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Discovery of anti-2019-nCoV agents from 38 Chinese patent drugs toward respiratory diseases 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 A, rutin, corosolic acid, verbascoside, baicalin, glycyrrhizin, mulberroside A, cynaroside, and bilirubin, can directly bind to both host cell target ACE2 receptor and viral target main protease. In combination of the docking results, the natural abundance of the substances, and botanical knowledge, we proposed that artemisinin, rutin, glycyrrhizin, cholic acid, hyodeoxycholic acid, puerarin, oleanic acid, andrographolide, matrine, codeine, morphine, chlorogenic acid, and baicalin (or Yinhuang Injection containing chlorogenic acid and baicalin) might be of value for clinical trials during a 2019-nCov outbreak.

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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 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 38 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 38 marketed CPDs (bold line in Table 1) containing 93 herbs used for the treatment of respiratory diseases were selected. Totally we docked 95 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 A, rutin, corosolic acid, verbascoside, baicalin, glycyrrhizin, mulberroside A, cynaroside, and bilirubin, and their binding sites toward 6LU7 and 1R4L are listed in Table 4. A close analysis found that 19 compounds directly bind to ACE2 receptor with high affinities (docking score <-10 kcal/mol), these compounds are hesperidin, saikosaponin A, mulberroside A, rutin, bilirubin, verbascoside, vincetoxicoside B, baicalin, prim-*O*-glucosylcimifugin, corosolic acid, cynaroside, orientin, corynoline, astragaloside A, protostemonine, ilexgenin A, amygdalin, paeoniflorin, and ursolic acid （Table 2). Whereas, in M protease docking screening, 12 phytochemicals, rutin, glycyrrhizin, dipsacoside B, saikosaponin A, corosolic acid, puerarin, morusin, hesperidin, polyphyllin I, verbascoside, baicalin, and cynaroside have been identified as potential M protease inhibitors (docking score ≤-8.4 kcal/mol), indicating their potential for 2019-nCov. Notably, artemisinin,

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berberine, rutin, glycyrrhizin, chlorogenic acid, baicalin, cholic acid, hyodeoxycholic acid, puerarin, oleanic acid, andrographolide, catalpol, matrine, codeine, morphine, caffeic acid, α-asarone, α-pinene, and taurine are commercially available with good supply (already marketed drugs). However, a combination of their docking results, natural abundance, and traditional knowledge from their source herbs allows us to recommend artemisinin, rutin, glycyrrhizin, chlorogenic acid, baicalin, cholic acid, hyodeoxycholic acid, puerarin, oleanic acid, andrographolide, matrine, codeine, and morphine for clinical trials during a 2019-nCov outbreak. Yinhuang Injection, a marketed drug in China, might be also worth recommendation because it is mainly composed of chlorogenic acid and baicalin. In addition, the results of Table 5 in combination of the literature data indicate the natural sources of these active compounds with relatively high content. Basically, around 34 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, tectoridin, timosaponin BII, dryocrassin, oleanic acid, genistein, trisalbaspidin ABA, daidzein, andrographolide, rosmarinic acid, quercetin (source plant: *Sophorae Flos*), curcumin (source plant: *Curcumae Longae Rhizoma*), dipsacoside B (source plant: *Lonicerae Dasystylae Flos*), rutin (source plant: *Potentilla chinensis*), and harpagide (source plant: *Ajuga pantantha*). This natural abundance information in combination with the docking results and the medicinal values of the source herbs suggests that the plants or herbs or their extracts with the above enriched active compounds might be valuable for fighting against

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2019-nCoV. Although the content of magnolol, lobetyolin, pulegone, citrulline, L-menthol, 6-gingerol, catalpol, caffeic acid, and *trans*-cinnamaldehyde is also more than 1%, it might be not potential either from their docking resluts or botanical knowledge (Table 5). Despite that 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.

Acknowledgments

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Competing interest statement

The authors declare no conflict of interest.

