Review

Chemical constituents and pharmacological effects of *Lonicerae japonicae*

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Abstract

***Lonicera japonica*, also known as honeysuckle, is an evergreen shrub in the family of *Syzygium*. By consulting Sciencedirect databases and Web of Science databases, 79 related articles were found, of which 22 were related to chemical composition and pharmacological activity. These articles show that *L. japonica* has a wide range of pharmacological activities, including antiviral, anti-tumor, and antioxidant effects. These activities have important applications in the pharmaceutical, food, and fragrance industries. This review focuses on the chemical composition and pharmacological effects of *L. japonicae*, which is of great significance to the development of new drugs and therapeutic methods.**

Keywords: *Lonicerae japonicae*; chemical composition; pharmacological activity

1 Introduction

Lonicera japonica is an evergreen shrub in the family of *Syzygium*. It blooms from March to May every year. These flowers are white at first, but later turn yellow, hence the name honeysuckle. *L. japonica* generally grows in humid and sunny areas. It can adapt well to various soils, including acidic, alkaline, and humid fertile sandy soils, and can also grow on gneiss and limestone. It is an important medicinal herb with extensive pharmacological activities and medicinal value. It is widely used in TCM clinical practice. Meanwhile, the beautiful flowers also make it a popular plant.

In recent years, *L. japonicae* performed well in fighting viruses. Studies have found that the active components in *L. japonicae* extract have anti-influenza virus, anti-hepatitis B virus and anti-HIV virus effects. *L. japonicae* is also widely used for the prevention

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and treatment of COVID-19. The researchers found that compounds in *L. japonicae* extract can inhibit the replication and dissemination of the new virus, which is helpful to control the epidemic.

In this study, the chemical constituents and pharmacological effects of *L. japonicae* were reviewed in order to provide reference for further research and development of *L. japonicae*. The chemical compositions were divided into five categories, namely volatile oils, organic acids, triterpenes and triterpene saponins, flavonoids, and iridoid glycosides. The pharmacological activities included antiviral effect, anti-tumor effect, antioxidant activity, anti-inflammatory effect, antipyretic and analgesic effects, immune regulatory effect, effects of lowering blood lipids and blood sugar, and so on.

2 Chemical compositions

2.1 Volatile oils

Volatile oils are the chemical components with the most kinds extracted and separated from *L. japonicae*. The volatile components include cyclohexene oxide (**1**), (*Z*)-Hex-4-en-1-ol (**2**), hexylformate (**3**), styrene (**4**), 2-hydroxyheptane (**5**), 5-methylfurfural (**6**), 5-methylfurfural (**7**), 2-isopropyl-5-methy-2-hexenal (**8**), hexanoic acid (**9**), 1-octen-3-ol (**10**), myrcene (**11**), (*E*,*E*)-2, 4-heptadienal (**12**), *α*-terpinene (**13**), *m*-cymene (**14**), *D*-limonene (**15**), 2-pinene (**16**), phenylacetaldehyde (**17**), (*Z*)-3,7-dimethylocta-1,3,6,-triene (**18**), (*Z*)-3-octen-1-ol (**19**), *γ*-terpinene (**20**), *o*-methoxyphenol (**21**), 1-octanol (**22**), (*Z*)-linalool oxide (furanoid) (**23**), 1-nonen-4-ol (**24**), linalool (**25**), 2-nonanol (**26**), (5*E*)-3,7-dimethylocta-1,5,7-trien-3-ol (**27**), nonanal (**28**), phenethyl alcohol (**29**), 1-methyl-4-(1-methylethyl)-2-cyclohexen-1-ol (**30**), eugenol (**31**), eugenol (**32**), methyl 2-formylbenzoate (**33**), 3,4-dimethoxy styrene (**34**), *β*-damascenone (**35**), jasmone (**36**), methyleugenol(**37**), geranyl acetone (**38**), *β*-ionone (**39**), 1,10-decanediol (**40**), 2,5-Di-tert-butyl-1,4-benzoquinone (**41**), 2,6-Di-tert-butyl-4-methylpheno (**42**), 2,6-Di-tert-butyl-4-methylpheno (**43**), methyl laurate (**44**), methyl laurate (**45**), spathulenol (**46**), lupeol acetate (**47**), nerolidol acetate (**48**), *β*-eudesmol (**49**), and trans-nerolidol (**50**). The structural formulas of volatile oil compounds are shown in Fig. 1.

