224 | Alpha-ylangole                        | Xia et al. (2012)        |
| 225 | A-ylangene                            | Xia et al. (2012)        |
| 226 | T-ylangol                             | Wang et al. (2008b)      |
| 227 | Iso-pinemone                          | Wang et al. (1992)       |
| 228 | Isocinol                              | Wang et al. (2008b)      |
| 229 | 5-isopropenyl-2-methylcyclopent-1-one formaldehyde | Wang et al. (2008b) |
| 230 | Lauric acid                           | Xiao et al. (2013)       |
| 231 | Linolenic acid                        | Wang (2015)              |
| 232 | F-linolenic acid                      | Wang et al. (2008b)      |
| 233 | Methyl linolenate                     | Xia et al. (2017)        |
| 234 | Linoleic acid                         | Xia et al. (2017)        |
| 235 | Methyl linoleate                      | Wang et al. (2008b)      |
| 236 | Ethyl linoleate                       | Xiao et al. (2013)       |
| 237 | Methyl stearate                       | Wang et al. (2008b)      |
| 238 | Hexyl stearate                        | Wang et al. (2008b)      |
| 239 | Ethylene-phenylacetaldehyde           | Wang et al. (2008b)      |
| 240 | Folate                                | Xiao et al. (2013)       |

(Continued on following page)
Anti-inflammatory effect

The antipyretic effect of LJF is closely related to its anti-inflammatory effect, and it is called “traditional Chinese medicine antibiotic”. Yan Xuelong et al. found that LJF exerts its anti-inflammatory effect by inhibiting pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), IL-1β and IL-6, regulating the balance of TH1/TH2, increasing cytokines secreted by TH1 cells or reducing cytokines secreted by TH2 cells (Yan et al., 2016). However, its material basis and mechanism of action are not clear. Song Yaling et al. investigated the effects of LJF on NO, TNF-α and IL-6 produced by macrophage RAW264.7 cells stimulated by lipopolysaccharide (LPS), and studied the anti-inflammatory activity of phenolic acids in LJF in vitro. It was found that caffeic acid, methyl caffeate, chlorogenic acid, neo-chlorogenic acid, crypto-
chlorogenic acid, iso-chlorogenic acid A, iso-chlorogenic acid B and iso-chlorogenic acid C could inhibit the inflammatory cytokines produced by RAW264.7 cells stimulated by LPS in different degrees, among which caffeic acid had the strongest inhibitory activity (Song et al., 2015). However, the study lacked a positive drug group. Miao Yanyan et al. established the fingerprint of LJF and studied the spectrum-activity relationship of its anti-inflammatory action. The results showed that 17 compounds had close positive correlation with the anti-inflammatory efficacy (Miao et al., 2020).

Li Kangning et al. used LPS-induced acute anterior uveitis (AAU) mice to explore the anti-inflammatory effect of LJF and clarify its mechanism of action. The results showed that the inflammatory cell infiltration in uveal tissue was reduced to different degrees in the low, medium and high doses of LJF extract group. The mRNA and protein expression levels of Toll-like receptor 4 (TLR4) and nuclear transcription factor-kB (NF-kB) in the eye tissue of mice in the LJF extract group were significantly reduced, while the levels of TNF-α, IL-6 and IL-10 were significantly reduced. LJF extract down-regulated the expression of inflammatory cells through the TLR4/NF-kB signaling pathway to reduce the inflammatory response in the eye tissue of AAU mice, in a dose-dependent manner (Li et al., 2021).

Lou et al. studied the mechanism of chlorogenic acid on rheumatoid arthritis. The results showed that chlorogenic acid could reduce the expression of p-signal transducer and activator of transcription 3 (p-STAT3) and Janus kinase 1 (JAK1) in the JAK/STAT pathway and the expressions of p50 and IKK in the NF-kB pathway, and inhibit the inflammatory proliferation of fibroblast like synoviocytes caused by IL-6, thereby exerting the anti-inflammatory effect (Lou et al., 2016). Kao et al. studied the therapeutic effect of LJF 50% ethanol extract on LPS-induced acute lung inflammation mice. Studies had found that LJF could down-regulate the expression of TNF-α, IL-6 and inducible nitric oxide synthase (iNOS), and upregulate the expression of IL-10. At the same time, FLJ also inhibited the expressions of NF-kB, STAT3, IκB, JNK and p38 phosphorylation, and increased the phosphorylation of Sp1 to produce an effective anti-inflammatory effect on the lung (Kao et al., 2015).

LJF is effective for a variety of diseases, such as acute anterior uveitis, rheumatoid arthritis, and acute lung inflammation, caused by inflammation. The anti-inflammatory mechanism of LJF has been studied primarily at the in vitro and in vivo levels. At present, it has been found that LJF can inhibit the expression of inflammatory factors such as TNF-α, IL-6 and iNOS, and regulate TLR4/NF-kB signaling pathway and JAK/STAT pathway, thus playing an anti-inflammatory role. Organic acids are the main anti-inflammatory components. However, anti-inflammatory components and mechanism have not been adequately researched. Future scholars can expand their scope to explore other components of anti-inflammation in LJF, such as saponins and essential oils.

Antimicrobial effect

LJF has broad-spectrum antibacterial effect, which has been verified by many pharmacological experiments in vitro and in vivo. Feng Xiuli et al. used agar diffusion method to study the in vitro antibacterial activity of LJF against Escherichia Coli, Candida Albicans, Bacillus Subtilis, Aspergilus Niger and Staphylococcus Aureus. The results showed that all the five kinds of bacteria were sensitive to the water extract of LJF (Feng et al., 2013). However, only a single concentration of water extract of LJF and the lack of positive drug group are the two limitations of this experiment.

Hu Xuan et al. found that the aqueous extract of LJF has bacteriostatic and bactericidal effects on escherichia coli, candida albicans, klebsiella pneumoniae, staphylococcus aureus, pseudomonas aeruginosa and streptococcus B (Hu et al., 2015a). Great efforts have been made by the researchers in the search for the antibacterial active ingredient of LJF. (Han et al., 2014) conducted a comparative study of the antibacterial effects of 3, 4-di-O-cafeoylquinic acid (3, 4-diCQA), 3, 5-di-O-cafeoylquinic acid (3, 5-diCQA), and 4,5-di-O-cafeoylquinic acid (4, 5-diCQA) on Bacillus subtilis. The order of efficacy was determined to be 3, 5-diCQA > 4, 5-diCQA > 3, 4-diCQA by comparing the IC50 values of each compound. This experiment has shown that slight differences in chemical structures of similar compounds can also greatly affect their drug efficacy. In this experiment, the changes of the position and distance of caffeoyl ester groups greatly affected the antibacterial effect (Han et al., 2014). Yang et al. studied the antibacterial activity of 7-acetyl-8,9-dihydroxy thymol, first isolated from LJF, and the known 7,8-dihydroxy-9-buuryl thymol. Two compounds were found to have antibacterial activity against Staphylococcus aureus, Escherichia coli, Micrococcus luteus, and Bacillus cereus. IC50 values range from 27.64 ± 2.26 to 128.58 ± 13.26 μg/ml (Yang et al., 2018). Wang Qing et al. showed that LJF had good inhibitory effect on standard staphylococcus aureus, staphylococcus epidermidis, escherichia coli, diplococcus pneumoniae, staphylococcus aureus, bacillus subtilis, staphylococcus aureus, pseudomonas cepacia and streptococcus B. The minimum inhibitory concentration was 37.5–100.00 mg. Different concentrations of LJF extract could also reduce the mortality of mice caused by diplococcus pneumoniae and staphylococcus aureus and prolong the survival time of infected mice (Wang Q. et al., 2008). Guan Zhongying et al. found that LJF extract could well inhibit streptococcus pneumoniae and pseudomonas aeruginosa, the diameter of bacteriostatic zone was more than 19mm, and the minimum inhibitory concentration of LJF extract to escherichia coli, streptococcus pyogenes, staphylococcus aureus, shigella dysenteriae and streptococcus agalactis was less than 0.125 g/
ml (Guan et al., 2009). However, the above studies are lack of research on the basis and mechanism of anti-bacterial substances of LJF.

