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.

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Screening out anti-inflammatory or anti-viral targets in Xuanfei Baidu Tang through a new technique of reverse finding target

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ABSTRACT

Traditional Chinese herbal compound prescription in Xuanfei Baidu Tang (XBT) has obvious effects in the treatment of COVID-19. However, its effective compounds and targets for the treatment of COVID-19 remain unclear. Computer-Aided Drug Design is used to virtually screen out the anti-inflammatory or anti-viral compounds in XBT, and predict the potential targets by Discovery Studio 2020. Then, we searched for COVID-19 targets using Genecards databases and Protein Data Bank (PDB) databases and compared them to identify targets that were common to both. Finally, the target we screened out is: TP53 (Tumor Protein P53). This article also shows that XBT in the treatment of COVID-19 works in a multi-link and overall synergistic manner. Our results will help to design the new drugs for COVID-19.

1. Introduction

At the end of 2019, the novel coronavirus disease (COVID-19) appeared and caused global concern. It is a highly infectious disease characterized by respiratory symptoms [1]. COVID-19 pandemic has caused an unprecedented and uncontrollable health crisis. Since the outbreak of this disease, it has been characterized by strong infectivity, long treatment time after infection, and high mortality of patients with severe illness [2–11]. The main physiological and pathological feature of severe COVID-19 is "cytokine storm", also known as inflammatory storm [12]. It is an immune response produced by a positive feedback loop between cytokines and immune cells, and it is also the state which the body's immune system has evolved from "self-protection" to "over-protection" [13,14]. Therefore, the outbreak of inflammation is the core pathological factor leading to aggravation and even death of patients in lung injury induced by COVID-19 [15–17]. Over expression and release of pro-inflammatory cytokines will lead to tissue damage [18–24]. In response to the inflammatory mechanism caused by the novel coronavirus (SARS-CoV-2) infection, a variety of methods have emerged to treat COVID-19, such as oxygen therapy, plasma therapy, drug (lopinavir, favipiravir, ribavirin, PegIFN-α2a, traditional Chinese herbal compound prescription) therapy [25,26]. Various traditional Chinese herbal compound prescriptions have been proved to be highly effective in the treatment of COVID-19 and have been widely used in the market and clinic, such as Sijunzi Decoction, Yupingfeng Powder, Buzhong Yiqi Decoction, Xuanfei Baidu Tang (XBT) and so on. In this article, we studies XBT in terms of anti-inflammatory or anti-viral effects. XBT is composed of 13 traditional Chinese herbal medicines, namely Ephedra, Bitter almond, Coix Seed, Atractylodes, Patchouli, Artemisia annua, Polygonum cuspidatum, Verbena, Reed root, Semen Lepidii, Exocarpium, licorice and Gypsum. XBT is a traditional Chinese herbal compound prescription for the treatment of anti-epidemic, which is designed for the pathological characteristics of wet toxin [27]. It has the effects of inhibiting viral infections, reducing inflammatory factors, and promoting the absorption of lung inflammation. Because of its outstanding efficacy, it is widely used as a recommended prescription in clinical practice [28].

Computer-Aided Drug Design (CADD) is to design and optimize lead compounds through calculating and estimating the relationship between ligand and receptor based on computer chemistry [29]. With the development of CADD, our understanding of disease pathogenesis, drug signal transduction pathways, target interactions, and other aspects is becoming more and more mature [30–32]. The modules of drug analysis, synthesis design, and drug molecular optimization in Discovery Studio 2020 (DS2020) make the later experimental operation more convenient. This not only reduces the cost of money and time, but also improves the safety of medicines. CADD builds a bridge between traditional Chinese medicine and modern pharmacology, and plays an important role in scientific development.

XBT is widely used in the treatment of clinical diseases [27,33,34],

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Table 1
The compounds screened out in Traditional Chinese Medicines Database.

Name	ID	Activities	Screened Compounds
Ephedra	6816	anti-inflammatory	(4S,5R) Ephedroxane
	11,642	anti-inflammatory	Isoquercitrin
Bitter almond	12,849	antiviral	Linalool
	5699	anti-inflammatory	Dihydroquercetin
	7278	anti-inflammatory	Eriodictyol
	7821	anti-inflammatory	Flavoxanthin
Atractylodes	1965	anti-inflammatory	Atractylenolide I
	1971	anti-inflammatory	Atractylone
	7495	anti-inflammatory	(+)-Eudesma-4(15),7(11)-dien-8-one
	20,569	anti-inflammatory	Syringin
Patchouli	16,498	antiviral	Pachypodol
Artemisia annua	2044	antiviral	Axillarin
	4354	antiviral	Cumaldehyde
	12,849	antiviral	Linalool
	18,376	antiviral	Quercetin-3-methyl ether
	19,777	antiviral	Sesamin
	3743	anti-inflammatory	Cirsiliol
	7951	anti-inflammatory	Friedelan-3-one
	11,259	anti-inflammatory	D-Isoborneol
	11,260	anti-inflammatory	L-Isoborneol
	11,642	anti-inflammatory	Isoquercitrin
	13,137	anti-inflammatory	Luteolin
	17,377	anti-inflammatory	beta-Pinene
	19,540	anti-inflammatory	Scoparone
	19,545	anti-inflammatory	Scopolin
	19,983	anti-inflammatory	beta-Sitosterol
	19,087	antiviral,anti-inflammatory	Rutin

Table 2
The compounds screened out in Traditional Chinese Medicines Database (continued).

Name	ID	Activities	Screened Compounds
Polygonum cuspidatum	3308	antiviral	(+)-Catechin
	1367	anti-inflammatory	Anthraquinone
	8095	anti-inflammatory	Gallic acid
	10,887	anti-inflammatory	Hyperin
	11,642	anti-inflammatory	Isoquercitrin
	19,087	antiviral, anti-inflammatory	Rutin
	18,411	antiviral, anti-inflammatory	Quercitrin
Exocarpium	15,286	antiviral,anti-inflammatory	Naringin
licorice	6402	antiviral	3,3′-Dimethylquercetin
	2455	anti-inflammatory	6,8-Bis(C-beta-glucosyl)-apigenin
	8841	anti-inflammatory	Glycyrrhetinic acid
	11,505	anti-inflammatory	Isoliquiritin
	11,642	anti-inflammatory	Isoquercitrin
	12,766	anti-inflammatory	Licochalcone A
	12,907	anti-inflammatory	Liquiritic acid
	17,403	anti-inflammatory	Pinocembrin
	19,983	anti-inflammatory	beta-Sitosterol
	8846	antiviral,anti-inflammatory	Glycyrrhizic acid
	19,087	antiviral,anti-inflammatory	Rutin

but its effective compounds and targets for the treatment of COVID-19 need to be further clarified. In this study, we aim to use DS2020 to screen out the anti-inflammatory or anti-viral compounds and targets in XBT, which will make contribution to treat COVID-19.

