

Molecular Basis for Treating COVID-19 with Official Chinese Herbal Formula LCTE

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Abstract

Chinese herbal formulas, notably the *lung-cleaning and toxicity-excluding* (LCTE) soup has played an important role in treating an ongoing and life-threatening worldwide pandemic, COVID-19 (caused by SARS-CoV-2). Applying LCTE outside of China may be difficult for medical society to approach due to the unfamiliar rationale behind its application in terms of Traditional Chinese Medicine. To overcome this barrier, we illuminate the chemical and biological mechanisms behind LCTE's effects, by exploring the chemical compounds contained in LCTE ingredients, the proteins targeted by these compounds as well as undertaking the network pharmacology analysis. The results disclosed that LCTE contains compounds with the potential to directly inhibit SARS-CoV-2 and inflammation, and that the compounds targeted proteins significantly related to the main symptoms seen in COVID-19. The general effect of LCTE was to affect the pathways involved in viral and other microbe infection, inflammation/cytokine response, and lung diseases. Our work provided chemical biological explanations for using LCTE to treat COVID-19.

Introduction

Towards the end of December 2019, a new type of pneumonia (COVID-19) originating in Wuhan, China, was identified. It is caused by the novel coronavirus SARS-CoV-2 and transmitted from human-to-human¹⁻³. This virus has affected many persons in China and spread to other countries in a very short time. On March 14, 2020, the World Health Organization (WHO) pronounced it a worldwide pandemic. According to WHO Daily Report, there have been a total of 142,649 confirmed COVID-19 cases with 5,393 deaths in nearly 135 countries, areas or territories as of this writing on March 14, 2020. This pandemic is ongoing, so quickly identifying new preventive and therapeutic agents is a top priority.

Specific vaccines and antiviral agents are the most effective methods for preventing and treating viral infections, yet no such anti-SARS-CoV-2 agents are currently available. Development of these treatments may require months or years, meaning that a more immediate treatment should be found if at all possible. Herbs used in Traditional Chinese Medicine (TCM) present a potentially valuable resource to this end. The effectiveness of herbal treatment in controlling contagious disease was demonstrated during the 2003 severe acute respiratory syndrome (SARS) outbreak⁴. As such, the Chinese government was encouraging the use of herbal medication in fighting this new viral pneumonia, which had brought about good clinical results⁵. The State Administration of TCM reported to official media (chinadaily.com.cn, March 6, 2020) that up to February 17 a total of 60,107 patients with SARS-CoV-2 infections, accounting for 85.2 percent of the infections, had been treated with TCM nationwide. The Chinese government, encouraged by the evident clinical benefits⁵, had recommended several herbal formulas in its continuously modified plans to prevent and treat SARS-CoV-2 infection. The lung-cleaning and toxicity-excluding soup (LCTE, with Chinese name as *qingfei paidu tang*) formula has the highest recommendation, based on its clinical effectiveness and preparatory simplicity (the preparation protocol is provided in supplementary Doc). Containing 20 herbal plants and one mineral component

(detailed in the following section), LCTE has been officially recommended by Chinese government since February 6, 2020 and remains on the list of recommended treatments in the 7th, most recent version of the National Plan for Preventing and Treating SARS-CoV-2 Infection.

At present, the rate of occurrences for COVID-19 infection is declining in China while soaring in some other parts of the world. The successful application of LCTE suggests this formula as an attractive means for fighting COVID-19. Yet, the rationale for LCTE application may be difficult to understand when explained in terms of TCM, making it less approachable to modern medical society, especially outside of China. This barrier severely limits the potential benefits gained by introducing LCTE treatment to medical professionals treating COVID-19 worldwide.

Fortunately, thanks to advancements in identifying the chemical compounds contained in Chinese herbs⁶⁻⁸ and the emergence of network pharmacology technology⁹, the mechanisms behind LCTE's effects may be explained through chemical biology. It is well realized that the therapeutic effects of herbal treatments are due to the pharmacological compounds contained in them¹⁰. For example, it has been proven that the anti-malarial effect of *Artemisia apiacea* is due to its component artemisinin¹¹. Accordingly, the curative effects of LCTE should reside in the chemical compounds contained in the formula's plant ingredients. Network pharmacology highlights a multiple drug component/multiple target model over the single component/single target model in drug development and assessment⁹. The use of this modeling has evolved and expanded over the last several decades¹². Traditional Chinese herbal formulas, which potentially contain many active compounds, are a typical example of the network pharmacology paradigm^{13,14}.

In this work, we provide an explanation for the working mechanisms behind LCTE in modern biochemical language. We achieved this by screening the compounds of related plants and undertaking a network pharmacology analysis. Our work disclosed that two of the main compounds contained in LCTE have the potential to directly inhibit SARS-CoV-2, and that most of the active constituent compounds are anti-inflammatory. Moreover, these compounds could significantly target the proteins related to the main symptoms of COVID-19. The general in vivo therapeutic effect of LCTE was regulation of pathways related to viral and other microbial infection, inflammation/ cytokine response, and lung diseases.