Zhang Zhongbin et al. found that phenolic acids in LJF were positively correlated with antibacterial activity (Zhang et al., 2019). Future scholars can use this as a reference to conduct in-depth study on the antibacterial material basis and mechanism of LJF, so as to provide a scientific basis for clinical application. Zeng Huaqian et al. determined the minimum inhibitory concentration of LJF on Staphylococcus mutans UA159 by liquid double dilution method. LJF could inhibit the growth, acid production and adhesion of Staphylococcus mutans UA159 and reduce the formation of biofilm (Zeng et al., 2022). Shi et al. through the construction of spectrum-activity relationship found that LJF had an antibacterial effect against P. aeruginosa, a common strain in wound sites, and chlorogenic acid and 3,4-dicaffeoylquinic acid were the main components of LJF that had antibacterial effect through the construction of spectrum-activity relationship (Shi et al., 2016). Yang et al. studied the antibacterial activity of five kinds of iridoid glycosides firstly isolated from LJF against Staphylococcus aureus ATCC 25923. The results showed that all the compounds showed slight inhibitory activity, with MIC values ranging from 13.7 to 26.0 g/ml (Yang et al., 2019).

The above studies have found that LJF extract has a significant antibacterial effect, and the effective components include phenolic acids, thymol derivatives and iridoid glycosides. These experimental results further enriched our understanding of the antibacterial activity of LJF and provided a scientific basis for the clinical treatment of drug-resistant pathogens. However, the antibacterial mechanism has not been studied in depth, and the mechanism by which these compounds inhibit the synthesis of bacterial cell walls or interfere with the synthesis of protein or inhibit the transcription and replication of nucleic acids has not been elucidated. In addition, most studies did not set up a positive group, and did not study the targets and pathways of compound action. LJF has a broader antibacterial spectrum than other common antibacterial agents. Further studies should also be conducted on the antibacterial components in LJF, such as polysaccharides and essential oils. At the same time, most bacteria develop drug resistance due to the abuse of antibiotics, and further research should be conducted on the efficacy of LJF against drug-resistant bacteria.

Antiviral effect

Mi Huijuan et al. established the antiviral spectral effect model of LJF and found that the IC50 of 10 batches of LJF was between 0.911 and 2.441 μg/ml (Mi et al., 2015). Wang Bianli et al. studied LJF and its antiviral activity by spectrum-effect relationship, and found that LJF had significant inhibitory activity on influenza A virus H1N1, and the treatment index of 80 batches of LJF against influenza A virus H1N1 was 14.57–39.85, which in some batches was higher than that of positive control drug ribavirin (16.78). However, it had no significant effect on herpes simplex virus type I and hand-foot-mouth disease virus EV71 strain in the LJF (Wang et al., 2015).

Li Meiyu et al. observed the inhibitory effect of LJF on human respiratory syncytial virus type 3 in human cervical cancer cell line (Hela). It was found that LJF could directly inactivate Hela cells (IC50 = 0.16 mg/ml, TI = 31.2), and LJF could also inhibit respiratory syncytial virus biosynthesis (IC50 = 1.0 mg/ml, TI = 5). The results showed that LJF had antiviral effect in vitro mainly through direct inactivation, inhibition of virus adsorption and inhibition of biosynthesis (Li, 2010). The experiments of Liu Ying et al. in vitro showed that the extract of LJF had obvious antiviral effect on vero cells infected with herpes simplex virus type I. The maximum non-toxic concentration was 384 mg/L and the therapeutic index was 26.56. The results of in vivo experiments showed that LJF had a good therapeutic effect on herpes simplex keratitis, which could reduce the degree of keratopathy and shorten the cure time (Liu and Wang, 2011). However, the above studies are lack of research on the active material basis of LJF. Ma Shuangcheng et al. screened the anti-virus components in LJF, and finally determined that luteolin-7-O-glucoside and luteolin were the active components of LJF with strong anti-respiratory virus components (Ma et al., 2006). Chen Juanshuang et al. found that chlorogenic acid in LJF has a good anti-HCMV effect. The maximum non-toxic concentration was 100 μg/ml, the minimum effective concentration was 1 μg/ml, and the therapeutic index was 100 (Chen et al., 2009).

Ding Jie et al. established the fingerprint of LJF polysaccharide and investigated its inhibition effect on respiratory syncytial virus (RSV). The results showed that there were 12 common peaks in the GC fingerprint of 12 batches of LJF medicinal materials with the similarity ≥ 0.994. The EC50 values of the total polysaccharide, 80% alcohol-precipitated polysaccharide, 50% alcohol-precipitated polysaccharide and 20% alcohol-precipitated polysaccharide of LJF (S12) were 0.76, 0.61, 1.03 and 3.04 μg/L, respectively. The TI values were 15.36, 18.51, 11.69 and 4.22, respectively. The results showed that LJF had certain RSV inhibitory activity in vitro (Ding et al., 2020).

In addition, LJF also has effects in anti-avian influenza virus, anti-coxsackie virus, anti-Eco virus, anti-rubella virus, anti-poliovirus, anti-varicella zoster virus, anti-adenovirus, anti-porcine reproducton and respiratoriosyndrome virus, anti-pseudorabies virus, anti-human immunodeficiency virus and other effects (Zhang et al., 2016). Kashiwada et al. studied the antiviral activity of six secoridoids compounds in LJF against influenza A virus. Studies have shown that vogelosine, 7-epi-Vogelosine, secoxyloganin, dimethyl secologanoside and sweroside can inhibit the virus at 100 μg/ml, and the
inhibition range is 53.1–28.4%. Among them, secoxyloganin showed the best inhibition effect, reaching 53.1% (Kashiwada et al., 2013).

To sum up, the current research shows that LJF has good antibacterial and antiviral effect. The antiviral components in LJF are flavonoids, polysaccharides and secoiridoid glucosides. As a medicinal material with homology of medicine and food, it is expected to become an important screening target of new antibacterial and antiviral drugs because of its natural properties, low-toxic and high in efficacy, as well as broad spectrum antibacterial properties and heat-clearing and detoxification effects. The symptoms of novel coronavirus (COVID-19) that broke out in 2019 are generally fever, cough and dyspnea. With Lianhua Qingwen capsule, a Chinese medicine preparation containing LJF, playing a preventive and therapeutic intervention in COVID-19 patients. Traditional Chinese medicine, particularly LJF, has demonstrated that it can significantly reduce fevers and improve breathing in COVID-19 patients by relieving their symptoms (Luo et al., 2021; Yao et al., 2022).

Antioxidation

Liu Hao et al. analyzed the antioxidant activity of ethanol extracts of LJF with different concentrations. The results showed that 95% ethanol LJF extract had the strongest scavenging effects on OH and DPPH, with the scavenging rate of 90.69% and 65.64%, respectively. Further studies showed that the content of chlorogenic acid, flavonoids and polyphenols in the 95% ethanol extract was also the highest, indicating that the content of these compounds was positively correlated with antioxidant activity (Liu et al., 2016). Tian Lei et al. found that different proportions of LJF extract had good inhibitory effects on DPPH, OH and superoxide anion radical (O2-[O]), increased the content of NO in the supernatant of damaged HUVECs cells, decreased the release of lactate dehydrogenase (LDH), and played a good role in anti-free radicals and antioxidation (Tian et al., 2014). Xu Xiaobo et al. compared the antioxidant activity of extracts from the stems, leaves and flowers of LJF. The results showed that when the concentration of flower extract was 0.22 mg/ml and 0.18 mg/ml, the DPPH free radical and ABTS + free radical scavenging rates were the highest among the three, reaching 90% and 90%, respectively. The IC50 values for DPPH radical scavenging and ABTS + radical scavenging of the flower, stem and leaf extracts were 0.07, 0.13, 0.17 and 0.05, 0.10, 0.15 mg/ml, respectively. Chlorogenic acid and caffeic acid were also found to have the highest contents in the flower extracts (Xu et al., 2018). Liu Changping et al. also found that flavonoids in LJF can block the autoxidation of linoleic acid and lard (Liu, 2009). The antioxidant activity of LJF was studied from different parts, extraction methods and doses of LJF in the above experiments, and good antioxidant activity of LJF in vitro was obtained. However, drugs should eventually be administered in vivo, which is different from a single in vitro environment and contains many cytokines. The results of antioxidant experiments in vitro may not be achieved in vivo. Therefore, the antioxidant effect and mechanism of LJF in animals should be further studied.