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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	Docking score (kcal/mol)		
	6LU7	1R4L	SUM
Hesperidin	-8.5	-11.4	-19.9
Saikosaponin A	-8.8	-11	-19.8
Rutin	-8.9	-10.7	-19.6
Corosolic acid	-8.8	-10.2	-19
Verbascoside	-8.4	-10.6	-19
Baicalin	-8.4	-10.5	-18.9
Glycyrrhizin	-8.9	-9.9	-18.8
Mulberroside A	-7.7	-11	-18.7
Cynaroside	-8.4	-10.2	-18.6
Bilirubin	-7.8	-10.7	-18.5
Vincetoxicoside B	-7.9	-10.6	-18.5
Morusin	-8.6	-9.8	-18.4
Puerarin	-8.6	-9.8	-18.4
Orientin	-8.1	-10.2	-18.3
Cynancersicoside A	-8.3	-9.9	-18.2
Protostemonine	-8.1	-10.1	-18.2
Amygdalin	-8.1	-10	-18.1
Ilexgenin A	-7.9	-10.1	-18
Prim-*O*-glucosylcimifugin	-7.6	-10.4	-18
Corynoline	-7.7	-10.2	-17.9
Astragaloside A	-7.6	-10.2	-17.8
Paeoniflorin	-7.7	-10	-17.7
Polyphyllin I	-8.5	-9.1	-17.6
Nodakenin	-7.9	-9.6	-17.5
Tectoridin	-7.9	-9.5	-17.4
Ursolic acid	-7.4	-10	-17.4

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Swertiajaponin	-8	-9.4	-17.4
Berberine	-7.5	-9.7	-17.2
Timosaponin BII	-7.7	-9.4	-17.1
Dryocrassin	-7.4	-9.5	-16.9
Columbianadin	-7.2	-9.6	-16.8
Arctiin	-7.3	-9.5	-16.8
Oleanic acid	-7.4	-9.3	-16.7
Luteolin	-7.6	-9.1	-16.7
Quercetin	-7.7	-9	-16.7
Forsythiaside A	-7.6	-9.1	-16.7
Radix isatidis A	-7.6	-9.1	-16.7
Genistein	-7.5	-9.1	-16.6
Indirubin	-7.3	-9.3	-16.6
Curcumin	-7	-9.5	-16.5
Trisalbaspidin ABA	-7.2	-9.3	-16.5
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
Daidzein	-7.4	-8.8	-16.2
Xanthiside	-7.3	-8.9	-16.2
Chlorogenic acid	-7.3	-8.8	-16.1
Verbenalin	-7.4	-8.7	-16.1
Poricoic acid A	-6.9	-9.2	-16.1
Andrographolide	-6.9	-8.8	-15.7
Dipsacoside B	-8.9	-6.7	-15.6
Codeine	-7	-8.5	-15.5
Rosmarinic acid	-7	-8.4	-15.4
Notopterol	-7	-8.4	-15.4

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Harpagide	-7	-8.3	-15.3
Imperatorin	-7.1	-8.2	-15.3
Papaverine	-6.9	-8.3	-15.2
Geniposide	-6.7	-8.5	-15.2
Catalpol	-7.1	-7.9	-15
Salidroside	-6.9	-7.9	-14.8
Morphine	-6.6	-8.1	-14.7
Atractylenolide I	-6.3	-8.2	-14.5
Magnolol	-6.4	-7.9	-14.3
Lobetyolin	-6.4	-7.7	-14.1
Matrine	-6.1	-7.9	-14
Pterodontic acid	-6	-7.7	-13.7
Isoevodionol	-6.2	-7.1	-13.3
Esculetin	-6.2	-6.9	-13.1
Platycodin D	-7.5	-5.5	-13
Scopoletin	-5.8	-6.8	-12.6
Dhelwangin	-5.2	-7.1	-12.3
Caffeic acid	-5.7	-6.5	-12.2
Ferulic acid	-5.4	-6.5	-11.9
6-Gingerol	-4.8	-6.6	-11.4
L(+)–Ascorbic acid	-5.1	-6.1	-11.2
Atractylodin	-4.9	-6.3	-11.2
Ephedrine	-5.1	-6.1	-11.2
Pulegone	-4.9	-6.2	-11.1
α–Asarone	-5.1	-5.9	-11
Coumalic acid	-4.9	-5.9	-10.8
Citrulline	-4.9	-5.8	-10.7
Linolenic acid	-4.6	-6.1	-10.7
Amantadine Hydrochloride	-4.4	-6.2	-10.6

