separations

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Review

Research Progress on Extraction and Separation of Active Components from Loquat Leaves

Siqiu Xiao [2,3,4,†], Wei Wang [1,2,3,*,†] and Ying Liu [2,3,4,*]

[1] Institute of Advance Carbon Conversion Technology, Huaqiao University, Xiamen 361021, China
[2] College of Chemistry, Chemical Engineering and Resource Utilization, Northeast Forestry University, Harbin 150040, China
[3] Key Laboratory of Forest Plant Ecology, Northeast Forestry University, Ministry of Education, Harbin 150040, China
[4] Engineering Research Center of Forest Bio-Preparation, Northeast Forestry University, Ministry of Education, Harbin 150040, China
* Correspondence: wangwei1978@hqu.edu.cn (W.W.); arrive100@163.com (Y.L.)
† These authors contributed equally to this work.

Abstract: Loquat is an evergreen tree belonging to the genus Loquat in Rosaceae. It is widely used in the processing of food and medicine. Based on the literature findings, the anti-tumor, antibacterial, anti-inflammatory and anti-oxidation activities of the extracted loquat leaves are related to its active components. The extracted loquat leaves, in addition, demonstrated remarkable, and privileged medicinal and commercial values, and recently attracted the interest of researchers. The current review aimed to summarize several important bioactive components in loquat leaves, their extraction and separation techniques, pharmacological activities, and research progress. In addition, the application prospect of bioactive components from loquat leaves was prospected, which provided a theoretical basis for its further development and utilization.

Keywords: loquat leaves; active components; extraction and separation; pharmacological action

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1. Introduction

Loquat (Latin name: *Eriobotrya Japonica (Thunb.)* Lindl) (Figure 1) is a small evergreen tree plant belonging to Rosaceae, Maloideae, and Loquat [1], which is native to the southeast of China and has a long history of cultivation. Later, it was introduced to the United States, Spain, Japan, India, and other countries and planted on a large scale [2]. Loquat fruit is rich in various nutritional elements needed by the human body, and it is a nutritious healthy fruit. It is an important subtropical economic fruit tree and has become an ornamental green plant in many places. There are many varieties of loquat in China, which are widely planted in southern areas such as Sichuan, Yunnan, Zhejiang, Fujian, Guangdong, Jiangsu, and other places [3,4]. Among them, the planting area and yield in Fujian area are the highest, reaching more than half of the total area in China [5,6]. This area has a long history, and is the main planting area in South China, as well as a world-famous producing area [7,8].

Loquat leaves (Figure 1), also known as Baye and Luju leaves, are dried leaves of loquat in rosaceae [9]; they are oval, with saw steps on the edge; a thick leather, wrinkled surface; and fine fluff on the back [10], and they have a long history of medicinal use. According to *China Pharmacopoeia*, loquat leaves are a traditional Chinese medicine, with a bitter taste, mild cold, antitussive, and expectorant effects, and it belongs to the lung and stomach meridians [11,12]; it is mainly used to treat cough due to lung heat, cough due to yin deficiency, eczema, and other symptoms. Medicinal loquat leaves are divided into broad leaves and subalpine leaves, which can be harvested all year round. When they are dried to 70% or 80%, they are tied into small leaves and then dried in the sun [13]. Modern medical scientists have found that a variety of active ingredients extracted from loquat leaves [14–16]—such as terpenes, flavonoids, saponins, polyphenols, and other substances, which

have strong anti-tumor, anti-virus, anti-oxidation, blood sugar and blood lipid lowering, immune system regulation, anti-inflammation, cough relieving, expectorant, and other effects [17–24], therefore have high medicinal value. As a plant with homology of medicine and food homology, many values of active components in loquat leaves have attracted much attention [25–27]. In this paper, the active components, pharmacological effects, and extraction and separation techniques of loquat leaves in recent years are reviewed.

Figure 1. Loquat (*Eriobotrya Japonica (Thunb.)* Lindl) and loquat leaves.

2. Active Components in Loquat Leaves

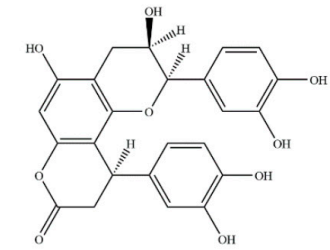
Loquat leaves are rich in a variety of active compounds, including polyphenols, flavonoids, triterpenes, organic acids, sugars, alkaloids, sesquiterpenes, and so on. The main active compounds in Loquat leaves are exemplified in Table 1 and Figure 2.

Table 1. The main compounds in loquat leave.

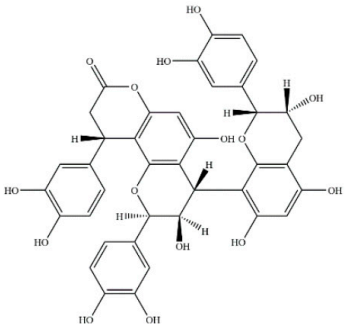
Classification	No.	Compounds	References
Polyphenols	1	Cinchonain I a	[25]
	2	Cinchonain II b	[25]
	3	Chorogenic acid	[25]
	4	Methyl chlorogenate	[25]
	5	Procyanidin B-2	[25]
	6	L-Epicatechin	[25]
Flavonoids	7	Quercetin	[15]
	8	Kaempferol	[15]
	9	Rutin	[15]
	10	Quercetin-3-O-sangbu disaccharide	[15]
	11	Flavan-3-ol	[15]
	12	Galangin	[15]
	13	Hesperidin	[15]
	14	Kaempferol-3-O-neohesperidin	[15]
	15	Isoquercitrin	[15]
	16	Quercetin-3-O-β-galactoside	[15]
Triterpenoids	17	Ursolic acid	[15]
	18	Oleanolic acid	[15]
	19	Koroso acid	[15]
	20	Poamic acid	[15]
	21	Masri acid	[15]
	22	Potentilla acid	[15]
	23	2α-hydroxy oleanolic acid methyl ester	[15]
	24	Methyl betulinic acid	[15]
	25	Maslinic acid	[15]
	26	2α-hydroxy ursolic acid methyl ester	[15]

Table 1. *Cont.*

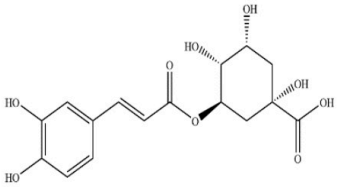
Classification	No.	Compounds	References
Sesquiterpenes	27	Sesquiterpene glycoside I	[28]
	28	Nerolidol-3-O-α-L-rhamnopyranosyl(1→4)-α-L-rhamnopyranosyl(1→2)-[α-L-rhamnopyranosyl(1→6)]-β-D-glucopyranosid	[29]
	29	α-L-rhamnopyianosyl(1→4)-α-L-rhamnopyranosyl(1→2)-[α-L-rhamnopyranosyl(1→6)]-β-D-glucopyranosyl-6,7-trans-nerolidol	[10]
Saponins	30	2α,3β,19α,23-tetrahydroxy-12-double bond-28-O-β-D glucose ursulosin	[10]
	31	Amygdalin	[30]
	32	Amygdaloside	[30]
	33	Roseoside	[30]
Organic acids	34	Alic acid	[15]
	35	Tartaric acid	[15]
	36	Boletic acid	[15]
	37	Oxaloacetic acid	[15]
	38	Citric acid	[15]
	39	α-ketoglutaric acid	[15]
	40	Rosanic acid	[15]
	41	Ferulic acid	[15]



