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Discovery of anti-2019-nCoV agents from Chinese patent drugs via docking screening

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Running Title: Natural agents against 2019-nCoV by docking screening

Keywords: 2019-nCoV, novel coronavirus pneumonia, docking, ACE2, viral main protease

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Abstract

The 2019 novel coronavirus (2019-nCoV) causes novel coronavirus pneumonia (NCP). Given that approved drug repurposing becomes a common strategy to quickly find antiviral treatments, a collection of FDA-approved drugs can be powerful resources for new anti-NCP indication discoveries. In addition to synthetic compounds, Chinese Patent Drugs (CPD), also play a key role in the treatment of virus related infections diseases in China. Here we compiled major components from 38 CPDs that are commonly used in the respiratory diseases and docked them against two drug targets, ACE2 receptor and viral main protease. According to our docking screening, 10 antiviral components, including hesperidin, saikosaponin, rutin, baicalin, glycyrrhizin, mulberroside A, puerarin, orientin, amygdalin, and ilexgenin A, can directly bind to both host cell target ACE2 receptor and viral target main protease, indicating their potential for 2019-nCoV treatment.

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Introduction

The 2019 novel coronavirus (2019-nCoV), named as the Wuhan coronavirus [the pneumonia caused by it is now named as novel coronavirus pneumonia (NCP)], is a positive-sense, single-strand RNA coronavirus (1). Up to date, global infections of 2019-nCoV surge past 40,000 (WHO website). Given that drug repurposing is the common strategy to search antiviral treatments, several approved drugs were reported to benefit patients (2). Besides synthetic compounds, natural products, especially Chinese Patent Drug (CPD), also play a key role in the treatment of virus related infections diseases in China. Although the mechanisms of CPDs might be associated with immune regulation, we focus on their antiviral properties. In this study. we compiled major components from 14 out of 38 CPDs that are commonly used in the respiratory diseases and docked them against two drug targets, ACE2 receptor and viral main protease.

Like severe acute respiratory syndrome-related coronavirus (SARS-CoV), the 2019-nCoV attach to host cells through S protein and angiotensin converting enzyme 2 (ACE2) receptor interaction (3). The catalytic inhibitor of ACE2 receptor is likely to induce a conformational change of ACE2, therefore blocking the interaction between S protein and ACE2 receptor (4). S protein of 2019-nCoV is not currently available but the structure of ACE2 receptor is well-known (5). Thus ACE2 receptor was selected to quickly identify entry inhibitors of 2019-nCoV using marketed CPDs-derived natural products.

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In addition to entry inhibitors, the replication inhibitors are also good strategies for antiviral drug discovery and development (6). Given that 2019-nCoV is a (+)SS RNA virus, its main protease is likely to be required to mediate viral replication and transcription through extensive cleavage of two replicase polyproteins. Therefore inhibition of viral main protease might block virus replication (7). Up to date, Rao et al reported the crystal structure of M protease of 2019-nCoV (PDB: 6LU7) and several drug repurposing docking screening studies were reported. We herein docked natural product database to main protease to look for antiviral replication agents.

Due to the limited time and lack of the available 2019-nCoV in hand, it is impossible to develop novel compounds against 2019-nCoV by biological screening. We here used docking screening to identify natural products from marketed CPDs that inhibit both virus entry and replication, therefore providing a potential prevention/treatment alternative against 2019-nCoV.

Material and Methods

The major components of each herb in the selected 14 CPDs were collected as the ligands, and all the ligands were in PDBQT format. The protein model 1R4L was selected as ACE2 receptor docking model while 6LU7 was selected as M protease docking model. Both PDB files of protein models were fetched from Protein Data Bank. The docking screenings were conducted by using AutoDock Vina v.1.0.2. The docking parameters for AutoDock Vina were kept at their default values. The grid box was 25 Å by 25 Å by 25Å, encompassing the catalytic pocket. The binding modes

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were clustered through the root mean square deviation (RMSD) among the Cartesian coordinates of the ligand atoms.

Results and Discussion

A total of 14 marketed CPDs (bold line in Table 1) containing 63 herbs used for the treatment of respiratory diseases were selected. Totally we docked 52 components (Table 2) and the top 10 hits were summarized in Table 3. All of them provide good binding affinities against both two targets. The key residues for each ligand binding were also summarized in Table 4.