Results

The main chemical compounds and protein targets of the LCTE soup formula

It is well held that Chinese herbal plants contain bioactive compounds and that the therapeutic effects of herbal treatments are achieved via compound/target interaction. We started our work by researching LCTE-contained chemical compounds and their protein targets. The LCTE formula consists of 20 herbal ingredients and one mineral material (raw gypsum, *Rudis Gypsi Miscueris* (Table 1). The main component of raw gypsum is inorganic $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$, and the inclusion of gypsum in the formula is

explainable by findings that it reduces body temperature¹⁵ as well as attenuates heat-induced hypothalamic inflammation via down-regulating IL-1 β ¹⁶. As such, we focused our study on the 20 herbal plants used to formulate LCTE. We found a complete chemical compound list for each plant as recorded in three Chinese herbal databases⁶⁻⁸ (detailed in the Methods section). The listed compounds were then filtered using ADME (absorption, distribution, metabolism, and excretion) indices to find and keep which might be absorbable via oral administration¹⁷. ADME filtration for oral bioavailability is necessary in that Chinese herbal plants are boiled with water and the obtained soup then orally administered. The passing rates ranged from 0.026 to 0.37 with an average of 0.11 (Table 1), indicating that the majority of the compounds present in the related plants would not be absorbed. After finding which compounds were most likely to be absorbed, we again checked the three Chinese herbal databases to find which proteins would be affected by each of these compounds. Each herbal ingredient, their total number of compounds, number of orally absorbable compounds, and their number of protein targets are listed in Table 1. More detailed information on plants and their compounds that passing filtration, and the proteins targeted by each compound screened out are available in the supplementary Table S1 and S2.

Table 1. The constitution and protein targets of LCTE

Chinese names	Latin names	Dosage (g)	No. of total ingredients	No. of ingredients passing ADME filtration	No. of protein targets
<i>Bai Shu</i>	Rhizoma Atractylodis Macrocephalae	9	117	7	35
<i>Ban Xia</i>	Rhizoma Pinelliae	9	138	12	206
<i>Chai Hu</i>	Radix Bupleuri	16	356	11	192
<i>Chen Pi</i>	Pericarpium Citri Reticulatae	6	79	6	72
<i>Dong Hua</i>	Farfarae Flos	9	160	16	185
<i>Fu Ling</i>	Poria	15	89	7	29
<i>Gan Cao</i>	Radix Glycyrrhizae	6	283	73	231
<i>Gui Zhi</i>	Cinnamomi Ramulus	9	245	7	90
<i>Huang Qin</i>	Radix Scutellariae	6	155	33	116
<i>Huo Xiang</i>	Pogostemon Cablin	9	122	12	180
<i>Ma Huang</i>	Herba Ephedrae	9	373	17	227
<i>Shan Yao</i>	Rhizoma Dioscoreae	12	120	13	70
<i>She Gan</i>	Rhizoma Belamcandae	9	108	11	104
<i>Sheng Jiang</i>	Rhizoma Zingiberis Recens	9	191	5	50
<i>Xi Xin</i>	Herba Asari	6	157	9	108
<i>Xing Ren</i>	Semen Armeniacae Amarum	9	42	15	113
<i>Ze Xie</i>	Rhizoma Alismatis	9	61	7	6
<i>Zhi Shi</i>	Fructus Aurantii Immaturus	6	91	14	123
<i>Zhu Ling</i>	Polyporus Umbellatus	9	31	8	5
<i>Zi Wan</i>	Radix Asteria	9	305	10	206
<i>Sheng Shi Gao</i>	Rudis Gypsi Miscoeris	15-30	/	/	/

The potentials to directly inhibit SARS-CoV-2 and the anti-inflammatory properties of the main LCTE-contained compounds

In all, the 20 herbal ingredients in the LCTE formula contain 207 different chemical components that may be absorbed through oral administration. 27 of these components were present in at least 2 of the plant

sources. 5 components were of high concurrence, existing in 6 or more plant sources (supplementary Table S3). Stigmasterol was present in 8 plants, quercetin was present in 7 plants, luteolin and beta-sitosterol and kaempferol were present in 6 plants (Fig. 1). Notably, we recently found that two of the five most prevalent compounds, kaempferol and quercetin, have the potential to directly inhibit papain-like protease (PLpro) and 3C-like protease (3CLpro), two enzymes which are critical to the replication of COVID-19-causing pathogen SARS-CoV-2¹⁸.