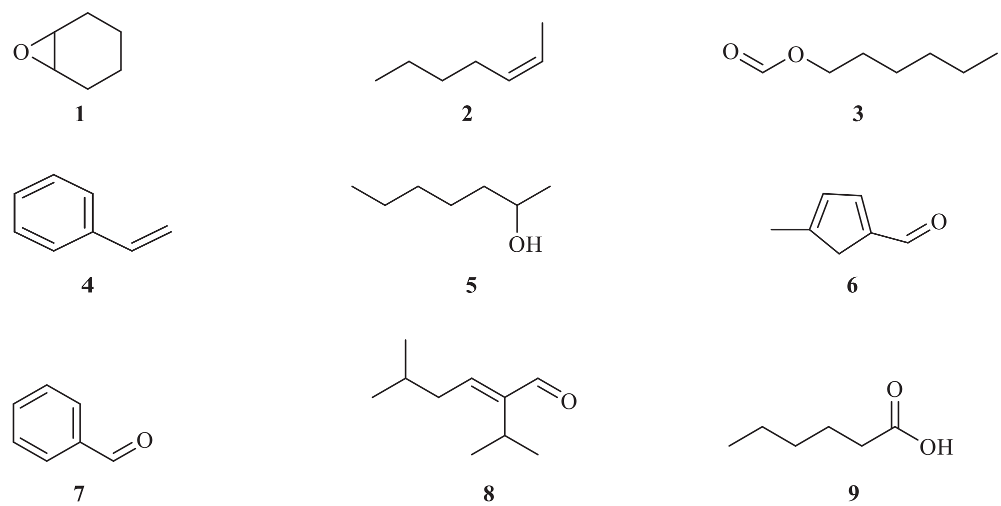

Fig. 1 Structural formulas of volatile oil compounds in *L. japonicae*

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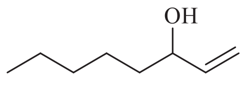
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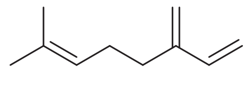
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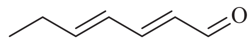
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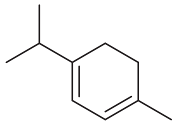
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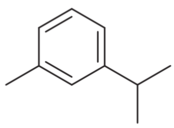
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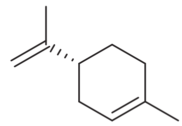
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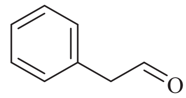
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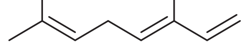
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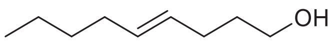
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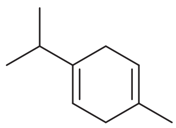
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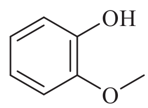
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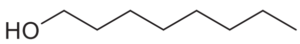
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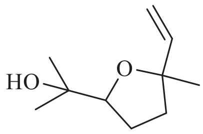
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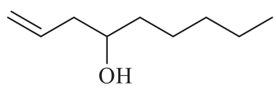
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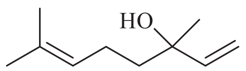
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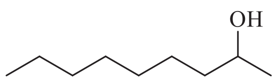
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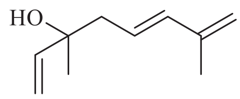
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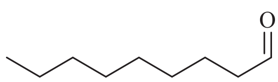
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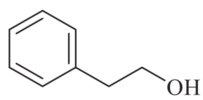
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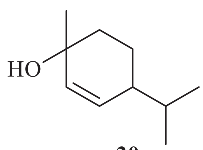
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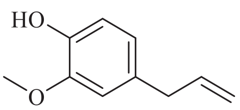
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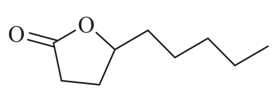
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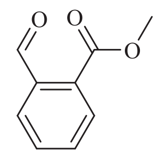
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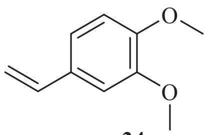
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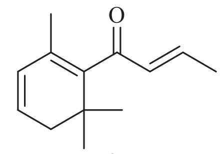
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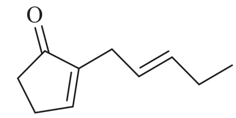
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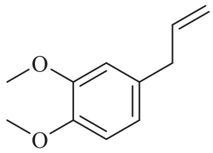
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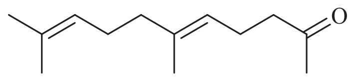
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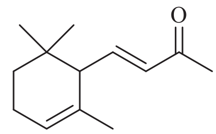
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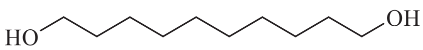
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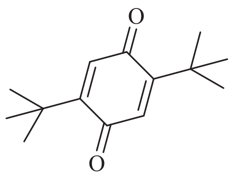
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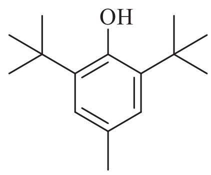
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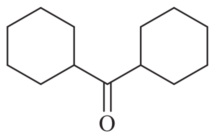
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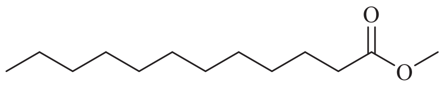
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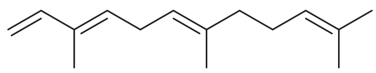
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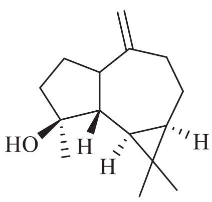
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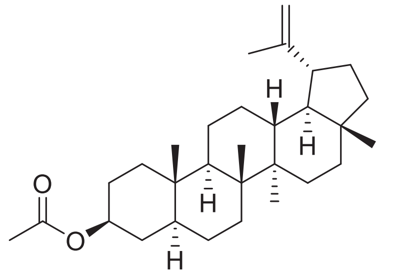
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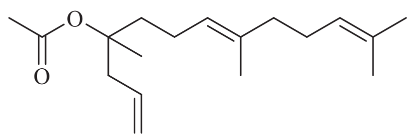
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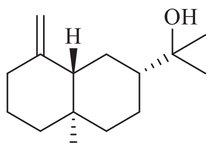
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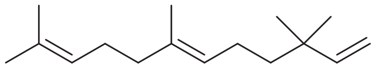
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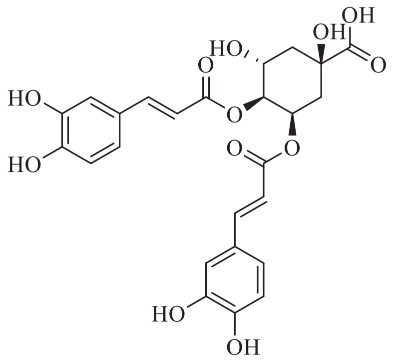
Continued fig. 1