Analysis of the results from Table 3, it was found that the top 10 antiviral components are hesperidin, saikosaponin, rutin, baicalin, glycyrrhizin, mulberroside A, puerarin, orientin, amygdalin, and ilexgenin A, and their binding sites toward 6LU7 and 1R4L are listed in Table 4. A close analysis found that 29 compounds directly bind to ACE2 receptor with high or mild binding affinities (docking score <-8.5 kcal/mol). 14 out of 29 compounds exhibit strong interactions with ACE2 receptor (docking score < -9.7kcal/mol), these compounds are hesperidin, saikosaponin A (mulberroside A), rutin, baicalin, prim-*O*-glucosylcimifugin, orientin (astragaloside A), ilexgenin A, amygdalin (paeoniflorin), glycyrrhizin, puerarin, and berberine （Table 5). Whereas, in M protease docking screening, 6 phytochemicals, rutin (glycyrrhizin), saikosaponin A, puerarin, hesperidin, baicalin, have been identified as potential M protease inhibitors (docking score ≤-8.4 kcal/mol), indicating their potential for 2019-nCov. Notably, artemisinin, berberine, rutin, glycyrrhizin, chlorogenic acid, baicalin, cholic

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acid, hyodeoxycholic acid, and puerarin are commercially available with good supply, suggesting a future new drug development is of necessity. In addition, the results of Table 5 in combination of the literature data indicated the natural sources of these active compounds with relatively high content. Basically, around 19 compounds are present in natural sources more than 1% (g/g), which are respectively hesperidin, baicalin, glycyrrhizin, puerarin, amygdalin, paeoniflorin, berberine, arctiin, forsythiaside A, chlorogenic acid, geniposide, magnolol, lobetyolin, pulegone, citrulline, L-menthol, 6-gingerol, rutin (source plant: *Potentilla chinensis*), and harpagide (source plant: *Ajuga pantantha*) (Table 5). This information in combination with the docking results suggests that these plants or herbs or their extracts with enriched active compounds might be valuable for fighting against 2019-nCoV. Although the other herbs or CPDs are not found to be active toward 2019-nCoV, this doesn't mean that they are not useful for NCP because only limited compounds in herbs were selected which couldn't exclude more compounds or their analogues in herbs of CPDs are active. In addition, the principles of formulating Chinese herbal prescription include eliminating evil and strengthening the body resistance, therefore, we couldn't exclude that these CPDs do work against NCP via regulating immune system. Further efforts on docking of the structures from the rest 24 CPDs are undergoing. Validation of these docking results is also undergoing.

Acknowledgments

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Competing interest statement

The authors declare no conflict of interest.

References

1. Huang CL, Wang YM, Li XW, Ren LL, Zhao JP, Hu Y, Zhang L, Fan GH, Xu, JY, Gu, XY, Cheng ZS, Yu, T, Xia JA, Wei A, Wu, WJ, Xie XL, Yin W, Li H, Liu, M, Xiao Y, Gao H,Guo L, Xie JG, Wang GF, Jiang RM, Gao ZC, Jin Q, Wang JW, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 2020; doi: 10.1016/S0140-6736(20)30183-5.

2. Wang ML, Cao RY, Zhang LK, Yang XL, Liu J. Xu MY, Shi ZL, Hu ZH, Zhong W, Xiao GF. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res., 2020; doi: 10.1038/s41422-020-0282-0.

3. Wan YS, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J. Virol., 2020; doi: 10.1128/JVI.00127-20.

4. Du LY, He YX, Zhou YS, Liu SW, Zheng BJ, Jiang SB. The spike protein of SARS-CoV -a target for vaccine and therapeutic development. Nat. Rev. Microbiol., 2009; 7(3): 226–236.

5. Towler P, Staker B, Prasad SG, Menon S, Tang J, Parsons T, Ryan D, Fisher M, Williams D, Dales NA, Patane MA, Pantoliano MW. ACE2 X-ray structures reveal a large hinge-bending motion important for inhibitor binding and catalysis. J. Biol.

 doi:10.20944/preprints202002.0254.v1

Chem., 2004; 279(17):17996–8007.