COVID-19's basic pathology is viral-caused inflammation. Based on publications in PubMed, we found that 19 of the 27 compounds present in 2 or more of the LCTE herbal plants possess anti-inflammatory properties (supplementary Table S3). The indication is that the main compounds of LCTE have the potential to directly inhibit SARS-CoV-2 and down-regulate inflammation (Fig. 1).

Enrichment of proteins targeted by LCTE in protein sets related to common COVID-19 symptoms

Fifteen main symptoms have been reported in COVID-19 patients^{19,20}. These include fever, cough, myalgia, fatigue, and dyspnea and etc., which could be catalogued as general, respiratory and digestive symptoms. The LCTE formula's clinical effectiveness in relieving these symptoms has been confirmed in China. To understand the molecular basis for LCTE's relief of COVID-19 symptoms, we used DisGeNET²¹ to download the proteins related to each symptom and then studied the correspondence between these and the protein targets of LCTE's orally-absorbable compounds. The exact proteins related to each symptom and the results for the DisGeNet search 'viral respiratory infection' are available in supplementary Table S4.

Hypergeometric distribution probability computation showed that the component-targeted proteins were significantly enriched in 11 of the symptoms-related proteins ($P < 0.05$) (Fig.2 and supplementary Table S5), including 5 of the highest occurrence symptoms, fever, coughing, myalgia, fatigue, and dyspnea. The protein sets for anoxia, diarrhea, nausea, headache, vomiting, and abdominal pain also significantly correlated to proteins targeted by LCTE. Computational enrichment for dry cough, pharyngalgia, dizziness, and sputum proteins did not yield significant results, which might be due to the low number of proteins recorded for these symptoms in the DisGeNET database. The proteins related to the search query 'viral respiratory infection' in DisGeNET also correlated significantly with LCTE-targeted proteins. Since COVID-19 is a viral respiratory disease, such results further support the effectiveness of LCTE in treating COVID-19.

Key compounds and proteins for LCTE's symptoms relief

The field of network pharmacology suggests that the effects of a drug containing multiple components can be predicted by a network constructed of the linkages between the multiple components and their targets⁹. Inspired by this methodology, we built a network using the following linkages: herbal plants and

their corresponding chemical compounds, chemical compounds and their affected proteins, and proteins related to each symptom. By calculating the degree for each vertex, we were able to derive which plants, compounds, and proteins are key to LCTE's symptom alleviation. For example, in LCTE there are two herbal ingredients, *Gan Cao* and *Huang Qin*, and 6 compounds (quercetin, luetolin, stigmasterol, kaempferol, beta-sitosterol, and wogonin) useful in treating fever, and the key proteins affected by these components are PTGS2 (prostaglandin-endoperoxide synthase 2) and PRSS1 (Serine Protease

1) (Fig. 3). While for treating cough, three LCTE's plants (*Gan Cao*, *Huang Qin*, and *Zhi Shi*) and five compounds (quercetin, luetolin, stigmasterol, kaempferol, and beta-sitosterol) were involved, targeting the proteins TOP2B (DNA topoisomerase II beta) and ADRB2 (adrenoceptor beta 2) (supplementary Fig S1). The network data for the key herbal plants, their compounds, the proteins involved in LCTE's effects on other COVID-19 symptoms, and information related to LCTE treatment of 'viral respiratory infection' are available in supplementary Fig S1 to Fig S15 and Table S6.

The general effects of LCTE soup

To predict the general in vivo effects of LCTE soup, we mapped all the proteins targeted by the orally-absorbable compounds to the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Disease Ontology (DO) database and to find which pathways or diseases were enriched. The top 30 enriched KEGG pathways were mainly related to viral and other microbial infections, and inflammation/cytokine responses (Fig. 4). The full list of enriched KEGG pathways and the genes involved are given in supplementary Table S7. The top 2 diseases enriched in DO were 'chronic obstructive pulmonary disease' and 'lung disease' (the full list of enrichment is in supplementary Table S8). Taken as a whole, our findings suggest that that this formula's general effects are well suited to treating viral infection in the respiratory system.

Discussion

A fundamental requirement in prescribing any medicine to a patient is understanding the medicine's mechanisms. With this doctrine in mind, and to provide an alternative medicine for fighting the pandemic COVID-19, we have explored the biochemical basis for LCTE's pathogen-targeting and symptom-relieving effects. Our examination into this formula's constituents showed that LCTE contains at least two compounds, kaempferol and quercetin, that may directly inhibit the COVID-19-causing pathogen SARS-CoV-2. It also showed that most of LCTE's main compounds are anti-inflammatory agents. Pharmacology network analysis indicated that the formula's compounds significantly target proteins related to this disease's main symptoms, such as fever, coughing, etc., and that LCTE is generally directed toward the key disease-related pathological processes, *i.e.*, viral infection response, inflammation/cytokine signaling, and lung diseases.

