Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Updated pharmacological effects of *Lonicerae japonicae flos*, with a focus on its potential efficacy on coronavirus disease–2019 (COVID-19)

Hui Zhao[1], Sha Zeng[1], Li Chen[1], Qiang Sun[1], Maolun Liu[1], Han Yang[1], Shan Ren[1], Tianqi Ming[1], Xianli Meng[2] and Haibo Xu[1]

Abstract

Lonicerae japonicae flos (LJF), known as Jin Yin Hua in Chinese, is one of the most commonly used traditional Chinese herbs and nutraceuticals. Nowadays, LJF is broadly applied in an array of afflictions, such as fever, sore throat, flu infection, cough, and arthritis, with the action mechanism to be elucidated. Here, we strove to summarize the main phytochemical components of LJF and review its updated pharmacological effects, including inhibition of inflammation, pyrexia, viruses, and bacteria, immunoregulation, and protection of the liver, nervous system, and heart, with a focus on the potential efficacy of LJF on coronavirus disease–2019 based on network pharmacology so as to fully underpin the utilization of LJF as a medicinal herb and a favorable nutraceutical in daily life.

Addresses

[1] State Key Laboratory of Southwestern Chinese Medicine Resources, Department of Pharmacology, Chengdu University of Traditional Chinese Medicine, Chengdu, 611137, China

[2] State Key Laboratory of Southwestern Chinese Medicine Resources, Innovative Institute of Chinese Medicine and Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, 611137, China

Corresponding author: Haibo, Xu (haibo.xu@cdutcm.edu.cn)

Current Opinion in Pharmacology 2021, **60**:200–207

This review comes from a themed issue on **Nutraceuticals (2022)**

Edited by **Yong Tang**

For complete overview about the section, refer Nutraceuticals (2022)

Available online 10 August 2021

https://doi.org/10.1016/j.coph.2021.07.019

Introduction

Lonicerae japonicae flos (LJF), known as Jin Yin Hua in Chinese and recorded in the Chinese Pharmacopoeia, refers to the dried flower buds or the initial flowers of *Lonicera japonica* Thunb., which mainly grows in eastern Asia, particularly including China and Japan. In traditional Chinese medicine, LJF is known to possess the potencies of clearing heat and toxin, and it is broadly utilized for the treatment of diverse clinical afflictions, including fever, sore throat, flu infection, cough, and arthritis. Other than clinical use, LJF is a common type of nutraceutical, with significant nutritional and health care functions [1]. In addition, LJF is also applied to some cosmetics for prevention of acne and eczema [2]. Currently, it is well established that LJF contains numerous bioactive compounds including phenolic acid, iris, saponins, and flavonoids. In addition, LJF exhibits multiple pharmacological effects, involving inhibition of inflammation, pyrexia, viruses, and bacteria, immunoregulation, and protection of the liver, nervous system, and heart, which underpin the management of various physical disorders with LJF.

Coronavirus disease−2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Symptoms of COVID-19 are variable, but often include fever, cough, and breathing difficulties. The pathogenesis of COVID-19 is facilitated by host suppressed immune function and hyperactive inflammatory response, leading to the development of cytokine storm that is a vital factor in COVID-19 progression [3]. A growing body of evidence reveals that traditional Chinese medicine, particularly LJF, may exert substantial efficacies on COVID-19, by alleviating fever and ameliorating respiration of patients with COVID-19 [4–7]. However, the effective constituents of LJF and the in-depth mechanisms underlying the therapeutic action of LJF on COVID-19 remain obscure. Hereby, we sought to summarize the main phytochemical components of LJF and review the updated pharmacological effects of LJF, particularly with a focus on the potential efficacy of LJF on COVID-19 based on network pharmacology so as to fully support the utilization of LJF as a medicinal herb and a favorable nutraceutical in daily life.

Phytochemical components

It is well known that LJF has varieties of phytochemical ingredients, which are mainly phenolic acid, iris, saponins, and flavonoids. Chlorogenic acid (CGA) is the largest family of phenolic acid, consisting of quinic acid

and cinnamic acid, with the latter mainly composed of caffeic acid and ferulic acid.

In the traditional Chinese medicine systems pharmacology database and analysis platform, 236 phytochemical constituents in LJF are recorded. Among them, 23 bioactive elements are characterized, with the oral bioavailability values at over 30% and drug-like property values at more than 0.18 (Table 1).

Updated pharmacological effects

A large amount of updated data show that LJF exerts various novel pharmacological actions, involving the effects on inflammation, pyrexia, viruses, bacteria, immune response, the liver, the nervous system, and the heart, and the potential efficacy on COVID-19 based on network pharmacology.

Anti-inflammatory effect

In the 12-O-tetradecanoylphorbol-13-acetate—induced mouse ear edema, chrysoeriol, a flavone in LJF, was demonstrated to alleviate acute skin inflammation, with the reduction in ear thickness, ear weight, and the number of inflammatory cells in inflamed ear tissues, by downregulating the protein levels of phospho-p65, phospho-STAT3, inducible nitric oxide synthases, cyclooxygenase-2, interleukin 6 (IL-6), interleukin 1 beta (IL-1β), and tumor necrosis factor α (TNF-α) in inflamed ear tissues. In addition, chrysoeriol suppresses the JAK2/STAT3 and IκB/p65 nuclear factor-kappa B (NF-κB) pathway activity in lipopolysaccharide (LPS)-stimulated RAW264.7 cells [8]. It was reported that LJP-1, a polysaccharide isolated from LJF, potently diminishes picryl chloride—caused allergic contact dermatitis in the mouse ear, with substantial attenuation in ear thickness, the serum level of IgE, and histamine, as well as tissue TNF-α [9]. In addition, all five novel iridoid glucosides in LJF were discovered to moderately diminish platelet-activating factor—induced β-glucuronidase release in rat polymorphonuclear leukocytes, indicative of the an ti-inflammatory action of LJF [10].