2. Experimental section

2.1. Screening out compounds in XBT

The Traditional Chinese Medicines Database is currently the world's largest non-commercial Chinese medicine database. This online database contains more than 20,000 purified compounds of 453 Chinese medicine ingredients [35,36]. Using the database to obtain plant information, the components of traditional Chinese herbal medicines in XBT were screened separately. The "Plant Source" field in query mode was activated, entering the following informations (Ephedra, Bitter almond, Coix Seed, Atractylodes, Patchouli, Artemisia annua, Polygonum cuspidatum, Verbena, Reed root, Semen Lepidii, Exocarpium, licorice, and Gypsum) one by one. Then execute the query and output the ID of all compounds related to each traditional Chinese herbal medicines, as well as their name, source, structure, efficacy, etc. After exporting the data of all compounds, we only keep the compounds that have the functions of "anti-inflammatory" or "anti-virus".

2.2. Optimization of small molecules and prediction of absorption, distribution, metabolism, excretion and toxicity (ADMET) properties

In view of the uncertain numbers of ligands and isomers, we used Prepare Ligands to modify the compound system, and then optimized the structure of small molecule ligands through the Minimize Ligands function. The optimized small molecules need to be evaluated by the prediction of ADMET properties. In the early stage of drug development, compounds can be predicted and selected based on the properties of the drug's ADMET. The properties of ADMET we mentioned refer to the absorption, distribution, metabolism, excretion, and toxicity of drug molecules in the body [37,38]. This operation can lower the expense of excessive structural modification and recombination in the later stage, and can improve the success rate of medical research and development to a certain extent. The ADMET properties that can be calculated in DS2020 include: aqueous solubility, blood brain barrier penetration (BBB), Cytochrome P450 2D6 inhibition [39], hepatotoxicity, Human intestinal absorption (HIA) and plasma protein binding [40,41]. After the job is completed, open the ADMET plot window. Because the point within the 99% confidence interval means that the predictive properties of this molecule are reliable, it is necessary to delete the BBB model and the HIA model points outside the 99% confidence interval. For a more comprehensive analysis of drug toxicity, toxicological properties prediction process (TOPKAT) is required after the prediction of ADMET properties.

2.3. TOPKAT

TOPKAT is based on the 2D structure of the molecule to calculate and verify the toxicity and environmental effects of the compound[42]. Toxicity prediction has the characteristics of low cost and high efficiency in drug development and drug risk reduction. Enter the compounds retained after the ADMET screening, and the factors we need to consider in this screening are: mutagenicity, aerobic biodegradability, oral LD50 in rats, and rodent carcinogenicity [43,44]. After the results are obtained, we need to verify whether all compounds are true in the ranges of "With Optimum Prediction Space (OPS)" and "Within OPS Limits". Among them, "With OPS" evaluates whether the prediction results are in the best prediction space of the model, and "Within OPS Limits" evaluates whether the prediction result is within the best prediction space limit of the model. If "With OPS" and "Within OPS Limits" are both true for one compound, this compound is credible and will been kept.

2.4. Ligand small molecule filtration

According to the Lipinski Rule of Five and Veber Rule [45,46], we evaluated the druggability of the compounds obtained after the

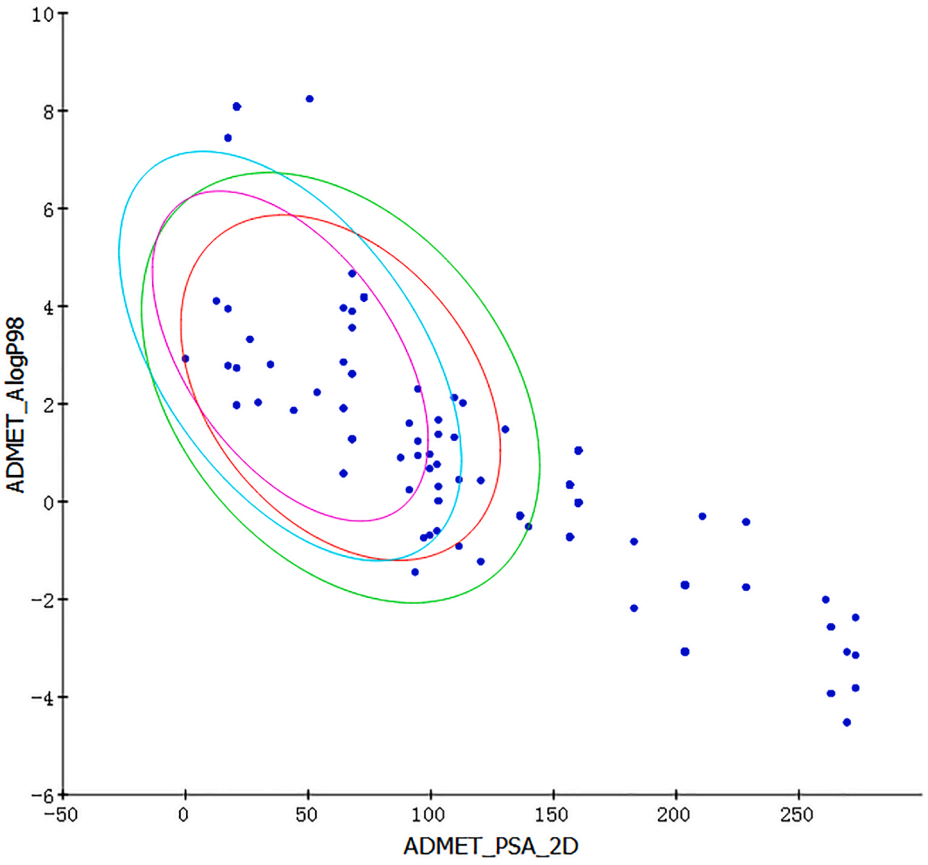


Fig. 1. ADMET property prediction results of 8 kinds of traditional Chinese herbal medicines (Ephedra, Bitter almond, Atractylodes, Artemisia annua, Polygonum cuspidatum, Licorice, Patchouli, Exocarpium).