6. Clercq ED. Strategies in the design of antiviral drugs. Nat. Rev. Drug Discov., 2002; 1: 13–25.

7. Wit ED, van Doremalen NV, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat. Rev. Microbiol., 2016; 14: 523–534.

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Table 1. Commercial names of 38 Chinese patent drugs (CPDs)

No.	CPDs	No.	CPDs
1	**Fengre Ganmao Granules**	20	Kangbingdu Capsules
2	**Xiaochaihu Granules**	21	Fufang Banlangen Granules
3	**Qingkailing Capsules**	22	Ganmao Shufeng Capsules/Granules
4	**Jinlianhua Capsules**	23	Ganmao Qingre Granules
5	**Zhongganling Capsules**	24	Fufang Jinyinhua Granules
6	**Lianhua Qingwen Capsules/Granules**	25	Yinqiao Jiedu Pills/Granules
7	**Lanqin Oral Solution**	26	Vitamin C Yinqiao Tablets
8	**Qingwen Jiedu Tablets**	27	Fufang Yinqiao Anfen Capsules
9	**Fangfeng Tongsheng Pills**	28	Xiasangju Granules
10	**Shuanghuanglian Oral Solution**	29	Vitamin C Effervescent Tablets
11	**Huoxiang Zhengqi Oral Solution**	30	Xiaoer Ganmao Granules
12	**Huoxiang Zhengqi Capsules**	31	Banlangen Granules
13	**Maxing Zhike Syrup**	32	Qingkailing Oral Solution
14	**Choulingdan Oral Solution**	33	Yinqiao Jiedu Granules
15	Erding Capsules	34	Fufang Yinqiao Anfen Vitamin C Tablets
16	Zhiganjia Granules	35	Ganmao Soft Capsules
17	Kanggan Granules	36	Fenghan Ganmao Granules
18	Kangbingdu Granules	37	Qiangli Pipa Syrup
19	Kangbingdu Oral Emulsion	38	Fufang Anwanan Tablets

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Table 2. Appendix total docking ranking

Ligand	6LU7	1R4L	Sum
Hesperidin	-8.5	-11.4	-19.9
Saikosaponin A	-8.8	-11	-19.8
Rutin	-8.9	-10.7	-19.6
Baicalin	-8.4	-10.5	-18.9
Glycyrrhizin	-8.9	-9.9	-18.8
Mulberroside A	-7.7	-11	-18.7
Puerarin	-8.6	-9.8	-18.4
Orientin	-8.1	-10.2	-18.3
Amygdalin	-8.1	-10	-18.1
Ilexgenin A	-7.9	-10.1	-18
Prim-*O*-glucosylcimifugin	-7.6	-10.4	-18
Astragaloside A	-7.6	-10.2	-17.8
Paeoniflorin	-7.7	-10	-17.7
Nodakenin	-7.9	-9.6	-17.5
Swertiajaponin	-8	-9.4	-17.4
Berberine	-7.5	-9.7	-17.2
Arctiin	-7.3	-9.5	-16.8
Forsythiaside A	-7.6	-9.1	-16.7
Radix isatidis A	-7.6	-9.1	-16.7
Indirubin	-7.3	-9.3	-16.6
Artemisinin	-7.3	-9.1	-16.4
Emodin	-7.2	-9.2	-16.4
Cholic acid	-7	-9.3	-16.3
Hyodeoxycholic acid	-7	-9.3	-16.3
Xanthiside	-7.3	-8.9	-16.2
Chlorogenic acid	-7.3	-8.8	-16.1

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Verbenalin	-7.4	-8.7	-16.1
Poricoic acid A	-6.9	-9.2	-16.1
Notopterol	-7	-8.4	-15.4
Harpagide	-7	-8.3	-15.3
Imperatorin	-7.1	-8.2	-15.3
Geniposide	-6.7	-8.5	-15.2
Salidroside	-6.9	-7.9	-14.8
Atractylenolide I	-6.3	-8.2	-14.5
Magnolol	-6.4	-7.9	-14.3
Lobetyolin	-6.4	-7.7	-14.1
Pterodontic acid	-6	-7.7	-13.7
Platycodin D	-7.5	-5.5	-13
Dhelwangin	-5.2	-7.1	-12.3
Ferulic acid	-5.4	-6.5	-11.9
6-Gingerol	-4.8	-6.6	-11.4
Atractylodin	-4.9	-6.3	-11.2
Ephedrine	-5.1	-6.1	-11.2
Pulegone	-4.9	-6.2	-11.1
Citrulline	-4.9	-5.8	-10.7
Linolenic acid	-4.6	-6.1	-10.7
L-Menthol	-4.7	-5.7	-10.4
Arecoline	-4.6	-5.4	-10
Glutamic acid	-4.5	-5.3	-9.8
Tetramethyl pyrazine	-4.5	-5.1	-9.6
Succinic acid	-4.4	-4.9	-9.3
Decanoy acetaldehyde	-3.9	-4.9	-8.8