The toll-like receptor (TLR) signaling pathway plays a critical role in the pathogenesis of sepsis. HS-23, an ethanol extract of LJF, was found to mitigate septic injury through inhibiting TLR4 signaling, evidenced by increasing bacterial clearance, reducing sepsis-induced mortality, and retarding multiple organ failure and TLR4 expression in septic mice, with downregulation in protein levels of myeloid differentiation primary response protein 88, c-Jun N-terminal kinase, p38 kinase, TIR-domain-containing adapter-inducing interferon-β, and interferon regulatory factor 3 [11].

Table 1

The main bioactive components in *Lonicerae japonicae flos*.

Number	Main phytochemical components	OB (%)	DL
1	(–)-(3R,8S,9R,9aS,10aS)-9-ethenyl-8-(beta-D-glucopyranosyloxy)-2,3,9,9a,10,10a-hexahydro-5-oxo-5H,8H-pyrano [4,3-d]oxazolo [3,2-a] pyridine-3-carboxylic acid_qt	87.47	0.23
2	Ioniceracetalides B_qt	61.19	0.19
3	Centauroside_qt	55.79	0.50
4	Caeruloside C	55.64	0.73
5	Secologanic dibutylacetal_qt	53.65	0.29
6	5-hydroxy-7-methoxy-2-(3,4,5-trimethoxyphenyl)chromone	51.96	0.41
7	Dinethylsecologanoside	48.46	0.48
8	Kryptoxanthin	47.25	0.57
9	Quercetin	46.43	0.28
10	7-epi-vogeloside	46.13	0.58
11	Ethyl linolenate	46.10	0.20
12	ZINC03978781	43.83	0.76
13	Stigmasterol	43.83	0.76
14	Phytofluene	43.18	0.50
15	Xylostosidine	87.47	0.23
16	Mandenol	42.00	0.19
17	Kaempferol	41.88	0.24
18	Eriodyctiol (flavanone)	41.35	0.24
19	Beta-carotene	37.18	0.58
20	Beta-sitosterol	36.91	0.75
21	Luteolin	36.16	0.25
22	Chryseriol	35.85	0.27
23	4,5′-Retro-.beta.,.beta.-carotene-3,3′-dione,4′,5′-didehydro	31.22	0.55

OB, oral bioavailability; DL, drug-like property.

Chronic obstructive pulmonary disease (COPD) is a type of obstructive lung disease characterized by long-term breathing problems and poor airflow. Inhalational delivery of LJF microparticle (LJFmp) may be a promising approach for the treatment of COPD, as LJFmp lessens the levels of TNF-α and IL-6 in bronchoalveolar fluid, decreases the number of inflammatory cells including neutrophils in peripheral blood, induces the recovery of elastin and collagen distribution, and suppresses caspase-3 expression in lung tissues of COPD mice [12]. A relatively recent study revealed that LJF may weaken the cytokine storm by attenuation of arachidonic acid metabolism, suggesting the potential therapeutic effect of LJF on COVID-19 [13].

Colorectal cancer, predominantly caused by colitis, is one of the most severe malignancies in the world nowadays [14]. In the dextran sulfate sodium—induced mouse colitis, LJF prevents colon shortening, the loss of recessive glands, and histological damage and decreases the levels of inflammatory cytokines in colonic mucosa, including IL-1β, TNF-α, interferon-γ, IL-6, IL-12, and IL-17, demonstrating the prophylactic role of LJF in mouse colitis by suppression of inflammation [15]. It was reported that SARS-CoV-2 gastrointestinal infection causes hemorrhagic colitis in the patients with COVID-19; LJF may potentially alleviate the intestinal inflammation to facilitate the treatment of COVID-19 [16].

Antipyretic effect

In a rat model of baker's yeast—caused pyrexia, both LJF and LJF-containing Shuang-Huang-Lian, a famous traditional Chinese medicinal formula, lessen the rectal temperature, with elevation in the AUC (area under the concentration time curve) (0-t) and plasma concentrations of CGA, a bioactive constituent of LJF, in the febrile rats versus the normal control, providing the pharmacokinetic evidence for the antipyretic effect of LJF [17]. Furthermore, LJF alleviates LPS-induced fever in rats, accompanied by decreased expression of TNF-α, IL-1β, and IL-6 [18]. As fever is one of the most common symptoms of COVID-19, the antipyretic effect of LJF may improve the outcome of the patients with COVID-19.

Antiviral effect

Cumulative evidence reveals that LJF exhibits inhibitory effects on a broad spectrum of viruses, including the influenza virus, respiratory syncytial virus, avian influenza virus H9 subtype, enterovirus EV71, and herpes virus [19].

For influenza A, secoxyloganin and dimethylsocologanoside of LJF drastically inhibit its growth and replication [20]. In addition, LJF exerts the therapeutic intervention in influenza by regulating the activities of NF-κB, mTOR, and T cell signaling pathways [21].

In addition, it was documented that most terpenoids of LJF display remarkable inhibition on the secretion of HBsAg (hepatitis B surface antigen) and HBeAg (hepatitis B e antigen) and the replication of HBV (hepatitis B virus) DNA in human hepatocellular carcinoma HepG 2.2.15 cells, justifying that LJF may serve as a dietary supplement against HBV infection [22].

Antibacterial effect

In a study on the spectrum—effect correlation between chemical fingerprints and antibacterial effect, LJF was unveiled to inhibit *Pseudomonas aeruginosa* replication, which was dominantly contributed by its two major bioactive compounds, such as CGA and 3,4-dicaffeoylquinic acid [23]. In a microcalorimetric determination, three di-O-caffeoylquinic acids (diCQAs) of LJF were noted to suppress *Bacillus shigae* growth, and the order of inhibitory actions was 3, 5-diCQA > 4, 5-diCQA > 3, 4-diCQA [24].