Luo Lei et al. found that different doses of LJF flavonoids could significantly promote the proliferation of RAW264.7 cells, increase the total antioxidant capacity and the activities of catalase (CAT), glutathione peroxidase (GSH-px) and superoxide dismutase (SOD), decrease the activity of LDH and malondialdehyde (MDA) content, and protect RAW264.7 cells from hydrogen peroxide-induced injury in a dose-dependent manner (Luo et al., 2018). Liang Conglian et al. established the spectral effect model of scavenging DPPH free radicals in LJF, in order to find the active components with scavenging DPPH free radicals in LJF. The results showed that there was a significant negative correlation between the contents of isochlorogenic acid B and isochlorogenic acid C and the scavenging activity of DPPH free radicals (Liang et al., 2015). Li Ying et al. found that methyl 3,4-dicaffeoylquinic acid (IC50 = 8.36 μmol/L), quercetin (IC50 = 6.46 μmol/L) and luteolin (IC50 = 2.08 μmol/L) in LJF had good xanthine oxidase inhibitory activity. Among them, the antioxidant activity of flavonoid aglycone > flavonoid glycosides, dicaffeoylquinic acid methyl ester > dicaffeoylquinic acid > monocafeoylquinic acid, and the 5-position substitution of dicaffeoylquinic acid made the greatest contribution to the antioxidant activity of the compounds (Li et al., 2011). This provides a scientific basis for the preparation of antioxidants from LJF.

Zhao Minmin et al. established an offline two-dimensional-High Performance Liquid Chromatography-DPPH-Electrospray ionization-Quadrupole-Time of Flight/mass (2D-HPLC-DPPH-ESI-Q-TOF/MS) technique to screen the antioxidant components in LJF. The results showed that a total of 36 components with antioxidant activity were screened out, and seven components including isochlorogenic acid B, isochlorogenic acid A, 1,3-dicaffeoylquinic acid, isochlorogenic acid C, rutin, cryptochlorogenic acid, and chlorogenic acid were verified to have good antioxidant activity in vitro (Zhao et al., 2020). Lv Rui et al. applied HPLC to determine the contents of multiple organic acids, luteolin-glucoside and anthocyanin components in LJF at different florescence and the relationship between functional components and antioxidant activity during different florescence. The results showed that there was a significant positive correlation between the content of chlorogenic acid and DPPH and ABTS + clearance, and there was a significant positive correlation between the content of neochlorogenic acid, crypto-chlorogenic acid and luteolin and ABTS + clearance. Florescence was negatively correlated with anthocyanin content and DPPH clearance (Lv and Xu, 2022).

Xiao et al. studied the antioxidant effects of 4,5-di-O-cafeoylquinic acid methylester (4,5-CQME) isolated from
LJF on the liver oxidative damage HepG2 cells model induced by H2O2. They found that 4,5-CQME could up-regulate the mRNA and protein expressions of NAD (P)H:quinone oxidoreductase 1 (NQO1), and HO-1 and down-regulate the expression of Kelch-like ECH-associated protein 1 (Keap1) and promote nuclear factor erythroid-2 related factor 2 (Nrf2) translocation, thus inhibiting oxidative stress by regulating Keap1/Nrf2 pathway. While the Nrf2 inhibitor ML385 can reduce the protection of 4,5-CQME (Xiao et al., 2020). Han et al. studied the antioxidant effect of chlorogenic acid on osteoblast MC3T3-E1 cell oxidative stress model induced by H2O2. Chlorogenic acid was found to significantly reduce H2O2-induced oxidative damage and activate the phosphorylation of Protein kinase B (Akt) by up-regulating the protein expression of HO-1 and the upstream mediator Nrf2. After administration of LY294002 (Phosphoinositide 3-kinase (PI3K)/Akt inhibitor), the expression of HO-1 and Nrf2 was inhibited again, indicating that chlorogenic acid protected cells from oxidative damage through PI3K/Akt-mediated activation of the Nrf2/HO-1 pathway (Han et al., 2017).

The main antioxidant components in the above study were organic acids and flavonoids in LJF, and most of the indicators involved were the DPPH free-radicals scavenging activity. Studies have shown that the antioxidant effects of organic acids may be achieved by regulating the Keap1/Nrf2/HO-1 pathway and PI3K/Akt pathway. However, the current experiments are limited to cell-level research. Future researchers should also verify this mechanism at animal and clinical levels to study the antioxidant mechanism and ability of LJF in vivo. Synthetic antioxidants often have some toxic and side effects, and LJF is expected to become a low-toxicity and high-efficiency food antioxidant. Organic acids and flavonoids are also abundant in the stems and leaves of LJF. The pruning of LJF produces a large number of stems and leaves that should not be discarded as medicinal or natural antioxidant preparation.

**Immunomodulatory effect**

Pi Jianhui et al. showed that flavonoids in LJF could significantly increase the organ index of immunosuppressed mice, increase the activities of acid phosphatase (ACP), alkaline phosphatase (AKP) and lysozyme (LSZ) in plasma, increase the levels of total antioxidant capacity (T-AOC) and SOD, and decrease the contents of monoamine oxidase (MAO) and MDA. It has good immunomodulatory function (Pi et al., 2015). Yin Hongmei et al. found that LJF polysaccharides had obvious immunomodulatory effect, and the efficacy was positively correlated with the dose (Yin et al., 2010). Zhou Xiuping et al. have shown that LJF can increase the phagocytic index of macrophages, enhance the transformation rate of lymphocytes, and enhance the secretion of IL-2, Interferon-γ (IFN-γ) by Th1 cells. The mRNA expression of TNF-α is well developed and plays an immunomodulatory role (Zhou et al., 2011). The above experiments studied the optimal extraction process of LJF in terms of immune activity, and discussed the mechanism of LJF at the molecular level, and proved that LJF has a good immune regulatory effect at the animal level. However, the optimal dose of LJF in immune regulation still needs to be studied to lay a foundation for future practical application.

Zhang Wenwen et al. analyzed the proliferation effect of LJF on mouse lymphocytes through lymphocyte trans-formation experiment. The results showed that all the essential oils from LJF could significantly promote the transformation of mouse lymphocytes, but the pharmacological activity of the essential oil from LJF in enhancing immunity was more significant (Zhang et al., 2020). Zhou et al. studied the immunomodulatory effect of LJF polysaccharide on immunosuppressed mouse models induced by cyclophosphamide. It has been discovered that LJF can significantly increase the thymus and spleen indices of mice, facilitate the activation of spleen lymphocyte proliferation, enhance the phagocytosis of macrophages and natural killer (NK) cell activity, and enhance the immune function of mice. LJF also upregulated IL-2, TNF-α, and IFN-γ levels and increased the percentage of CD4 and CD8 T-cell subsets and the CD4/CD8 ratio. Experiments have shown that LJF can be used as a potential immunomodulator (Zhou et al., 2018). Bai et al. also performed in vivo studies on the immunoregulatory effects of LJF polysaccharides. The mouse model of allergic rhinitis was established by ovalbumin induction. LJF significantly inhibited the sneezing frequency and the number of nasal wipe movements, and inhibited the infiltration of inflammatory cells in the nasal mucosal tissue of model mice after administration. Biologically, LJF inhibited serum levels of immunoglobulin E (IgE), TNF-α, IL-1β, and IL-17. LJF also inhibited mRNA expression levels of IL-4, IL-5, IL-6, IL-17, IL-23, retinoic acid receptor-related orphan receptor γt (ROR-γt) and STAT3, inhibited protein expression levels of ROR-γt and STAT3, and increased mRNA and protein expression levels of Suppressor Of Cytokine Signaling 3 (SOCS3). The results showed that LJF had a therapeutic effect on allergic rhinitis by regulating the immune response of Th17 cells (Bai et al., 2020). This study provided the basis data for further application of LJF to functional foods.

