Supplementary Materials

Mining of 97 abnormal pain prescriptions

For 97 abdominal pain prescriptions, it was found that the top ten herbs in THScore are Gancao, Fuling, Baishao, Danggui, Huanglian, Chaihu, Danshen, Baizhu and Chenpi (Fig. S1A). Gancao has the highest THScore and most related literatures (No.=1371). Traditional Chinese medicine assumes that Gancao can relieve pain. Modern science has proven that Gancao can relieve gastrointestinal smooth muscle spasm and relieve pain [1]. The second-ranked herb is Fuling, which may be related to its sedative effect [1]. The third-ranked herb is Baishao. The mechanism is that Radix Paeoniae Rubra and Gancao have a synergistic analgesic effect on writhing reactions [1].

In the related literature on abdominal pain, Dahuang has the second-highest frequency of occurrence, with a total of 1200, but it is not in the top 10 of THScore. This may be due to the side effects of Dahuang itself, which can easily cause digestive system discomfort [1]. It is clinically applied the scope is smaller. After reviewed the literatures and we found that the relevant literatures are mainly about animal experiments. A correaltion analysis showed that THScore of top 100 herbs are highly consistent with the number of queried literatures on CNKI using headache and each herb as the keyword(cor=0.77, pvalue<0.0001).

The top 10 of the herb pairs analysis table(Fig. S1B) contains the classic drug pairs of Baishao and Gancao. The main component of Radix Paeoniae Rubra is paeoniflorin, which works synergistically with Gancao, can significantly inhibit the contraction of smooth muscle and skeletal muscle, and has a good antispasmodic and analgesic effect on the pain caused by muscle spasm [2]. The number one Shenqu and Sharen are rarely recorded in the literature. This could be a novel drug pair, synergy mechanism of which deserved to be further explored.

Besides, Among top 10 significant symptoms-herb associations (Fig. S1C), there are more than 2,000 literatures on treatment of rapid pulse by Huangqin. The mechanism is that the sedative effect of Huangqin is reducing heart rate [1,3].

Mining of 125 hiccup prescriptions

For 125 hiccup prescriptions, it was found that the top ten herbs in THScore are Gancao, Chenpi, Renshen, Dingxiang, Banxia, Baizhu, Fuling, Shidi, Muxiang ,and Zhuru (Fig. S2A). The first-ranked is Gancao, who has the effect of relieving smooth muscle spasm [1]. The second-ranked is Chenpi, who have be proved have the effect of relaxing muscles [1]. And the third-ranked is Renshen, which can improve human immunity. TCM assumes that one of the causes of hiccups is frailty, while Renshen has the effect of improve these symptoms[1,4].

In the herb pairs analysis(Fig. S2B), the top-10 herb pairs contain two classic herb pairs: Renshen and Baizhu, Dingxiang and Shidi. TCM assumes that Renshen and Baizhu macrocephala have a synergistic effect, which can improve human immunity, strengthen physique, and achieve the purpose of treating hiccups [5]. The ginsenoside Rg1 contained in Renshen can replenish vitality of spleen and lungs, and can significantly improve the immune function [6]. Baizhu I contained in Baizhu macrocephala is the effective component of invigorating the spleen[7], and Baizhu lactones can inhibit gastrointestinal motility and antispasmodic effects in rats[8]. Traditional Chinese medicine assumes that Dingxiang is an important herb for hiccups. Its active ingredient, volatile oil, can stimulate the secretion of gastric acid and pepsin, there it can help digestion, increase gastrointestinal motility, reduce abdominal distension, and relieve hiccups[9]. The carbohydrate compound contained in Shidi pedicle can inhibit diaphragm contraction and treat hiccups [10].

In the symptom-herb analysis**(Fig. 2C)**, the top 10 symptom-herb association include vomiting and Gancao, a total of 1451 related literatures. In addition, Renshen treatment of stomach deficiency [11], Dingxiang treatment of stomach cold [12], all are proved to have mechanism evidence.