Table 3
Toxicity properties of the most promising compounds.

Compounds	Rodent Carcinogenicity	Ames	Rat Oral LD50	Aerobic Biodegradability
(4S,5R) Ephedroxane	Non-Carcinogen	0.668916	0.991625	0.562176
(+)-Eudesma-4(15), 7(11)-dien-8-one	Non-Carcinogen	0.122225	2.38961	0.724887
Pachypodol1	Non-Carcinogen	0.669673	1.14754	0.481777
Pachypodol2	Non-Carcinogen	0.512067	0.866841	0.621833
Pachypodol3	Non-Carcinogen	0.599349	0.381132	0.490207
Pachypodol4	Non-Carcinogen	0.704909	0.393169	0.471899
Pachypodol5	Non-Carcinogen	0.577077	0.299591	0.616676
Pachypodol6	Non-Carcinogen	0.661746	0.452941	0.536422
Cirsiliol1	Non-Carcinogen	0.157938	0.24355	0.538137
Cirsiliol2	Non-Carcinogen	0.603944	0.220941	0.572221
Cirsiliol3	Non-Carcinogen	0.380653	0.133455	0.550077
Scoparone	Non-Carcinogen	0.636048	1.14097	0.7564
Luteolin1	Non-Carcinogen	0.238779	0.194719	0.467705
Luteolin2	Non-Carcinogen	0.630162	0.149287	0.513354
Luteolin2Quercetin-3-methyl ether	Non-Carcinogen	0.689358	0.163154	0.475555
Sesamin	Non-Carcinogen	0.535598	0.489369	0.609635
Gallic acid	Non-Carcinogen	0.687047	0.736671	0.404672
Anthraquinone	Non-Carcinogen	0.776107	2.33633	0.171863
Glycyrrhetinic acid1	Non-Carcinogen	8.87E-06	1.27097	0.730006
Glycyrrhetinic acid2	Non-Carcinogen	8.87E-06	1.27097	0.730006

Table 4
Toxicity properties of the most promising compounds (continued).

Compounds	Rodent Carcinogenicity	Ames	Rat Oral LD50	Aerobic Biodegradability
Liquiritic acid1	Non-Carcinogen	8.87E-06	1.27097	0.730006
Liquiritic acid2	Non-Carcinogen	8.87E-06	1.27097	0.730006
Liquiritic acid3	Non-Carcinogen	8.87E-06	1.27097	0.730006
Liquiritic acid4	Non-Carcinogen	8.87E-06	1.27097	0.730006
Liquiritic acid5	Non-Carcinogen	8.87E-06	1.27097	0.730006
Liquiritic acid6	Non-Carcinogen	8.87E-06	1.27097	0.730006
Liquiritic acid7	Non-Carcinogen	8.87E-06	1.27097	0.730006
Liquiritic acid8	Non-Carcinogen	8.87E-06	1.27097	0.730006
Pinocembrin1	Non-Carcinogen	0.0779542	0.544404	0.535875
Pinocembrin2	Non-Carcinogen	0.627138	0.419365	0.631557
Pinocembrin3	Non-Carcinogen	0.594698	0.41769	0.654128
Pinocembrin4	Non-Carcinogen	0.167847	0.301578	0.542622
Pinocembrin5	Non-Carcinogen	0.621283	0.229593	0.644483
Pinocembrin6	Non-Carcinogen	0.594698	0.41769	0.654128
Pinocembrin7	Non-Carcinogen	0.627138	0.419365	0.631557
Pinocembrin8	Non-Carcinogen	0.167847	0.301578	0.542622
Pinocembrin9	Non-Carcinogen	0.0779542	0.544404	0.535875
Pinocembrin10	Non-Carcinogen	0.621283	0.229593	0.644483
3,3′-Dimethylquercetin1	Non-Carcinogen	0.631479	0.528344	0.518521
3,3′-Dimethylquercetin2	Non-Carcinogen	0.550035	0.636029	0.622739
3,3′-Dimethylquercetin3	Non-Carcinogen	0.55875	0.218344	0.493588
3,3′-Dimethylquercetin4	Non-Carcinogen	0.688634	0.180996	0.502659
3,3′-Dimethylquercetin5	Non-Carcinogen	0.604492	0.21979	0.609962