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L-Menthol	-4.7	-5.7	-10.4
trans–Cinnamaldehyde	-4.4	-5.7	-10.1
β–Pinene	-4.3	-5.7	-10
Arecoline	-4.6	-5.4	-10
Glutamic acid	-4.5	-5.3	-9.8
α–Pinene	-4.1	-5.6	-9.7
Tetramethyl pyrazine	-4.5	-5.1	-9.6
Succinic acid	-4.4	-4.9	-9.3
Decanoy acetaldehyde	-3.9	-4.9	-8.8
Taurine	-3.7	-4.2	-7.9
Betaine	-3.5	-4.1	-7.6

Table 3. Natural products from CPDs docking results

Ligand	Docking score (kcal/mol)		
	6LU7	1R4L	SUM
Hesperidin	-8.5	-11.4	-19.9
Saikosaponin A	-8.8	-11	-19.8
Rutin	-8.9	-10.7	-19.6
Corosolic acid	-8.8	-10.2	-19
Verbascoside	-8.4	-10.6	-19
Baicalin	-8.4	-10.5	-18.9
Glycyrrhizin	-8.9	-9.9	-18.8
Mulberroside A	-7.7	-11	-18.7
Cynaroside	-8.4	-10.2	-18.6
Bilirubin	-7.8	-10.7	-18.5

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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 A	His41, Glu166, Arg188, Gln189, Thr190, Gln192	Ala348, Glu402, Arg514, Tyr515, Arg518
Rutin	His163, Phe140, Glu166, Arg188	Asn149, Arg273, His345, Thr445, His505, Tyr515
Corosolic acid	Gly143, Ser144, Cys145	Lys363, Thr371
Verbascoside	Phe140, Gly143, Glu166, Thr190, Gln192	Ser128, Glu145, Asn277, Cys344, His345, Arg518
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
Cynaroside	Thr24, Thr25, Thr26, Gly143	Asn149, Pro346, Lys363, Asp368
Bilirubin	Leu141, Ser144, His163, Gln189	Thr371, Glu406, Tyr515

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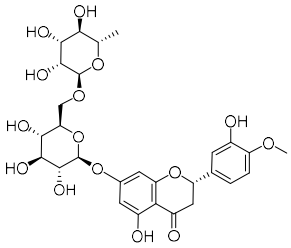
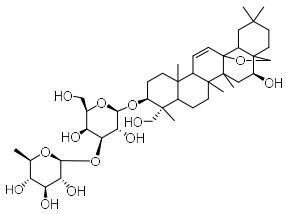
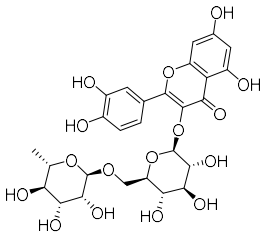
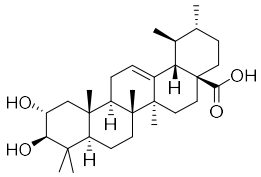
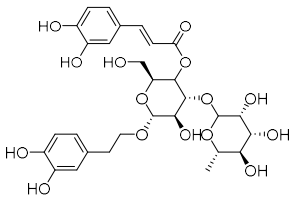
Table 5. The structure, natural source and content of active components, and weight ratio of a herb in Chinese patent drugs

Ligand	Structure	Herb origin	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
Corosolic acid		Eriobotryae Folium	34 (42.86%)	7.64
Verbascoside		Rehmanniae Radix	19[c], 20[c], 30 (9.09%)	0.39–0.42

