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

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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.
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.
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
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,
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
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 results 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.

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Competing interest statement

The authors declare no conflict of interest.

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| 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       |
| 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 |
| Substance                  | Value 1 | Value 2 | Value 3 |
|----------------------------|---------|---------|---------|
| 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   |
| Columbianadina             | -7.2    | -9.6    | -16.8   |
| Arctiin                    | -7.3    | -9.5    | -16.8   |
| Oleanic acid               | -7.4    | -9.3    | -16.8   |
| 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   |
| Andrographolid             | -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   |
| Compound                  | Value1 | Value2 | Value3 |
|---------------------------|--------|--------|--------|
| 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  |
| Atractyloidin             | -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  |
| Ligand                | Docking score (kcal/mol) |
|----------------------|--------------------------|
|                      | 6LU7 | 1R4L | SUM    |
| 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             | 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                     |
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         | ![Structure](structure1.png) | Citri Reticulatae Pericarpium | 11 (10.66%), 12 (10.10%), 36 (7.69%) | 21.60–75.70 |
| Saikosaponin A     | ![Structure](structure2.png) | Bupleuri Radix | 2 (30.86%), 8 (4.00%), 23 (8.47%) | 3.93–7.80 |
| Rutin              | ![Structure](structure3.png) | Mori Folium | 1$^c$, 28 (23.18%) | 0.32–3.25 |
| Corosolic acid     | ![Structure](structure4.png) | Eriobotryae Folium | 34 (42.86%) | 7.64 |
| Verbascoside       | ![Structure](structure5.png) | Rehmanniae Radix | 19$^c$, 20$^c$, 30 (9.09%) | 0.39–0.42 |
**Baicalin**

Scutellariae Radix 2 (11.52%), 3, 7, 9 (7.55%), 10 (50.00%), 24 (14.29%), 32, 35 (11.43%) 99.40–183.20

**Glycyrrhizin**

Glycyrrhizae Radix et Rhizome 2 (11.52%), 6, 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 4.97–13.14

**Cynaroside**

Lonicerae Flos 26 (17.01%) 5.1–9.4

**Bilirubin**

Atificial Cow–bezoar 38 6.7–9.1

**Vincetoxicosid e 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, 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

Cynancersicosi de 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-\(\text{O-glucosylcimifugin}\) (Saposhnikovi ae 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
Paeoniflorin

Paeoniae Radix Rubra: 8 (4.00%), 17 (42.87%) 20.00–25.00

Polyphyllin I

Paridis Rhizoma 18c 2.87–10.10

Nodakenin

Notopterygii Rhizoma Et Radix 5c, 8 (6.00%), 16c, 35 (5.71%) 0.50–28.60

Tectoridin

Iridis Tectori Rhizoma 18c 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

Phellodendr i Chinensis Cortex 7c 17.76–80.32

Timosaponin BII

Anemarrhena e Rhizoma 19c, 20c 50.00–92.50
Dryocrassin (Dryopteridis Crassirhizomatous Rhizoma)

Columbianadin (Angelicae Pubescentis Radix)

Arctiin (Arctii Fructus)

Oleanic acid (Helicteres Angustifolia)

Luteolin (Lonicerae Japonicae Caulis)

Quercetin (Desmodium Triquetrum)

Forsythiaside A (Forsythiae Fructus)
Radix isatidis  
\[\text{Isatidis Radix} \]
\[1^\text{c}, 3^\text{c}, 5^\text{c}, 6^\text{c}, 7^\text{c}, 15^\text{c}, \text{No report}\]

Genistein  
\[\text{Sojae Semen Praeparatum} \]
\[25 (8.93\%), 26 (8.51\%), 33 (8.93\%) \]
\[29.38\pm11.65\]

Indirubin  
\[\text{Isatidis Folium} \]
\[8^\text{c}, 21 (60.00\%), 30 (15.15\%) \]
\[0.02–4.15\]

Curcumin  
\[\text{Curcumae Radix} \]
\[19^\text{c}, 20^\text{c} \]
\[0.84–1.12\]

Trisalbaspidin  
\[\text{Dryopteris Setosa} \]
\[18^\text{c} \]
\[17.8\]

Artemisinin  
\[\text{Artemisiae Annuae Herba} \]
\[5^\text{c} \]
\[1.91–5.19\]

Emodin  
\[\text{Rhei Radix Et Rhizoma} \]
\[6^\text{c}, 9 (3.77\%) \]
\[0.29–0.66\]

Cholic acid  
\[\text{Cholic acid} \]
\[3^\text{c}, 32^\text{c} \]

Hyodeoxycholic acid  
\[\text{Hyodeoxycholic acid} \]
\[3^\text{c}, 32^\text{c} \]

Daidzein  
\[\text{Sojae Semen Praeparatum} \]
\[25 (8.93\%), 26 (8.51\%), 33 (8.93\%) \]
\[18.69\pm1.28\]
Xanthiside