Supplemental Figures

Figure S1 Cross-validation for abdominal pain prescription mining results. 97 prescriptions of abdominal pain were collected from *Chinese Medicine Prescriptions Dictionary* and *TCM Knowledge Database (Zhong Yi Zhi Ku)*. A: Her importance rank. The left is top 10 THScore-ranked herb. The right are the correlation analysis of THScore and number of literatures for top 100 ranked herb. B. Herb-herb co-occurrence (Co-occurrence Level=4, Co-occurrence event ⩾ 10, top 10 ranked by Co_ratio). C. Symptom-herb associations (Co-occurrence event ⩾ 5, top 10 ranked by symptom-herb association).

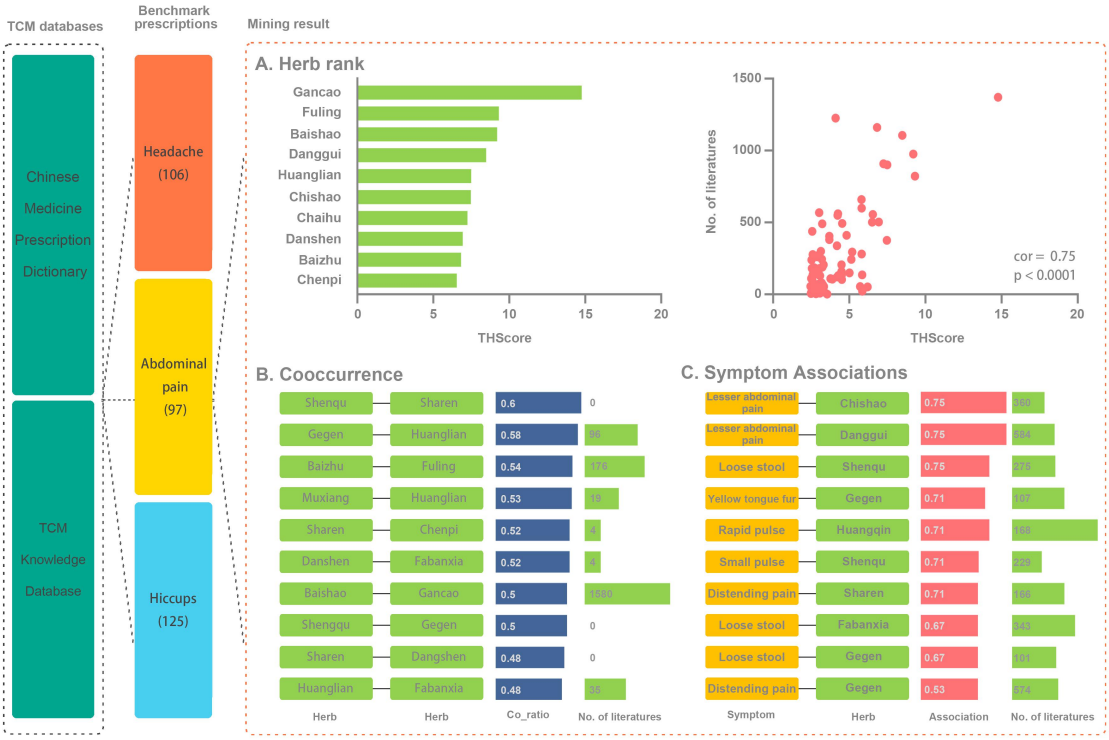
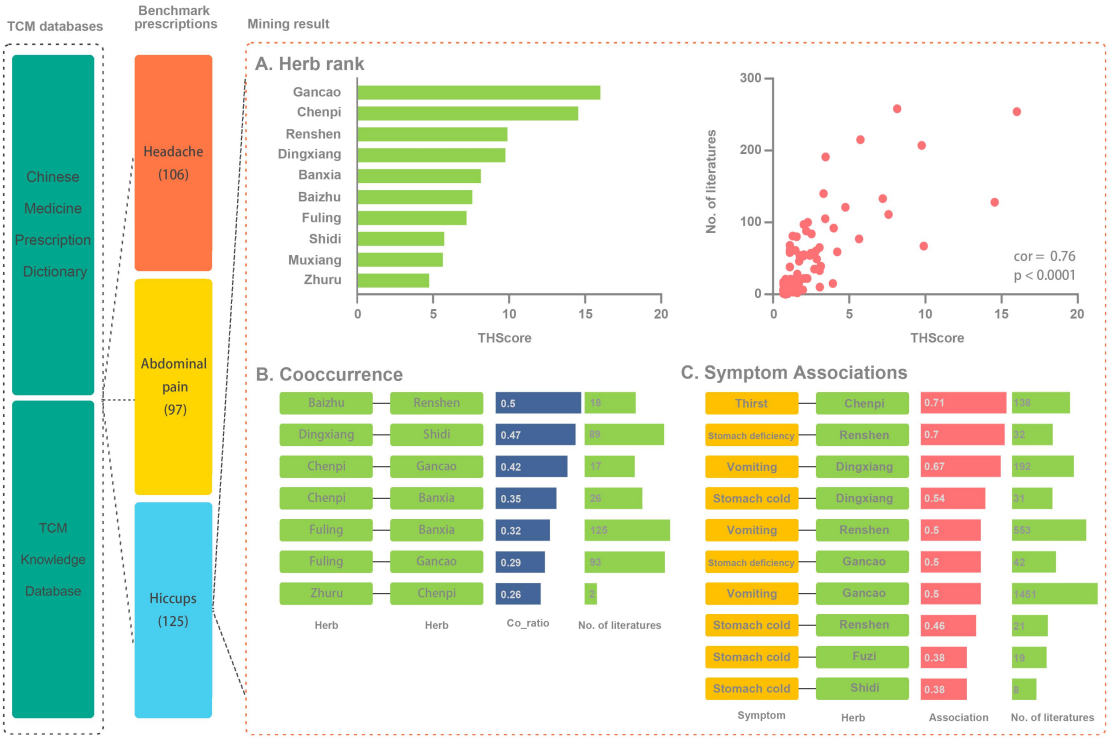