In the above studies, polysaccharides, essential oils and flavonoids are the main components of LJF that play an immune regulation. Particularly, polysaccharides are the most studied and also play a major role in LJF. LJF regulates immune diseases mainly by regulating inflammatory and immune factors in immune T cells and promoting NK cell activity, and can also act on STAT3/ROR-γt pathway, which is the key part of TH17 cell differentiation. However, there is currently no unified specification for the extraction of polysaccharides from LJF, resulting in uneven polysaccharide content and lack of relevant research on the optimal and effective dose of LJF for...
immune regulation. This has created great difficulties for its clinical application. In the future, new preparation technologies such as microspheres, nanoparticles, and liposomes should be applied to the research and development of LJF polysaccharide preparations to improve the stability and bioavailability in vivo.

Hepatoprotective effect

Li Xiansheng et al. have shown that total saponins in 70% alcohol extract of LJF at different doses can increase the activity of serum SOD, reduce the content of MDA, and inhibit hepatomegaly induced by CCl4 in mice, thus protecting the liver (Li, 2009). Liu Chang et al. used network pharmacology and experimental verification to predict the targets of LJF for the prevention of acute alcoholic liver injury and established an SD rat model of acute alcoholic liver injury. The results showed that serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and liver tissue MDA levels of rats in the high, medium and low dose groups of LJF were significantly reduced, serum IL-6 content of rats in the low and high dose groups of LJF was significantly reduced, and the SOD and GSH-Px contents of liver tissue in the medium and high dose groups of LJF were significantly increased. The PCR results showed that high, medium and low dose groups of LJF could significantly reduce the expression levels of mitogen-activated protein kinase 4 (MAP2K4) and MAPK3 genes (Liu et al., 2021).

Tu Suiping et al. determined the testosterone metabolism rate of cytochrome P450 family 3 subfamily A (CYP3A) substrate in rat liver microparticles by HPLC, and determined the mRNA expression levels of CYP3A1 and CYP3A2 enzymes in rat liver by PCR technology, to investigate the effects of LJF extract on CYP3A enzyme activity and gene expression in rats. The results showed that long-term administration of LJF had no significant effect on CYP3A enzymes in rats (Tu et al., 2020). Yan Shihao et al. used a C57 mouse model of hepatic fibrosis to explore the effect of the combination of LJF and Forsythia suspensa extract on hepatic fibrosis. The results showed that after intervention with different doses of LJF-Forsythia suspensa composition, the mRNA expressions of Collagen type I alpha 1 (Col1a1), Collagen alpha-1(III) chain (Col3a1), fibronectin (FN) and transforming growth factor-β (TGF-β) in the liver of model mice were significantly down-regulated, as well as the mRNA and protein expressions of alpha-smooth muscle actin (α-SMA) (Yan et al., 2021). Other studies have shown that LJF can protect the liver by reducing the levels of γ-glutamyl transpeptidase (γ-GT) and alkaline phosphatase (ALP) in serum, increasing the levels of albumin (ALB) and total protein (TP), and reducing the content of GSH-Px in liver (Teng et al., 2014; Teng et al., 2016).

Xu Xiaoyan et al. used SD rats with liver fibrosis to explore the effect and mechanism of total flavonoids of LJF on the improvement of CCl4-induced liver fibrosis. The results showed that compared with the model group, the liver fibrosis was significantly alleviated in the low-dose and high-dose groups of total flavonoids of LJF. The ALT activity in serum, hydroxyproline (Hyp) content and MDA content in liver tissue were significantly decreased, and the activities of T-SOD and GSH-Px were significantly increased. The total flavonoids of LJF can inhibit the proliferation and promote the apoptosis of hepatic stellate cells (HSC) in different degrees (Xu et al., 2020). Ge et al. studied the liver protection effects of four newly isolated flavonoids (japoflavone A-D) and ten known flavonoids on H2O2-induced in SMCC 7721 cells and HepG2 cells. It was found that japoflavone D could improve H2O2-induced apoptosis of hepatocytes and reverse the decreases of CAT and SOD in the model group in a dose-dependent manner. Japoflavone D can be used as a new hepatoprotective drug for further study (Ge et al., 2018). Tzeng et al. studied the liver protection of LJF ethanol extract on nonalcoholic steatohepatitis (NASH) model mice after induction of methionine-choline deficiency diet for 8 weeks. LJF was found to significantly improve inflammation and fibrosis in the liver of model mice, and inhibit ALT, AST in plasma and MDA levels in liver tissues. LJF also inhibited the mRNA expression of Cytochrome P450 Family 2 Subfamily E Member 1 (CYP2E1), TNF-α, TGF-β1, α-SMA, Collagen 1, matrix metalloproteinase 2 (MMP2), MMP9, and diacylglycerol o-acyltransferase 2 (DGAT2) in liver tissue and up-regulated the mRNA Expression of peroxisome proliferator-activated receptor-α (PPAR-α). The liver protective effect of LJF on NASH is also related to up-regulating the expression of p-ERK and reducing the expression of p-JNK in MAPK signaling pathway (Tzeng et al., 2015).

In summary, LJF has effects in treating acute liver injury, non-alcoholic steatohepatitis, and liver fibrosis. In recent years, more and more studies have preliminarily confirmed the effect of LJF on the liver. Saponins and flavonoids are the components of LJF with hepatoprotective effect. It was found that the pathway in which LJF worked involved the extracellular regulated protein kinases (ERK) and JNK pathways in the mitogen-activated protein kinase (MAPK) signaling pathway, but had no effect on the p38 pathway. Although the research on liver protection is getting deeper and deeper, there are still some problems need to be further discussed. For example, at present, the pathways involved in liver injury also include NF-κB signaling pathway and STAT3 signaling pathway, and whether LJF also acts on these pathways needs further verification (Xu et al., 2014; Kim et al., 2020). The key components for hepatoprotective effect of LJF are mainly concentrated on LJF extract, and the mechanism of action of saponins and flavonoids in LJF extract is lack of research.

Anti-tumor effect

Liu Yuguo et al. found that polysaccharides in different doses of LJF could regulate b-cell lymphoma-2/bcl-2-associated x (Bcl-
2/Bax) apoptosis pathway; middle and high doses of LJF polysaccharides could increase the content of TNF-α in serum (p < 0.05) and inhibit S180 sarcoma (the inhibition rate was 23.85%, 30.02% respectively) (Liu et al., 2012). Liu Bei et al. found that LJF polysaccharides (10-250 μg/ml) had antitumor activity by promoting the proliferation of spleen lymphocytes in mice, especially at the concentration of 100 μg/ml (p < 0.01) (Liu and Liu, 2013). These provide a scientific reference for the further study of the anti-tumor mechanism of LJF. However, these studies lack the validation of the anti-tumor target of LJF and the optimal extraction method and dose size for its clinical application.