2.2 Organic acids

Organic acids are one of the main chemical components of *L. japonicae*, and they are the key components for clearing heat and detoxifying. Organic acids identified from *L. japonicae* are 4,5-dicaffeoylquinic acid (**51**), cynarine (**52**), 4-feruloylquinic acid (**53**), isochlorogenic acid B

(**54**), caffeic acid (**55**), 3-*O*-feruloylquinic acid (**56**), and palmitic acid (**57**). Among them, isochromogenic acid B and caffeic acid have strong antiviral effects. The structural formulas of organic acid compounds are shown in Fig. 2.



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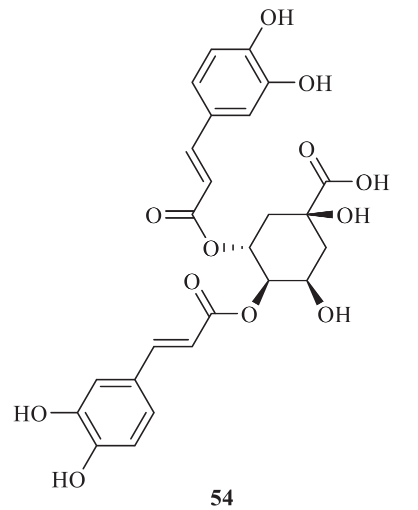

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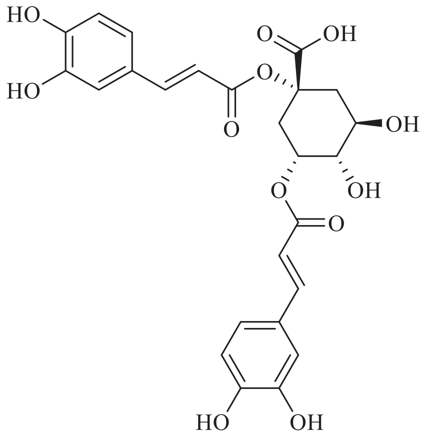

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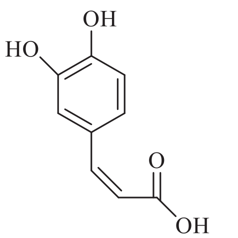

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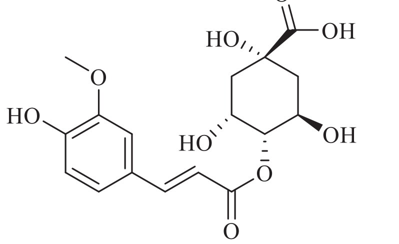

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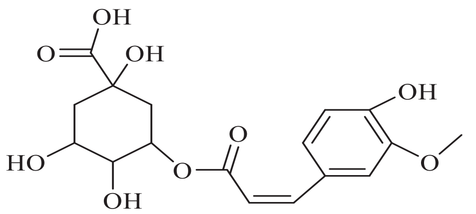