Figure S2 Cross-validation for hiccups prescription mining results. 125 prescriptions of hiccups were collected from *Chinese Medicine Prescriptions Dictionary* and *TCM Knowledge Database (Zhong Yi Zhi Ku)*. A: Her importance rank. The left is top 10 THScore-ranked herb. The right are the correlation analysis of THScore and number of literatures for top 100 ranked herb. B. Herb-herb co-occurrence (Co-occurrence Level=4, Co-occurrence event≥10, 7 herb-herb pairs are filtered). C. Symptom-herb associations (Co-occurrence event≥5, top 10 ranked by symptom-herb association).



Supplementary Tables

Table S1. Level defined by **Co-occurrence ratio and P value**.

Co-occurrence ratio	P value	Level
[0,0.001]	[0,0.01]	-4
(0.001,0.002]	[0,0.01]	-3
(0.002,0.005]	[0,0.01]	-2
(0.005,0.01]	[0,0.01]	-1
[0.1,0.15)	[0,0.01]	1
[0.15,0.2)	[0,0.01]	2
[0.2,0.25)	[0,0.01]	3
[0.25,1)	[0,0.01]	4

Table S2. Count and Frequency of the top 10 herb(Headache).

Herb	Support	THscore	Dosage_SD	Cooccurrence	Classification
Chuanxiong	0.63	15.27	5.18	Danggui/Baizhi	driver
Baishao	0.42	11.59	14.85	Gouteng	driver
Gancao	0.44	11.49	4.17	NA	driver
Danshen	0.26	7.55	7.63	Chishao/Quanxie	driver
Fuling	0.26	7.41	7.34	Baizhu	driver
Tianma	0.29	7.33	2.55	Duzhong/Gouteng/Zaoren	driver
Gouteng	0.24	7.09	7.66	Tianma/Baishao	driver
Danggui	0.28	7.03	2.43	Chuanxiong /Baizhu	driver
Shengdi	0.28	6.83	4.41	NA	driver
Juhua	0.25	6.40	2.93	NA	driver

Table S3.12 herb pairs with high level of co-occurrence and mutual exclusivity(Headache).