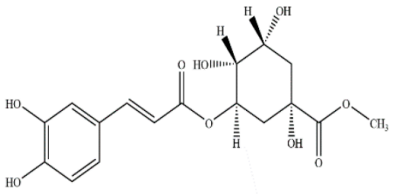
No.1 Cinchonain I a



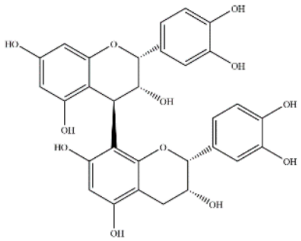
No.2 Cinchonain Ⅱb



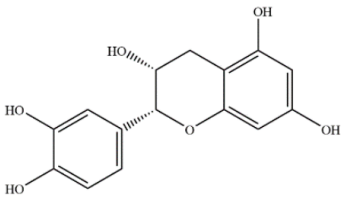
No.3 Chorogenic acid



No.4 Methyl chlorogenate

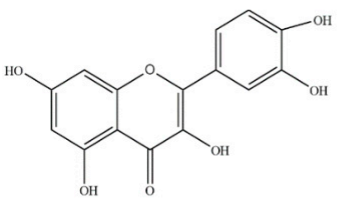


No.5 Procyanidin B-2

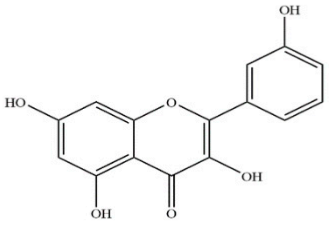


No.6 L-Epicatechin

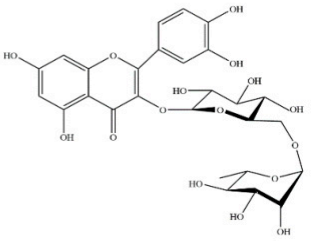
Figure 2. *Cont.*



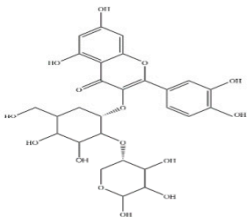
No.7 Quercetin



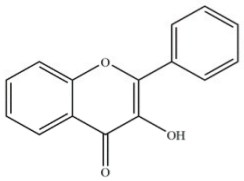
No.8 Kaempferol



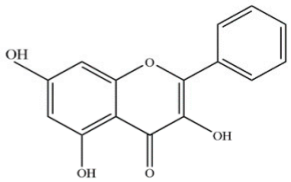
No.9 Rutin



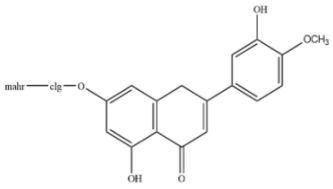
No.10 Quercetin-3-O-sangbu disaccharide



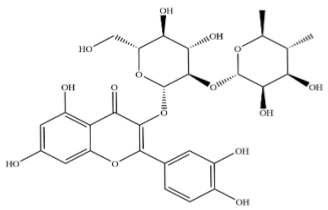
No.11 Flavan-3-ol



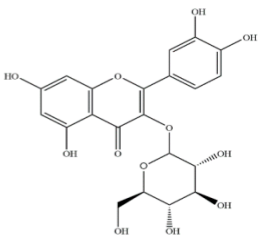
No.12 Galangin



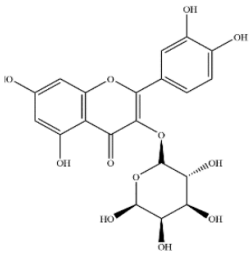
No.13 Hesperidin



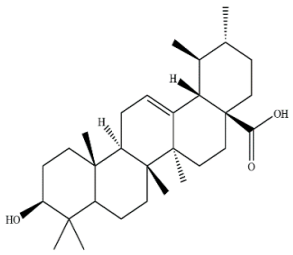
No.14 Kaempferol-3-O-neohesperidin



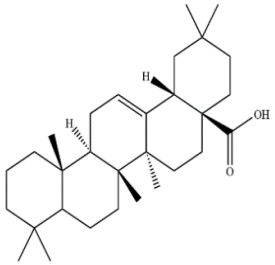
No.15 Isoquercitrin



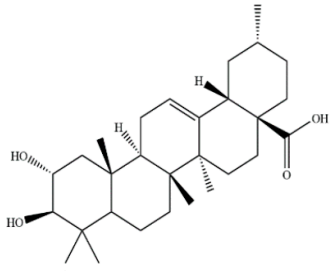
No.16 Quercetin-3-O-β-galactoside



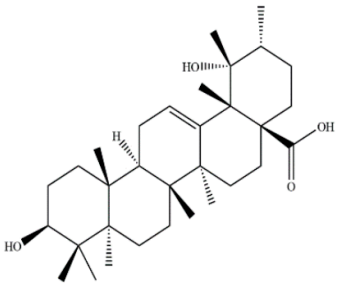
No.17 Ursolic acid



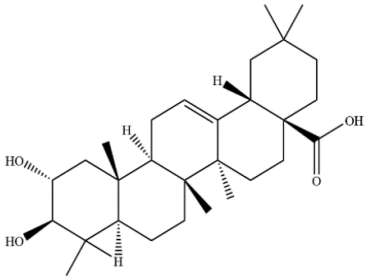
No.18 Oleanolic acid



No.19 Koroso acid

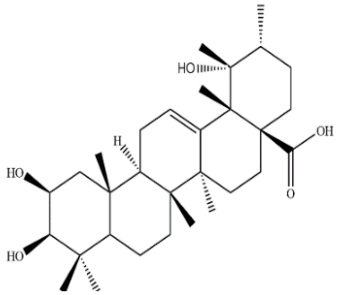


No.20 Poamic acid

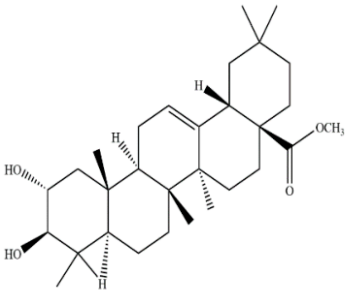


No.21 Masri acid

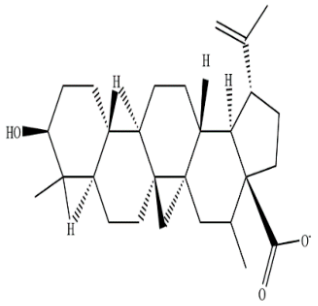
Figure 2. *Cont.*



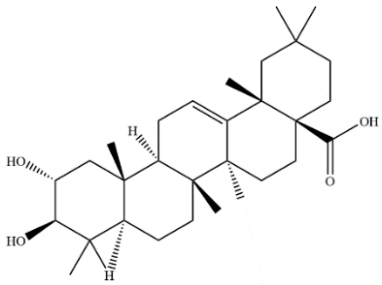
No.22 Potentilla acid



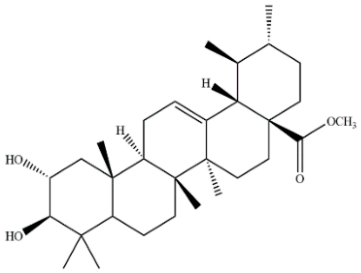
No.23 2α-hydroxy oleanolic acid methyl ester