By searching three comprehensive Chinese herbal databases⁶⁻⁸ and filtering the results with ADME indices¹⁷ (based on the fact that Chinese herbal treatments are mainly boiled with water and the

produced soup then orally administered), we were able to screen out which of LCTE's chemical components are both water-soluble and orally-absorbable. Only about 10% of the compounds passed the ADME filtration test (Table 1), indicating that when LCTE is administered as TCM, the number of bioactive compounds that enter the body is relatively small. The exclusion of such a large proportion of constituents from absorption into the body might contribute to the relative safety of traditional herbal treatments.

The usefulness of LCTE in treating COVID-19 is explainable by the pharmacological properties of the main compounds in this formula. Importantly, two ingredients have the potential to directly inhibit SARS-CoV-2. One of our recent studies screened out 13 natural compounds with the potential to directly inhibit SARS-CoV-2¹⁸. Two of these thirteen compounds, kaempferol and quercetin, were predicted to block SARS-CoV-2 viral replication by inhibiting 3CLpro and PLpro¹⁸. Kaempferol and quercetin are contained in 8 of the plants used to formulate LCTE (Fig. 1), meaning there is a high probability that LCTE also directly inhibits this COVID-19 cause. Moreover, of the 27 prevailing LCTE compounds, 19 are reportedly anti-inflammatory agents (Fig. 1 and supplementary Table S3). Since inflammation response is the key propagating force in COVID-19 advancement²², such a pharmacological profile seems well-suited to treatment.

Our protein enrichment analysis helped provide an explanation for how LCTE relieves symptoms. Proteins are key body molecules in maintaining physical functions and causing diseases, as well as principal targets for drugs. With this in mind, we identified 304 different proteins targeted by the compounds in LCTE and, based on hypergeometric distribution probability analysis, we found that many of these proteins significantly correlated to the protein sets belonging to 11 of the 15 most common COVID-19 symptoms (Fig. 2 and supplementary Table S5). These results indicate that LCTE may specifically target proteins closely related to the symptoms of this disease, especially high-occurrence symptoms such as fever, cough, and fatigue. That significant enrichment of proteins was not found for dry cough, pharyngalgia, and sputum might be due to the low number of proteins linked to these symptoms in the DisGeNET database (3,6 and 7, respectively) (supplementary Table S5). In addition, when DisGeNET was searched using the parameter 'viral respiratory infection', we found that a significant number of proteins related to this disease were targeted by LCTE ingredients (Fig. 2 and supplementary Table S5). This is of note, as COVID-19 is a viral respiratory disease.

Through constructing and analyzing the herb-component-protein-symptom network, we disclosed the key molecules involved in relieving each symptom of COVID-19. For example, the proteins PRSS1 and PTGS2, targeted by quercetin, luteolin, and stigmasterol, are important in curing fever (Fig. 3). Similar information related to other symptoms is presented in supplementary Fig. 1S to Fig. S15 and Table S6.

Finally, to predict the general in vivo effects, we mapped all the proteins targeted by LCTE's compounds to the KEGG pathways and DO pathways. The results showed that the top 30 enriched KEGG pathways were related to viral and other microbial infection diseases, inflammation/cytokine signaling (Fig 4). These pathways are closely related to pneumonia caused by coronavirus²²⁻²⁴. In addition, the top two diseases

enriched in DO were 'chronic obstructive pulmonary disease' and 'lung disease', giving even more support to the assertion that LCTE is useful in treating COVID-19 (supplementary Table S8).

In conclusion, the clinical effectiveness of LCTE in treating COVID-19 is rational in terms of chemical biology in that it contains ingredients with the potential to directly inhibit SARS-CoV-2 and inflammation, target proteins related to prevalent COVID-19 symptoms, and affect the disease's key pathological processes. This formula is worth serious medical consideration worldwide as a useful alternative and complementary means for fighting COVID-19, especially at present, as a specific SARS-CoV-2 vaccine or inhibitor is unavailable.

Methods

Data collection

The chemical compounds of each of the twenty plants used to make LCTE were found by examining three comprehensive Chinese herbal databases: the Traditional Chinese Medicine Systems Pharmacology database (TCMSP, <http://www.tcmspw.com/>)⁶, the Encyclopedia of Traditional Chinese Medicine (ETCM, <http://www.nrc.ac.cn:9090/ETCM/>)⁸ and SymMap (<https://www.symmap.org/>)⁷. Since Chinese herbal treatments are prepared by boiling with water and the collected soup are taken orally, an *in silico* integrated model of absorption, distribution, metabolism, and excretion (ADME) was used to screen the bioactive compounds of orally-administered LCTE. The indices used for the screening included oral bioavailability evaluation, Caco-2 permeability, drug-like value, and drug half-life. The threshold values indicating effectiveness for these four indices were > 30%, > -0.4, > 0.18, and > 3 h, respectively as recommend¹⁷. The values of these four indices can be obtained from the TCMSP database. Each compound passing ADME screening was cross-checked in the three aforementioned Chinese herbal databases to find the compound's protein targets.