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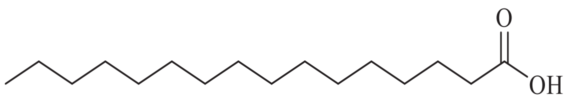

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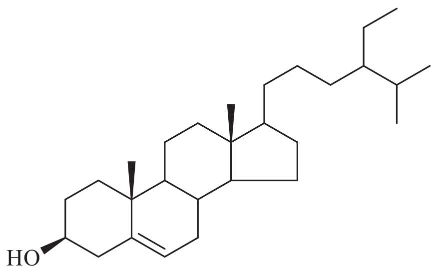
Fig. 2 Structural formulas of organic acid compounds in *L. japonicae*

2.3 Triterpenes and triterpene saponins

Triterpenoid saponins in *L. japonicae* include sitostero (**58**), *β*-amyrin (**59**), *α*-amyrin (**60**), tremulone (**61**), friedelin (**62**), oleanolic acid (**63**), cycloart-23-ene-3,25-diol (**64**), ursolic acid (**65**).

loganic acid (**66**), secoxyloganin (**67**), sweroside (**68**),and *β-sitosterol* (**69**). The structural formulas of triterpene saponin compounds are shown in Fig. 3.



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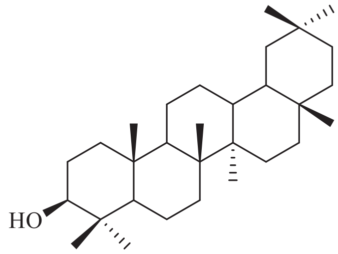

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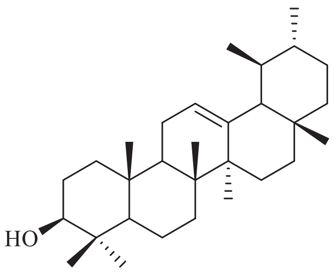

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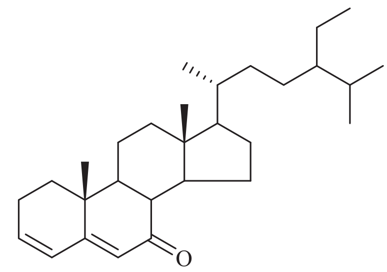

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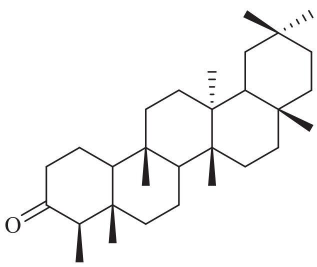

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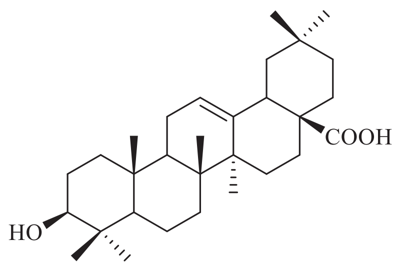

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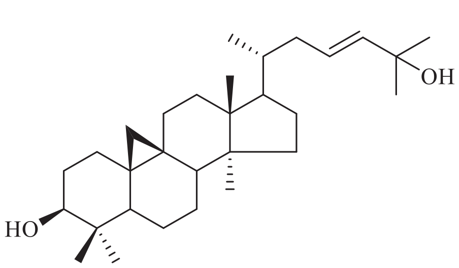

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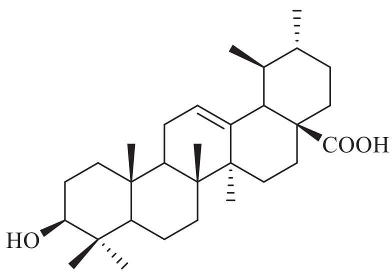

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Fig. 3 Structural formulas of triterpene saponin compounds in *L. japonicae*

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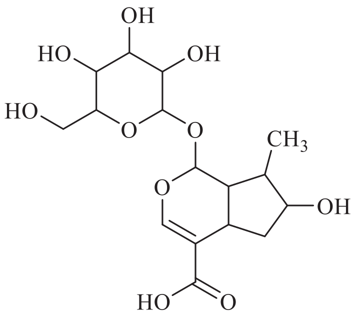

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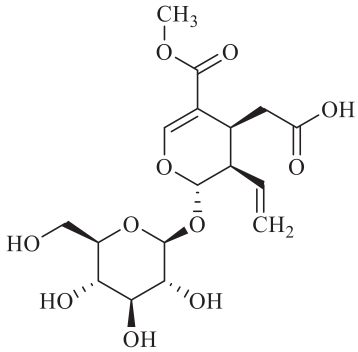