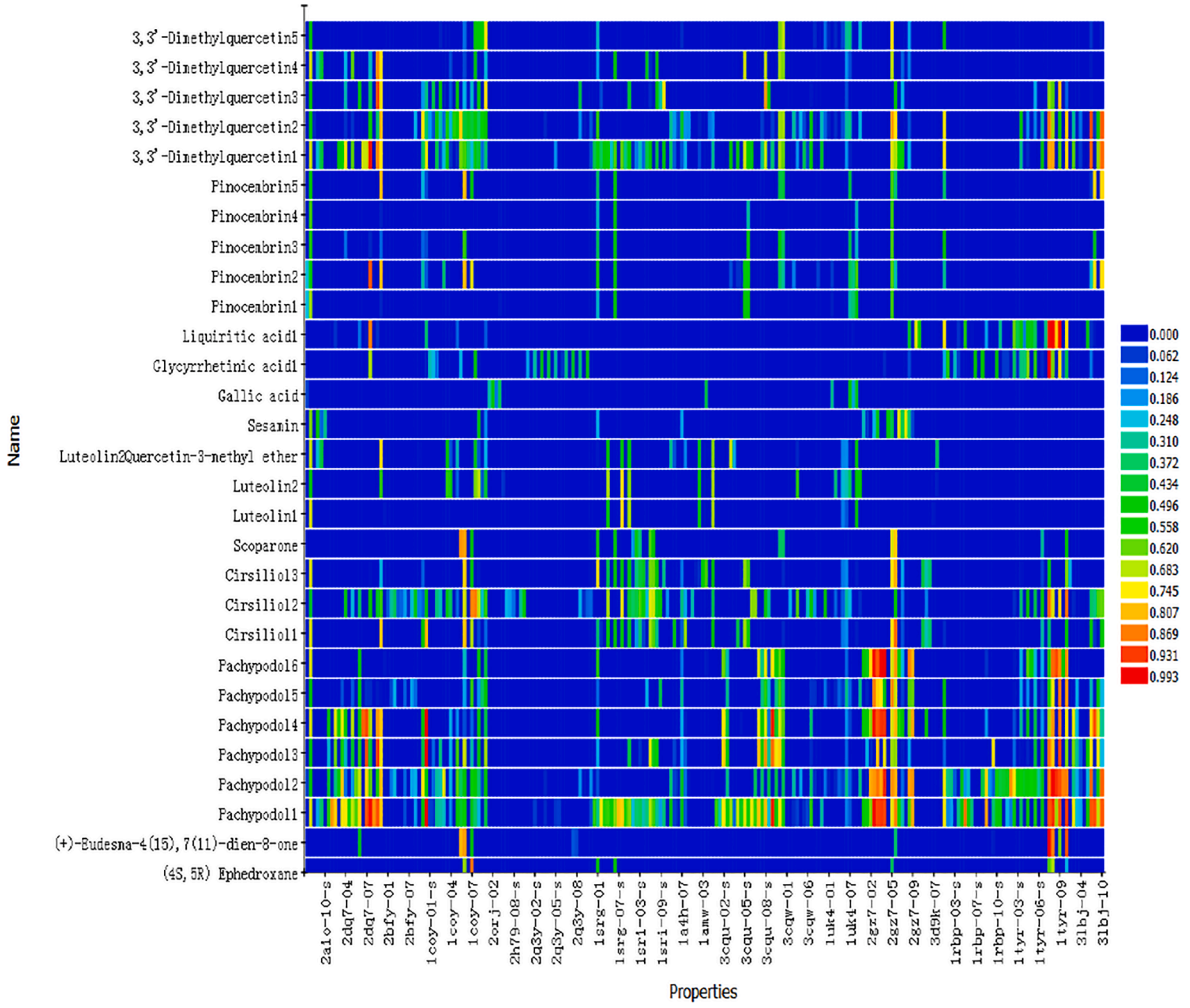
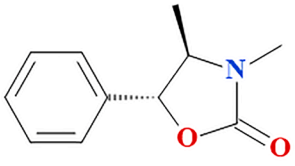
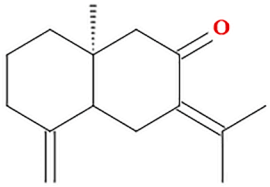


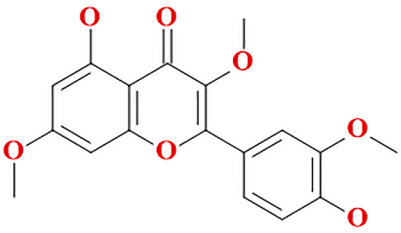
Fig. 2. Reverse finding target results of 6 kinds of traditional Chinese herbal medicines (Ephedra, Atractylodes, Patchouli, Artemisia annua, Polygonum cuspidatum, Licorice). The horizontal axis represents the pharmacophores, and the vertical axis represents the compounds obtained through reverse finding target. (4S,5R) Ephedroxane is from Ephedra; (+)-Eudesma-4(15),7(11)-dien-8-one is from Atractylodes and 3,3′-Dimethylquercetin1-5 are from licorice, et al (more information is shown in Table 6).



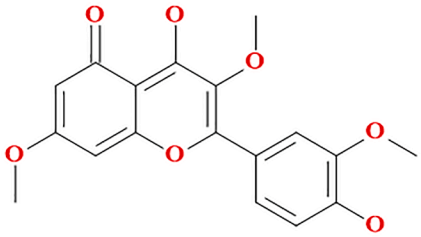
(4S,5R) Ephedroxane



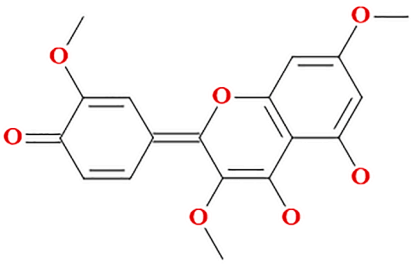
(+)-Eudesma-4(15),7(11)-dien-8-one



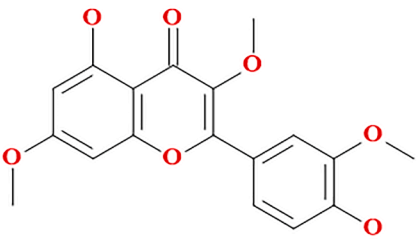
Pachypodol1



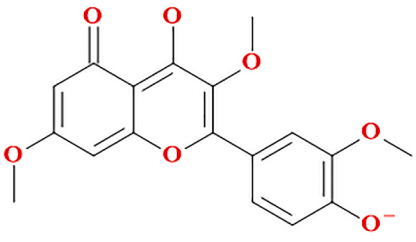
Pachypodol2



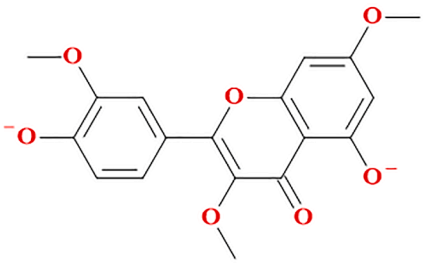
Pachypodol3



Pachypodol4

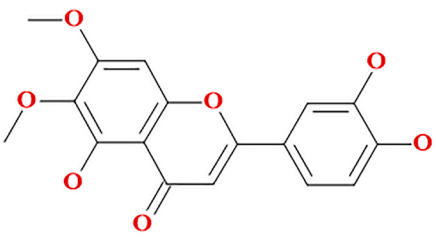


Pachypodol5

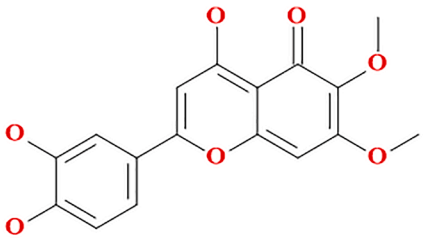


Pachypodol6

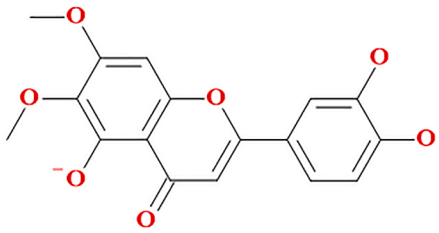
Fig. 3. (1). The structures of 29 compounds. **(2).** The structures of 29 compounds. **(3).** The structures of 29 compounds. **(4).** The structures of 29 compounds.