Herb1	Herb2	Co_ratio	pValue	Co_event	Ex_event	Total_event	Co_level
Danggui	Chuanxiong	0.42	1.6E-05	28	40	68	4
Gouteng	Tianma	0.40	3.4E-05	16	24	40	4
Baizhi	Chuanxiong	0.34	6.7E-05	23	44	67	4
Baizhu	Danggui	0.32	4.9E-04	12	25	37	4
Gouteng	Baishao	0.32	5.0E-03	17	36	53	4
Chishao	Danshen	0.32	2.0E-03	12	26	38	4
Fuling	Baizhu	0.31	1.3E-03	11	25	36	4
Tianma	Duzhong	0.30	2.0E-04	10	24	34	4

Zaoren	Tianma	0.29	5.7E-04	10	25	35	4
Quanxie	Danshen	0.28	6.1E-03	10	26	36	4
Gancao	Zhuru	0	4.2E-03	0	56	56	-4
Chuanxiong	Zhizi	0	6.5E-03	0	71	71	-4

Table S4. 10 significant associations between symptom and herb(Headache).

Symptom	Herb	Association	Event	Symptom_support	Herb_support
Tight pulse	Shengjiang	0,75	6	0.75	0.22
Palpitation	Gegen	0.71	5	0.66	0.20
Poor sleep	Juhua	0.71	5	0.66	0.25
Flusteredness	Danshen	0.71	5	0.07	0.26
Insomnia	Shengdi	0.67	6	0.08	0.27
Fatigue	Baishao	0.83	5	0.06	0.42
Dry Mouth	Chaihu	0.53	8	0.14	0.20
Distending pain	Gancao	0.75	6	0.08	0.44
Tight pulse	Gancao	0.75	6	0.08	0.44

Table S5. Count and Frequency of the top 10 herb (abdominal pain).

Herb	Support	THScore	Class	No.of literature
Gancao	0.68	14.77	driver	1,371
Fulin	0.42	9.32	driver	822
Baishao	0.42	9.21	driver	976
Danggui	0.27	8.49	driver	1,106
Huanglian	0.30	7.50	driver	901
Choshao	0.25	7.47	driver	376
Chaihu	0.30	7.25	driver	908
Dangshen	0.30	6.94	driver	503
Baizhu	0.34	6.83	driver	1,161
Chenpi	0.33	6.55	driver	556

Table S6.10 herb pairs with high level of co-occurrence and mutual exclusivity (abdominal pain).

Herb1	Herb2	pValue	Co_event	Ex_event	Total_event	Level	No.of literature
Baishao(Shaoyao)	Gancao	0.001	29	29	58	4	68
Baizhu	Fulin	0.001	21	18	39	4	176
Gancao	Gegen	0.001	17	37	54	4	24
Dangshen	Fulin	0.001	17	23	40	4	10
Muxiang	Huanglian	0.001	16	14	30	4	19
Dangshen	Baizhu	0.001	16	19	35	4	25
Shenqu	Gancao	0.001	16	38	54	4	1
chenpi	Fulin	0.01	16	26	42	4	4

Gegen	Huanglian	0.001	15	11	26	4	96
Huanglian	huangqin	0.001	15	19	34	4	267

TableS7. 10 significant associations between symptom and herb (abdominal pain).

Symptom	Herb	Association	Event	Symptom_support	Herb_support	index	No.of literature
lesser abdominal pain	Chishao	0.83	5	0.07	0.25	0.62	18
lesser abdominal pain	Danggui	0.83	5	0.07	0.27	0.61	44
loose stool	Shenqu	0.67	6	0.10	0.20	0.53	47
yellow tongue fur	Gegen	0.63	5	0.09	0.22	0.49	105
rapid pulse	Huangqi	0.67	8	0.13	0.32	0.46	2031
small pulse	Shenqu	0.56	9	0.17	0.20	0.45	14
distending pain	Shanren	0.56	5	0.10	0.20	0.44	106
loose stool	Fabanxia	0.56	5	0.10	0.22	0.44	274
loose stool	Gegen	0.56	5	0.10	0.22	0.44	51
distending pain	Gegen	0.56	5	0.10	0.22	0.44	61

Table S8. Count and Frequency of the top 10 herb (hiccups).