The proteins related to the main symptoms of COVID-19 were found through searching the DisGeNET (<https://www.disgenet.org/>)²¹ database using the term of each symptom as input. Since COVID-19 is a viral respiratory infection, we also searched the DisGeNET database using the input 'viral respiratory infection' to find which proteins relate to this disease.

The literatures about anti-inflammation by main compounds were carried out by searching PubMed with the chemical compounds names and 'inflammation' as query terms.

Protein enrichment

Enrichment of the COVID-19 symptom-related proteins targeted by LCTE ingredients were assessed by the probability (P) value of hypergeometric distribution:

$$P(x = k) = \frac{C_k^M C_{n-k}^{N-M}}{C_n^N}, \text{ with } C_n^N = \frac{N!}{n!(N-n)!}$$

k represents the number of overlapping proteins between the protein set targeted by LCTE-contained compounds and the set of protein related to each symptom or 'viral respiratory infection'. M represents the number of proteins in the set related to a single symptom or 'viral respiratory infection', n stands for the number of proteins in the set targeted by LCTE ingredients. N (the total number of proteins) was set as 17,549, which is the number of genes included in the latest version of DisGeNET RDF (v6.0).

Network analysis

The constructions and degree calculations of the plants-compound-protein-symptom network were performed using R package *igraph* (v1.2.4.2) and the results are presented with Cytoscape (v3.7.2). The network constructions are based on using these data as edges: herbal plants and their corresponding chemical compounds, chemical compounds and their affected proteins, and proteins related to each symptom.

General in vivo effects prediction

The general effects of LCTE were predicted by KEGG pathway and Disease Ontology (DO) enrichment. The full list of proteins targeted by the LCTE-containing compounds is mapped to these two databases, significant enriched (with the adjusted P value cutoff set to 0.05) were extracted. The analyses were carried out by the R package *clusterProfiler* (v3.14.2).

All data were processed using statistical language R (v3.6.2) unless otherwise specified. $P < 0.05$ was considered to be of statistical significance.

Declarations

Data availability

The authors declare that all data supporting the findings of this study are available within the manuscript and its supplementary files.

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Footnotes

The authors declare no competing interests.

Descriptions Of Supplementary Material

Supplementary Fig S1 to Fig S15. The protocol for preparing LCTE medicine. The network of plants, chemical ingredients and target proteins for relieving each symptom of COVID–19 and treating viral respiratory infection by LCTE

Supplementary Table S1. The chemical ingredients contained in each plant of LCTE

Supplementary Table S2. The protein targets of each chemical ingredient in LCTE

Supplementary Table S3. The occurrences of the chemical ingredients in LCTE and the anti-inflammatory reports for the main ingredients

Supplementary Table S4. The proteins related to main symptoms of COVID–19

Supplementary Table S5. The enrichment and proteins overlapped between ingredients-targeted and symptoms or disease-related

Supplementary Table S6. The summary of important plants, chemical ingredients, protein targets for relieving each symptom of COVID–19 and treating viral respiratory infection by LCTE

Supplementary Table S7. The full list of KEGG pathways enriched for the proteins targeted by chemical ingredients of LCTE

Supplementary Table S8. The full list of Disease Ontology pathways enriched for the proteins targeted by chemical ingredients of LCTE