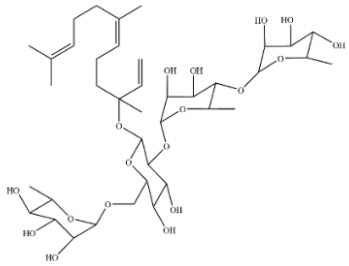
No.24 Methyl betulinic acid



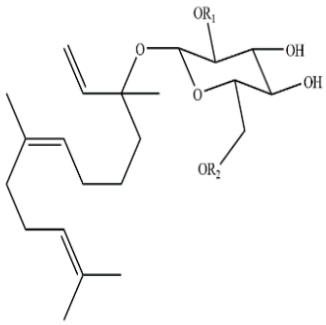
No.25 Maslinic acid



No.26 2α-hydroxy ursolic acid methyl ester



No.27 Sesquiterpene glycoside I

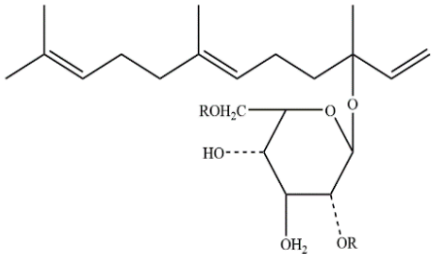


No.28 R_1=Rha-Rha,R_2=Rha

Nerolidol-3-O-α-L-rhamnopyranosyl

(1→4)-α-L-rhamnopyranosyl(1→2)-

[α-L-rhamnopyranosyl(1→6)]-β-D-glucopyranosid



No.29 R=α-L-Rha(1→4)-α-L-Rha(1→)

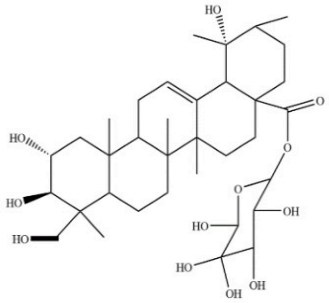
R′-α-L-Rha(1→4)-

α-L-rhamnopyianosyl(1→4)-α-L-rhamnopyranosyl

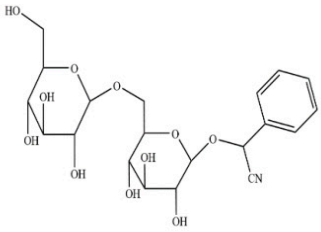
(1→2)-[α-L-rhamnopyranosyl(1→6)]-β-D

-glucopyranosyl-6,7-trans-nerolidol

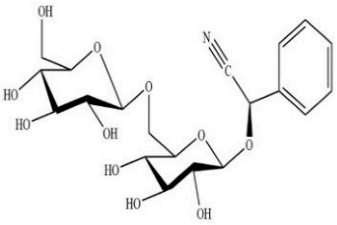
Figure 2. *Cont.*



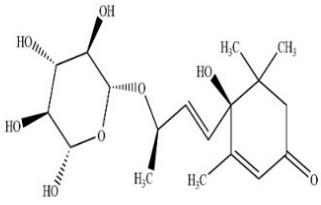
No.30 2α,3β,19α,23-tetrahydroxy-12-double bond-28-O-β-D glucose ursulosin



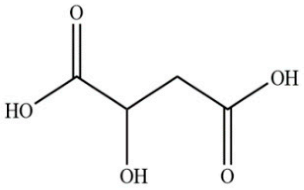
No.31 Amygdalin



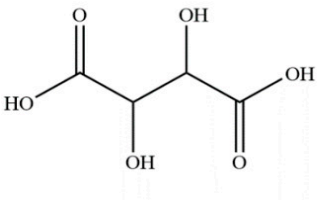
No.32 Amygdaloside



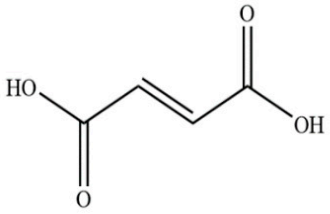
No.33 Roseoside



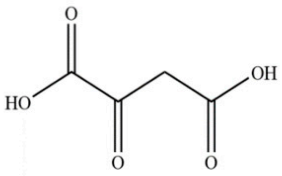
No.34 Alic acid



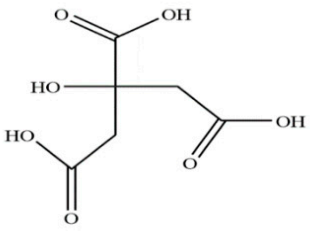
No.35 Tartaric acid



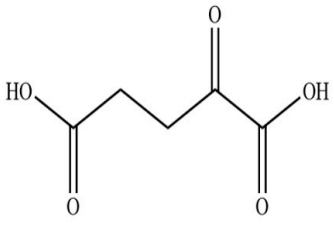
No.36 Boletic acid



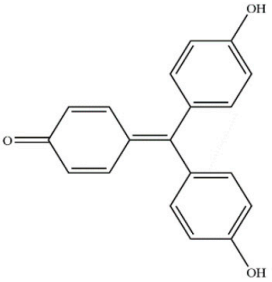
No.37 Oxaloacetic acid



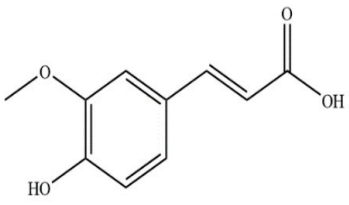
No.38 Citric acid



No.39 α-ketoglutaric acid



No.40 Rosanic acid



No.41 Ferulic acid

Figure 2. The structures of Polyphenols, Flavonoids, Triterpenoids, Sesquiterpenes, Saponins, and Organic acids in Loquat leaves.

2.1. Polyphenols

The polyphenols contained in loquat leaves are a kind of multi-hydrocarbon phenolic compounds [25], including flavonoids, tannins, phenolic acids and anthocyanins [31,32]. Polyphenols are ubiquitous in the plant kingdom and are one of the most important secondary metabolites of plants [33]. In loquat leaves, flavonoids and flavonoids-3-ol are mostly used as the core of polyphenols [24], and the main components are (-)epicatechin, chlorogenic acid, procyanidin B-2, cinchonain la, procyanidinoligomer [34], 4-O-p-coumaroylquinic acid, 4-O-caffeoylquinic acid [35], (2R)-Naringenin8-c-a-Rhamnopyranoyl(1→2)-β-D-glucopyranoside [36], mechlorogenate, ueresionl, cinchonain II b [37]. Ito et al. [36] isolated 3 flavonoid glycosides and 15 flavonoid compounds from loquat leaves, which were characterized by (2s) and (2r) naringin 8-c-α-l-rhamnosyl(1-2)-β-d-pyranoside and cinchona respectively.

2.2. Flavonoids

Flavonoids exist in almost all plants, and are compounds formed by connecting two benzene rings through three carbon atoms. The aglycones of flavonoids in loquat leaves are mainly kaempferol and quercetin, and the glycosides are composed of 1-3 monosaccharides, such as glucose, rhamnose, galactose and arabinose, and the connection position is mostly 3-position. 3, 5, 7 trihydroxyflavone (galangin), hesperidin and kaempferol-3 were isolated from loquat leaves and loquat plants for the first time [30]. In addition, acetylated flavonoid glycosides were found, and loquat leaves were extracted by dichloromethane, ethyl acetate and butanol in turn. The ethyl acetate components were separated and purified by various chromatograms, and the structures of three compounds were determined, namely kaempferol-3-O-α-L-(2″,4″-di-E-p-coumaroyl)rhamnoside [38,39].