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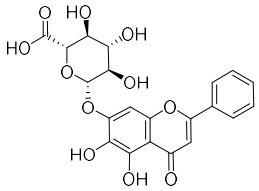
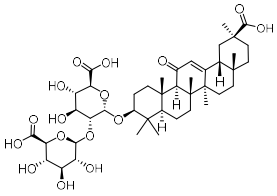
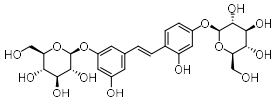
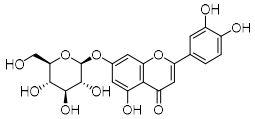
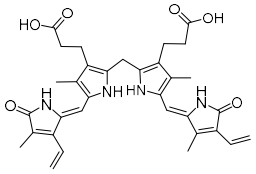
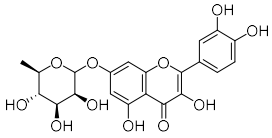
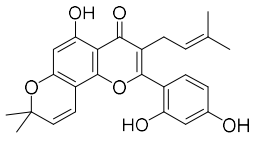
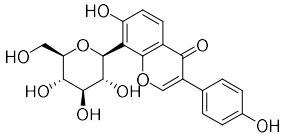
Baicalin		Scutellariae Radix	2 (11.52%), 3[c], 7[c], 9 (7.55%), 10 (50.00%), 24 (14.29%), 32[c], 35 (11.43%)	99.40–183.20
Glycyrrhizin		Glycyrrhizae Radix et Rhizome	2 (11.52%), 6[c], 8 (6.00%), 9 (15.09%), 11 (1.33%), 12 (10.10%), 13 (12.00%), 22 (5.88%), 25 (8.93%), 26 (8.51%), 33 (8.93%), 36 (7.69%)	20.30–71.70
Mulberroside A		Mori Ramulus	1[c]	4.97–13.14
Cynaroside		Lonicerae Flos	26 (17.01%)	5.1–9.4
Bilirubin		Atificial Cow–bezoar	38[c]	6.7–9.1
Vincetoxicoside B		Cynanchi Stauntonii Rhizoma et Radix	37 (5.60%)	No report
Morusin		Mori Cortex	37 (3.72%)	4.40–6.10
Puerarin		Puerariae Lobatae radix	5[c], 8 (8.00%), 23 (8.47%), 35 (8.57%), 36 (11.54%)	11.30–38.93

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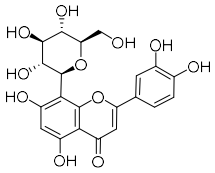
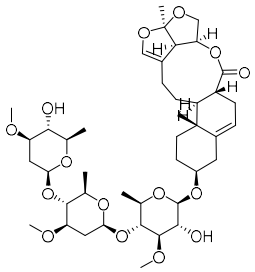
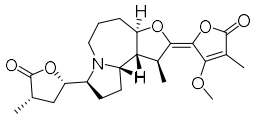
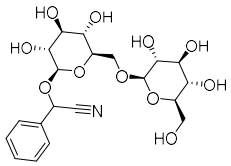
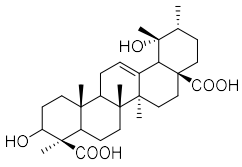
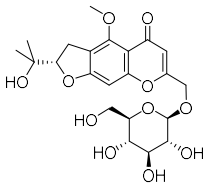
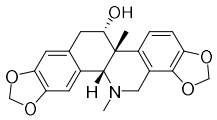
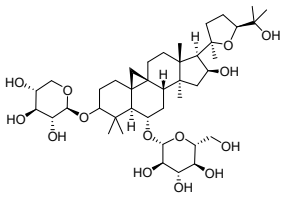
Orientin		Trollius Chinensis	4 (100%)	8.56–20.51
Cynancersicoside A		Cynanchi Atrati Radix et Rhizoma	30 (9.09%)	0.04–0.11
Protostemonine		Stemonae Radix	37 (9.31%)	2.80–3.80
Amygdalin		Armeniacae Semen Amarum	1[c], 6[c], 13 (16.00%), 22 (8.82%), 23 (6.78%), 35 (11.43%), 36 (11.54%)	36.7–45.8
Ilexgenin A		Ilicis Pubescentis Radix et Caulis	5[c]	4.1–15.6
Prim-*O*-glucosylcimifugin		Saposhnikoviae Radix	8 (4.00%), 9 (3.77%), 22 (8.82%), 23 (8.47%), 35 (5.71%), 36 (11.54%)	1.16–9.49
Corynoline		Corydalis Bungeanae Herba	23 (16.95%)	1.93–5.80
Astragaloside A		Astragali Radix	8 (8.00%)	0.26–2.13