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Table 3. Natural products from CPDs docking results

Ligand	Binding affinity (kcal/mol)		
	6LU7	1R4L	Sum
Hesperidin	-8.5	-11.4	-19.9
Saikosaponin	-8.8	-11	-19.8
Rutin	-8.9	-10.7	-19.6
Baicalin	-8.4	-10.5	-18.9
Glycyrrhizin	-8.9	-9.9	-18.8
Mulberroside A	-7.7	-11	-18.7
Puerarin	-8.6	-9.8	-18.4
Orientin	-8.1	-10.2	-18.3
Amygdalin	-8.1	-10	-18.1
Ilexgenin A	-7.9	-10.1	-18

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Table 4. Key residues for potential inhibitors binding

Ligand	Key residues	
	6LU7	**1R4L**
Hesperidin	Gly143, Ser144, Cys145, Glu166	Cy3344, His345, Asp368, Arg514, Tyr515, Arg518
Saikosaponin	His41, Glu166, Arg188, Gln189, Thr190, Gln192	Ala348, Glu402, Arg514, Tyr515, Arg518
Rutin	His163, Phe140, Glu166, Arg188	Asn149, Arg273, His345, Thr445, His505, Tyr515
Baicalin	Thr25, Thr26, Leu141, Gly143, Ser144, Cys145	His345, Lys363, Thr371, His505, Arg518
Glycyrrhizin	Phe140, His163, His164, Arg188	Arg273, His345, Thr365, Thr371, Tyr515, Arg518
Mulberroside A	Thr24, Thr26, Gly143, Ser144, Cys145, Gln189	Asn149, Arg273, Lys363, Asp367, Asp368, Tyr515, Arg518
Puerarin	Thr26, His41, Leu141, Ser144, His163, Glu166	Asn149, Asp367, Glu402, Tyr515
Orientin	Phe140, Glu166, Gln189, Thr190	Arg273, Thr371, Glu406, Tyr515, Arg518
Amygdalin	Leu141, Gly143, Ser144, Glu166, Arg188	Asn149, Pro346, Lys363, Arg518
Ilexgenin A	Thr24, Leu141, Gly143	His345, Lys363, Thr371

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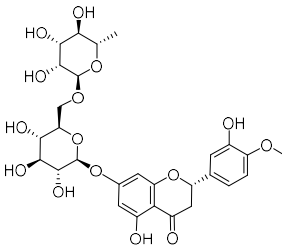
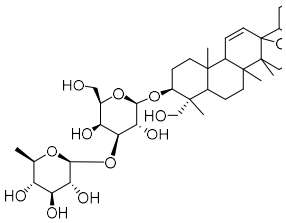
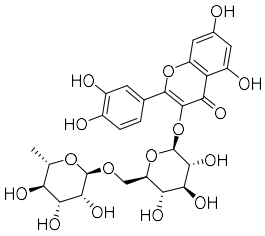
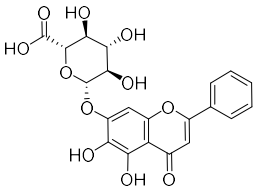
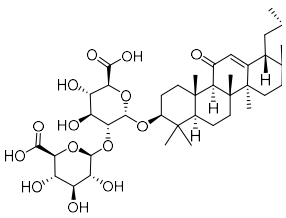
Table 5. The structure, natural source and content of active components, and weight ratio of a herb in Chinese patent drugs

Compound	Structure	Source	Weight ratio[a]	Content (mg/g)[b]
Hesperidin		Citri Reticulatae Pericarpium	11 (10.66%), 12 (10.10%), 36 (7.69%)	21.60–75.70
Saikosaponin A		Bupleuri Radix	2 (30.86%), 8 (4.00%), 23 (8.47%)	3.93–7.80
Rutin		Mori Folium	1[c], 28 (23.18%)	0.32–3.25
Baicalin		Scutellariae Radix	2 (11.52%), 3[c], 7[c], 9 (7.55%), 10 (50.00%), 24 (14.29%), 32[c], 35 (11.43%)	99.40–183.20
Glycyrrhizin		Glycyrrhizae Radix et Rhizome	2 (11.52%), 6[c], 8 (6.00%), 9 (15.09%), 11 (1.33%), 12 (10.10%), 13 (12.00%), 22 (5.88%), 25 (8.93%), 26 (8.51%), 33 (8.93%), 36 (7.69%)	20.30–71.70