2.3. Triterpenoids

Triterpenoids exist in plants in free form or in the form of glycosides or esters combined with sugar, and are compounds with relatively high content in loquat leaves [40], mainly ursulane and oleanane pentacyclic triterpenoids [41]. Ju Jianhua et al. [42] isolated six triterpene acids from the n-butanol extract of loquat leaves, and isolated pomolic acid from this plant for the first time. Lu Han et al. [43] isolated 9 triterpenoids from loquat leaves, and identified them as methyl betulinic acid, ursolic acid, oleanolic acid, 2α-hydroxy oleanolic acid methyl ester, koroso acid methyl ester, potentilla acid, 2α-hydroxy oleanolic acid, koroso acid, roseic acid, etc. Among them, methyl betulinic acid and oleanolic acid were isolated from loquat and its genus for the first time [1]. The triterpenoids in loquat leaves are ursolic acid and koroso acid.

2.4. Sesquiterpenes

Sesquiterpene compounds contain three isoprene units, and have various skeleton structures such as chain and ring. Some scholars have isolated six sesquiterpene glycosides from loquat leaves, and their glycosides are composed of D-glucopyranose and L-rhamnose [44,45]. Loquat leaves contain nerolidol-3-O-α-L-rhamnosyl(1-4)-α-L-rhamnosyl(1-2)-[α-L-rhamnosyl(1-6)]-β-D-glucopyranoside. Sesquiterpenes such as nerolidol-3-0-α-L-rhamnosyl(1-4)-[α-L-rhamnosyl(1-2)]-β-D-glucopyranoside, loquatifolin [29,46,47]. Cyclosesquiterpenes include: Isohumbertiol-3-O-{α-L-Rhamnopyranosyl-(1-4)-α-L-RH-Amnopyranosyl-(1-2)-[-α-L-Rhamnopyranosyl-(1-6)]}-β-D-glucopyranoside and Isohum-Bertiol-3-O-{-α-L-Rhamnopyranosyl-(1-4)-α-L-Rhamnopyranosyl-(1-2)-[-α-L-(4-trans-Feruloyl)-rhamnopyranosyl-(1-6)]}-β-D-glucopyranoside [47].

2.5. Saponins

Saponins are a class of glycosides [48] whose aglycones are triterpenes or spirostanes, and saponins are composed of sapogenins and sugars. The main components contained in loquat leaves are loquat glycoside and amygdalin [49], and amygdalin is composed of 1 molecule of amygdanitrile and 2 molecules of glucose. It exists in all parts of loquat and is the most effective component in loquat core [50]. Saponins in loquat leaves include

roseoside, vomifoliol-9-o-β-d-apiofuranozyl(1-6)-β-D-glucopyranoside, 3-oxo-α-ionyl-9-O-β-D-apiofuranosyl(1-6)-β-D-glucopyranside, vomifoliol-9-O-β-xy-lopyranosyl(1-6)-β-D-glucopyranside, eriojaposide A, eriojaposide B, etc [51].

2.6. Organic Acids

Organic acid is a common acidic organic compound in plants, and the most common one is carboxylic acid. Chen Faxing et al. [52] extracted the organic acids from fresh loquat leaves, and the results showed that the organic acids in loquat leaves were mainly quinic acid, with a high expression, and also contained a small amount of L- malic acid [53], tartaric acid, fumaric acid, α-ketoglutarate [54], oxaloacetic acid, citric acid and trace amounts of isocitric acid, cis-aconitic acid, β-coumaric acid and ferulic acid (trans), etc.

3. Extraction and Separation Technologies of Active Compounds in Loquat Leaves

Efficient extraction and separation technology is very important for further research and application of natural products, and how to extract active ingredients quickly and effectively is the basis of its development and utilization [55]. Considering the diverse health benefits and wide applications of active compounds in loquat leaves, and many studies have established effective extraction and separation techniques, which are summarized and discussed below.

3.1. Solvent Extraction

Solvent extraction is a traditional and commonly used extraction technology. It includes cold extraction and hot extraction, and it is a technology that makes use of the solubility difference of each component in a sample in a specific solvent to completely or partially separate it. Under normal pressure, water or organic solvent is usually used as the extraction solvent. Li Kaiquan et al. [56] used ethanol as an extractant to extract triterpenoids from loquat leaves, and the extraction rate reached 7.41%. Wentao et al. [57] used acetone solution as the extraction solvent to extract anthocyanins from loquat leaves, and the extraction rate of anthocyanins was 2.37%. Pan Xin [58] used water, ethanol, ethyl acetate, and n-butanol as solvents to extract the active components from loquat leaves. The results showed that the highest extraction rate of mixed natural products among the four solvents was water extraction, with a yield of 22.10%. Zhao Honghong et al. [59] studied the extraction technology of flavonoids from loquat leaves with methanol as the extraction solvent, and found that the concentration of flavonoids was 8.11% under the best conditions. The traditional solvent extraction method takes a long time, the product loss is large, the extraction rate is low, and the use of organic solvents may have residues harmful to health. Therefore, with the development of science and technology, modern environmentally friendly and efficient extraction technology is widely used.

3.2. Ultrasonic-Assisted Extraction

Ultrasonic-assisted extraction (UAE) refers to the mechanical effect, cavitation effect, and thermal effect of an ultrasonic wave under the action of organic solvent, so that the effective ingredients in raw materials can quickly enter the organic solvent, and extract solutions of various active ingredients can be obtained. It has the advantages of high efficiency, rapidness, simplicity, wide applicability, and low cost [60]. Wang Juan et al. [61] used ultrasonic-assisted extraction to extract polysaccharide from loquat leaves. Taking the ratio of liquid to material, ultrasonic time, ultrasonic power, and ethanol concentration as influencing factors, the extraction conditions were optimized, and the optimum process was obtained as follows: the ratio of liquid to material was 25:1 mL/g, ultrasonic power was 425 W, ultrasonic time was 13 min, ethanol concentration was 50%, and the extraction rate of loquat leaves polysaccharide was 3.36%. Fu Xianming et al. [62] used the ultrasonic method to extract total flavonoids from loquat leaves in Putian in order to develop and utilize the plant resources of loquat leaves. The optimum extraction process was determined as follows: ultrasonic power of 140 W, ultrasonic time of 30 min, ultrasonic temperature of

70 °C, ethanol concentration of 50%, and solid–liquid ratio of 1:40. Under these conditions, the extraction rate of total flavonoids could reach 10.534%. Ma Xiong et al. [63] optimized the ultrasonic extraction conditions of ursolic acid from loquat leaves, and obtained the best technological conditions as follows: ultrasonic time 35 min, ultrasonic temperature 69 °C, ethanol concentration 82%, and liquid-to-material ratio 21:1 mL/g. Under these conditions, the extraction rate of ursolic acid was 3.567 mg/g. Feng Hang [64] used the ultrasonic extraction method to extract polyphenols from loquat leaves. The experimental results showed that the optimum extraction parameters of polyphenols from loquat leaves were as follows: ultrasonic time 80 min, solid–liquid ratio of 1:40, and ethanol concentration of 60%. In recent years, ultrasonic extraction technology has been widely used in the research of active ingredients in Chinese herbal medicines. Ultrasonic-assisted extraction can effectively avoid the influence of high temperature on active ingredients in loquat leaves, and the extraction efficiency is better than that of traditional extraction technology [65]. However, there are many problems in loquat leaves, such as diverse active ingredients and complex structures, different properties of different extraction solvents, and different working mechanisms of various brands of ultrasonic instruments, which will affect the ultrasonic-assisted extraction efficiency to some extent [66]. In order to ensure the extraction rate of effective components, it can be combined with other extraction technologies such as homogenization method to achieve the effects of high efficiency, environmental protection, convenience, and quickness [67].