Herb	Support	THScore	Class	No.of literature
Gancao	0.48	64.04	driver	254
Chenpi	0.44	58.21	driver	128
Renshen	0.36	39.58	driver	67
Dingxiang	0.32	39.04	driver	207
Banxia	0.23	32.59	driver	258
Baizhu	0.23	30.31	driver	111
Fuling	0.20	28.83	driver	133
Shidi	0.20	22.94	driver	215
Muxiang	0.15	22.61	driver	77
Zhuru	0.13	19.01	driver	121

Table S9. 7 herb pairs with high level of co-occurrence and mutual exclusivity (hiccups).

Herb1	Herb2	Co_ratio	pValue	Co_event	Ex_event	Total_event	Level	No.of literature
Baizhu	Renshen	0.50	0.001	25	25	50	4	18

Dingxiang	Shidi	0.47	0.001	21	24	45	4	89
Chenpi	Gancao	0.42	0.01	34	47	81	4	17
Chenpi	Banxia	0.35	0.001	22	40	62	4	26
Fuling	Banxia	0.32	0.001	13	28	41	4	125
Fuling	Gancao	0.29	0.001	19	47	66	4	93
Zhuru	Chenpi	0.26	0.001	15	42	57	4	2

TableS10. 10 significant associations between symptom and herb (hiccups).

Symptom	Herb	Association	Event	Symptom_support	Herb_support	index	No.of literature
Vomiting	Dingxiang	0.67	8	0.10	0.32	0.45	192
Stomach deficiency	Renshen	0.70	7	0.08	0.37	0.44	32
thirst	Chenpi	0.71	5	0.06	0.44	0.40	138
Stomach cold	Dingxiang	0.54	7	0.10	0.32	0.37	31
Stomach cold	Fuzi	0.38	5	0.10	0.13	0.34	19
Vomiting	Renshen	0.50	6	0.10	0.37	0.32	553
Stomach cold	Shidi	0.38	5	0.10	0.21	0.30	8
Stomach cold	Renshen	0.46	6	0.10	0.37	0.29	21
Stomach deficiency	Gancao	0.50	5	0.08	0.48	0.26	42
Vomiting	Gancao	0.50	6	0.10	0.48	0.26	1451

Table S11. Count and Frequency of the top 50 herb.

Herb	Count	Frequency
Danggui	2241	0.36
Fuling	2143	0.34
Gancao	2119	0.34
Baizhu	2097	0.33
Dangshen	1639	0.26
Baishao	1583	0.25
Danshen	1555	0.25
Chucmxiong	1416	0.23
Chenpi	1272	0.20
Chaihu	1256	0.20
Huangqin	1242	0.20
NA	1062	0.17
Zhiqiao	986	0.16
Chishao	976	0.16
Zhigancao	873	0.14

Yujin	823	0.13
Wuweizi	815	0.13
Ezhu	798	0.13
Huanglian	797	0.13
Maidong	767	0.12
Guizhi	717	0.11
Sharen	715	0.11
Jiegeng	692	0.11
Taoren	677	0.11
Nuzhenzi	664	0.11
Taizishen	652	0.10
Gouqizi	636	0.10
Yiyiren	633	0.10
Yuanzhi	623	0.10
Fangfeng	612	0.10
Suanzaoren	598	0.10
Honghua	595	0.09
Xiangfu	586	0.09
Houpo	579	0.09
Zexie	574	0.09
Gegen	562	0.09
Zhishi	533	0.08
Lianqicio	520	0.08
Fabanxia	499	0.08
Yimucao	482	0.08
Tusizi	463	0.07
Pugongying	459	0.07
Zhimu	448	0.07
Huangbo	444	0.07
Muli	444	0.07
Muxiang	444	0.07
Banxia	441	0.07
Tianma	439	0.07
Duzhong	425	0.07