Lin et al. studied the anti-tumor effect of LJF polysaccharide LJ-02-1 with molecular weight of 54 kDa on pancreatic cancer cells, and they found that the inhibition rates of LJF polysaccharide on BxPC-3 and PANC-1 pancreatic cancer cells at the concentration of 1 mg/ml were 66.7% and 52.1%, respectively (Lin et al., 2016). Park et al. studied the anti-cancer effect of LJF polyphenol extract on human HepG2 cells. Polyphenol extracts were found to inhibit HepG2 cell migration in a dose-dependent manner and reduce the expression of MMP-2 proteins associated with cell migration. The polyphenol extract can prevent cell G2/M phase and induce apoptosis, inhibit the expression of mitotic-related cyclin dependent kinase 1 (CDK1), cell division cycle 25c (CDC25C), and cyclin B1 proteins, inhibit the expression of apoptosis-related proteins Bcl-xL, pro-caspase-3, pro-caspase-9 and poly(ADP-ribose) polymerase (PARP), and promote Bax expression. The polyphenol extract can dose-dependently inhibit p-P13K, p-Akt expression, promote p-ERK1/2, p-JNK and p-38 MAPK expression, and exert anti-tumor effect by regulating P13K/Akt and MAPKs pathways (Park et al., 2012).

Patil et al. synthesized LJF gold nanoparticles and found that it could inhibit HeLa cells by 10.54, 29.38, 47.58 and 62.73% at 200, 300, 400 and 500 μg/ml (Patil et al., 2019). Rajivgandhi et al. synthesized LJF silver nanoparticles using the nano-silver technology and found that it effectively inhibited the viability of A549 lung cancer cells by increasing ROS production at 75 μg/ml (Rajivgandhi et al., 2022).

The above research has revealed that LJF has good anti-tumor effect on pancreatic cancer, liver cancer, cervical cancer and lung cancer, and its active components are polysaccharides and polyphenols. The anticancer effect and mechanism of LJF may be related to the regulation of PI3K/Akt and MAPKs pathways and intrinsic apoptotic pathway. In addition, LJF has been studied in recent years with respect to its nano-silver and nano-silver composites, which exhibit a good anticancer effect. However, in the above studies, no anticancer study was conducted on the single compound of LJF, and no in-depth verification of the related mechanisms was conducted in animals and clinic, which makes it difficult to ensure the clinical safety and effectiveness of LJF. In the future, researchers can study the anti-cancer effects of luteolin and chlorogenic acid, and use the popular drug nano controlled release system to study the targeted and localized administration of LJF.

Hypoglycemic and hyperlipidemic effect

Chen Xiaolin et al. found that the water extract of LJF could reduce glucose by inhibiting the activities of α-amylase and α-glucosidase, and the inhibitory effect increased with the increase of the concentration of the extract (Chen, 2010). However, this study lacks positive drug group and control group. Ye Qinghua used streptozotocin (STZ) to induce type II diabetic rat model. After 42 days of administration of LJF extract, it was found that the levels of blood glucose and insulin in the treatment group were lower than those in the control group and model group (p < 0.05, p < 0.01). The levels of ALT, AST and gamma-glutamyl transferase (GGT) in serum decreased significantly (p < 0.05). Low density lipoprotein cholesterol (LDL-C) (71.2%–76.3%, p < 0.01), high-density lipoprotein cholesterol (HDL-C) (21.6%–24.3%, p < 0.05), very low-density lipoprotein cholesterol (VLDL-C) (45.2%–50.0%, p < 0.01), triglyceride (TG) (50.6%–53.8%, p < 0.01), total cholesterol (TC) (45.8%, 51.0%, p < 0.05) significantly increased. CAT, SOD and GSH in liver increased significantly (Ye, 2018). To sum up, LJF has a significant hypoglycemic effect. LJF (4.2 g/kg) can not only reduce the level of triglyceride in serum and liver tissue of hyperlipidemic model mice, but also reduce the level of blood glucose in alloxan diabetic model mice and sucrose-induced hyperglycemia model mice (Wang et al., 2007).

Zhang et al. found that LJF polyphenol extract significantly reduced the postprandial blood glucose level of diabetic rats and inhibited the α-glucosidase activity related to glucose absorption, with 3,5-dicaffeoyl quinic acid playing the main role, while chlorogenic acid and rutin had relatively weak inhibitory activity (Zhang et al., 2014). Wang et al. studied the hypoglycemic and hypolipidemic effects of LJF polysaccharide on diabetic SD rats induced by streptozotocin. Compared with the last experiment, the polysaccharides had inhibitory activity on both α-amylase and α-glucosidase. The IC50 values against the inhibitory activity of the positive drug acarbose against α-amylase and α-glucosidase were 59.4 and 39.7 μg/ml, with LJF polysaccharides reaching 61.2 and 45.6 μg/ml. LJF polysaccharides (800 mg/kg) reduced serum glucose and improved insulin resistance, and increased liver and skeletal muscle glycogen content. This mechanism might be related to the recovery of pyruvate kinase and hexokinase activities. In terms of reducing blood lipid, LJF polysaccharide can reduce the content of TC, TG, LDL-C and VLDL-C and increase the content of HDL-C to achieve the effect of reducing blood lipid. The study also showed that the hypoglycemic and hypolipidemic effects of LJF polysaccharide were related to the inhibition of antioxidant enzymes ALT, AST and GGT, the increase of CAT, SOD and
GSH, and the inhibition of oxidative stress response in vivo (Wang et al., 2017).

The above studies have shown that LJF has good therapeutic effects on diabetes and complications, coronary heart disease, atherosclerosis and other diseases caused by hyperglycemia and hyperlipidemia. Similar to the anti-tumor effect, the most studied components are still polyphenols and polysaccharides. However, most of the above studies lack positive drug comparison, and only detect the biochemical factors related to insulin resistance, glucose metabolism and lipid metabolism, and lack in-depth research on the targets, pathways and related protection mechanisms. Known antidiabetic drugs, including biguanides and sulfonylureas, are compared as positive agents. Foxo1 and Foxo3, AMPK pathway, INSR/IRS-1/PI3K/Akt/GSK-3/GLUT-4 pathway, and PI3K-Akt/PKB pathway are currently the key targets and pathways for lowering blood glucose and blood lipid. Future scholars can study the hypoglycemic and hypolipidemic effects of LJF in vivo and in vitro based on the above pathways.

Toxic effect

There was no significant difference in acute toxicity between the aqueous extract of LD50 (72.12 g/kg) and diploid (69.92 g/kg). The administration dose is equivalent to 412 and 400 times of the safe dose of human body (body mass 60 kg). Hu Xuan et al. studied the acute toxicity of LJF and found that LJF was given four times by intra-gastric administration (Hu et al., 2015b).

Pu Hanlin et al. studied the long-term toxicity of LJF in mice. The mortality rate of LJF (3 g/100 ml) within 5 days was 70%. Before and after 5 days, the mortality rate reached 90%. The content of phosphorus, copper, magnesium and zinc in liver tissue increased significantly, the content of manganese increased slightly, the content of iron decreased significantly, the color of liver darkened and the spleen became smaller. The results show that LJF has certain toxicity to the body (Pu et al., 2011).

LJF and its active components not only have a broad-spectrum antibacterial effect, but have been used for thousands of years to treat influenza infection, as new natural food antioxidants and tumor specific drugs, but also have their own characteristics in liver specific protection, diabetes and other pharmacological effects. Among them, the active ingredient 3,5-dicaffeoyl quinic acid has the effect of lowering blood glucose, japo flavone D has the effect of protecting liver, 4,5-CQME and chlorogenic acid have the effect of anti-oxidation, and 3,4-dicaffeoyl quinic acid and chlorogenic acid have the effect of anti-bacteria. The components of Chinese medicine are complex, and the study of monomeric active components is an important way to obtain lead compounds and prepare drugs, as well as an effective way to promote the clinical application of Chinese medicine and in-depth study of its pharmacological mechanism. However, the current pharmacological studies on LJF are still mostly studies on alcohol extracts and water extracts. Most of the pathways identified by current studies are still incomplete and not thorough, and have only been confirmed on cells or animals alone. In addition, large doses of LJF have a certain toxicity, and there is currently a lack of research on its clinical safe dose. At present, there are few studies on antipyretic, antibacterial and antiviral effects, and almost no clear mechanism is clarified. Future scholars can continue in-depth research from the above aspects. In this study, we reviewed most of the current pharmacological research results of LJF and proposed the shortcomings and solutions, in the hope of providing a basis and reference for future research on LJF.