It was demonstrated that two thymol derivatives of LJF, 7-acetyl-8,9-dihydroxy thymol and 7,8-dihydroxy-9-butyryl thymol, both manifest significant inhibition on *Staphylococcus aureus*, *Escherichia coli*, *Micrococcus luteus*, and *Bacillus cereus in vitro*, with IC_{50} values ranging from 27.64 ± 2.26 to 128.58 ± 13.26 μg/mL [25]. Moreover, five novel iridoid glucosides in LJF also display mild inhibitory potentials against *S. aureus* with minimal inhibitory concentration values ranging from 13.7 to 26.0 μg/mL [10]. After gastrointestinal SARS-CoV-2 infection, some patients with COVID-19 may develop alterations in the gastrointestinal microbiota. Hence, the antibacterial effect of LJF may be beneficial to the restoration of gut microbiota [26].

Immunoregulation

It was documented that some phytochemical compounds in LJF may present diversified immunoregulatory effects. For instance, CGA, abundant in LJF, improves LPS-induced expressions of IL-10 and IL-6 in RAW264.7 cells and elevates the activities of NF-κB, Sp1, and C/EBPβ and δ. However, these actions of CGA may be impeded by luteolin of LJF through alleviating the phosphorylation of IκB and p38 kinase, NF-κB activity, and IL-6 expression in LPS-challenged RAW264.7 cells [27]. It is well known that the healthy immune system can protect against SARS-CoV-2; the immunoregulatory action of LJF may be helpful to the treatment of COVID-19 with LJF [28].

Liver protection

Liver fibrosis is very likely to cause hepatic cirrhosis. LJF was reported to alleviate carbon tetrachloride—induced liver fibrosis in mice, accompanied by the decrease in hepatic hydroxyproline content, serous

collagen IV level, hepatic stellate cell activation, epithelial–mesenchymal transition process, and oxidative stress injury in the liver, through increasing the antioxidative activity of the nuclear factor erythroid 2–related factor 2 signaling pathway cascade. In addition, the phenolic acids in LJF, particularly CGA, sharply mitigate hepatic stellate cell activation *in vitro*. These data suggest the antifibrotic activity of LJF [29], which is consistent with another report that LJF extract exhibits marked protection against liver fibrosis in dimethylnitrosamine-induced rat hepatic injury, with alteration in the levels of 9 metabolites [30].

Besides amelioration of liver fibrosis, LJF also shows liver protection by antagonizing reactive oxygen species activity. Under oxidative stress, a biflavonoid of LJF named japoflavone D attenuates the activation of ERK and mTOR and activates the KEAP1/NRF2/ARE signaling axis in SMMC-7721 hepatoma cells, indicative of the potent antioxidative function of LJF [31]. Furthermore, some phytochemical constituents of LJF present significant activities against the viabilities of HepG 2 and SMMC-7721 cells *in vitro*, by inducing cell apoptosis via the intrinsic apoptotic pathway [22].

Neuroprotective effect

It is being brought to light that inflammation is implicated in the pathogenesis of chronic neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. In LPS-stimulated BV2 microglial cells, polyphenols isolated from LJF showed to attenuate the levels of proinflammatory cytokines, including IL-1β, TNF-α, nitric oxide (NO) synthase 2, prostaglandin E_2, NO synthase, and cyclooxygenase-2, through inhibiting the phosphoinositol 3-kinase/Akt/NF-κB signaling axis, supporting the neuroprotective function of LJF via anti-inflammatory reaction [32].

Cardioprotective effect

Heart failure is a serious medical situation in the clinical setting. The CGA of LJF was reported to protect cardiomyocytes in transverse aortic constriction–caused mouse heart failure, by reducing TNF-α–induced toxicity. In addition, CGA lessens TNF-α–induced cardiac injury in human induced pluripotent stem cell–derived cardiomyocytes, accompanied by increased cell viability and mitochondrial membrane potential and decreased apoptosis in cardiomyocytes. These results are attributed to the inhibition of CGA on the NF-κB signal by attenuation of NF-κB/p65 phosphorylation and c-Jun N-terminal kinase activity [33].

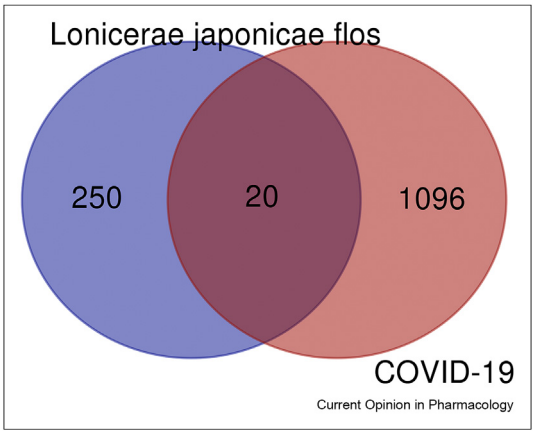
Potential efficacy on COVID-19 based on network pharmacology

As per the traditional Chinese medicine systems pharmacology database, LJF contains 23 high orally bioavailable and drug-like phytochemicals (Table 1) that target 270 genes, 20 of which are among the 1116 genes involved in the pathogenesis of COVID-19, based on the Therapeutic Target Database [34] and Online Mendelian Inheritance in Man database. Therefore, these 20 overlapped genes are the potential targets of LJF in COVID-19, including heat shock protein family B (small) member 1, plasminogen activator, urokinase, collagen type I alpha 1 chain, paraoxonase 1, interleukin 6 receptor, TNF, myeloperoxidase, neutrophil cytosolic factor 1, alcohol dehydrogenase 1C, estrogen receptor 1, IL6, heme oxygenase 1, IL10, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma, epidermal growth factor receptor, interferon-gamma, nitric oxide synthase 3, albumin, glycogen phosphorylase, muscle associated, and amyloid-beta precursor protein (Figure 1).