Table S12. 27 herb pairs with high level of co-occurrence and mutual exclusivity

Herb1	Herb2	Interaction	Event	pValue	Event_ ratio	Class	Nember in the CNKI
Honghua	Taoren	0.47	Co_Occurence	6.86E-296	401/459	4	74
Baizhu	Fuling	0.37	Co_Occurence	1.08E-129	1116/1917	4	175
Baizhu	Dangshen	0.33	Co_Occurence	2.61E-138	856/1737	4	25

Maidong	Wuweizi	0.31	Co_Occurence	4.69E-161	378/824	4	5
Chucmxiong	Danggui	0.31	Co_Occurence	2.45E-120	791/1759	4	195
Gouqizi	Nuzhenzi	0.29	Co_Occurence	3.08E-133	247/609	4	3
Tusizi	Shudihuang	0.29	Co_Occurence	9.16E-117	170/423	4	3
Chucmxiong	Honghua	0.28	Co_Occurence	7.16E-174	426/1080	4	28
Fuling	Chenpi	0.28	Co_Occurence	1.01E-86	729/1914	4	4
Baishao	Danggui	0.27	Co_Occurence	2.74E-57	765/2051	4	25
Chenpi	Baizhu	0.27	Co_Occurence	7.84E-77	696/1915	4	11
Tusizi	Gouqizi	0.27	Co_Occurence	9.40E-111	186/515	4	2
Fuling	Shanyao	0.26	Co_Occurence	1.43E-96	646/1850	4	18
Taoren	Chuanxiong	0.25	Co_Occurence	2.95E-125	407/1193	4	11
Yuanzhi	Suanzaoren	0.25	Co_Occurence	1.96E-106	245/721	4	9
Dangshen	Fuling	0.25	Co_Occurence	8.22E-48	704/2106	4	8
Danggui	Baizhu	0.25	Co_Occurence	1.58E-19	810/2424	4	28
Banxia	Fabanxia	0.00	Mutually_Exclusive	7.54E-17	0/939	-4	1
Jineijin	Shudihuang	0.00	Mutually_Exclusive	3.14E-09	0/696	-4	0
Zhizi	Zhishi	0.00	Mutually_Exclusive	1.93E-12	1/873	-3	0
Xiakucao	Fabanxia	0.00	Mutually_Exclusive	1.56E-11	1/836	-3	0
Yimucao	Muxiang	0.00	Mutually_Exclusive	5.84E-11	1/804	-3	0
Chuanniuxi	Muxiang	0.00	Mutually_Exclusive	1.68E-09	1/761	-3	0
Dilong	Jiangcan	0.00	Mutually_Exclusive	1.51E-08	1/721	-3	0
Huangjing	Tusizi	0.00	Mutually_Exclusive	3.16E-08	1/705	-3	0
Bajitian	Rougui	0.00	Mutually_Exclusive	7.48E-08	1/695	-3	0
Xiakucao	Rougui	0.00	Mutually_Exclusive	8.47E-07	1/644	-3	1