Conclusion and future perspectives

LJF, as a natural food and medicine with development value, has been widely used in China for thousands of years. People have developed many ways to eat them, such as raw food, tea, and steaming with other food, etc. Scholars have studied its chemical constituents and pharmacological effects deeply. So far, more than 600 components have been isolated from LJF, including essential oils, organic acids, flavonoids, iridoids, saponins, trace elements and so on. It has the functions of anti-inflammation, anti-virus, anti-bacteria, anti-oxidation, anti-tumor, protecting liver and gallbladder, anti-hyperlipidemia, anti-thrombosis, anti-allergy, immune regulation and so on. It provides great help for clinical application. However, there is still a lot of work to be done on the development and utilization of LJF:

First, compounds in plants are directly related to pharmacological effects and determine their therapeutic effects on diseases. However, the studies on the effective components of LJF are not comprehensive due to the imprecise instruments and analytical methods. The compounds isolated at present may only be a small part of LJF, and it is still recommended to continue developing new compounds in the future, which may be the key components for its efficacy. The probability of developing a drug similar to anticancer drug paclitaxel is very low, but it is still hopeful. LJF has been planted on a large scale, but the annual supply still cannot keep up with the demand. And leaves and stems also exist a large number of active ingredients, and their access is easy. Therefore, more analysis of leaves and stems is also proposed in the future to expand the development of multiple sources.

Second, LJF is a medicinal and edible drug, and its therapeutic effects on various diseases have attracted attention from researchers in China and abroad. However, the molecular targets related to pharmacological effects and the pathways to exert the pharmacological basis remain to be clarified. Current research mainly focuses on preliminary animal experiments, and
more in vitro studies at the cellular level and more comprehensive clinical applications are needed to further clarify its pharmacological mechanism of action and optimize the clinical medication standards of LJF.

Third, as a traditional Chinese medicine, LJF is widely used in medicine books, and thousands of years of experience in the clinical application of LJF has been accumulated. However, the current research on its pharmacological effects is only limited to some of the most concerned diseases, such as cancer and diabetes. This limits the application of LJF. We hope that LJF will become not only a common medicine for the above serious diseases, but also a specific medicine for other minor diseases in the future. Through in-depth exploration of the wealth recorded in ancient medical books, a broader range of modern clinical applications of LJF can be explored in the future.

Fourth, the acute, subacute and chronic toxicity evaluation of LJF is not only a prerequisite for clinical trials and the development of new drugs, but also a powerful experimental basis for its potential to become a new drug. Attention should also be paid to the toxicity study to provide a basis for the development of natural antitumor drugs and natural antioxidant cosmetics. It is believed that with the deepening of chemical and pharmacological work, more active components will be extracted and the action mechanism, action target and action channel will be clarified, in order to give full play to the clinical application value of LJF.

This study summarized the botany, ethnopharmacology, phytochemistry and pharmacological effects of LJF, hoping to comprehensively elaborate the medicinal value of LJF and promote its application. As a kind of health food with high value, LJF is worthy of further promotion and development.