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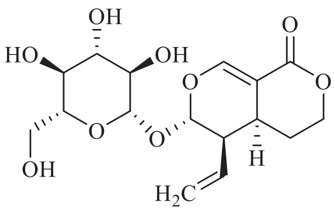

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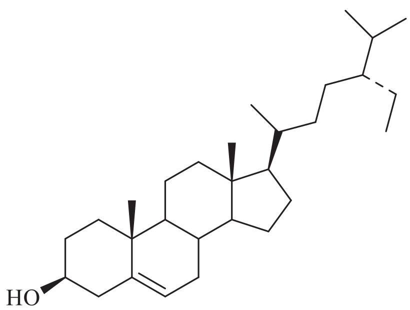

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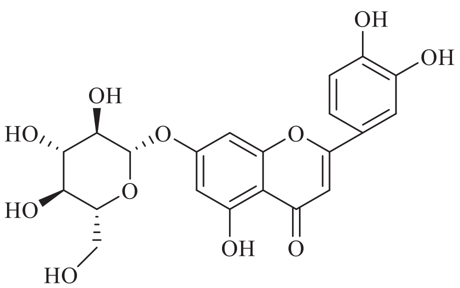
Continued fig. 3

2.4 Flavonoids

Flavonoids are one of the main active components of *L. japonicae* and have antiinffuenza effect and good protection of viscera and organs. They have strong antioxidant capacities. Flavonoids are the compounds that exist in nature and contain 2-phenylchromone structure. In plants, flavonoids combine with sugars to form glycosides. Flavonoids in *L. japonicae* include luteolin-7-*O*-glucoside (**70**), luteolin 7-galacturonide (**71**), quercetin 3-*O*-(6''-galloyl)-*β*-*D*-glucopyranoside (**72**), hyperoside (**73**), corymbosin (**74**), diosmetin (**75**), and hesperidin (**76**). Among them, luteolin-7-*O*-glucoside has a strong antiviral effect. The structural formulas of flavonoid compounds are shown in Fig. 4.



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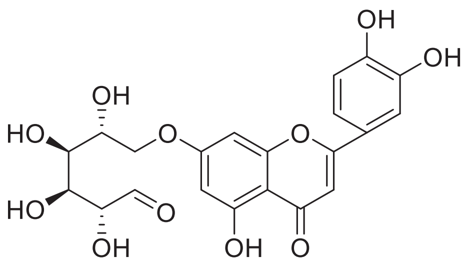

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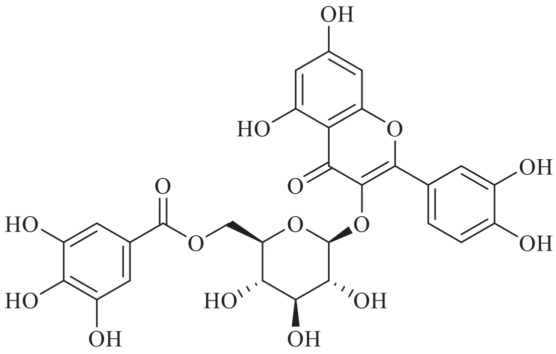
Fig. 4 Structural formulas of flavonoid compounds in *L. japonicae*

(to be continued)



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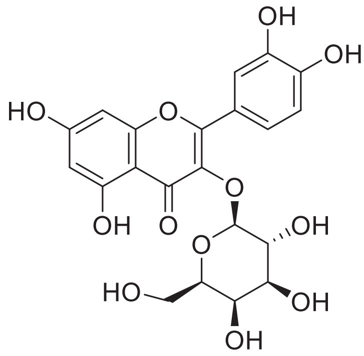

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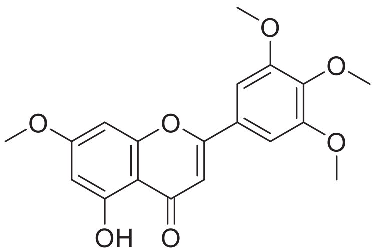

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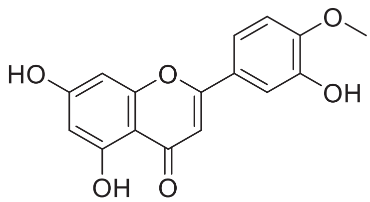

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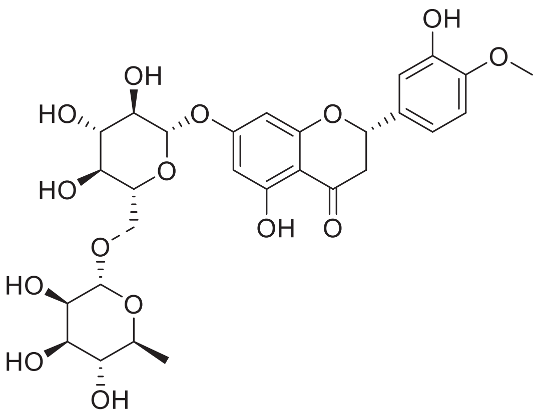