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Figures

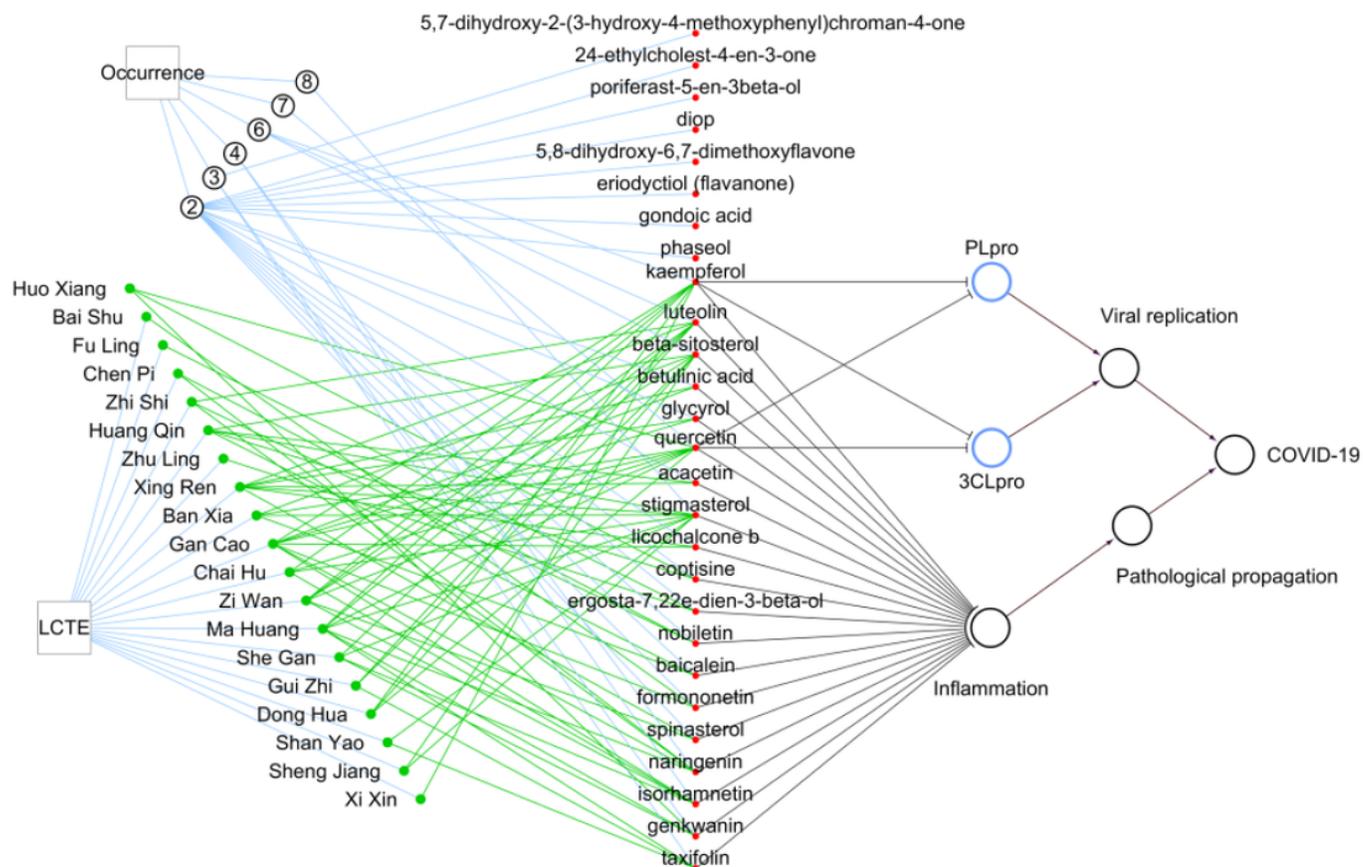


Figure 1

The virus-inhibiting potential and anti-inflammatory property of the main chemical components in LCTE. The circled number indicates the number of occurrences of compounds contained in multiple plants, for example, quercetin is contained in 8 plants. Black lines with a blunt end indicate that the source vertex has inhibiting effects on the target vertex, while those ending in an arrow have activation effects. Green networks connect herbal ingredients to the main chemical compounds contained in the plants. PLpro and 3CLpro stand for papain-like protease and 3C-like protease of SARS-CoV-2, respectively.