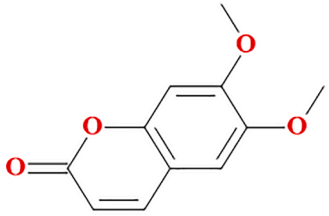
Cirsiliol1



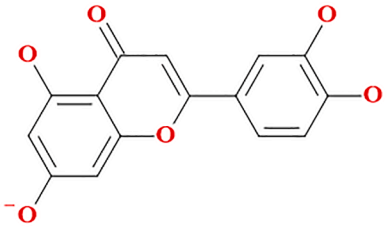
Cirsiliol2



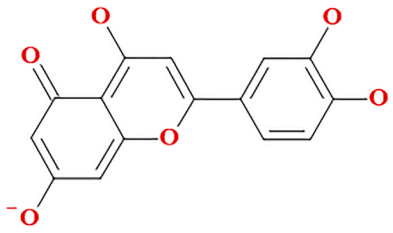
Cirsiliol3



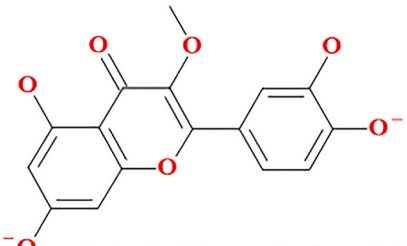
Scoparone



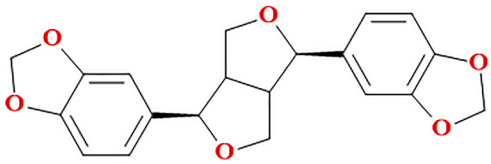
Luteolin1



Luteolin2



Luteolin2Quercetin-3-methyl ether



Sesamin

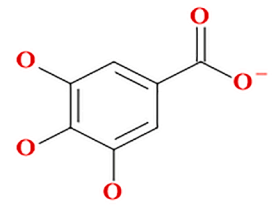
Fig. 3. (*continued*).

preliminary screening. The Lipinski Rule of Five includes: the number of hydrogen bond donors does not exceed 5, the molecular weight does not exceed 500, the number of hydrogen bond acceptors does not exceed 10, the molecular weight does not exceed 500, and AlogP (The upper limit of the logarithm of the octanol–water partition coefficient) is not more than 5. The Veber Rule includes: The number of rotatable keys does not exceed 10, the polar surface area does not exceed 140 Å, and the sum of hydrogen bond donors and acceptors does not exceed 12. The range of these parameters correlates with the degree of oral availability of the drug.

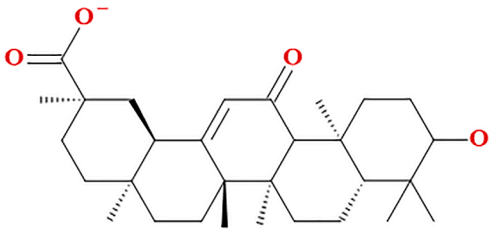
After the evaluation, the small molecule compounds that do not meet the criteria are deleted, and the small molecules with good druggability are retained.

2.5. Performing DS2020 reverse finding target

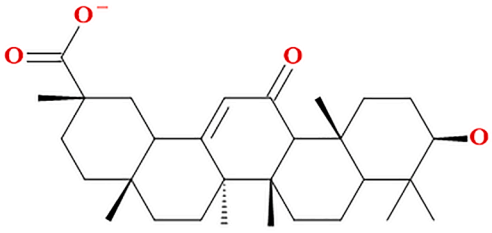
After the prediction and screening of reverse finding target, the higher matching value of the pharmacophore and the compound, the more reliable it is. Then the targets corresponding to the pharmacophores are more likely to be the target of the compounds. The Fit Value of the entered compounds and pharmacophores can be got through the calculated results pages of PharmacophoreFits link and the



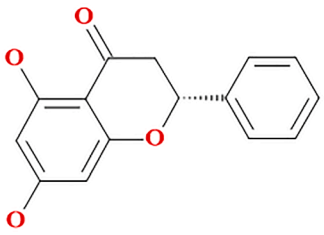
Gallic acid



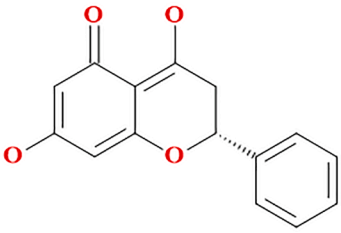
Glycyrrhetinic acid1



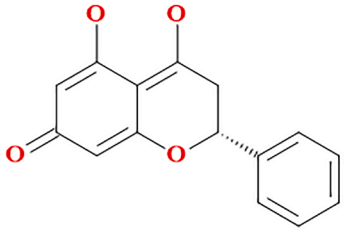
Liquiritic acid1



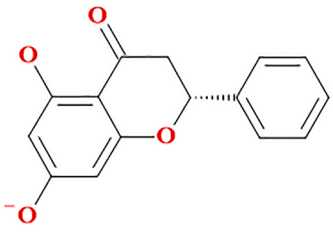
Pinocembrin1



Pinocembrin2



Pinocembrin3



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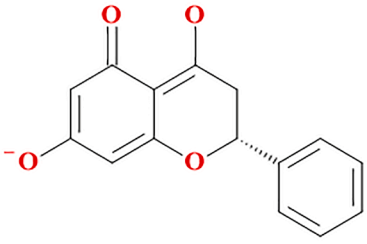


Pinocembrin5

Fig. 3. (*continued*).

"LigandProfiler" heat map.