Of these 20 postulated targets of LJF, the heat shock protein family B (small) member 1 [35], plasminogen activator, urokinase [36], interleukin 6 receptor [37], TNF [38], myeloperoxidase [39], estrogen receptor 1 [40], IL6 [41], heme oxygenase 1 [42], IL10 [43], epidermal growth factor receptor [44], nitric oxide synthase 3 [45], and albumin [46] have been validated to be highly correlated with the initiation and development of COVID-19, and these target genes of LJF are implicated in the inflammatory reaction, oxidative stress, immune regulation, and respiratory function, implying the actions of LJF on these multiple targets orchestrate its efficacy on COVID-19.

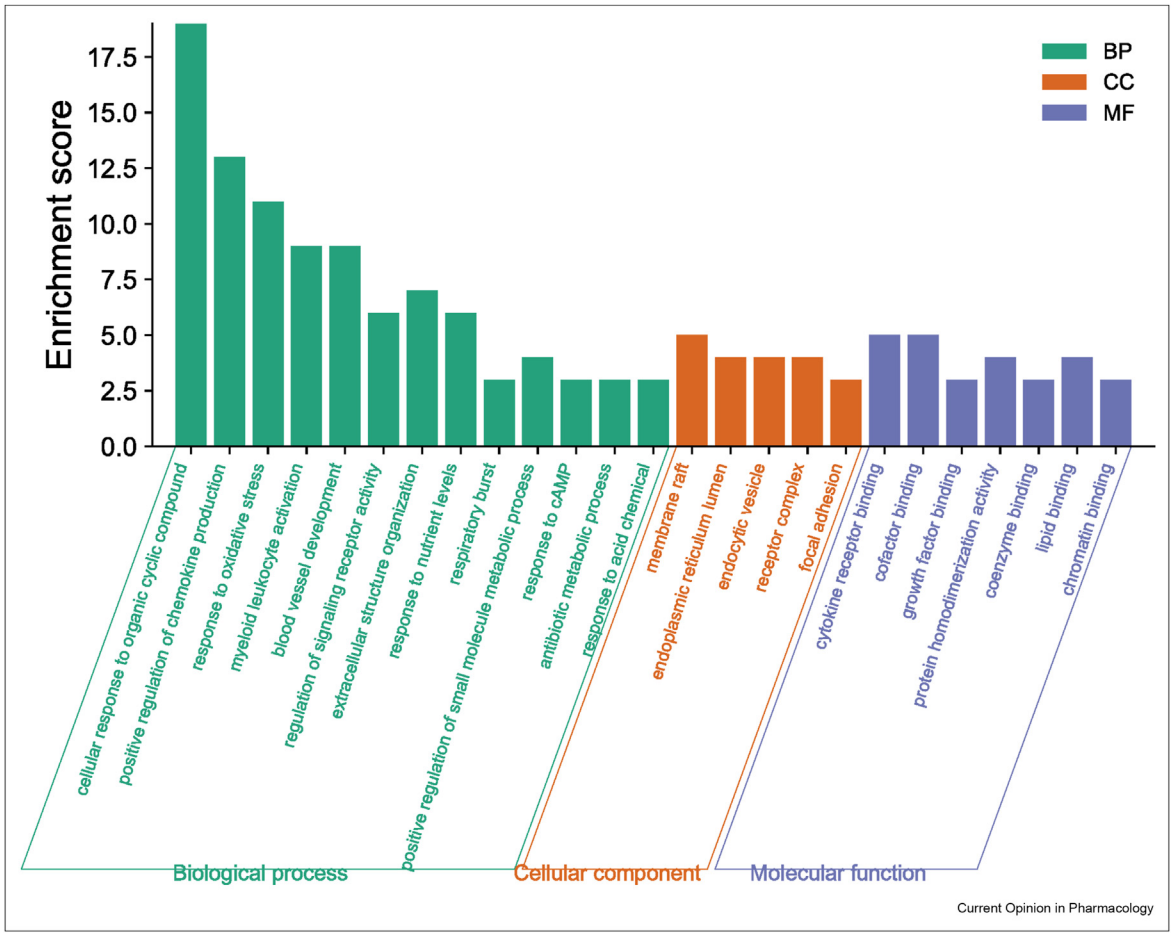
Moreover, gene ontology enrichment analysis of these 20 target genes indicates that LJF may exert its anti–COVID-19 potential through the regulation of the biological process, cellular component, and molecular

Figure 1



The Venn diagram depicts the target genes of LJF in COVID-19. In TCMSP database, 270 target genes are screened out for LJF, and 1116 pathogenic genes of COVID-19 are retrieved in TTD and OMIM database, generating 20 overlapped genes that are the potential targets of LJF in COVID-19. TCMSP, traditional Chinese medicine systems pharmacology; TTD, Therapeutic Target Database; OMIM, Online Mendelian Inheritance in Man.

Figure 2



Gene ontology (GO) enrichment analysis of the functions of the 20 LJF-targeted genes in COVID-19. The 20 LJF-targeted genes in COVID-19 are subject to GO enrichment analysis, revealing that LJF-targeted genes are associated with the regulation of the biological process, cellular component, and molecular function in COVID-19.