Massa Medicata Fermentata 1c 1.52–3.79

Lonicerae Japonicae Flos: 3c, 6c, 10
Lonicera Japonicae (25.00%), 17
(42.87%), 24
(42.86%), 25
(17.86%), 27c, 32c, 33
(17.86%), 34c
Chrysanthemi Flos: 28
(10.59%), 30 (9.09%)

Chlorogenic acid

Verbenalin

Verbenae Herba 5c 1.52–3.35

Poricoic acid A

Poria 11 (16.00%), 12
(5.05%) 0.24–0.40

Andrographolide

Andrographi s Herba 16c 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
Notopterol 
*Notopterygii Rhizoma Et Radix*  
5°, 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°, 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°, 7°, 9 (1.89%), 32 26.25–60.28

Catalpol 
*Rehmanniae Radix*  
19°, 20° 30 (9.09%)  
2.03–11.40

Salidroside 
*Rhodiolae Crenulatae Radix Et Rhizoma*  
6°  
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
Magnolol 11 (10.66%), 12 (10.10%) 9.50–67.80

Lobetyolin Codonopsis Radix: 2 (11.52%) 29.50–59.40

Matrine Sophorae Tonkinensis Radix et Rhizoma 18c 0.24–9.62

Pterodontic acid Lagerae Herba 14 (100%) Unknown 4.77

Isoevodionol Evodia Lepta 16c 2.02–3.67

Esculetin Violae Herba 8 (6.00%), 9 (7.55%), 12 (10.10%), 22 (5.88%), 23 (5.08%), 25 (10.71%), 26 (10.21%), 35 (5.71%), 36 (7.69%), 37 (3.72%) 1.85–4.06

Platycodin D Platycodonis Radix 25 (10.71%), 26 (10.21%), 33 (10.71%), 35 (5.71%), 36 (7.69%), 37 (3.72%) 1.35–5.71

Scopoletin Lycii Cortex 30 (9.09%) 0.07

Dhelwangin Pogostemonis Herba 6c, 11 (5.33%), 12 (15.15%), 19c, 20c, 30 (9.09%) 1.35–5.71

Caffeic acid Taraxaci Herba 15c 1.84
| Compound          | Source                          | Concentration          | Value       |
|-------------------|---------------------------------|------------------------|-------------|
| Ferulic acid      | Phragmites Rhizoma:             | 1, 19, 20, 23          | 0.46–1.65   |
|                   | Angelicae Sinensis Radix:       |                        |             |
|                   | 1, 19, 20, 23                   | 8.47%, 26 (10.21%)     |             |
| 6-Gingerol        | Zingiberis Rhizoma:             | 2, 12                  | 9.96–28.64  |
|                   | Recens                          | 36                     |             |
| L(+)-Ascorbic acid| Atractylodis Rhizoma:           | 11                     | 3.98–10.96  |
| Atractylodin      | Ephedrae Herba:                 | 13, 22, 35             | 4.80–10.20  |
| Ephedrine         | Ephedrae Herba:                 | 13, 22, 35             | 4.80–10.20  |
|                   | 6c                              | 1 (1.89%), 23          |             |
|                   | Schizonepetae Spica:            | 26, 27, 33             | 294.27–754.02|
| Pulegone           | Schizonepetae Spica:            | 26, 27, 33             | 294.27–754.02|
|                   | 7.14%, 34, 35                   | (7.14%), 34, 35        |             |
|                   | Acori Tatarinowii Rhizoma:      | 19, 20, 35             | 0.84–1.07   |
| α-Asarone          |                                 | 19, 20, 35             | 0.84–1.07   |
| Coumalic acid     | Phragmites Rhizoma:             | 1, 19, 20, 23          | 7.00–12.10  |
| Citrulline        | Trichosanthis Radix:            | 8                      | 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

Amantadine Hydrochloride

9 (3.77%), 16°, 23 (5.08%), 25 (10.71%), 26 (4.73%), 27°, 30 (6.06%), 33 (10.71%), 34°, 35°, 1°, 37 (3.72%)

25.76–226.10

L-Menthol

Menthae Haplocalycis Herba

9 (3.77%), 16°, 23 (5.08%), 25 (10.71%), 26 (4.73%), 27°, 30 (6.06%), 33 (10.71%), 34°, 35°, 1°, 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°, 34°

2.40–9.34

Arecoline

Arecae Pericarpium

11 (16.00%), 12 (5.05%)

1.92–3.80

Glutamic acid

Bubali Cornu

32°

2.25

α–Pinene

Forsythiae Fructus Oil

27°, 34°

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°, 18°

Volatile oils

7.2%
Taurine

\[
\text{H}_2\text{N} \xrightarrow{\text{SO}_{3}^\text{H}} \text{Lycii Cortex} 30 \text{ (9.09%)} \quad 3.12–6.20
\]

Betaine

\[
\text{N} \xrightarrow{\text{CH}_{3}} \text{Lycii Cortex} 30 \text{ (9.09%)} \quad 5.40–10.10
\]

\(a\) The number of Chinese patent drugs is same as that in table 1.

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

\(c\) Unknown.