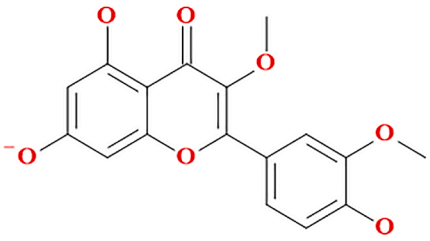
2.6. Target point network construction

First, we use reverse finding target technology to get the targets that have anti-inflammatory or antiviral effects in XBT. Then we use Genecards databases (https://www.genecards.org) and Protein Data Bank (PDB) databases to search all targets related to COVID-19 with the key word of "SARS-CoV-2". By comparing the results of these two parts, we can find anti-inflammatory or antiviral targets related to COVID-19 in XBT. Finally, we use Cytoscape 3.8.0 to establish the interaction network diagram of "XBT-Compounds-Targets-Efficacy". After the construction is completed, it can clearly show the active components of each the traditional Chinese herbal medicine, as well as the common targets related to anti-inflammation or antivirus in these components.

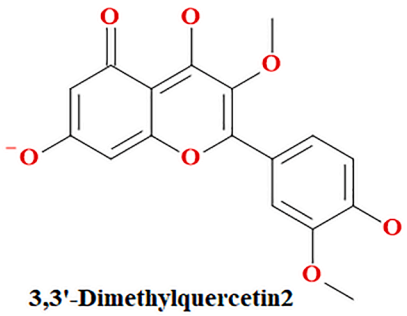
3. Results and discussion

3.1. Screening the compounds of XBT in the traditional Chinese medicines Database

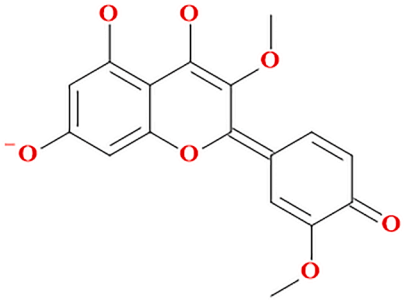
In the Traditional Chinese Medicines Database, if you query with



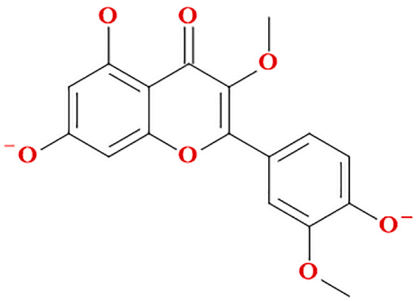
3,3'-Dimethylquercetin1



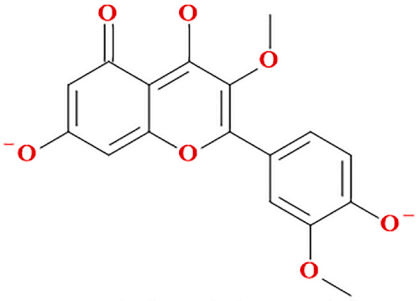
3,3'-Dimethylquercetin2



3,3'-Dimethylquercetin3



3,3'-Dimethylquercetin4



3,3'-Dimethylquercetin5

Fig. 3. (*continued*).

"Ephedra" as the key word, the output results show that there are 53 compounds related to ephedra, including 2 compounds with anti-inflammatory effects and 0 compounds with antiviral effects. By analogy, it can be seen from table (Table 1, 2) that a total of 46 compounds from 13 traditional Chinese herbal medicines have been screened. According to the screening results, we have not found any compound with anti-inflammatory or anti-viral effects in 5 traditional Chinese herbal medicines (Gypsum, Coix Seed, Verbena, Reed root and Semen Lepidii). Then they will be excluded in the next calculation process. At this time there are only 8 traditional Chinese herbal medicines left.

3.2. Optimization of small molecules and prediction of ADMET properties

After the small molecule optimization process, the ADMET property prediction is carried out. Most drugs need to be discontinued and search for other candidate compounds during the development process. The main reason for this result is that the prediction results of ADMET properties are unreliable. From Fig. 1, we can see that if a compound is reliable, the points shown in the prediction must be within the blue ellipse (99% confidence interval of the BBB model) and the green ellipse (99% confidence interval of the HIA model). Therefore, as shown in the Fig. 1, only 1 compound remains in Ephedra. In the same way, finally, 1 compound is retained in Bitter almond, 3 compounds in Atractylodes, 13 compounds in Artemisia annua, 3 compounds in Polygonum cuspidatum, and 30 compounds in Licorice. The compounds in Patchouli all meet the requirements of ADMET, while the compounds in Exocarpium do not meet the requirements of ADMET. Therefore, Exocarpium is excluded from the next calculation.

3.3. TOPKAT and ligand small molecule filtration

The calculated result is exported to PDF format. Open the calculated result (Table 3, Table 4) to check whether all the properties and OPS components of each small molecule are within the expected range. Then, we remove compounds that do not meet the requirements. After screening, 1 compound is retained in Ephedra, 0 compound in Bitter

Table 5
All pharmacophores and their corresponding targets obtained by reverse finding target technology.

Pharmacophore	Target(gene name)	Efficacy
1tyr-01, 1tyr-01-s, 1tyr-02, 1tyr-02-s, 1tyr-03, 1tyr-03-s, 1tyr-04, 1tyr-05, 1tyr-05-s, 1tyr-06, 1tyr-06-s, 1tyr-07, 1tyr-08, 1tyr-08-s, 1tyr-09, 1tyr-09-s, 1tyr-10, 1tyr-10-s	1tyr(TTR)	anti-inflammatory
1uk4-01,1uk4-02,1uk4-03,1uk4-04,1uk4-05,1uk4-06,1uk4-07, 1uk4-08, 1uk4-09, 1uk4-10	1uk4(rep)	antiviral
2gz7-01, 2gz7-01-s, 2gz7-02, 2gz7-03, 2gz7-03-s, 2gz7-04, 2gz7-04-s, 2gz7-05, 2gz7-05-s, 2gz7-06, 2gz7-07, 2gz7-07-s, 2gz7-08, 2gz7-08-s, 2gz7-09	2gz7(rep)	antiviral
2dq7-01, 2dq7-02, 2dq7-02-s, 2dq7-03, 2dq7-04, 2dq7-05, 2dq7-05-s, 2dq7-06, 2dq7-06-s, 2dq7-07, 2dq7-07-s, 2dq7-08, 2dq7-09, 2dq7-10	2dq7(FYN)	anti-inflammatory
2x0v-01	2x0v(TP53)	anti-inflammatory
2x0u-01	2x0u(TP53)	anti-inflammatory
3cqu-01, 3cqu-01-s, 3cqu-02, 3cqu-02-s, 3cqu-03, 3cqu-03-s, 3cqu-04, 3cqu-04-s, 3cqu-05, 3cqu-05-s, 3cqu-06, 3cqu-06-s, 3cqu-07, 3cqu-07-s, 3cqu-08, 3cqu-08-s, 3cqu-09, 3cqu-09-s, 3cqu-10, 3cqu-10-s	3cqu (AKT1)	antiviral, anti-inflammatory
3cqw-01, 3cqw-02, 3cqw-03, 3cqw-04, 3cqw-05, 3cqw-06, 3cqw-06-s, 3cqw-07, 3cqw-08, 3cqw-09, 3cqw-10, 3cqw-10-s	3cqw (AKT1)	antiviral, anti-inflammatory