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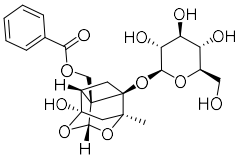
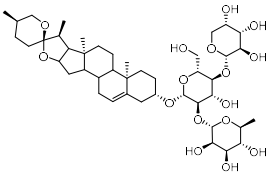
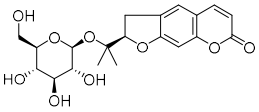
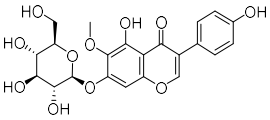
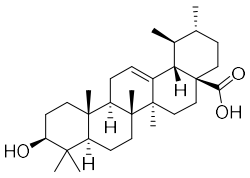
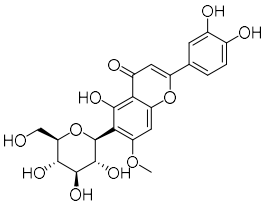
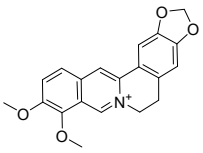
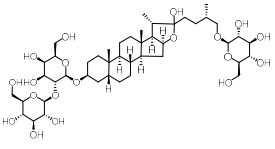
Paeoniflorin		Paeoniae Radix Rubra Paeoniae Radix Alba	Paeoniae Radix Rubra: 8 (4.00%), 17 (42.87%) Paeoniae Radix Alba: 9 (3.77%), 22 (14.70%)	20.00–25.00
Polyphyllin I		Paridis Rhizoma	18[c]	2.87–10.10
Nodakenin		Notopterygii Rhizoma Et Radix	5[c], 8 (6.00%), 16[c], 35 (5.71%)	0.50–28.60
Tectoridin		Iridis Tectori Rhizoma	18[c]	33.27–58.63
Ursolic acid		Prunellae Spica	28 (66.22%)	2.21–4.15
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
Timosaponin BII		Anemarrhenae Rhizoma	19[c], 20[c]	50.00–92.50

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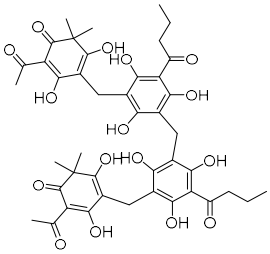
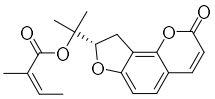
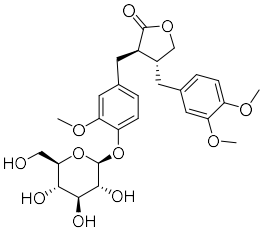
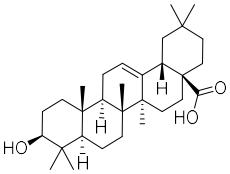
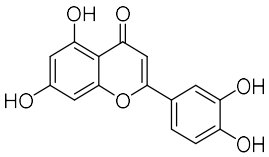
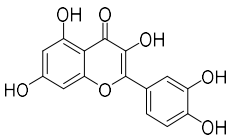
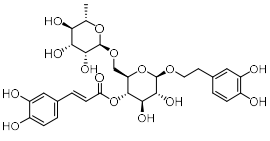
Dryocrassin		Dryopteridis Crassirhizomatis Rhizoma	6[c], 17 (14.27%)	26.10–61.00
Columbianadin		Angelicae Pubescentis Radix	22 (5.88%)	0.58–7.78
Arctiin		Arctii Fructus	1[c], 8 (8.00%), 25 (10.71%), 26 (10.21%), 33 (10.71%)	47.5–73.3
Oleanic acid		Helictercs Angustifolia	16[c]	10.18–25.58
Luteolin		Lonicerae Japonicae Caulis	18[c]	2.35–2.45
Quercetin		Desmodium Triquetrum	16[c]	No report
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