3.3. Microwave-Assisted Extraction

Microwave-assisted extraction (MAE) refers to the use of high-frequency microwaves to break the cell wall of plants, so that the effective components in cells are dissolved by extraction solvent. This extraction method has strong microwave frequency penetration, high heating efficiency, and high selectivity, so microwave extraction can extract the active components in plants efficiently, in a short time and simply [68]. Huang Zhenghong [69] optimized the extraction process of polyphenols from loquat leaves. The optimum extraction agent with 70% ethanol was determined. The optimum technological parameters of microwave-assisted extraction were as follows: extraction temperature 80 °C, extraction time 30 min, ratio of extract to material 60 mL/g, and microwave power 3.0 W. Under the optimum conditions, the highest polyphenol yield in loquat leaves could reach 9.34 mg/g, which indicated that microwave extraction could significantly improve the extraction rate of polyphenols in loquat leaves, and showed the superiority of this method. Zhou Fang et al. [70] used dried loquat leaves as raw materials to optimize the technological conditions of microwave-assisted extraction of polysaccharides from loquat leaves. Through the single factor experiment and orthogonal experiment, the optimum technological conditions were determined as follows: the ratio of material to liquid was 1:20 (g/mL), the microwave power was 640 W, the microwave time was 150 s, and the extraction rate of polysaccharides from loquat leaves was 10.350 mg/g. Li Bingjie [71] optimized the extraction of total flavonoids from loquat leaves by orthogonal test on the basis of the single factor experiment. The results showed that the optimum technological conditions of microwave extraction were: ethanol volume fraction 60%, solid–liquid ratio 1:25 (g/mL), microwave time 7 min, and microwave temperature 65 °C. Under these conditions, the extraction rate of total flavonoids from loquat leaves reached 16.24%. Fan Aiping et al. [72] used the microwave method to extract oleanolic acid from loquat leaves, and determined the optimum process of microwave extraction as follows: ethanol concentration of 95%, extraction power of 630 W, microwave time of 70 s, solid–liquid ratio of 1:20 (g/mL), and the extraction rate of oleanolic acid was 84.8%. The higher the extraction power used in microwave extraction, the shorter the extraction time. Therefore, it is necessary to set the extraction power and time according to the characteristics of extracting active ingredients from medicinal plants. Microwave extraction technology is a technology and method for extracting various chemical components from natural plants, minerals, or animal tissues, which is widely used [73].

3.4. Macroporous Adsorption Resin

Macroporous adsorption resin (MAR) technology is a newly developed technology. It is a purification and refining method in which the decoction of traditional Chinese medicine compound passes through a macroporous resin to adsorb the effective components, and then it is eluted and recovered to remove impurities. As a rapid, economical, and effective purification method, macroporous adsorption resin is generally used for the separation and purification of a certain kind of total components such as flavonoids, saponins, polyphenols, or terpenoids in natural medicines [74]. Han Wei [75] took loquat leaves as the research object, used macroporous adsorption resin to separate and purify the crude extract of triterpene acids from loquat leaves, screened and investigated the static and dynamic adsorption and desorption properties of the best macroporous resin for triterpene acids from loquat leaves, and obtained the best separation and purification process conditions: the model of macroporous resin is HZ-816, the loading flow rate is 2 BV/h (1 BV is about 32 mL), and the loading mass concentration is 0.6 mg. The purity of triterpene acid was 92.29% when the sample volume was 470 mL, the ethanol concentration of eluent was 95%, the elution flow rate was 2 BV/h, and the dosage of eluent was 6 BV. Huang Baiqi et al. [76] optimized the macroporous adsorption resin and purified ursolic acid and oleanolic acid from loquat leaves through static and dynamic experiments. The results showed that S-8 macroporous resin was selected, and the optimized purification process was as follows: the ratio of resin column diameter to height was 1:7, the total concentration of the sample solution was 0.338 mg/mL, pH value was 7.0, 1 BV/h flow rate for sampling 16 BV, the washing volume was 3 BV, and pH value was 11. After purification, the total content of two acids in eluent is 93.28%, and the recovery rate is 87.42%. The process conditions are simple and feasible, and can be used to purify ursolic acid and oleanolic acid in loquat leaves. Liu Yun et al. [77] compared the adsorption and desorption effects of six kinds of macroporous resins on total flavonoids in loquat leaves, selected the best macroporous resin model, and discussed its adsorption and desorption conditions. The results showed that HPD 100 macroporous resin was most suitable for the purification of total flavonoids from loquat leaves. The purification process was as follows: the concentration of sample solution was 3 g/L, the sample loading rate was 2 BV/h, the sample loading volume was 2.5 BV, deionized water was used for washing, 5 BV 70% ethanol was used for elution at the flow rate of 1 BV/h, and the eluent was collected. Under this condition, the yield of total flavonoids was 78.7% and the purity was 47.3%. Macroporous adsorption resin separation method has a good purification effect on the extraction of active components from loquat leaves, and the process is reasonable, stable, and feasible.

3.5. Supercritical Fluid Extraction

Supercritical fluid extraction (SFE) means that when a substance is in a supercritical state, the environmental pressure and temperature are closely related to the solubility of the extracted substance in the supercritical fluid. When the supercritical fluid is mixed with the extracted substance, the supercritical fluid will be extracted and separated according to the polarity, boiling point, and other properties of each substance [78]. Zhang Huien et al. [79] studied the process of supercritical carbon dioxide extraction of ursolic acid from loquat leaves, established the mathematical model of supercritical extraction of ursolic acid from loquat leaves, and determined the optimum process conditions of supercritical extraction of ursolic acid as follows: extraction temperature 61.6 °C, extraction pressure 25.8 MPa, and dynamic extraction time 40 min. Under these conditions, the theoretical extraction rate of ursolic acid was 3.96 mg/g. Jiang Yan et al. [80] also used supercritical CO_2 fluid extraction technology to extract ursolic acid from loquat leaves, and optimized the extraction conditions to determine the appropriate process parameters. The results showed that the influencing factors of supercritical CO_2 extraction of ursolic acid from loquat leaves were as follows: extraction temperature > extraction time > amount of carrier > extraction pressure. The best parameters were extraction temperature 30 °C, extraction pressure 15 MPa, amount of carrier 50 mL and extraction time 90 min. Under the optimum

conditions, the crude extract contained 15.66 mg ursolic acid, with a content of 7.83%. Supercritical fluid extraction technology is widely used in agricultural production, food processing, traditional Chinese medicine, chemical industry, and other industries, and has the advantages of a good separation effect, high extraction rate, and environmental protection [81]. However, the application of extracting active ingredients from loquat leaves is less, so the research on extracting active ingredients from loquat leaves by supercritical fluid technology can be expanded to obtain higher quality products.

3.6. Column Chromatography

Column chromatography (CC) is a method of separating and measuring multi-component mixtures by using the different physical properties of each component. It uses the different distribution ratios of substances between the stationary phase and mobile phase to achieve the purpose of separation. The whole chromatographic process is the process of adsorption, desorption, re-adsorption, and re-desorption. Song Xing [82] optimized the best technological conditions for the extraction and separation of koroso acid by silica gel column chromatography as follows: the dry loading amount is: sample: silica gel = 1:50, and the eluent is petroleum ether: ethyl acetate = 2:1. The final purity of koroso acid is 53.28%, and the purity of koroso acid is 96.43% after the separated sample is recrystallized with 90% ethanol. Huang Yuanyuan [83] used industrial CH_3CH_2OH extraction, organic solvent extraction, and column chromatography techniques such as normal silica gel, ODS silica gel, Toyopearl HW-40, and Sephadex LH-20 to obtain three monomer compounds from the n-BuOH extraction layer of the water-soluble extract of loquat leaves. He Chuanbo et al. [84] determined that the injection condition of loquat leaf polysaccharide by ion exchange column chromatography was pH 8.0, and the buffer solution without NaCl was selected. After ion exchange column chromatography, loquat leaf polysaccharide was divided into three components, and the yields were 32.66%, 1.22%, and 3.12%, respectively. The biggest feature of chromatography is its high separation efficiency, which can separate various substances with very similar properties. As an important analytical separation method, chromatography is widely used in scientific research and industrial production.