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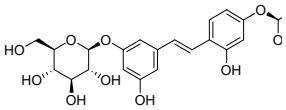
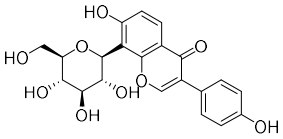
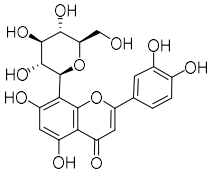
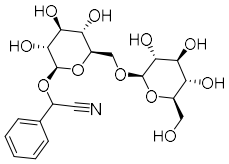
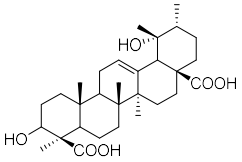
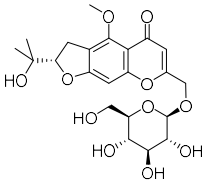
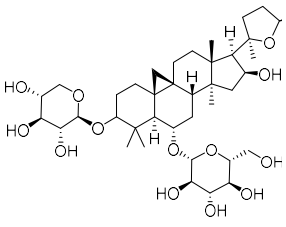
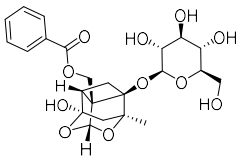
Iberroside A		Mori Ramulus	1[c]	4.97–13.14
Puerarin		Puerariae Lobatae radix	5[c], 8 (8.00%), 23 (8.47%), 35 (8.57%), 36 (11.54%)	11.30–38.93
Orientin		Trollius Chinensis	4 (100%)	8.56–20.51
Amygdalin		Armeniacae Semen Amarum	1[c], 6[c], 13 (16.00%), 22 (8.82%), 23 (6.78%), 35 (11.43%), 36 (11.54%)	36.7–45.8
Ilexgenin A		Ilicis Pubescentis Radix et Caulis	5[c]	4.1–15.6
Prim-*O*-glucosyl cimifugin		Saposhnikoviae Radix	8 (4.00%), 9 (3.77%), 22 (8.82%), 23 (8.47%), 35 (5.71%), 36 (11.54%)	1.16–9.49
Astragaloside A		Astragali Radix	8 (8.00%)	0.26–2.13
Paeoniflorin		Paeoniae Radix Rubra Paeoniae Radix Alba	Paeoniae Radix Rubra : 8 (4.00%), 17 (42.87%) Paeoniae Radix Alba : 9 (3.77%), 22 (14.70%)	20.00–25.00

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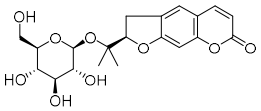
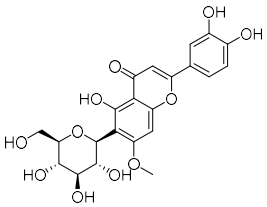
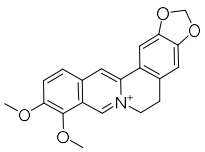
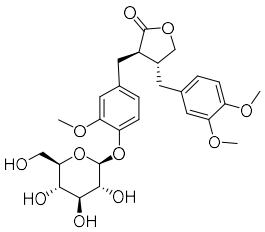
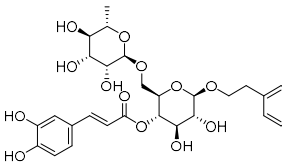
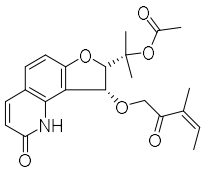
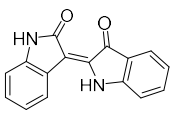
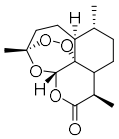
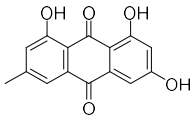
Nodakenin		Notopterygii Rhizoma Et Radix	5[c], 8 (6.00%), 16[c], 35 (5.71%)	0.50–28.60
Swertiajaponin		Lophatheri Herba	8 (8.00%), 25 (7.14%), 26, 33 (7.14%)	0.31–2.29
Berberine		Phellodendri Chinensis Cortex	7[c]	17.76–80.32
Arctiin		Arctii Fructus	1[c], 8 (8.00%), 25 (10.71%), 26 (10.21%), 33 (10.71%)	47.5–73.3
Forsythiaside A		Forsythiae Fructus	1[c], 6[c], 8 (6.00%), 9 (3.77%), 10 (25.00%), 19[c], 20[c], 24 (42.86%), 25 (17.86%), 26 (17.01%), 27[c], 30 (9.09%), 33 (17.86%), 34[c]	146.2–172.1
Radix isatidis A		Isatidis Radix	1[c], 3[c], 5[c], 6[c], 7[c], 15[c], 16[c], 18[c], 19[c], 20[c], 21 (40.00%), 30 (9.09%), 31 (100%), 32[c]	Unknown
Indirubin		Isatidis Folium	8[c], 21 (60.00%), 30 (15.15%)	0.02–4.15
Artemisinin		Artemisiae Annuae Herba	5[c]	1.91–5.19
Emodin		Rhei Radix Et Rhizoma	6[c], 9 (3.77%)	0.29–0.66