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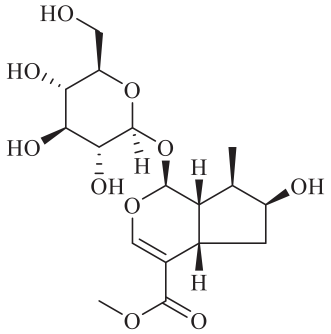
Continued fig. 4

2.5 Iridoid glycosides

Iridoid glycosides are one of the main chemical components of *L. japonicae*, and they are the key components for clearing heat and detoxifying. Iridoid glycosides identified from *L. japonicae* include loganin (**77**), sweroside (**78**), secologanin (**79**), secoxyloganin (**80**), and loganic acid (**81**). The structural formulas of iridoid glycoside compounds are shown in Fig. 5.



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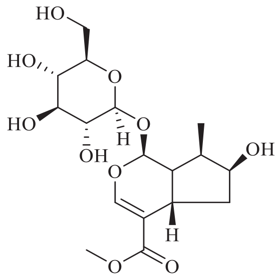

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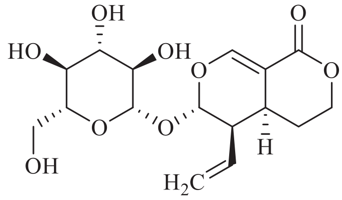

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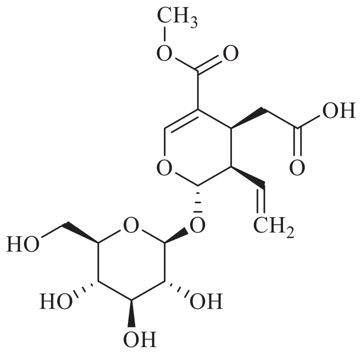

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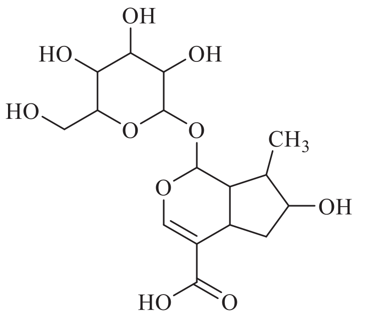

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Fig. 5 Structural formulas of iridoid glycoside compounds in *L. japonicae*

3 Pharmacological effects

3.1 Antiviral effect

The research results show that the extract of *L. japonicae* has antiviral activity against H1N1 and H3N2 influenza viruses, among which acid and flavonoid extracts have the most significant inhibitory effect on the virus. Extracts of *L. japonicae* mainly inhibit viral replication and release by inhibiting the neuraminidase activity of the virus. Therefore, *L. japonicae* extracts have broad-spectrum anti-influenza virus activity and have potential application value in clinical management of influenza virus infection [1]. In the battle against COVID-19, compared to the utilization of conventional therapy alone, combination therapy involving *L. japonicae* has demonstrated significant improvement in lung CT and clinical cure rate [2]. *L. japonicae* also plays an important role in the adjuvant treatment of hepatitis B virus [3], HIV [4] and other infectious diseases.

3.2 Anti-tumor effect

β-sitosterol has an inhibitory effect on some tumor cells [5]. *β*-sitosterol can induce apoptosis of tumor cells, interfere with the growth and spread of tumor cells, and inhibit tumor angiogenesis [6]. It can also inhibit tumor development by regulating the cell cycle and cell signaling pathways. *β*-sitosterol disrupts the cross-talk between RIG-I and IFN/STAT signaling. It inhibits the activation of p38 MAP kinase and NF-*κ*B, which are involved in the initiation of IFN transcription. *β*-sitosterol also inhibits the induction of RIG-I, leading to decreased IFN production and IFN-*β* signal transduction. This disruption of the RIG-I and IFN/

STAT signaling pathway by *β*-sitosterol contributes to the amelioration of influenza virus-induced proinflammatory response and acute lung injury in mice [7]. At the same time, chlorogenic acid also has anti-tumor effect [8], and neochlorogenic acid enhances the anti-tumor effect of pingyangmycin by regulating TOP2A [9].