3.7. Enzyme-Assisted Extraction

Enzyme-assisted extraction (EAE) is often combined with ultrasonic-assisted extraction and microwave extraction. The active components in loquat leaves are very similar to those in loquat cores. The ultrasonic-assisted enzymatic extraction of loquat core polysaccharides was studied by Wu zhuqing et al. [85]. Cellulase dosage, enzymolysis pH, enzymolysis temperature, and enzymolysis time were selected as the influencing factors, and the yield of loquat core polysaccharides was the response value. Response surface analysis showed that the optimized extraction conditions were as follows: solid–liquid ratio of 1:15, ultrasonic treatment temperature of 60 °C, ultrasonic treatment time of 30 min, the enzymolysis temperature was 49 °C, the enzymolysis time was 1.8 h, and the enzymolysis was pH 4.7, with a cellulase dosage of 1.8%. Under the optimized conditions, the yield of loquat kernel polysaccharide after drying was 9.96% [85,86]. He Chuanbo et al. [84] obtained the optimum conditions of enzymatic extraction of loquat leaf polysaccharide by experiments: extraction time 2.95 h, extraction temperature 41 °C, enzyme dosage 15.6 mg/g, and polysaccharide extraction rate 8.03%. The sample injection condition of loquat leaf polysaccharide ion exchange column chromatography was determined to be pH 8.0, and the buffer solution without NaCl was selected. After ion exchange column chromatography, loquat leaf polysaccharide was divided into three components, and the yield was divided respectively.

4. Pharmacological Activity

4.1. Eliminating Phlegm and Relieving Cough

Loquat leaves are a very effective medicine for relieving cough and resolving phlegm. It has been reported in the literature that the water extract of loquat leaves can effectively eliminate phlegm and relieve cough [87], which may be related to the fact that it can stimulate the secretion of respiratory glands and make the respiratory tract smooth, thus reducing cough and diluting sputum, eliminating phlegm and relieving cough [88]. Ye Guangyi et al. [89]. prepared the extract from loquat leaves, observed the antitussive effect of loquat leaf extract with ammonia water in mice and citric acid in guinea pigs, observed the expectorant effect in mice's trachea, and observed the antiasthmatic effect in guinea pigs' asthma model induced by histamine and acetylcholine. The results showed that the extract from loquat leaves could reduce the number of coughs in mice, increase the excretion of the respiratory tract, and had a good effect in relieving cough, resolving phlegm, and relieving asthma. Qian Pingping [90] also studied the expectorant and antitussive effects of loquat leaves, and proved that adult loquat leaves have better antitussive and expectorant effects than juvenile loquat leaves. Ge Jinfang [91] orally administered loquat leaf triterpene acid to rats, which can significantly treat chronic bronchitis, reduce bronchial mucosal inflammation and epithelial cell shedding, reduce internal secretion, inhibit bronchial mucosal epithelial cell proliferation, and increase bronchial inner diameter and ventilation. Huang Suhua et al. [92] studied the active ingredients in loquat leaves: flavonoids, triterpene acids, polysaccharides, and polyphenols all have antitussive and expectorant activities. Among them, flavonoids and triterpene acids have similar antitussive and expectorant effects, while polysaccharides are poor. Analysis of the correlation between the content of ingredients and activity shows that flavonoids can reduce cough times, and total terpenes can prolong cough latency and have certain expectorant effects. Amygdalin in loquat leaves is also a commonly used expectorant and antitussive agent in modern medicine emulsin, and intestinal microbial enzymes decompose amygdalin in the intestines to produce trace hydrocyanic acid, which inhibits the respiratory center and achieves the effect of relieving cough and asthma [50].

Chinese patent medicine "loquat paste" made of loquat leaves has the effects of clearing away lung-heat, moistening the throat, relieving cough, and eliminating phlegm, and is mainly used to treat acute and chronic tracheitis and cough, with a remarkable curative effect. At present, Chinese patent medicines "loquat cough granule", "Qiangli loquat dew", and "Ganxing cough dew" have been developed clinically, and loquat leaves are expected to play a greater role in clinical medicine.

4.2. Anti-Inflammatory Activity

Modern pharmacological studies have shown that loquat leaves have an anti-inflammatory effect, and triterpenes are the main active ingredients of its pharmacological action. The triterpene acid extract from loquat leaves can effectively inhibit the lung inflammation of ALI mice, and reduce the infiltration of mononuclear inflammatory cells and thickening of alveolar septum, and the effect in the mixture state is better than that of single triterpene acid. Mao Huigao [93] screened out three catalpol derivatives with an anti-inflammatory effect. The structure–activity relationship analysis found that catalpol and picroside II were introduced into the compound with nonpolar groups through 6 phenolic hydroxyl groups, which could increase their anti-inflammatory activity. It was found that the diterpenoid ZH12167 is an anti-inflammatory active ingredient in Scrophularia dentata, and it can inhibit inflammation through JNK/STAT3 pathway. Ge Jinfang [94] studied the inhibitory effect of loquat leaf triterpene acid (TAL) on acute and chronic inflammation. The results showed that TAL (0.05, 0.5, 5, 50 mg/L) in vitro could increase the proliferation of spleen lymphocytes and the production of IL-2 induced by ConA and LPS in AA rats, while inhibiting the excessive production of IL-1 in PM ϕ in AA rats. It shows that the lung inflammation of mice can be effectively inhibited by total triterpenoids in loquat leaves, which provides a new idea for the clinical treatment of patients with acute lung injury. Wang

Liwei et al. [95] used xylene-induced ear swelling in mice, sulfur dioxide-induced cough in mice, and citric acid spray-induced cough in guinea pigs to observe the anti-inflammatory effects of different fractions and monomer components of loquat leaves. These components can be used as lead compounds or screened out of new drugs with biological activity and little toxic side effects, which has reference value for formulating quantitative indexes of loquat leaves quality standards and developing anti-inflammatory drugs.

4.3. Anti-Tumor Activity

In recent years, it has been found that koroso acid in loquat leaves plays an important role in anti-tumor activity [96]. Lin Jiangxiao et al. [97] studied the inhibitory effect of different samples on the growth of gastric cancer cell BGC823 during the separation of koroso acid from loquat leaves, and detected the effect of different samples on the growth of gastric cancer cell BGC823 by the MTT method. The results showed that koroso acid could inhibit the growth of gastric cancer cell BGC823, and other components (such as maslinic acid or mature fruit acid) and koroso acid could produce a synergistic effect to enhance the anti-tumor effect. Experimental studies have shown that ursolic acid extracted from loquat leaves has a cytotoxic effect on S180 cells. Daily intraperitoneal injection of ursolic acid extract at 10 and 20 mg/kg can obviously prolong the survival time of S180 mice bearing tumors, from 13.2 days in the control group to 20.0 and 28.7 days. Daily intraperitoneal injection of ursolic acid extract at 5, 10, and 20 mg/kg can reduce the tumor weight, and the tumor inhibition rate is 45.5, 59.2% and 67.8% respectively [98]. Ito et al. found that procyanidin oligomer in loquat leaves can effectively inhibit tumors and has cytotoxicity to oral tumor cells. [37]. EGFR belongs to the tyrosine kinase type I receptor family and is the product of proto-oncogene Cerb-1. Ren Weiguang et al. [99] found by high-throughput drug screening technology that triterpenoids and phenolic compounds contained in loquat leaves can inhibit the growth of tumors by inhibiting EGFR kinase activity, and anti-EGFR kinase selectively acts on intracellular targets, blocking EGFR function and inhibiting tumor spread. Therefore, triterpenoids and phenolic compounds in loquat leaves can provide a basis for screening EGFR kinase inhibitors. Studies have found that triterpene acids in loquat leaves can inhibit the activity and expression of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9), and inhibit cancer cells such as lung cancer [100]. Li Qi also found that triterpenoids in loquat leaves can induce apoptosis of white blood cells, which has a certain effect on the treatment of leukemia [101]. Huang Jing and others also proved that ursolic acid in loquat leaves has an anti-tumor effect [102]. Fan Tengyun et al. [103] summarized the anti-tumor action mechanism of flavonoids, which inhibited the proliferation of tumor cells by inducing the apoptosis of tumor cells and blocking the cell cycle. The active ingredients in loquat leaves have remarkable anti-tumor effects [104], and it has become a research hotspot at home and abroad to explore related anti-tumor drugs [105].