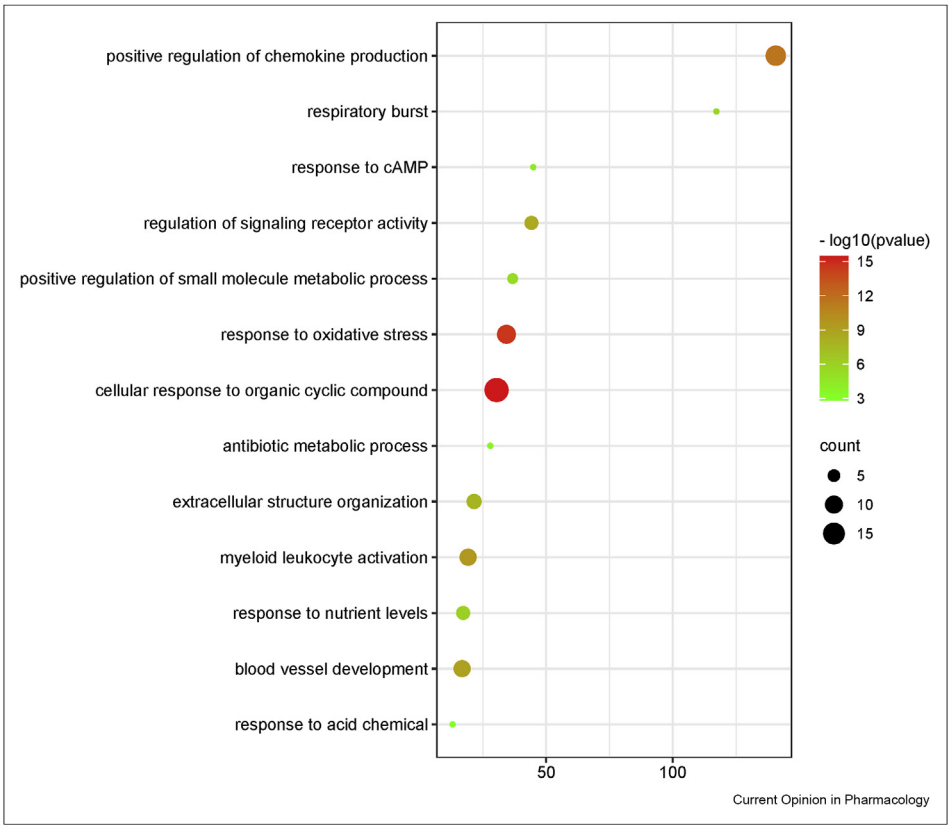
function (Figure 2). Particularly, for biological processes, LJF mainly modulates the pathways involved in the cellular response to organic cyclic compounds, positive regulation of chemokine production, response to oxidative stress, myeloid leukocyte activation, blood vessel development, regulation of signaling receptor activity, extracellular structure organization, response to nutrient levels, respiratory bust, positive regulation of small molecule metabolic processes, response to cAMP, antibiotic metabolic processes, and response to acid chemical.

Furthermore, these results are reinforced by Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis of the biological process enriched with the LJF-targeted genes, indicating that LJF substantially regulates the chemokine production, cellular response to organic cyclic compounds, and response to oxidative stress, with great significance (Figure 3).

Importantly, these potencies of LJF on COVID-19 are evidenced by numerous experimental reports. An orally absorbable plant microRNA in LJF, named MIR2911, was found to suppress the replication of SARS-CoV-2, by acting on the 28 binding sites for MIR2911 in the virus genome, which underpins the negative conversion of SARS-CoV-2–infected patients by MIR2911 [47]. Luteolin, the main flavonoid in LJF, was found to bind the main protease of the SARS-CoV-2 coronavirus with high affinity, implying the potential inhibitory action of LJF on SARS-CoV-2 [48]. A meta-analysis based on 7 English and Chinese databases revealed that the LJF-containing Lianhua Qingwen capsule exerts remarkably therapeutic intervention in common pneumonia and COVID-19 pneumonia [49, 50].

Moreover, it was well documented that LJF can mediate cellular response to organic cyclic compounds, response

Figure 3



KEGG pathway enrichment analysis of the biological process regulated by the LJF-targeted genes. The biological processes enriched with 20 LJF-targeted genes in COVID-19 are subject to KEGG pathway enrichment analysis, revealing that LJF may drastically regulate the chemokine production, cellular response to organic cyclic compounds, and response to oxidative stress. KEGG, Kyoto Encyclopedia of Genes and Genomes.

to oxidative stress [51], myeloid leukocyte activation [52], blood vessel development, and extracellular structure organization, coinciding with network pharmacology—based efficacy of LJF on COVID-19.

Conclusions and perspectives

To date, it is widely acknowledged that complementary and alternative therapy, including traditional Chinese medicine and nutraceutical, may play a pivotal role in the management of miscellaneous diseases, with favorable effects and fewer adverse reactions [53-55]. LJF is one of the most commonly used herbs and nutraceuticals, with multiple properties against a range of clinical disorders, such as inhibition of inflammation, pyrexia, viruses, and bacteria, immunoregulation, and protection of the liver, nervous system, and heart. However, the in-depth mechanisms underlying these properties are still in great need of extensive and intensive exploration with cutting-edge approaches and state-of-the-art technologies. In addition, on long-term dietary uptake, the side effects of LJF should not be neglected, although the toxicological data of LJF are extremely deficient at present.

For COVID-19, collectively, LJF may exert preventive and therapeutic intervention by host-directed regulation and certain antiviral effects [56]. With the progress of several clinical trials of LJF-containing Chinese medicinal preparations, including the Lianhua Qingwen capsule, Toujie Quwen granule, and Jinye Baidu granule [57], more convincing data will strongly evidence the utilization of LJF as a beneficial herb and functional nutraceutical in COVID-19.