Table S13. 76 significant associations between symptom and herb

Symptom	Herb	Symptom_ count	Herb_ count	Symptom_ herb_count	Ratio

Thin Nasal Secretion	Jiegeng	33	692	20	0.61
Nasal Obstruction	Jiegeng	33	692	20	0.61
Rhinocnesmus	Jiegeng	33	692	20	0.61
Purulent Nasal Discharge	Chaihu	51	1256	33	0.65
Purulent Nasal Discharge	Huangqin	51	1242	33	0.65
Purulent Nasal Discharge	Dilong	51	364	31	0.61
Purulent Nasal Discharge	Baizhi	51	312	36	0.71
Epistaxis	Chaihu	51	1256	33	0.65
Epistaxis	Huangqin	51	1242	33	0.65
Epistaxis	Dilong	51	364	31	0.61
Epistaxis	Baizhi	51	312	36	0.71
Sputum	Huangqin	61	1242	50	0.82
Sputum	Qingbanxia	61	247	44	0.72
Sputum	Gualou	61	305	45	0.74
Sputum	Dilong	61	364	49	0.80
Sputum	Zisuzi	61	83	49	0.80
Sputum	Qianhu	61	204	46	0.75
Sputum	Kuandonghua	61	96	44	0.72
Sputum	Baiqian	61	124	45	0.74
Dyspnea	Huangqin	61	1242	50	0.82
Dyspnea	Qingbanxia	61	247	44	0.72
Dyspnea	Gualou	61	305	45	0.74
Dyspnea	Dilong	61	364	49	0.80
Dyspnea	Zisuzi	61	83	49	0.80
Dyspnea	Qianhu	61	204	46	0.75
Dyspnea	Kuandonghua	61	96	44	0.72
Dyspnea	Baiqian	61	124	45	0.74
Neck Pain	Danggui	41	2241	34	0.83
Neck Pain	Danshen	41	1555	34	0.83
Neck Pain	Xiangfu	41	586	30	0.73
Neck Pain	Gancao	41	2119	30	0.73
Neck Pain	Tianma	41	439	33	0.80
Neck Pain	Guizhi	41	717	31	0.76
Neck Pain	Gegen	41	562	32	0.78
Neck Pain	Zexie	41	574	31	0.76
Neck Pain	Jianghuang	41	94	30	0.73
Neck Pain	Chishao	41	976	35	0.85
Lumbodynia	Tufuling	94	305	60	0.64
Lumbodynia	Baimaogen	94	189	65	0.69
Fatigue	TUfuling	94	305	60	0.64
Fatigue	Baimaogen	94	189	65	0.69
Facial Paralysis	Dangshen	54	1639	47	0.87
Facial Paralysis	Lianqiao	54	520	45	0.83

Facial Paralysis	Huangqin	54	1242	46	0.85
Facial Paralysis	Banlangen	54	102	45	0.83
Facial Paralysis	Quanxie	54	293	48	0.89
Facial Paralysis	Jiangcan	54	373	46	0.85
Facial Paralysis	Baifuzi	54	63	43	0.80
Facial Paralysis	Jinyinhua	54	271	45	0.83
Facial Paralysis	Daqingye	54	80	46	0.85
Facial Paralysis	Xixin	54	189	46	0.85
Pain	Fuling	356	2143	253	0.71
Pain	Shanyao	356	1062	245	0.69
Peaud Orange	Baizhu	242	2097	150	0.62
Peaud Orange	Fuling	242	2143	208	0.86
Peaud Orange	Shanyao	242	1062	209	0.86
Breast Pain	Jiegeng	33	692	28	0.85
Breast Pain	Zaojiaoci	33	106	22	0.67
Poor Milk Discharge	Jiegeng	33	692	28	0.85
Poor Milk Discharge	Zaojiaoci	33	106	22	0.67
Headache	Chuanxiong	113	1416	90	0.80
Flaccidity of Muscles	Danggui	177	2241	142	0.80
Flaccidity of Muscles	Chenqi	177	1272	132	0.75
Flaccidity of Muscles	Fangfeng	177	612	107	0.60
Increased frequency of defecation：Increased defecation	Baizhu	56	2097	37	0.66
Loose Stool	Baizhu	56	2097	37	0.66
Failing to sleep due to dyspnea：Insomnia	Danshen	250	1555	151	0.60
Lumbodynia	Danshen	82	1555	52	0.63
Lumbodynia	Jixueteng	82	328	52	0.63
Lumbodynia	Duzhong	82	425	58	0.71
Maculopapules	Gancao	42	2119	26	0.62
Maculopapules	Difuzi	42	137	26	0.62
Depression	Baizhu	49	2097	33	0.67
Depression	Danggui	49	2241	34	0.69
Depression	Fuling	49	2143	34	0.69
Depression	Gancao	49	2119	32	0.65

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