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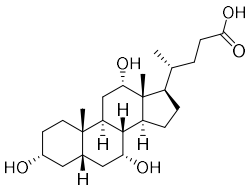
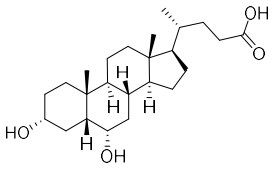
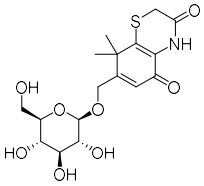
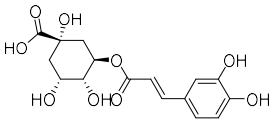
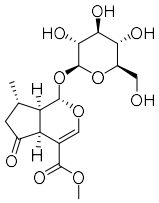
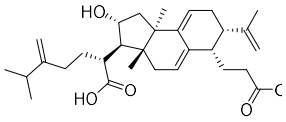
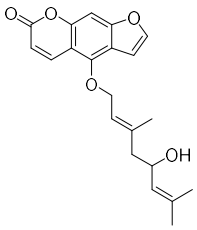
Cholic acid		Cholic acid	3[c], 32[c]	
Hyodeoxycholic acid		Hyodeoxycholic acid	3[c], 32[c]	
Xanthiside		Massa Medicata Fermentata	1[c]	1.52–3.79
Chlorogenic acid		Lonicerae Japonicae Flos Chrysanthemi Flos	Lonicerae Japonicae Flos: 3[c], 6[c], 10 (25.00%), 17 (42.87%), 24 (42.86%), 25 (17.86%), 27[c], 32[c], 33 (17.86%), 34[c] Chrysanthemi Flos: 28 (10.59%), 30 (9.09%)	22.30–31.60; 2.38–7.20
Verbenalin		Verbenae Herba	5[c]	1.52–3.35
Poricoic acid A		Poria	11 (16.00%), 12 (5.05%)	0.24–0.40
Notopterol		Notopterygii Rhizoma Et Radix	5[c], 16, 35 (5.71%)	3.50–15.00

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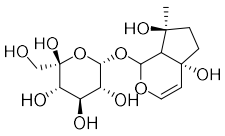
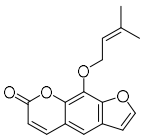
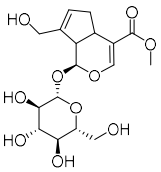
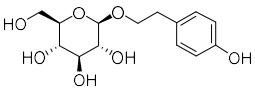
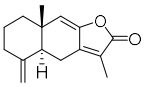
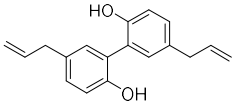
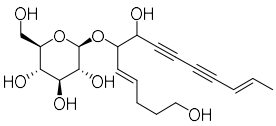
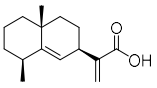
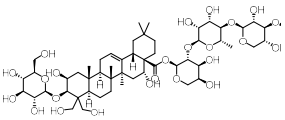
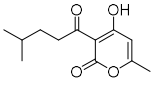
Harpagide		Scrophulariae Radix	8 (8.00%)	3.59–4.86
Imperatorin		Angelicae Dahuricae Radix	8 (4.00%), 11 (16.00%), 12 (5.05%), 18[c], 23 (5.08%), 35 (5.71%), 36 (7.69%)	0.75–1.37
Geniposide		Gardeniae Fructus	3[c], 7[c], 9 (1.89%), 32[c]	26.25–60.28
Salidroside		Rhodiolae Crenulatae Radix Et Rhizoma	6[c]	7.83–11.09
Atractylenolide I		Atractylodis Macrocephalae Rhizoma	9 (1.89%), 12 (10.10%)	1.93–2.54
Magnolol		Magnoliae Officinalis Cortex	11 (10.66%), 12 (10.10%)	9.50–67.80
Lobetyolin		Codonopsis Radix Lobeliae Chinensis Herba	Codonopsis Radix: 2 (11.52%) Lobeliae Chinensis Herba: 15[c]	29.50–59.40
Pterodontic acid		Laggerae Herba	14 (100%)	Unknown
Platycodin D		Platycodonis Radix	8 (6.00%), 9 (7.55%), 12 (10.10%), 22 (5.88%), 23 (5.08%), 25 (10.71%), 26 (10.21%), 33 (10.71%), 35 (5.71%), 36 (7.69%), 37 (3.72%)	1.85–4.06
Dhelwangin		Pogostemonis Herba	6[c], 11 (5.33%), 12 (15.15%), 19[c], 20[c], 30 (9.09%)	1.35–5.71