4.4. Antioxidant Activity

The active ingredients in loquat leaves are natural antioxidants. Studies have found that lignans and polyphenols in loquat leaves have good DPPH free radical scavenging capacity and total antioxidant capacity, and their antioxidant activity is equivalent to that of ascorbic acid with the same concentration [15]. Because polyphenols contain multiple hydroxyl groups in their structures, they can scavenge free radicals well, so they have a strong antioxidant capacity [106,107]. Ding Jianying et al. showed that the higher the content of polyphenols, the stronger the scavenging ability of hydroxyl radicals and DPPH radicals, and the better the antioxidant effect [108] through the experiment on the scavenging ability of loquat leaf polyphenols to hydroxyl radicals and DPPH radicals [109]. Flavonoids also have the ability to scavenge ·OH and DPPH, and the higher the concentration of flavonoids, the stronger its ability to scavenge free radicals [110]. Fu Xiaodan et al. [111] studied the antioxidant capacity of flavonoids extracts to lard with peroxide value as an index. The results showed that flavonoids in loquat leaves had a certain antioxidant capacity to lard, and had a strong scavenging capacity to DPPH free radicals and ABTS free

radicals. Xu Lixuan [112] studied that loquat leaf flavonoids with the mass concentration of 0.05–4.00 g/L have strong antioxidant capacity *in vitro*, and can reduce the production of MDA in mouse liver mitochondria and liver homogenate, and inhibit the hemolysis of mouse red blood cells induced by H_2O_2. Intraperitoneal injection of loquat leaf flavonoids has a significant inhibitory effect on MDA in mouse liver tissue. Hong et al. [113] studied the antioxidant activity of ethyl acetate extract from loquat leaves, and the results showed that different components in the extract had a strong antioxidant capacity, and the order of antioxidant capacity was: neocaine IB > neocaine ia > epicatechin > quercetin-3-O-a-L-rhamnoside > ursolic acid. Wang Jianchao [25] used an antioxidant experiment *in vitro*, and the results showed that loquat leaf polyphenol had better scavenging effects on DPPH, ABTS+, hydroxyl radical, and nitroso than ascorbic acid and tea polyphenols, so it could be used as a potential natural antioxidant source. Some researchers used antioxidant CoQ (2.81 mg/g) to feed relatively old mice (17.5 months) for 15 weeks. After feeding, the mice's special performance in the Morris water maze test was improved, the oxidative damage of protein was reduced, and the early aging was delayed. Therefore, it is beneficial for individuals with age-related symptoms of cognitive decline to take high CoQ [114]. Excessive free radicals produced in the human body will cause oxidative stress damage to cells and body, and then accelerate human aging [115–117]. The antioxidant effect of active ingredients in loquat leaves can remove reactive oxygen free radicals and reduce oxidative stress damage, which is beneficial to slowing down human aging [118].

4.5. Bacteriostasis

The decoction or ethyl acetate extract and ethanol extract of loquat leaves can inhibit *Staphylococcus albus*, *Diplococcus pneumoniae*, *Staphylococcus aureus*, and *Shigella flexneri in vitro* [119]. Xiao Xinsheng et al. [120] used the filter paper method [121] to study loquat leaf extract, and found that loquat leaf extract could effectively inhibit *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis*, and the bacteriostatic effect from strong to weak was: *Staphylococcus aureus* > *Escherichia coli* > *Bacillus subtilis*. The purified loquat leaf polyphenol has obvious an antibacterial effect on *Escherichia coli* and *Staphylococcus aureus*, and the inhibitory effect increases with the increase of polyphenol concentration. The inhibitory effect of loquat leaf polyphenol on *Bacillus subtilis* and *Pseudomonas aeruginosa* is poor or not [25]. Flavonoids have a strong inhibitory effect on *Escherichia coli* and *Bacillus subtilis*, but a poor inhibitory effect on *Aspergillus flavus* and *Saccharomyces cerevisiae* [122]. Ju-Sang Kim et al. [123] added 1% loquat extract to the feed of Epinephelus coioides, and after feeding for 4 weeks, the ability of Epinephelus coioides to inhibit Vibrio vulnificus was significantly improved. Tan Hui et al. [124] studied the inhibitory effects of 18 triterpene acids from loquat leaves on *Propionibacterium acnes*, among which 12 triterpene acids showed inhibitory effects on *Propionibacterium acnes*, among which ursolic acid, maslinic acid, koroso acid, and rosaric acid had the strongest inhibitory effects. Shen Yuting [125] explored the antibacterial mechanism of loquat leaf extract on Penicillium digitatum, and used the compound coating of loquat leaf extract and sodium alginate to preserve citrus fruits. The results showed that the antibacterial effect of loquat leaf extract on Penicillium digitatum was dose-dependent, and it could inhibit the germination of Penicillium digitatum spores, destroy the normal morphology of spores, and inhibit the growth of hypha. The effect of loquat leaf extract on Penicillium digitatum was observed under fluorescent staining, resulting in a large number of cell apoptosis. The loquat leaf extract can reduce the morbidity of fruits inoculated with Penicillium digitatum and the enlargement of plaque diameter, which has a significant effect on improving the resistance of fruits to green mold.

4.6. Hyperglycemic

The active ingredients in loquat leaves have a hypoglycemic effect [126]. Toshima et al. [127] made a fermented tea from loquat leaves and green tea. The components in this tea inhibited the activity of α-glucosidase, and showed the effect of inhibiting hyperglycemia in rats fed with maltose. Chen Rong et al. [128] studied the effects of loquat leaf extract on the growth and metabolism of intestinal probiotics before and after digestion, as well as on digestive enzyme activity during digestion, to explore the hypoglycemic effect of loquat leaf extract. The results showed that loquat leaf extract could reduce the blood sugar concentration by decreasing the activity of amylase and increasing the propionic acid content in probiotics metabolites. Shih et al. [129] fed mice with high fat content food for 10 weeks, and then fed them loquat extract for 4 weeks. It was found that the hyperglycemia, hyperlipidemia, and insulin levels of mice in the experimental group were significantly improved, and the weight of mice was significantly reduced. Xu Shuwen [130] studied the hypoglycemic activity and mechanism of koroso acid. The results showed that koroso acid could reduce blood sugar by improving insulin sensitivity, enhancing the effect of insulin, reducing postprandial blood sugar, improving lipid metabolism, and reducing the damage of free radicals to β cells through antioxidation. Li Feng et al. [131] used gliclazide and metformin hydrochloride as positive control drugs to study the effects of loquat leaf triterpene acid extract on fasting blood glucose, oral glucose, and starch tolerance in normal mice and blood glucose in diabetic mice. The results showed that the crude extract of triterpene acid from loquat leaves had no obvious effect on fasting blood glucose of normal mice, but had obvious inhibitory effect on the increase of blood glucose after fasting administration of glucose and starch, and the effect was stronger than that of gliclazide and metformin hydrochloride. Sesquiterpene glycosides isolated from loquat leaves also have significant hypoglycemic activity [132]. The active ingredients in loquat leaf extract show good blood sugar control activity and have no influence on the blood sugar level of the normal body, so it has a broad prospect in developing slimming products or related drugs.