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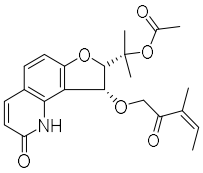
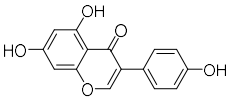
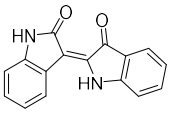
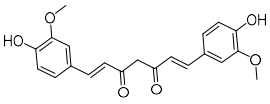
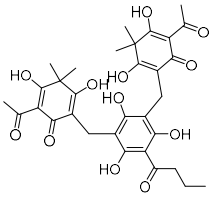
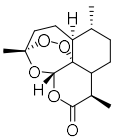
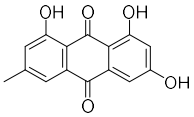
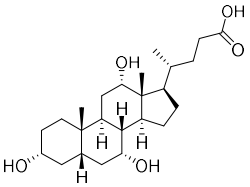
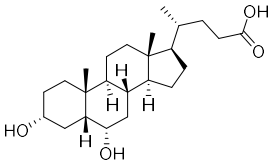
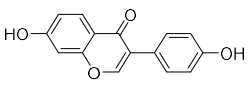
Radix isatidis A		Isatidis Radix	1[c], 3[c], 5[c], 6[c], 7[c], 15[c], 16[c], 18[c], 19[c], 20[c], 21 (40.00%), 30 (9.09%), 31 (100%), 32[c]	No report
Genistein		Sojae Semen Praeparatum	25 (8.93%), 26 (8.51%), 33 (8.93%)	29.38±11.65
Indirubin		Isatidis Folium	8[c], 21 (60.00%), 30 (15.15%)	0.02–4.15
Curcumin		Curcumae Radix	19[c], 20[c]	0.84–1.12
Trisalbaspidin ABA		Dryopteris Setosa	18[c]	17.8
Artemisinin		Artemisiae Annuae Herba	5[c]	1.91–5.19
Emodin		Rhei Radix Et Rhizoma	6[c], 9 (3.77%)	0.29–0.66
Cholic acid		Cholic acid	3[c], 32[c]	
Hyodeoxycholic acid		Hyodeoxycholic acid	3[c], 32[c]	
Daidzein		Sojae Semen Praeparatum	25 (8.93%), 26 (8.51%), 33 (8.93%)	18.69±1.28

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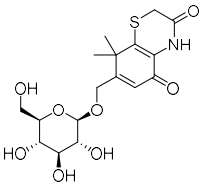
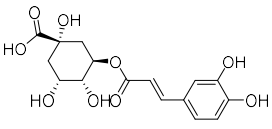
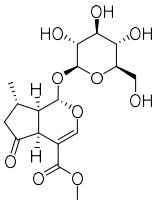
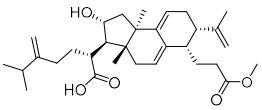
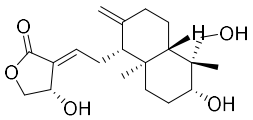
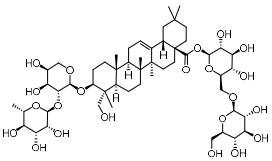
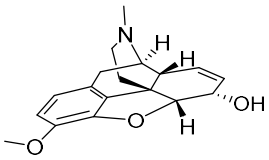
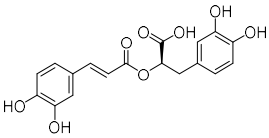
Xanthiside		Massa Medicata Fermentata	1[c]	1.52–3.79
Chlorogenic acid		Lonicerae Japonicae Flos Chrysanthemi Flos	Lonicerae Japonicae Flos: 3[c], 6[c], 10 (25.00%), 17 (42.87%), 24 (42.86%), 25 (17.86%), 27[c], 32[c], 33 (17.86%), 34[c] Chrysanthemi Flos: 28 (10.59%), 30 (9.09%)	22.30–31.60; 2.38–7.20
Verbenalin		Verbenae Herba	5[c]	1.52–3.35
Poricoic acid A		Poria	11 (16.00%), 12 (5.05%)	0.24–0.40
Andrographolide		Andrographis Herba	16[c]	14.9–17.2
Dipsacoside B		Lonicerae Flos	26 (17.01%)	4.30–9.30
Codeine		Papaveris Pericarpium	37 (31.05%)	0.23–0.60
Rosmarinic acid		Prunellae Spica	28 (66.22%)	19.23–25.67