Authors' contributions

H.Z., X.L.M., and H.B.X. conceived and designed the research project. H.Z., S.Z., L.C., Q.S., M.L.L., H.Y., S.R., and T.Q.M. carried out the study. H.Z. and H.B.X. wrote the manuscript. All authors have read and approved the manuscript for publication.

Conflict of interest statement

Nothing declared.

Acknowledgements

This work was funded by the National Natural Science Foundation of China (Nos. 81573813 and 81173598), Sichuan Provincial Administration

of Traditional Chinese Medicine of China (No. 2021MS447), the Excellent Talent Program of Chengdu University of Traditional Chinese Medicine of China (Nos. YXRC2019002 and ZRYY1917), and the Open Research Fund of the State Key Laboratory of Southwestern Chinese Medicine Resources of China (No. 2020XSGG006).

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Zhou W, Shan J, Wang S, Cai B, Di L: **Transepithelial transport of phenolic acids in Flos Lonicerae Japonicae in intestinal Caco-2 cell monolayers**. *Food & function* 2015, **6**:3072–3080.

2. Wang L, Jiang Q, Hu J, Zhang Y, Li J: **Research progress on chemical constituents of Lonicerae japonicae flos**. *BioMed Res Int* 2016, **2016**:8968940.

3. Rohilla S: **Designing therapeutic strategies to combat severe acute respiratory syndrome coronavirus-2 disease: COVID-19**. *Drug Dev Res* 2021, **82**:12–26.

4. * Yang Y, Islam MS, Wang J, Li Y, Chen X: **Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): a review and perspective**. *Int J Biol Sci* 2020, **16**:1708–1717.
This review summarizes the advantages of traditional Chinese medicine including LJF in the treatment of patients with COVID-19.

5. * Luo H, Tang QL, Shang YX, Liang SB, Yang M, Robinson N, Liu JP: **Can Chinese medicine Be used for prevention of corona virus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs**. *Chin J Integr Med* 2020, **26**:243–250.
The historical classics and research evidence indicate that traditional Chinese medicine including LJF may exert powerful efficacy on COVID-19.

6. Gao LQ, Xu J, Chen SD: **In silico screening of potential Chinese herbal medicine against COVID-19 by targeting SARS-CoV-2 3CLpro and angiotensin converting enzyme II using molecular docking**. *Chin J Integr Med* 2020, **26**:527–532.

7. Ye M, Luo G, Ye D, She M, Sun N, Lu YJ, Zheng J: **Network pharmacology, molecular docking integrated surface plasmon resonance technology reveals the mechanism of Toujie Quwen Granules against coronavirus disease 2019 pneumonia**. *Phytomedicine* 2020:153401.

8. Wu J, Chen Y, Bai L, Liu Y, Fu X, Zhu P, Li J, Chou J, Yin C, Wang Y, *et al.*: **Chrysoeriol ameliorates TPA-induced acute skin inflammation in mice and inhibits NF-κB and STAT3 pathways**. *Phytomedicine : international journal of phytotherapy and phytopharmacology* 2020, **68**:153173.

9. Tian J, Che H, Ha D, Wei Y, Zheng S: **Characterization and anti-allergic effect of a polysaccharide from the flower buds of Lonicera japonica**. *Carbohydr Polym* 2012, **90**:1642–1647.

10. Yang R, Fang L, Li J, Zhao Z, Zhang H, Zhang Y: **Separation of five iridoid glycosides from Lonicerae japonicae flos using high-speed counter-current chromatography and their anti-inflammatory and antibacterial activities**. *Molecules* 2019, **24**.

11. Kim S, Yoon S, Kim Y, Hong S, Yeon S, Choe K, Lee S: **HS-23, Lonicera japonica extract, attenuates septic injury by suppressing toll-like receptor 4 signaling**. *J Ethnopharmacol* 2014, **155**:256–266.

12. Park Y, Jin M, Kim S, Kim M, Namgung U, Yeo Y: **Effects of inhalable microparticle of flower of Lonicera japonica in a mouse model of COPD**. *J Ethnopharmacol* 2014, **151**:123–130.

13. Ren Y, Yao M, Huo X, Gu Y, Zhu W, Qiao Y, Zhang Y: **[Study on treatment of "cytokine storm" by anti-2019-nCoV prescriptions based on arachidonic acid metabolic pathway]**. *Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China journal of Chinese materia medica* 2020, **45**:1225–1231.

14. Chen L, He M, Zhang M, Sun Q, Zeng S, Zhao H, Yang H, Liu M, Ren S, Meng X, *et al.*: **The Role of non-coding RNAs in colorectal cancer, with a focus on its autophagy**. *Pharmacol Ther* 2021, **226**:107868.

15. Park J, Bae H, Lee G, Hong B, Yoo H, Lim S, Lee K, Kim J, Ryu B, Lee B, *et al.*: **Prophylactic effects of Lonicera japonica extract on dextran sulphate sodium-induced colitis in a mouse model by the inhibition of the Th1/Th17 response**. *Br J Nutr* 2013, **109**:283–292.

16. Carvalho A, Alqusairi R, Adams A, Paul M, Kothari N, Peters S, DeBenedet AT: **SARS-CoV-2 gastrointestinal infection causing hemorrhagic colitis: implications for detection and transmission of COVID-19 disease**. *Am J Gastroenterol* 2020, **115**:942–946.

17. Gao R, Lin Y, Liang G, Yu B, Gao Y: **Comparative pharmacokinetic study of chlorogenic acid after oral administration of Lonicerae Japonicae Flos and Shuang-Huang-Lian in normal and febrile rats**. *Phytother Res : PT* 2014, **28**:144–147.

18. Wu J, Zhang M, Cheng J, Zhang Y, Luo J, Liu Y, Kong H, Qu H, Zhao Y: **Effect of Lonicerae japonicae flos carbonisata-derived carbon dots on rat models of fever and hypothermia induced by lipopolysaccharide**. *Int J Nanomed* 2020, **15**:4139–4149.