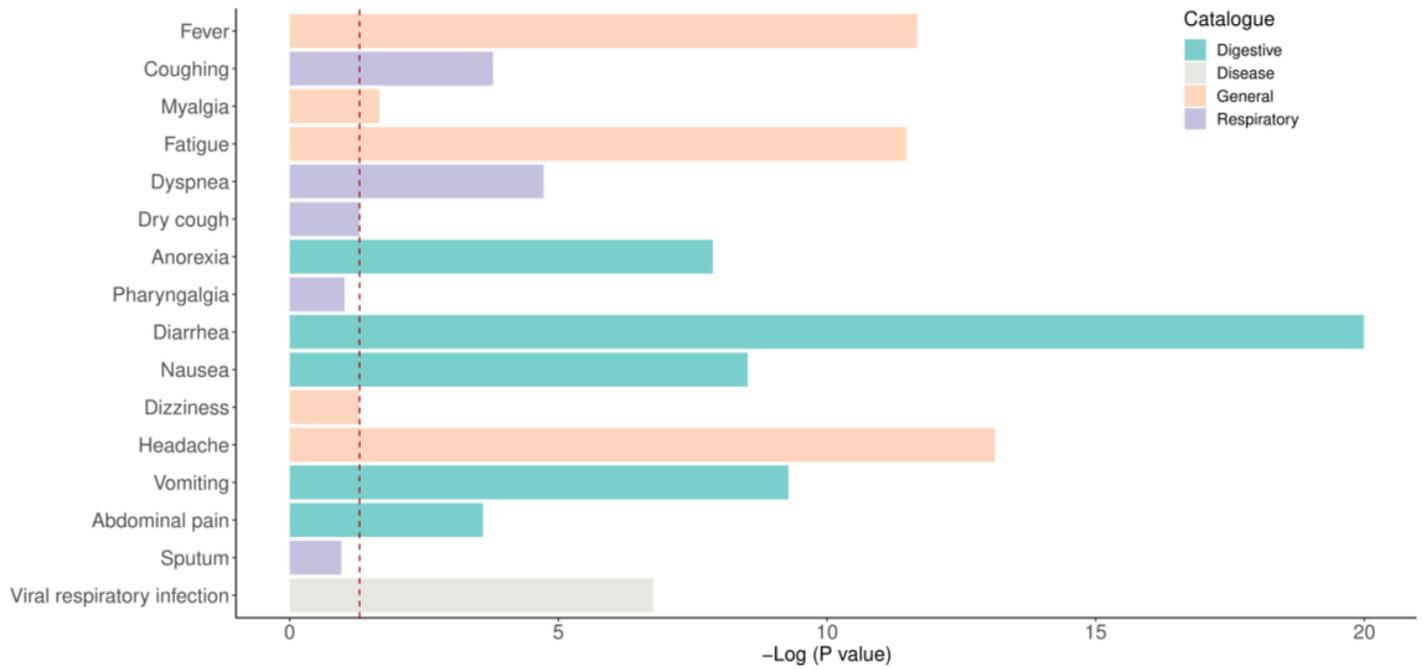


Figure 2

Enrichment of compound-targeted proteins and proteins related to symptoms. The enrichment is represented by the probability (P) value of hypergeometric distribution for overlap between chemically-targeted proteins and proteins related to symptoms or proteins related to viral respiratory infection. The bar colors correspond to the anatomic system affected by each symptom. The vertical dot line indicated the threshold (P = 0.05).