Author contributions

LY and HJ conceived and designed the review; AH, SW, SZ, SL, YN, JH searched the literature and downloaded the documents and made classification; AH and SW wrote the paper; and LY, SW and SZ checking the chemical structures and formula, HJ, AH, SW and SZ contributed comments for version of the manuscript. All authors read and approved the final manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China, Grant/Award Numbers: 81703684, 81973604; Heilongjiang Touyan Innovation Team Program; National Famous Old Traditional Chinese Medicine Experts Inheritance Studio Construction Program of National Administration of TCM, Grant/ Award Number: (2022) No. 75; The Seventh Batch of National Old Traditional Chinese Medicine Experts Academic Experience Inheritance Program [NO. (2022) No. 76], Traditional Chinese medicine Processing technology inheritance base project; Central Finance to Support the Development of Local Universities; the scientific research project of Heilongjiang Provincial Health Commission (No.20211313050171). Second affiliated hospital of heilongjiang university of chinese medicine (ZHY2022-170); Scientific research Project of Heilongjiang Administration of Traditional Chinese Medicine.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Bai, X., Chai, Y., Shi, W., Li, Y., Zhang, T., and Liu, P. (2020). Lonicera japonica polysaccharides attenuate ovalbumin-induced allergic rhinitis by regulation of Th17 cells in BALB/c mice. J. Funct. Foods 65, 103758. doi:10.1016/j.jff.2019.103758
Bang, B. W., Park, D., Kwon, K. S., Lee, D. H., Jang, M., Park, S. K., et al. (2019). BST-104, a water extract of Lonicera japonica, has a gastroprotective effect via antioxidant and anti-inflammatory activities. J. Med. Food 22 (2), 140–151. doi:10.1089/jmf.2018.4231
Chen, J. J., Fang, J., Wan, J., Feng, L., Zhang, Y., Zhao, J. H., et al. (2009). An in vitro study of the anti-cytomegalovirus effect of chlorogenic acid. Her. Med. 28 (9), 1138–1141.
Chen, L., Zhang, H. Y., Li, X., Dong, J. J., and Zhao, T. Z. (2015). Research progress on chemical constituents of Lonicera japonica. Drugs Clin. 30 (1), 108–114.
Chen, X. L. (2010). Effects of water extract from Lonicera japonicae flos on glycometabolism in vitro. Lichtschen Med. Mat. Med. Res. 21 (3), 628–629. doi:10.3966/j.issn.1008-0805.2010.03.056
Lonicera japonica is known for its application in modern functional foods. Enzymatic hydrolysis of Lonicera japonica flower buds and their anti-hepatotoxic and anti-inflammatory effects were reported. These properties are attributed to the presence of flavonoids and phenolic acids. Flavonoids were isolated from the flower buds of Lonicera japonica by distillation and its component analysis. The anti-inflammatory and protective liver effect of Lonicera japonica flower buds against acute alcoholic liver injury in rats was studied. Lonicera japonica polysaccharide on S180 sarcoma in mice. Experimental study on anti-inflammatory and anti-tumoral activities of tetraploid Lonicera japonica flowers in vitro. | Flavonoids and phenolic acids from Lonicera japonica flower buds: A systematic review of ethnopharmacology, phytochemistry and fingerprint analysis. The anti-inflammatory and protective liver effect of Lonicera japonica flower buds against acute alcoholic liver injury in rats. Extracts of Lonicera japonica flowers have been shown to possess anti-inflammatory and anti-hepatotoxic activities, as well as antioxidative properties. These studies support the traditional use of Lonicera japonica flowers in functional foods and traditional medicine.
Son, K. H., Park, J. O., Chung, K. C., Chang, H. W., Kim, H. P., Kim, J. S., et al. (1992). Flavonoids from the aerial parts of Lonicera japonica. J. Pharm. Pharmacol. 44 (5), 365–370. doi:10.1111/j.1365-203X.1992.tb12796.x
Song, J. H. (2011). Study on antipyretic and anti-inflammatory effect of Lonicera japonica. Chongqing Med. Coll. 41 (6), 2552–2556. doi:10.1671/2011.05.2024
Song, Y. L., Ni, F. Y., Zhao, Y. W., Xie, X., Wang, W. Z., Wang, Z. Z., et al. (2014). Research progress on chemical constituents from Lonicerae Flos. Chin. Tradit. Herb. Drugs 45 (24), 366–3664. doi:10.7506/j.1003-2767.2014.24.027
Song, Y. L., Wang, H. M., Ni, F. Y., Wang, X. J., Zhao, Y. W., Huang, W. Z., et al. (2015). Study on anti-inflammatory activities of phenolic acids from Lonicerae Japonicae Flos. Chin. Tradit. Herb. Drugs 46 (4), 490–495. doi:10.7506/j.1003-2767.2015.04.006
Sun, C., Teng, Y., Li, G., Yoshioka, S., Yokota, J., Miyamura, M., et al. (2010). Metabolomics study on the protective effect of Lonicera japonica extract on acute liver injury in dimethylsulfoxide treated rats. J. Pharm. Biomed. Anal. 53 (1), 98–102. doi:10.1016/j.jpba.2010.03.015
Tan, Z. W., Xia, W., Yu, Y. L., and, Center, S. (2018). Research progress on chemical constituents and pharmacology of honeysuckle. J. Anhui Agric. Sci. 46 (9), 26–28+123. doi:10.3989/j.cnki.11-7083/c.2018.09.008
Teng, Y., Luo, S. X., Guo, Y. X., Tan, T., Zhang, Y., Sun, C. H., et al. (2016). Protective effects of Lonicera japonica extract on acute liver injury in rats by the method of metabolomics. Food Res. Dev. 37 (4), 29–34.
Teng, Y., Tan, T., Luo, S. X., Zhang, Y., Xin, H. U., Jiang, D. T., et al. (2014). Protective effects of Lonicerae japonica extract on acute liver injury in rats and antioxidant activity. Food Res. Dev. 35 (4), 57–59. doi:10.3989/j.cnki.1003-6551.2014.02.015
Tian, L., Jiang, B. P., Miao, H. E., Shen, L. I., and Fan, X. F. (2014). Study on antioxidant activity of water extracts from different proportions of Lonicerae Japonicae Flos flower and wild Lonicerae Japonicae Flos flower in vitro. Pract. Pharm. Clin. Rem. 17 (10), 1294–1294. doi:10.14053/j.issn.0253-2670.2014.10.018
Tu, S. P., Huang, D., Huang, H., Wu, D., Wu, C. L., and Dai, J. (2020). The in vivo effects of Lonicera japonica thunb on CYP1A1 enzyme activity and gene expression in rats. J. Chengdu Med. Coll. 15 (2), 204–207+231. doi:10.1674/1674-2257.2020.02.017
Tzeng, T. F., Tzeng, Y. C., Cheng, Y. J., Liou, S. S., and Liu, I. M. (2015). The ethanol extract from Lonicera japonica thunb represses nonalcoholic steatohepatitis in a methionine and choline-deficient diet-fed animal model. Nutrients 7 (10), 8670–8684. doi:10.3390/nu7105423
Wang, B. L., Gao, Y., and Zhao, X. X. (2015). Study on Lonicera japonica thunb antiviral effect in vitro. Liaoning J. Tradit. Chin. Med. 42 (8), 1495–1497. doi:10.3391/j.issn.1000-1719.2015.08.047
Wang, D., Zhan, X., and Liu, Y. (2017). Hypoglycemic and hypolipidemic effects of a polysaccharide from flower buds of Lonicera japonica in streptozotocin-induced diabetic rats. Int. J. Biol. Macromol. 102, 396–404. doi:10.1016/j.ijbiomac.2017.04.056
Wang, G., Zhai, X., Wang, J., Liu, W., Yuan, Y., Nan, P., et al. (1992). Analysis of chemical constituent of essential oil in Lonicera japonica thunb cultivated on the northern plain of Henan Province. China J. Chin. Mat. Med. 17 (5), 240–246. doi:10.1016/j.issn.1003-2767.2014.02.034
Patil, M. P., Bayara, E., Subedi, P., Pud, L. A. L., Tarte, N. H., and Kim, G. D. (2019). Biogenic synthesis, characterization of gold nanoparticles using Lonicera japonica and their anticaner activity on Hela cells. J. Drug Deliv. Sci. Technol. 51, 83–90. doi:10.1016/j.disst.2019.02.021
Peng, L., Mei, S., Jiang, B., Zhou, H., and Sun, H. (2000). Constituents from Lonicera japonica. Fitoterapia 71 (6), 713–715. doi:10.1016/s0015-2705(00)00212-4
Peng, S., Hou, X. Q., Huo, M. Q., Liu, Y. N., Zhang, Y. L., and Qiao, Y. J. (2020). Study on efficacy markers of heat-clearing and detoxifying effect of Lonicerae Japonicae Flos based on systematic traditional Chinese medicine. China J. Chin. Mat. Med. 45 (14), 3275–3281. doi:10.19540/cjcn.cjcm.20200210.403
Pi, J. H., Tan, J., Liu, Z. T., and Xiang, D. B. (2015). Effects of Lonicera japonica flavone on immunomodulation in mice. Chin. J. Appl. Physiol. 31 (1), 89–92. doi:10.13459/cjcap.2015.01.026
Pi, H. L., Jiang, H., and Chen, R. R. (2011). Toxicity of lonicerae japonicae flos and dry ginger in mice. Pract. Pharm. Clin. Rem. 14 (4), 277–278. doi:10.14053/j.cnki.ppcr.2014.01.007
Qi, L., Chen, C., and Li, P. (2009). Structural characterization and identification of iridoid glycosides, saponins, phenolic acids and flavonoids in Flos Lonicerae japonicae by a fast liquid chromatography method with diode-array detection and time-of-flight mass spectrometry. Rapid Commun. Mass Spectrom. 23 (19), 3227–3242. doi:10.1002/rcm.4245
Rajavandgi, G. N., Chakkaravathu, G., Ramachandran, G., Manoharan, N., Raghunathan, R., Siddiqui, M. Z., et al. (2012). Synthesis of silver nanoparticle (Ag NPs) using glycosilbased rich medicinal plant Lonicera japonica for improve the cytotoxicity effect in cancer cells. J. King Saud Univ. - Sci. 34 (2), 101798. doi:10.1016/j.jksus.2011.10.058
Ren, M. T., Chen, J., Yue, S., Sheng, L. S., Ping, L. J., and Qi, L. W. (2008). Identification and quantification of 32 bioactive compounds in Lonicera species by high performance liquid chromatography coupled with time-of-flight mass spectrometry. J. Pharm. Biomed. Anal. 48 (5), 1351–1360. doi:10.1016/j.jpba.2008.09.037
Shang, X., Pan, H., Li, M., Zhao, X., and Ding, H. (2011). Lonicera japonica thunb. Ethnopharmacology, phytochemistry and pharmacology of an important traditional Chinese medicine. J. Ethnopharmacol. 138 (1), 1–21. doi:10.1016/j.1016-0811.2011.08.016
Shi, Z., Liu, Z., Liu, C., Wu, M., Su, H., Ma, X., et al. (2016). Spectrum-effect relationship between chemical fingerprints and antibacterial activities of Lonicerae Flos and Lonicera thunb base on UPLC and microcalorimetry. Front. Pharmacol. 7, 12. doi:10.3389/fphar.2016.00012
Zheng et al. 10.3389/fphar.2022.1013992
Frontiers in Pharmacology frontiersin.org
Wang, Z., Xiao, C. Y., Tian, L., and Zheng, Q. F. (2010). [Discussion on herbal textural research of Flos Lonicerae]. J. Chin. Mat. Med. 35 (8), 1086–1088. doi:10.4266/cjmm20100831

Wu, J., Wang, C., and Yu, H. (2019). Chemical constituents and pharmacological effect of lonicerae japonicae flos. Chin. J. Exp. Tradit. Med. Formulae 25 (4), 225–234. doi:10.13422/j.cnki.cjxj.20190408