3.3 Antioxidant activity

DPPH and FRAP assays show that *L. japonicae* has antioxidant activity. Different cultivars and genotypes of *L. japonicae* exhibit various levels of antioxidant activity. Certain cultivars, such as 'Amur', 'Jolanta', 'Klon 40', 'Kuvshinovidnaya', and 'Nympha', demonstrate high antioxidant activity. Additionally, there is a correlation between the antioxidant activity of *L. japonicae* extracts and the content of anthocyanins. The presence of flavonoids and phenolic acids in *L. japonicae* also provides evidence for their antioxidant activity. Therefore, the combination of anthocyanins, flavonoids, and phenolic acids in *L. japonicae* contributes to their antioxidant properties [10]. In addition. chlorogenic acid also acts as a free radical scavenger and antioxidant to protect the cardiovascular system [11].

3.4 Anti-inflammatory effect

L. japonicae exhibits an obvious anti-inflammatory effect by inhibiting the inflammatory response and the release of inflammatory mediators [12]. 3,5-dicaffeoylquinic acid enhances autophagy by inhibiting the MCP3/JAK2/STAT3 signaling pathway, thus alleviating the inflammatory pain mediated by microglial activation [13].

3.5 Antipyretic and analgesic effect

Global metabolic profiling and metabolomics analysis were used to identify the key metabolites in *L. japonicae* extract. The metabolites chlorogenic acid (CA) and swertiamarin (SWE) were found to be the main components responsible for the antipyretic effects of *L. japonicae*. CA targets the MAPK3 pathway and regulates the expression of IL-1 and IL-6, whereas SWE acts on the PI3K-AKT pathway and reduces IL-6 production. By reducing these proinflammatory cytokines, CA and SWE synergistically mimic the antipyretic effects of *L. japonicae* extract. These results indicate that chlorogenic acid has heat-clearing and detoxifying effects [14]. In addition, other components of *L. japonicae*, such as osmanthus glycosides and volatile oils, also play a certain role in antipyretic analgesia [15].

3.6 Immune regulation effect

Studies showed that the administration of *L. japonicae* extract resulted in a prolonged intestinal phase of trichinellosis and decelerated the expulsion of trichinella parasites from the intestines of infected mice. These observations strongly suggest that the extract possesses immunomodulatory properties, influencing the host immune response to infection. Furthermore, it was observed that the extract selectively influenced both the percentage and absolute count of B and T cells in peripheral blood, as well as the absolute count of B cells in mesenteric lymph nodes among infected mice. This indicates a potential impact on lymphocyte activity and cytokine production, further supporting its immunomodulatory effects. Notably, high levels of polyphenolic compounds present in this extract, particularly cyanidin-3-*O*-glucoside, may contribute significantly to its immunomodulatory effects. However, additional investigation is required to elucidate the specific mechanism underlying these actions and fully understand its precise immunomodulatory properties [16].

3.7 Effects of lowering blood lipids and blood sugar

L. japonicae binds with cholesterol and prevents its absorption in the intestine. Administration of Lonicerae japonicaedecoction can reduce the level of cholesterol in blood, and has the effect of lowering blood lipid in normal rabbits. Therefore, 3,5-DCQA can be widely developed and applied in functional foods to help reduce postprandial hyperglycemia [17].

3.8 Other pharmacological effects

Chlorogenic acid obtained by acetylation has obvious protective effect on the liver injury caused by carbon tetrachloride in mice [18], which proves that *L. japonicae* has the effect of protecting liver and gallbladder. *L. japonicae* also has many medicinal values, such as antagonizing inflammatory response [19], antagonizing oxidative stress response [20], reducing acneiform rashes caused by EGFR inhibitors [21], anti-thrombus formation [22], and nerve cell protection. These effects prove that it has broad development prospects.

4 Conclusion

In this review, the chemical compositions and pharmacological activities of *L. japonicae* were summarized based on the existing studies. As a kind of traditional Chinese medicine, *L. japonicae* is very rich in resources and is widely used in clinical practice. This review described 80 compounds in the five chemical classes of *L. japonica*, and their pharmacological activities such as antiviral effect, anti-tumor effect, antioxidant activity, anti-inflammatory effect, antipyretic and analgesic effects, immune regulatory effect, and effects of lowering blood lipids and blood sugar. The efficacy of *L. japonicae* has been widely recognized in the medical community, but more in-depth and systematic studies are needed to study the toxicology of *L. japonicae*. If the safety and efficacy of *L. japonicae* are further studied and discussed, the value of *L. japonicae* will be more widely recognized.

Acknowledgements

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References

[1] Li M, Wang Y, Jin J, et al. Inhibitory activity of Lonicerae japonicae extracts against /influenza A virus in vitro and in vivo. Virol Sin, 2021, 36: 490-500.

[2] Du XQ, Shi LP, Cao WF, et al. Add-on effect of Lonicerae japonicae in .the treatment of coronavirus disease 2019: a systematic review and meta-analysis. Front Pharm, 2021, 12: 708636.