19. ** Lee DYW, Li QY, Liu J, Efferth T: **Traditional Chinese herbal medicine at the forefront battle against COVID-19: clinical experience and scientific basis**. *Phytomedicine* 2021, **80**:153337.
The antiviral and anti-inflammatory effects of LJF underpin its efficacy on COVID-19.

20. Kashiwada Y, Omichi Y, Kurimoto S, Shibata H, Miyake Y, Kirimoto T, Takaishi Y: **Conjugates of a secoiridoid glucoside with a phenolic glucoside from the flower buds of Lonicera japonica Thunb**. *Phytochemistry* 2013, **96**:423–429.

21. Zhang FX, Li ZT, Li M, Yuan YL, Cui SS, Chen JX, Li RM: **Dissection of the potential anti-influenza materials and mechanism of Lonicerae japonicae flos based on in vivo substances profiling and network pharmacology**. *J Pharmaceut Biomed Anal* 2021, **193**:113721.

22. Ge L, Xiao L, Wan H, Li J, Lv K, Peng S, Zhou B, Li T, Zeng X: **Chemical constituents from Lonicera japonica flower buds and their anti-hepatoma and anti-HBV activities**. *Bioorg Chem* 2019, **92**:103198.

23. Shi Z, Liu Z, Liu C, Wu M, Su H, Ma X, Zang Y, Wang J, Zhao Y, Xiao X: **Spectrum-effect relationships between chemical fingerprints and antibacterial effects of Lonicerae japonicae flos and Lonicerae flos base on UPLC and microcalorimetry**. *Front Pharmacol* 2016, **7**:12.

24. Han J, Lv Q, Jin S, Zhang T, Jin S, Li X, Yuan H: **Comparison of anti-bacterial activity of three types of di-O-caffeoylquinic acids in Lonicera japonica flowers based on microcalorimetry**. *Chin J Nat Med* 2014, **12**:108–113.

25. Yang J, Li Y, Zhou X, Xu X, Fu Q, Liu C: **Two thymol derivatives from the flower buds of Lonicera japonica and their antibacterial activity**. *Nat Prod Res* 2018, **32**:2238–2243.

26. Alberca GGF, Solis-Castro RL, Solis-Castro ME, Alberca RW: **Coronavirus disease-2019 and the intestinal tract: an overview**. *World J Gastroenterol* 2021, **27**:1255–1266.

27. Cheng CY, Yeh CC: **Adaptive immunoregulation of luteolin and chlorogenic acid in lipopolysaccharide-induced interleukin-10 expression**. *Ci Ji Yi Xue Za Zhi* 2020, **32**:186–192.

28. Chowdhury MA, Hossain N, Kashem MA, Shahid MA, Alam A: **Immune response in COVID-19: a review**. *J Infect Public Health* 2020, **13**:1619–1629.

29. Miao H, Zhang Y, Huang Z, Lu B, Ji L: **Lonicera japonica attenuates carbon tetrachloride-induced liver fibrosis in mice: molecular mechanisms of action**. *Am J Chin Med* 2019, **47**:351–367.

30. Sun C, Teng Y, Li G, Yoshioka S, Yokota J, Miyamura M, Fang H, Zhang Y: **Metabonomics study of the protective effects of Lonicera japonica extract on acute liver injury in dimethylnitrosamine treated rats**. *J Pharmaceut Biomed Anal* 2010, **53**(1):98–102.

31. Wan H, Ge L, Li J, Zhang K, Wu W, Peng S, Zou X, Zhou H, Zhou B, Zeng X: **Effects of a novel biflavonoid of Lonicera japonica flower buds on modulating apoptosis under different oxidative conditions in hepatoma cells**. *Phytomedicine : international journal of phytotherapy and phytopharmacology* 2019, **57**:282–291.

32. Han MH, Lee WS, Nagappan A, Hong SH, Jung JH, Park C, Kim HJ, Kim GY, Kim G, Jung JM, *et al.*: **Flavonoids isolated from flowers of Lonicera japonica Thunb. Inhibit inflammatory responses in BV2 microglial cells by suppressing TNF-alpha and IL-beta through PI3K/akt/NF-kb signaling pathways**. *Phytother Res* 2016, **30**: 1824–1832.

33. Tian L, Su C, Wang Q, Wu F, Bai R, Zhang H, Liu J, Lu W, Wang W, Lan F, *et al.*: **Chlorogenic acid: a potent molecule that protects cardiomyocytes from TNF-α-induced injury via inhibiting NF-κB and JNK signals**. *J Cell Mol Med* 2019, **23**: 4666–4678.

34. Wang Y, Zhang S, Li F, Zhou Y, Zhang Y, Wang Z, Zhang R, Zhu J, Ren Y, Tan Y, *et al.*: **Therapeutic target database 2020: enriched resource for facilitating research and early development of targeted therapeutics**. *Nucleic Acids Res* 2020, **48**(D1):D1031–D1041.

35. O'Brien E, Sandhu J: **Sex differences in COVID-19 mortality: opportunity to develop HSP27 (HSPB1) immunotherapy to treat hyper-inflammation?** *Cell stress & chaperones* 2020, **25**: 725–729.

36. Hou Y, Ding Y, Nie H, Ji H: **Fibrinolysis influences SARS-CoV-2 infection in ciliated cells**. *bioRxiv* 2021. the preprint server for biology.

37. Buonaguro F, Puzanov I, Ascierto P: **Anti-IL6R role in treatment of COVID-19-related ARDS**. *J Transl Med* 2020, **18**:165.