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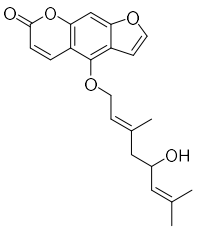
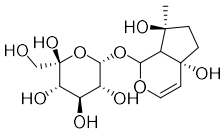
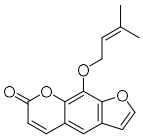
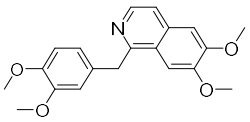
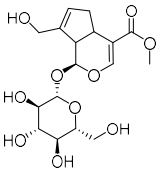
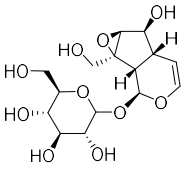
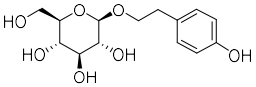
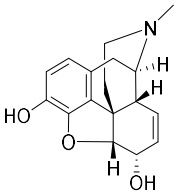
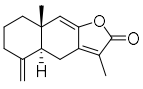
Notopterol		Notopterygii Rhizoma Et Radix	5[c], 16, 35 (5.71%)	3.50–15.00
Harpagide		Scrophulariae Radix	8 (8.00%)	3.59–4.86
Imperatorin		Angelicae Dahuricae Radix	8 (4.00%), 11 (16.00%), 12 (5.05%), 18[c], 23 (5.08%), 35 (5.71%), 36 (7.69%)	0.75–1.37
Papaverine		Papaveris Pericarpium	37 (31.05%)	0.10–0.33
Geniposide		Gardeniae Fructus	3[c], 7[c], 9 (1.89%), 32[c]	26.25–60.28
Catalpol		Rehmanniae Radix	19[c], 20[c] 30 (9.09%)	2.03–11.40
Salidroside		Rhodiolae Crenulatae Radix Et Rhizoma	6[c]	7.83–11.09
Morphine		Papaveris Pericarpium	37 (31.05%)	0.32–0.93
Atractylenolide I		Atractylodis Macrocephalae Rhizoma	9 (1.89%), 12 (10.10%)	1.93–2.54

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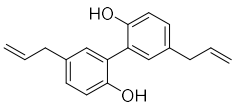
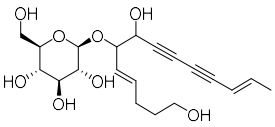
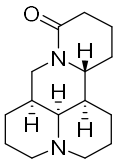
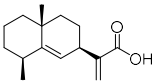
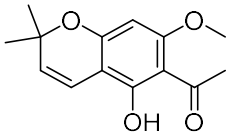
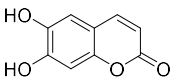
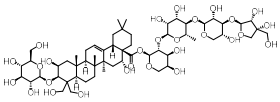
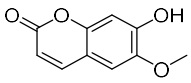
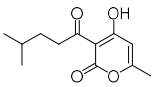
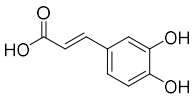
Magnolol		Magnoliae Officinalis Cortex	11 (10.66%), 12 (10.10%)	9.50–67.80
Lobetyolin		Codonopsis Radix Lobeliae Chinensis Herba	Codonopsis Radix: 2 (11.52%) Lobeliae Chinensis Herba: 15[c]	29.50–59.40
Matrine		Sophorae Tonkinensis Radix et Rhizoma	18[c]	0.24–9.62
Pterodontic acid		Laggerae Herba	14 (100%)	Unknown
Isoevodionol		Evodia Lepta	16[c]	4.77
Esculetin		Violae Herba	15[c]	2.02–3.67
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
Scopoletin		Lycii Cortex	30 (9.09%)	0.07
Dhelwangin		Pogostemonis Herba	6[c], 11 (5.33%), 12 (15.15%), 19[c], 20[c], 30 (9.09%)	1.35–5.71
Caffeic acid		Taraxaci Herba	15[c]	1.84