[3] Ge L, Wan H, Tang S, et al. Novel caffeoylquinic acid derivatives from Lonicera japonica Thunb. flower buds exert pronounced anti-HBV activities. RSC adv, 2018, 8: 35374-35385.

[4] Wang F, Li C, Zheng Y, et al. Study on the anaphylactoid of three phenolic acids in Lonicerae japonicae. J Ethnopharm, 2015, 170: 1-7.

[5] Li JX, Kadota S, Li HY, et al. The effect of traditional medicines on bone resorption induced by parathyroid hormone (PTH) in tissue culture: a detailed study on *Cimicifugae rhizoma*. J Trad Med, 1996, 13: 50-58.

[6] Wang K, Li W, Li ZF, et al. β-sitosterol inhibits the proliferation of hepatocellular carcinoma cells by targeting CDC25B. J Sun Yat-sen Univ, 2012, 43: 675-684

[7] Zhou B, Li J, Liang X, et al. β-sitosterol ameliorates influenza A virus-induced proinflammatory response and

acute lung injury in mice by disrupting the cross-talk between RIG-I and IFN/STAT signaling. Acta Pharm Sin, 2020, 41: 1178-1196.

[8] Gupta A, Atanasov AG, Li Y, et al. Chlorogenic acid for cancer prevention and therapy: Current status on efficacy and mechanisms of action. Pharmacol Res, 2022: 106505-106516.

[9] Che J, Zhao T, Liu W, et al. Neochlorogenic acid enhances the antitumor effects of pingyangmycin via regulating TOP2A. Mol Med Rep, 2021, 23: 1-8.

[10] Kucharska AZ, Sokół-Łętowska A, Oszmiański J, et al. Iridoids, phenolic compounds and antioxidant activity of edible *Lonicerae japonicaeberries* (*Lonicera caerulea* var. kamtschatica Sevast.). Molecules, 2017, 22: 405-411.

[11] Sharma A, Lee HJ. *Lonicera caerulea*: An updated account of its phytoconstituents and health-promoting activities. Trends Food Sci Technol, 2021, 107: 130-149.

[12] Wu S, He X, Wu X, et al. Inhibitory effects of blue *Lonicerae japonicae* (*Lonicera caerulea* L) on adjuvant-induced arthritis in rats: Crosstalk of anti-inflammatory and antioxidant effects. J Funct Foods, 2015, 17: 514-523.

[13] Park J, Kim Y, Lee C, et al. 3, 5-Dicaffeoylquinic acid attenuates microglial activation-mediated inflammatory pain by enhancing autophagy through the suppression of MCP3/JAK2/STAT3 signaling. Biomed Pharm, 2022, 153: 113549-113557.

[14] Wang H, Tian L, Han Y, et al. Mechanism assay of *Lonicerae japonicae* for heat-clearing based on metabolites and metabolomics. Metabolites, 2022, 12: 121-136.

[15] Wang Y. Research on Chinese medicine *Lonicerae japonicae* medicinal ingredients and pharmacological effects. Atlant Press, 2017, 3: 42-45.

[16] Piekarska J, Szczypka M, Gorczykowski M, et al. Evaluation of immunotropic activity of iridoid-anthocyanin extract of *Lonicerae japonicaeberries* (*Lonicera caerulea* L.) in the course of experimental trichinellosis in mice. Molecules, 2022, 27: 1949-1955.

[17] Gao D, Ma FT, Sun P. Biological function of *Lonicerae japonicae* extract and its application in breeding industry. Animal Nut, 2019, 31: 2045-2051.

[18] Zhang B, Niu L, Huang X. *Lonicera caerulea* juice alleviates alcoholic liver disease by regulating intestinal flora and the FXR-FGF15 signaling pathway. Nutrients, 2023, 15: 4025-4031.

[19] Lu Y, Huang WA, He ZB, et al. Network pharmacology-based strategy for exploring the pharmacological mechanism of *Lonicerae japonicae* (*Lonicer japonica* Thunb.) against Newcastle Disease. Evid Based Com Alt, 2022, 6: 1934-1946.

[20] Li C, Tang Y, Gu F, et al. Phytochemical analysis reveals an antioxidant defense response in *Lonicera japonica* to cadmium-induced oxidative stress. Sci Rep, 2022, 12: 6840-6852.

[21] Liu Z, Tian T, Wang B, et al. Reducing acneiform rash induced by EGFR inhibitors with *Lonicerae japonicae* therapy: A prospective, randomized, controlled study. Front Pharm, 2022, 13: 835166-835170.

[22] Kim K, Bae ON, Lim KM, et al. Novel antiplatelet activity of protocatechuic acid through the inhibition of high shear stress-induced platelet aggregation. J Pharmacol, 2012, 343: 704-711.