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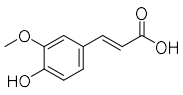
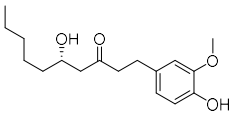
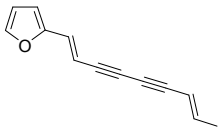
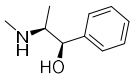
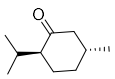
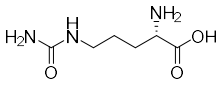
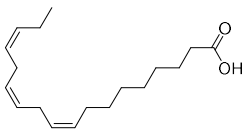
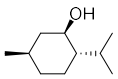
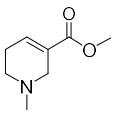
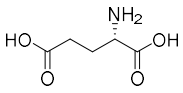
Ferulic acid		Phragmitis Rhizoma Angelicae Sinensis Radix	Phragmitis Rhizoma: 1[c], 19[c], 20[c], 23 (8.47%), 26 (10.21%) Angelicae Sinensis Radix: 9 (3.77%), 35 (5.71%)	0.46–1.65
6-Gingerol		Zingiberis Rhizoma Recens	2 (11.52%), 12 (1.51%), 22 (5.88%), 36 (7.69%)	9.96–28.64
Atractylodin		Atractylodis Rhizoma	11 (10.66%)	3.98–10.96
Ephedrine		Ephedrae Herba	13 (24.0%), 22 (5.88%), 35 (11.43%), 36 (7.69%), 9 (3.77%), 6[c]	4.80–10.20
Pulegone		Schizonepetae Spica	1[c], 9 (1.89%), 23 (16.95%), 25 (7.14%), 26 (6.80%), 27,33 (7.14%), 34, 35 (8.57%)	Volatile oils 294.27–754.02
Citrulline		Trichosanthis Radix	8 (8.00%)	20.20–60.20
Linolenic acid		Perillae Folium	11 (2.67%), 12 (5.05%), 22 (5.88%), 23 (5.08%), 36 (11.54%)	0.09–0.68
L-Menthol		Menthae Haplocalycis Herba	9 (3.77%), 16[c], 23 (5.08%), 25 (10.71%), 26 (4.73%), 27[c], 30 (6.06%), 33 (10.71%), 34[c], 35[c], 1[c], 37 (3.72%)	25.76–226.10
Arecoline		Arecae Pericarpium	11 (16.00%), 12 (5.05%)	1.92–3.80
Glutamic acid		Bubali Cornu	32[c]	2.25

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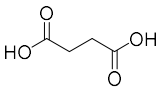
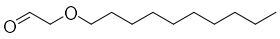
Tetramethyl pyrazine		Chuanxiong Rhizoma	35 (5.71%), 8 (4.00%), 9 (3.77%)	0.15–0.24
Succinic acid		Pinelliae Rhizoma	2 (11.52%), 11 (10.66%), 12 (10.10%)	3.24–4.43
Decanoy acetaldehyde		Houttuyniae Herba	6[c], 18[c]	Volatile oils 7.2%

[a] The number of Chinese patent drugs is same as that in table 1.

[b] Data source: China National Knowledge Infrastructure (CNKI).

[c] Unknown.