Table 6
Compounds in each traditional Chinese herbal medicine obtained by reverse finding target technology.

Name	Screened compounds
Ephedra	(4S,5R) Ephedroxane
Atractylodes	(+)-Eudesma-4(15),7(11)-dien-8-one
licorice	Glycyrrhetinic acid
	Liquiritic acid
	3,3′-Dimethylquercetin1
	3,3′-Dimethylquercetin2
	3,3′-Dimethylquercetin3
	3,3′-Dimethylquercetin4
	3,3′-Dimethylquercetin5
	Pinocembrin1
	Pinocembrin2
	Pinocembrin3
	Pinocembrin4
	Pinocembrin5
Patchouli	Pachypodol1
	Pachypodol2
	Pachypodol3
	Pachypodol4
	Pachypodol5
	Pachypodol6
Polygonum cuspidatum	Gallic acid
Artemisia annua	Cirsiliol1
	Cirsiliol2
	Cirsiliol3
	Scoparone
	Luteolin1
	Luteolin2
	Luteolin2Quercetin-3-methyl ether
	Sesamin

almond, 1 compound in Atractylodes, 6 compounds in Patchouli, 8 compounds in Artemisia annua, 2 compounds in Polygonum cuspidatum, and 25 compounds in licorice. Therefore, Bitter almond is excluded from the next calculation. At this time there are only 6 traditional Chinese herbal medicines left. Then evaluate through the two configuration principles of Lipinski Rule of Five and Veber Rule, and delete small molecules that do not meet the evaluation criteria in the results. The output results showed that the types and quantities of compounds retained in each traditional Chinese herbal medicine remained unchanged.

3.4. Reverse finding target

In order to show the matching degree of the pharmacophore with all the compounds participating in the test more concisely, we used the "Ligand Profiler" heat map (Fig. 2) to represent it. In Fig. 2, the horizontal axis represents the pharmacophores, and the vertical axis represents the compounds screened from traditional Chinese herbal medicines. The color changes from red to blue, indicating that the Fit Value is gradually decreasing. In order to explain the meaning of Fig. 2 more clearly, we take Ephedra as an example. After a series of screening, we extracted (4S, 5R) Ephedroxane from Ephedra. Because the pharmacophore with higher matching degree is red and yellow, the fitted value corresponding to 1coy is the highest. Therefore, the target corresponding to 1coy is very likely to be the target of (4S, 5R) Ephedroxane. It can be seen from Fig. 2, Fig. 3 that 29 compounds in XBT through reverse finding target were found.

3.5. Target point network construction

The reverse finding target technology was used to obtain pharmacophores whose corresponding targets were been predicted. The targets of XBT are rep (ATP- dependent DNA helicase Rep), TTR (Transthyretin), AKT1 (AKT Serine/Threonine Kinase 1), FYN (FYN Proto-Oncogene/Src Family Tyrosine Kinase) and TP53 (Tumor Protein P53). As the potential targets: TP53, FYN, FYN are against inflammation, rep is against virus, and AKTI is against inflammation and virus (Table 5). We compared these targets (rep, TTR, AKT1, FYN and TP53) with the targets searched by Genecards databases and PDB databases, and found the common target TP53 for COVID-19 (Figs. 4, 5).

As shown in Fig. 4, there are 29 compounds from 6 traditional Chinese herbal medicines (Ephedra, Atractylodes, Patchouli, Artemisia annua, Polygonum cuspidatum, Licorice) that have anti-inflammatory or antiviral effects in XBT. As shown in Fig. 5, Cirsiliol1-3 (extracted from Artemisia annua), Pachypodol1-4 (extracted from Patchouli), Liquiritic acid, Glycyrrhetinic acid, 3,3′-Dimethylquercetin1-3, Pinocembrin2, Pinocembrin3, Pinocembrin5 (extracted from Patchouli) could be used as candidate compounds for the treatment of COVID-19.

4. Conclusion

Based on the anti-inflammatory or anti-viral effects, we used DS2020 to optimize, screen out small molecule and predict ADMET, toxicological properties for various traditional Chinese herbal medicines in XBT. The pharmacophores are collected by reverse finding target, and then the targets are predicted. From Table 5, we found that the anti-inflammatory or antiviral targets corresponding to the compounds of XBT were mainly: rep, TTR, AKT1, FYN, TP53. Among them, TP53 is highly related to COVID-19. In addition, among these targets, each target is connected to two or more compounds, indicating that the same target can also be controlled by multiple compounds at the same time. The calculated results are expected to be used in the design of new drugs for the treatment of COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