Xia, W., Yu, Y., Yang, H., Tan, Z., Xu, L., Dong, W., et al. (2017). Research advances on chemical constituent and pharmacology effects of lonicerae japonicae flos. J. Anhui Agric. Sci. 45 (33), 126–127+165. doi:10.13988/j.cnki.0517-6611.2017.33.042

Xia, Y., Li, D., Pei, Z., and Zhang, Y. (2012). Review on the chemical constituents of the flower buds of Lonicera japonica. Mod. Chin. Med. 14 (4), 26–32. doi:10.13313/j.issn.1673-4890.2012.04.016

Xiao, L., Liang, S., Ge, L., Wan, H., Wu, W., Fei, J., et al. (2020). 4, 5-di-O-cafeoylquinic acid methyl ester isolated from Lonicera japonica Thumb. targets the Keap1/Nrf2 pathway to attenuate H2O2-induced liver oxidative damage in HepG2 cells. Phytomedicine 70, 153219. doi:10.1016/j.phymed.2020.153219

Xiao, M., Tan, H. J., Li, X. H., and Kang, H. P. (2013). Study on essential oil from leaf of Lonicera japonica by GC-MS. J. Anhui Agric. Sci. 41 (03), 947+996. doi:10.13989/j.cnki.0517-6611.2013.03.015

Xu, M. Y., Hu, J. J., Shen, J., Wang, M. L., Zhang, Q. Q., Qu, Y., et al. (2014). Stat5 signaling activation crosslinking of IFN-β in hepatic inflat cell exacerbates liver injury and fibrosis. Biochim. Biophys. Acta 1842 (11), 2237–2245. doi:10.1016/j.bbadis.2014.07.025

Xu, X. B., Xu, P., Mao, X. F., Li, J. F., and Ren, M. (2018). Content and antioxidant activity of three active components in different organs of lonicerae japonicae thumb. Sci. Technol. Food Ind. 39 (13), 41–45. doi:10.13386/j.issn1002-0306.2018.13.008

Xu, X. Y., Miao, F., Wang, X. D., Gao, Y. F., Zhang, Z. Y., and Su, S. Z. (2020). The effect and mechanism of Lonicera japonica total flavones on hepatic fibrosis induced by carbon tetrachloride in rats. J. Taishan Med. Coll. 41 (1), 1–4. doi:10.3986/j.issn.1004-7115.2020.01.001

Yan, S. H., Miao, H., Huang, Z. L., and Ji, L. L. (2021). Protective effects of extract combination of Lonicerae Japonicae Flos and Eusphybe Fruncus against CCl4 induced liver fibrosis in mice. Acad. J. Shanghai Univ. Tradit. Chin. Med. 35 (2), 50–56. doi:10.16306/j.issn.1008-8611.2021.02.010

Yan, X. L., Meng, A. F., and Pu, S. B. (2016). Research progress on activities of anti-inflammation and immunity from the flower of Lonicera japonica thumb. Chin. Wild Plant Resour. 35 (2), 41–44. doi:10.1006/j.wpr.2016.02.012

Yang, J., Li, Y. C., Zhou, X. R., Xu, X. J., Fu, Q. Y., and Liu, C. Z. (2018). Two thymol derivatives from the flower buds of Lonicera japonica and their antibacterial activity. Nat. Prod. Res. 32 (18), 2238–2243. doi:10.1080/14786419.2017.1371153

Yang, Q. R., Zhao, Y. Y., Hao, J. B., and Li, W. D. (2016). Research progress on chemical constituents and their differences between lonicerae japonicae flos and lonicerae flos. Chin. J. Chin. Mater. Med. 41 (7), 1204–1211. doi:10.4268/cjcm20160708

Yang, R., Fang, L., Li, J., Zhao, Z., Zhang, H., and Zhang, Y. (2019). Separation of five iridoid glycosides from Lonicerae japonicae flos using high-speed counter-current chromatography and their anti-inflammatory and antibacterial activities. Molecules 24 (1), 197. doi:10.3390/molecules2401197

Yang, S. K. (2019). Study on chemical constituents and biological activities of Lonicerae Japonicae Flos. Chem. Eng. Des. Commun. 45 (11), 149+177. doi:10.3969/j.issn.1630-6490.2019.11.098

Yao, C. L., Wei, W. L., Zhang, J. Q., Bi, Q. R., Li, J. Y., Khan, I., et al. (2022). Traditional Chinese medicines against COVID-19: A global overview. World J. Tradit. Med. Clin. Med. 8 (3), 279. doi:10.4103/wj3m.81.2021.353502

Ye, Q. H. (2018). Experimental studies on hypoglycemic effects of extracts from Lonicerae Japonicae Flos. Clin. J. Chin. Med. 10 (19), 4–7. doi:10.3969/j.issn.1674-7840.2018.19.002

Yin, H. M., Lv, X. Y., and Xiao, W. (2010). Study on preparation process optimization and immune activity of Lonicerae jactivica polysaccharide. China J. Chin. Med. 35 (4), 453–455.

Zeng, H. Q., Mao, L., Jin, Y. H., Li, S. T., and Xu, A. (2022). In vitro study of the effects of Lonicerae Japonicae Flos on Streptococcus mutans UA159. J. Prev. Treat. Stomatol. Dis. 38 (8), 542–548. doi:10.12016/j.physmed.2020.153219

Zhang, M. L., Li, F., Liu, W., Shi, L., and Yang, J. X. (2016). Research progress on the anti-virus effect of Lonicerae Flos. J. Liaoning Univ. Tradit. Chin. Med. 18 (9), 156–158. doi:10.13194/j.issn.1673-842x.2016.09.048

Zhang, W., Huang, L. Q., Li, C. X., Li, J., and Zhang, R. X. (2014). Literature study on species of honeysuckle flower. China J. Chin. Med. Mat. Med. 39 (12), 2239–2245. doi:10.4268/cjmm20141218

Zhang, W. W., Ren, Y., Zhang, R. C., and Hao, G. Z. (2020). Study on the effects of volatile oil from Flos Lonicerae and leaves of Lonicera japonica on lymphocyte proliferation in mice. J. Pharm. Res. 39 (4), 198–201+224. doi:10.13386/j.cnki.jpr.2020.04.003

Zhao, Z., Shen, H., Sun, Y., and Dung, W. (2019). Studied on phenolic acids extracting of Lonicera japonica Thumb. and its antimicrobial Effect. Chin. J. Ethnomed. Ethnopharm 28 (10), 27–29.

Zkao, A. Y. (2018). A brief analysis of the pharmacological action and clinical application of Lonicerae Japonicae Flos. Contemp. Med. Symp. 16 (4), 53–54.

Zhao, M. M., Zhao, Z. G., Liu, Q., Liu, W., Wang, X., and Zhao, H. Q. (2021). Rapid discovery of trace antioxidants in lonicerae japonicae flos by 2D-HPLC-DPPH-ESI-TOF/MS. Chin. Tradit. Herb. Drugs 52 (11), 3193–3200. doi:10.7501/j.issn.0253-2670.2021.11.005

Zhou, X., Dong, Q., Kan, X., Peng, L., Xu, X., Fang, Y., et al. (2018). Immunomodulatory activity of a novel polysaccharide from Lonicera japonica in immunosuppressed mice induced by cyclophosphamide. PloS one 13 (10), e0204152.

Zhou, Y. X., Li, Z. M., Liu, Z. J., Yang, D. Q., Qiu, H., and Lin, M. (2011). Effect of flos lonicerae on immunologic function of rats. Pract. Prev. Med. 18 (2), 214–216. doi:10.3969/j.issn.1006-3110.2011.02.008

Zhuang, L., Zhang, C., and Ali, M. S. (2013). Advances in pharmacological action and clinical application of flos lonicerae. Lianzu J. Tradit. Chin. Med. 40 (2), 378–380. doi:10.13192/j.jcm.2013.02.192.zhuangf.007