4.7. Protecting Liver and Kidney

Loquat extract has a protective effect on liver and kidney damage caused by ethanol and viruses [133]. He Yuqin et al. [134] studied the effect of loquat leaf extract on serum biochemical indexes and IBV antibody level of chickens artificially infected with IBV. The experiment showed that loquat leaf extract had a significant protective effect on the liver function and kidney function of chickens artificially infected with IBV, and could improve the level of IBV antibody, and the best group was 0.8% loquat leaf extract. El-Hossary et al. [135] found that the water extract and ethanol extract of loquat leaves can obviously improve the renal function and have a certain protective effect on the kidney, and the effect of the water extract is stronger than that of ethanol extract. Liang Shucai et al. [136] discussed the protective effect of total flavonoids of loquat leaves (TFL) on acute liver injury induced by carbon tetrachloride (CCl_4) in mice. Compared with the control group, TFL can significantly reduce the levels of serum ALT and AST, decrease the content of MDA in liver tissue, increase the content of GSH, and increase the levels of SOD and GSH-Px. Finally, it was concluded that total flavonoids of loquat leaves (TFL) have effects on acute liver injury induced by CCl4 in mice. The inhibitory effect of ursolic acid from loquat leaves on the proliferation of rat hepatic stellate cells was studied, and the mechanism of anti-hepatic fibrosis of ursolic acid from loquat leaves was discussed. It was shown that ursolic acid has a remarkable anti-hepatic fibrosis effect [137]. Wang Baikang [138] treated 80 cases of acute glomerulonephritis in children with modified loquat leaves decoction (treatment group). In the early stage, 50 cases were treated with conventional western medicine antibiotics (control group). The curative effect of the loquat leaves decoction on acute glomerulonephritis was observed. X~2 test showed that the cure rate of the treatment group (67.5%) was higher than that of the control group (14%). Zhang Yanwei and Jiao Jian [139] summarized the prescriptions of loquat leaves for the treatment of kidney diseases, including loquat leaves

decoction, Ganlu decoction, Euryale ferox mixture, and Siye decoction, and preliminarily discussed the characteristic efficacy, indications, and dose–effect relationship of loquat leaves prescriptions. The active ingredients in loquat leaf extract can effectively treat liver cirrhosis, liver injury, nephritis, renal failure [140] and other diseases, and have a significant effect in clinical medicine.

4.8. Anti-Pulmonary Fibrosis Activity

Pulmonary fibrosis is a chronic progressive pulmonary interstitial disease [141], which is caused by a variety of causes and eventually leads to changes in the normal lung tissue structure of patients. Liu Juan et al. [142] found that the preventive and therapeutic effects of loquat leaf triterpene acid on pulmonary fibrosis in rats can be achieved through anti-lipid peroxidation, which can improve the lung tissue structure of rats with pulmonary fibrosis, reduce the damage of alveolar structure and thickening of alveolar septum, and reduce the infiltration of inflammatory cells and collagen fiber content. At the same time, triterpene acid from loquat leaves has an effect on transforming growth factor β1 (TGF-β1) stimulating transdifferentiation, collagen synthesis, and ERK pathway of human embryonic lung fibroblasts. Triterpenoid acid can inhibit the proliferation of human embryonic lung fibroblasts, reduce the production of smooth muscle actin in activated human embryonic lung fibroblasts, and reduce the expression of connective tissue growth factor, collagen, and p-ERK 1/2 [143,144]. Jing Wong et al. [145] analyzed the mechanism and molecular targets of loquat leaves in treating pulmonary fibrosis based on the network pharmacology and molecular docking method. The results showed that there were 18 candidate active ingredients, 103 potential targets, and 138 pathways in loquat leaves in treating pulmonary fibrosis. Molecular docking showed that MOL012556 had good binding with three key candidate target proteins. This study provides a new research method for the mechanism of loquat leaves in treating pulmonary fibrosis.

4.9. Anti-Leukemia Activity

Studies have shown that four triterpene acids in loquat leaves have effects on anti-proliferation activity and apoptosis induction of human leukemia cells. It is found that koroso acid, oleanolic acid, ursolic acid, and maslinic acid all have anti-proliferation activity and apoptosis induction, among which koroso acid induces apoptosis through mitochondrial dysfunction and caspase activation, with the strongest activity [25]. Komiya et al. [146] found that oleanolic acid and ursolic acid could inhibit the proliferation of lymphocytic leukemia Molt4B cells. Ursolic acid inhibited the activity of island decarboxylase (ODC) *in vitro*, and oleanolic acid was not as strong as ursolic acid. These two substances can slightly inhibit the activity of S-adenosylmethionine decarboxylase (Ado Met Dc) and reduce the polyamine content, thus inhibiting the proliferation of lymphocytic leukemia Molt4B cells [47,147]. Elenilson et al. studied the anti-leukemia mechanism of ursolic acid. Ursolic acid is a natural pentacyclic triterpene with anti-leukemia activity, and its C-3 amino derivative can inhibit the activity of leukemia cells. This provides a strong theoretical basis for further treatment of leukemia with ursolic acid derivatives in preclinical research [148].

4.10. Other Pharmacological Effects

The active ingredients in loquat leaves also have the functions of protecting gastric mucosa, stopping vomiting, beauty, and anti-allergic activity [149–152]. Studies have shown that the active ingredients in loquat leaves can protect gastric mucosa, inhibit the formation of gastric ulcer, and have no effect on the secretion of gastric juice and gastric acid [19]. The amygdalin in loquat leaves can be decomposed into cyanic acid and benzaldehyde after being absorbed by human body. These two substances have anticancer, analgesic, and cosmetic effects. According to cosmetic experts, dried loquat leaves can be used for medicinal bath, making skin smooth and tender, and eliminating skin inflammation such as prickly heat and macula. It is a good skin care method [118]. Loquat leaves can also reduce the contents of 5-hydroxytryptamine (5-HT) and dopamine (DA) in the brain tissue

of the mice vomiting model induced by cisplatin, which indicates that loquat leaves have a good antiemetic effect [153].

5. Summary and Prospect

To sum up, loquat leaves are rich in active ingredients and have numerous pharmacological effects. There are many types of extraction and separation technologies for active ingredients, and the effects of different extraction and separation technologies are quite different. Therefore, it is necessary to select the appropriate separation and extraction technology according to the specific situation, so as to make full use of the maximum effect of the extraction and separation technology of effective components from loquat leaves, enhance pharmacological activity, and apply it to clinical research more efficiently.

The resources of loquat leaves in China are very rich. At present, the products developed with loquat leaves as raw materials are mostly concentrated in tea, beverages, and cough medicines, but their utilization rate and refinement degree are not high enough. In the future, the development and utilization of loquat leaves in the fields of medicines, health products, cosmetics, functional foods, etc. can be increased to form a loquat industrial chain, giving full play to its medicinal, edible, and economic values.

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