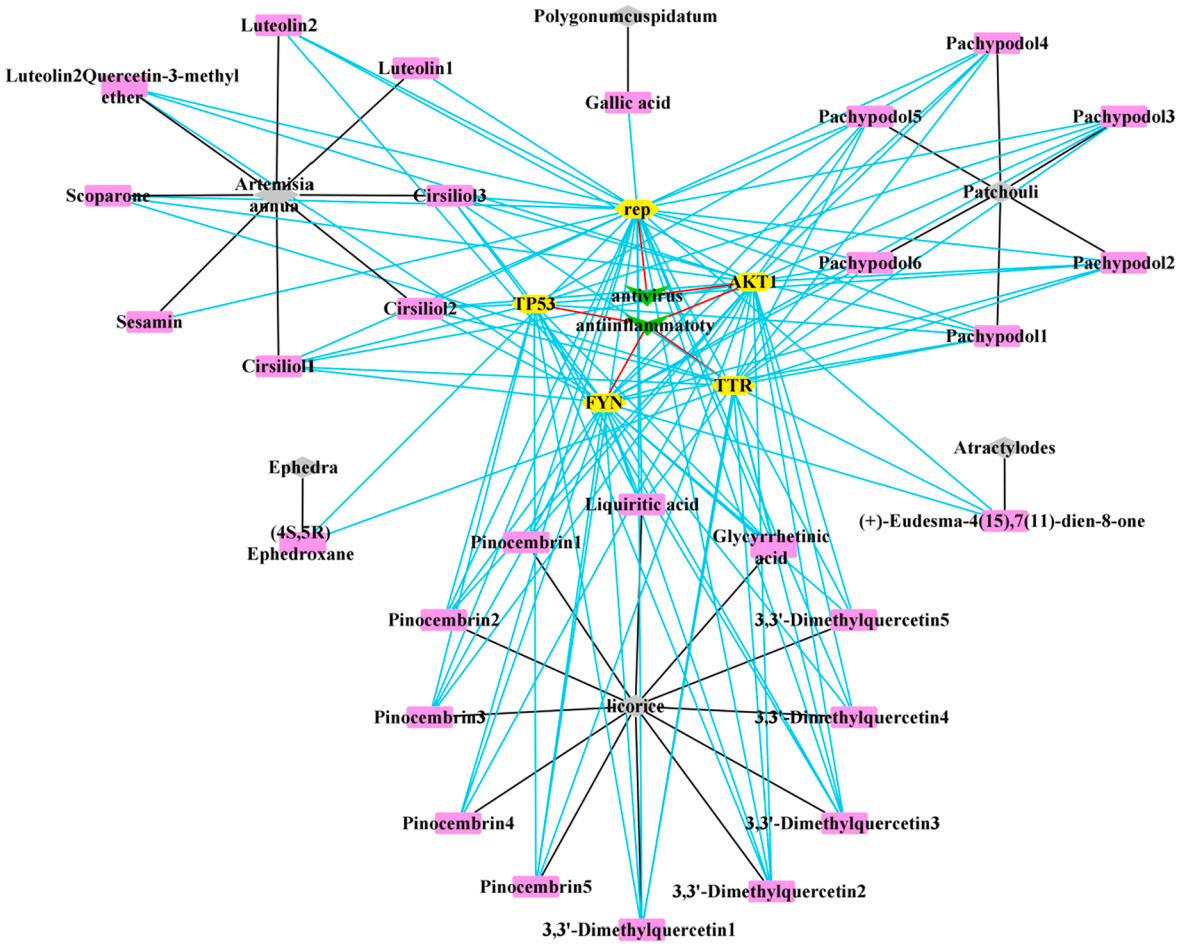


Fig. 4. "XBT-Compounds-Targets-Efficacy" Interaction Network Diagram. 6 traditional Chinese herbal medicines (Ephedra, Atractylodes, Patchouli, Artemisia annua, Polygonum cuspidatum, Licorice) in XBT are marked in gray; 29 compounds screened from 6 traditional Chinese herbal medicines with anti-inflammatory or antiviral effects are marked in pink; 5 targets are marked in yellow, and the properties of the targets are marked in green. The black line represents that a certain compound comes from a certain traditional Chinese herbal medicine; the blue line represents the interaction between the compound and the target, and the red line represents a certain target is against inflammation or virus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

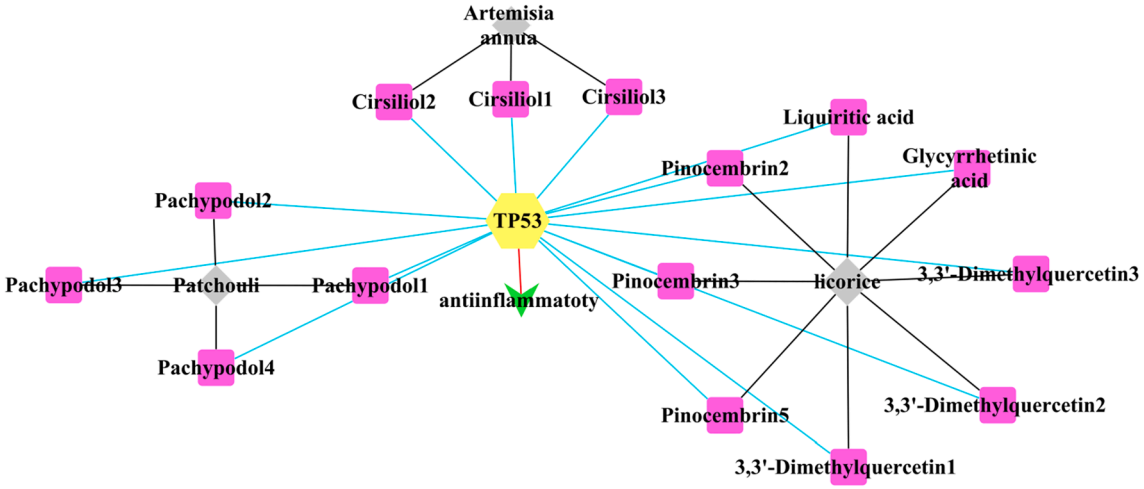


Fig. 5. "3 traditional Chinese herbal medicines-Compounds-Target-anti-inflammatory" Interaction Network Diagram related to COVID-19. 3 traditional Chinese herbal medicines (licorice, Artemisia annua, Patchouli) in XBT are marked in gray; 15 compounds screened from 3 traditional Chinese herbal medicines with anti-inflammatory or antiviral effects are marked in pink; 1target (TP53) is marked in yellow, and the property of the target is marked in green. The black line represents that a certain compound comes from a certain traditional Chinese herbal medicine; the blue line represents the interaction between the compound and the target, and the red line represents TP53 is against inflammation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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