38. Gao G, Zhu Z, Fan L, Ye S, Huang Z, Shi Q, Sun Y, Song Q: **Absent immune response to SARS-CoV-2 in a 3-month recurrence of coronavirus disease 2019 (COVID-19) case**. *Infection* 2021, **49**:57–61.

39. Zhang Y, Han K, Du C, Li R, Liu J, Zeng H, Zhu L, Li A: **Carboxypeptidase B blocks ex vivo activation of the anaphylatoxin-neutrophil extracellular trap axis in neutrophils from COVID-19 patients**. *Crit Care* 2021, **25**:51.

40. Cai Y, Zeng M, Chen Y: **The pharmacological mechanism of Huashi Baidu Formula for the treatment of COVID-19 by combined network pharmacology and molecular docking**. *Ann Palliat Med* 2021, **10**(4):3864–3895.

41. Islam A, Khan M, Ahmed R, Hossain M, Kabir S, Islam M, Siddiki A: **Transcriptome of nasopharyngeal samples from COVID-19 patients and a comparative analysis with other SARS-CoV-2 infection models reveal disparate host responses against SARS-CoV-2**. *J Transl Med* 2021, **19**:32.

42. Dattilo M: **The role of host defences in Covid 19 and treatments thereof**. *Mol Med* 2020, **26**:90 (Cambridge, Mass.).

43. Lu L, Zhang H, Dauphars D, He Y: **A potential role of interleukin 10 in COVID-19 pathogenesis**. *Trends Immunol* 2021, **42**:3–5.

44. Mukhopadhyay D, AlSawaftah N, Husseini G: **In Silicoldentification of novel MicroRNAs as promising therapeutics for SARS-CoV-2 by regulating the EGFR-ADAM17 Axis: an analysis**. *ACS pharmacology & translational science* 2021, **4**: 396–399.

45. Wiltshire E, Peña A, MacKenzie K, Shaw G, Couper J: **High dose folic acid is a potential treatment for pulmonary hypertension, including when associated with COVID-19 pneumonia**. *Med Hypotheses* 2020, **143**:110142.

46. Pasqualetti S, Aloisio E, Panteghini M: **Letter to the editor: serum albumin in COVID-19: a good example in which analytical and clinical performance of a laboratory test are strictly intertwined**. *Hepatology* 2021 (Baltimore, Md.).

47. ** Zhou LK, Zhou Z, Jiang XM, Zheng Y, Chen X, Fu Z, Xiao G, Zhang CY, Zhang LK, Yi Y: **Absorbed plant MIR2911 in honeysuckle decoction inhibits SARS-CoV-2 replication and accelerates the negative conversion of infected patients**. *Cell Discov* 2020, **6**:54.

MIR2911 in LJF was found to inhibit the replication of SARS-CoV-2, by acting on the 28 binding sites in the virus genome.

48. ** Yu R, Chen L, Lan R, Shen R, Li P: **Computational screening of antagonists against the SARS-CoV-2 (COVID-19) coronavirus by molecular docking**. *Int J Antimicrob Agents* 2020, **56**:106012.

Luteolin, the main flavonoid in LJF, was found to bind the main protease of SARS-CoV-2 with high affinity.

49. Hu C, Liang M, Gong F, He B, Zhao D, Zhang G: **Efficacy of Lianhua qingwen compared with conventional drugs in the treatment of common pneumonia and COVID-19 pneumonia: a meta-analysis**. *Evid Based Complement Alternat Med* 2020, **2020**:5157089.

50. * Zhang Q, Cao F, Ji G, Xu X, Sun Y, Li J, Qi X, Sun S, Wang Y, Song B: **The efficacy and safety of Lianhua Qingwen (LHQW) for coronavirus disease 2019 (COVID-19): a protocol for systematic review and meta analysis**. *Medicine (Baltim)* 2020, **99**, e20979.

A meta-analysis revealed that LJF-involving Lianhua Qingwen Capsule exerts therapeutic intervention in COVID-19.

51. Iddir M, Brito A, Dingeo G, Fernandez Del Campo S, Samouda H, La Frano M, Bohn T: **Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: considerations during the COVID-19 crisis**. *Nutrients* 2020:12.

52. Shaath H, Vishnubalaji R, Elkord E, Alajez N: **Single-cell transcriptome analysis highlights a role for neutrophils and inflammatory macrophages in the pathogenesis of severe COVID-19**. *Cells* 2020, **9**.

53. Tan L, Lei N, He M, Zhang M, Sun Q, Zeng S, Chen L, Zhou LJ, Meng XL, Xu HB: **Scutellarin protects against human colorectal cancer in vitro by down regulation of hedgehog signaling pathway activity**. *Int J Pharmacol* 2020, **16**:53–62.

54. Sun Q, He M, Zhang M, Zeng S, Chen L, Zhou L, Xu H: **Ursolic acid: a systematic review of its pharmacology, toxicity and rethink on its pharmacokinetics based on PK-PD model**. *Fitoterapia* 2020, **147**:104735.

55. Zhao H, He M, Zhang M, Sun Q, Zeng S, Chen L, Yang H, Liu M, Ren S, Meng X, *et al.*: **Colorectal cancer, gut microbiota and traditional Chinese medicine: a systematic review**. *Am J Chin Med* 2021, **49**:805–828.

56. Ni L, Chen L, Huang X, Han C, Xu J, Zhang H, Luan X, Zhao Y, Xu J, Yuan W, *et al.*: **Combating COVID-19 with integrated traditional Chinese and Western medicine in China**. *Acta Pharm Sin B* 2020, **10**:1149–1162.

57. Luo H, Yang M, Tang QL, Hu XY, Willcox ML, Liu JP: **Characteristics of registered clinical trials on traditional Chinese medicine for coronavirus disease 2019 (COVID-19): a scoping review**. *Eur J Integr Med* 2021, **41**:101251.