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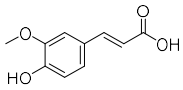
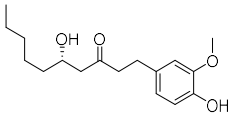
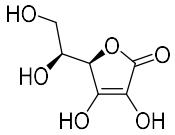
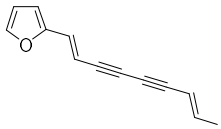
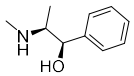
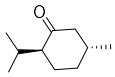
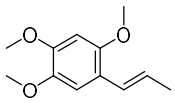
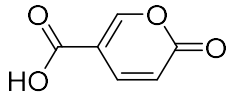
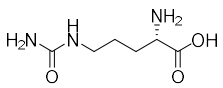
Ferulic acid		Phragmitis Rhizoma Angelicae Sinensis Radix	Phragmitis Rhizoma: 1[c], 19[c], 20[c], 23 (8.47%), 26 (10.21%) Angelicae Sinensis Radix: 9 (3.77%), 35 (5.71%)	0.46–1.65
6-Gingerol		Zingiberis Rhizoma Recens	2 (11.52%), 12 (1.51%), 22 (5.88%), 36 (7.69%)	9.96–28.64
L(+)–Ascorbic acid				
Atractylodin		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
α–Asarone		Acori Tatarinowii Rhizoma	19[c], 20[c], 35 (2.86%)	0.84–1.07
Coumalic acid		Phragmitis Rhizoma	1[c], 19[c], 20[c], 23 (8.47%), 26 (10.21%)	7.00–12.10
Citrulline		Trichosanthis Radix	8 (8.00%)	20.20–60.20

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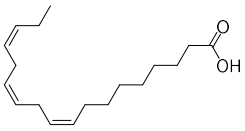
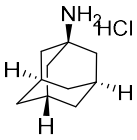
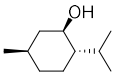
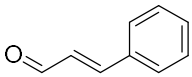
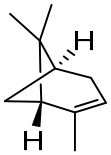
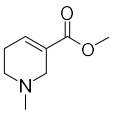
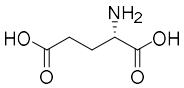
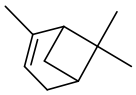
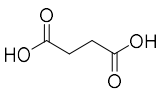
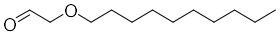
Linolenic acid		Perillae Folium	11 (2.67%), 12 (5.05%), 22 (5.88%), 23 (5.08%), 36 (11.54%)	0.09–0.68
Amantadine Hydrochloride				
L-Menthol		Menthae Haplocalycis Herba	9 (3.77%), 16[c], 23 (5.08%), 25 (10.71%), 26 (4.73%), 27[c], 30 (6.06%), 33 (10.71%), 34[c], 35[c], 1[c], 37 (3.72%)	25.76–226.10
trans–Cinnamaldehyde		Cinnamomi Ramulus	22 (8.82%), 35 (8.57%), 36 (7.69%)	12.70–16.02
β–Pinene		Forsythiae Fructus Oil	27[c], 34[c]	2.40–9.34
Arecoline		Arecae Pericarpium	11 (16.00%), 12 (5.05%)	1.92–3.80
Glutamic acid		Bubali Cornu	32[c]	2.25
α–Pinene		Forsythiae Fructus Oil	27[c], 34[c]	0.75–3.00
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%

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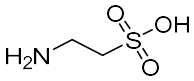
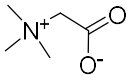
Taurine		Lycii Cortex	30 (9.09%)	3.12–6.20
Betaine		Lycii Cortex	30 (9.09%)	5.40–10.10

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

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

[c] Unknown.