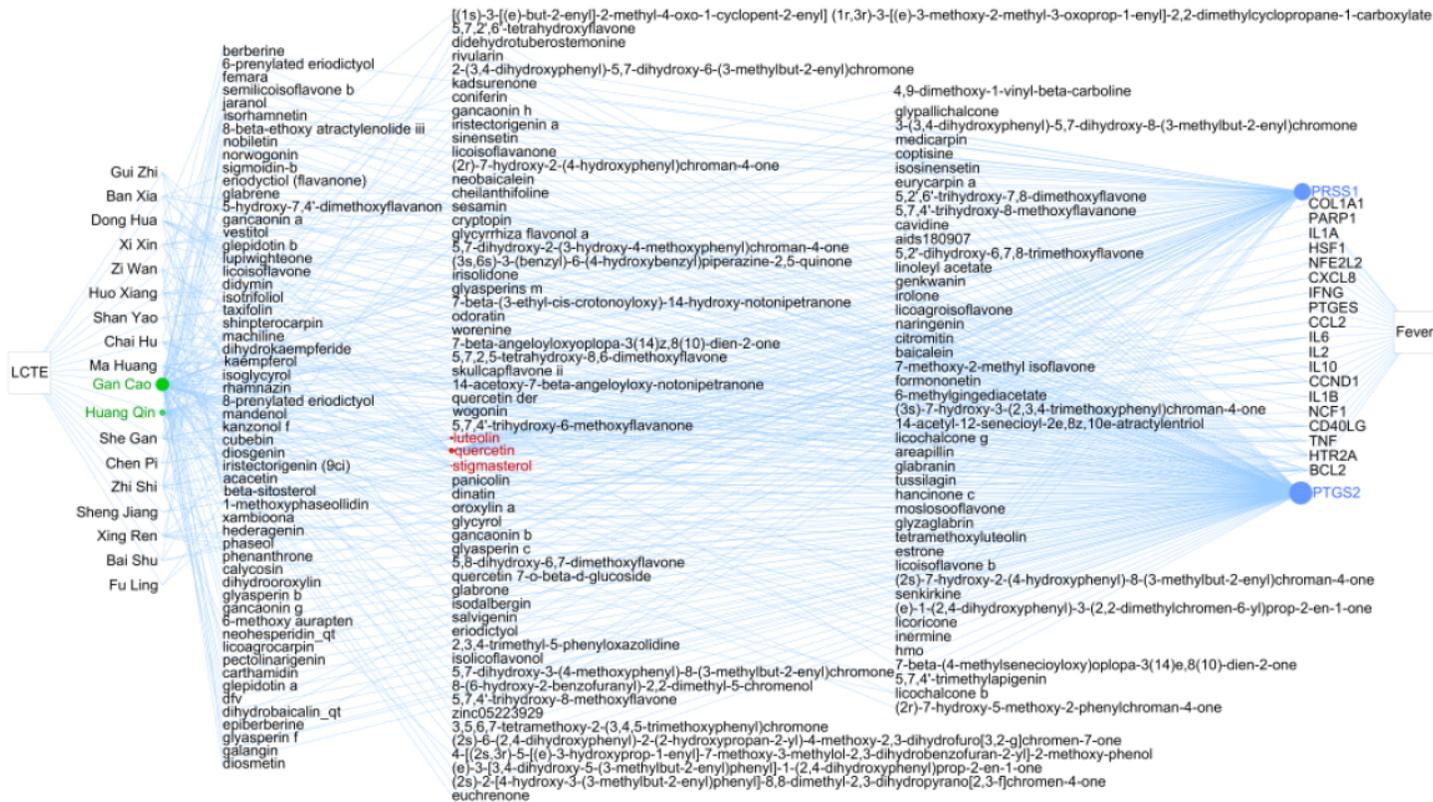


Figure 3

The network of LCTE herbal ingredients, chemical compounds, and target proteins for fever relief. Vertex sizes are proportional to their degree. Vertices with higher degrees indicate a more important role in the network. Green, red and blue vertices represent plants, chemical compounds, and protein targets, respectively. PPSS1 stands for prostaglandin-endoperoxide synthase and PRSS1 for Serine Protease 1.

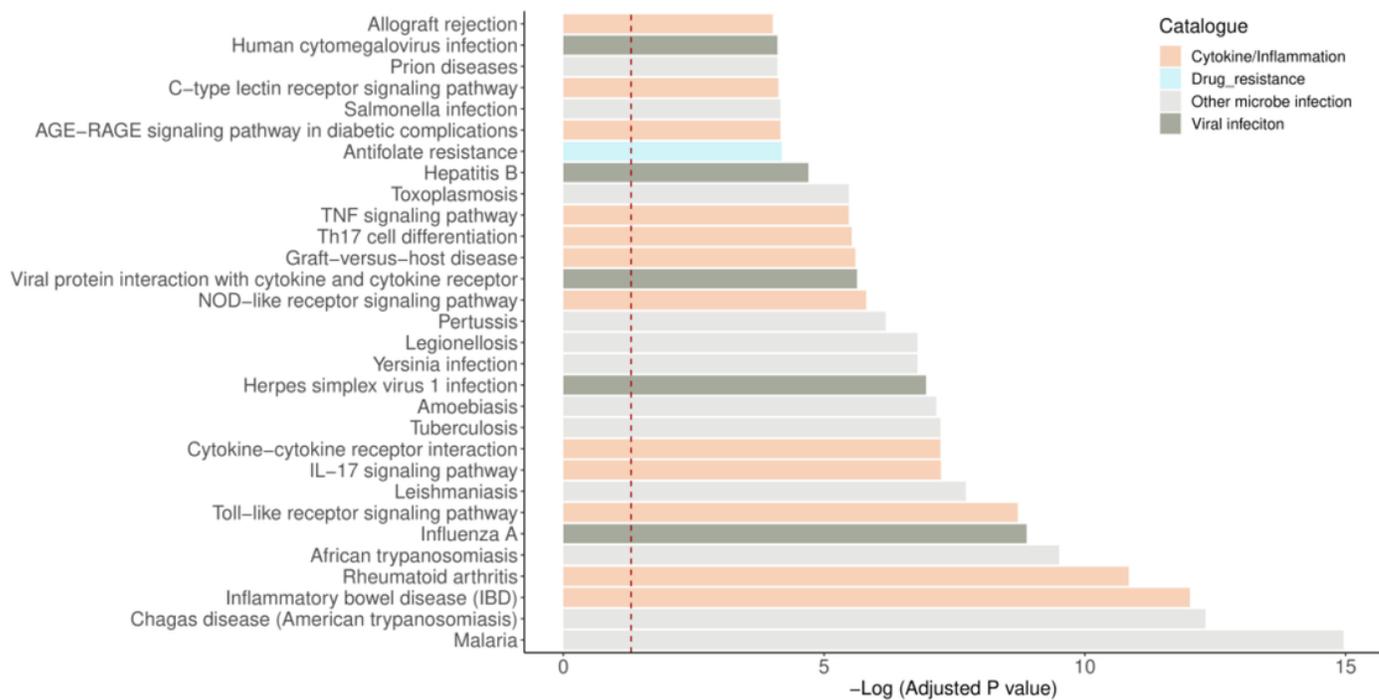


Figure 4

Enrichment of compound-targeted proteins in KEGG pathways. Enrichment was performed using R package clusterprofiler with the proteins targeted by the LCTE-contained chemical compounds as input. The bar colors correspond to different pathway functions. The vertical dot line indicated the threshold (adjusted P = 0.05).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable3.xlsx](#)
- [SupplementaryTable4.xlsx](#)
- [SupplementaryTable5.pdf](#)
- [SupplementaryTable6.xlsx](#)
- [SupplementaryTable7.xlsx](#)
- [SupplementaryTable8.xlsx](#)
- [SupplementaryTable1.pdf](#)
- [SupplementaryTable2.pdf](#)
- [SupplementaryFiguresS1S15.pdf](#)