Chinese herbal medicines for Rheumatoid Arthritis: text-mining the Classical literature for potentially effective natural products

Xuan Xia\textsuperscript{1,2}, Brian H May\textsuperscript{3}, Anthony Lin Zhang\textsuperscript{3}, Xinfeng Guo\textsuperscript{1,2}, Chuanjian Lu\textsuperscript{1,2}, Charlie C. Xue\textsuperscript{1,3}, Qingchun Huang\textsuperscript{1,2}

Affiliation

1. The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China
2. Department of Rheumatology and Immunology, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China.
3. China-Australia International Research Centre for Chinese Medicine, RMIT University, Bundoora, Victoria, Australia.

Supplementary materials

TABLE SUPP 1: Frequency of citations for formula interventions identified by the search terms at different stages in the selection procedure

| Search term in pin yin | Search term in Chinese | All data (after duplicate removal) | Included citations | Earliest dynasty | Earliest Book |
|-----------------------|------------------------|-----------------------------------|-------------------|-----------------|---------------|
| 1: Bi                 | 痹                    | 2147                              | 258               | Dong han dynasty | Jin Gui Yao Lue |
| 2: Li jie             | 历节                  | 473                               | 175               | Song dynasty    | Tai Ping Sheng Hui Fang |
| 3: Tong feng          | 痛风                  | 363                               | 89                | Song dynasty    | Ren Zhai Zhi Zhi Fang |
| 4: He xi feng         | 鹤膝风                | 150                               | 14                | Song dynasty    | Sheng Ji Zong Lu |
| 5: Bai hu bing        | 白虎病                | 11                                | 5                 | Ming dynasty    | Yi Xue Gang mu |
| 6: Ji zhua feng       | 鸡爪风                | 11                                | 2                 | Yuan dynasty    | Ren Shu Bian Lan |
| 7: Gu chui feng       | 鼓槌风                | 9                                 | 3                 | Ming dynasty    | Sun Wen Heng Yi An |
| 8: Wang               | 觊                    | 10                                | 2                 | Qing dynasty    | Yi Zong Jin Jian |
| Total                 |                       | 3174                              | 548               |                 |               |
**SUPP 2: Glossary of Pin yin, Chinese and scientific names for traditional medicines, books, formulas and other terms cited in the text and tables**

*Ben Cao Pin Hui Jing Yao* 本草品汇精要 (c. 1505), book name

*Ben Cao Gang Mu* 本草纲目 (c. 1593), book name

Bai fu ling 白茯苓, *Poria cocos* (Schw.) Wolf [sclerotium] (see Table 3)

bai hu bing 白虎病, disease name ‘white tiger disease’

bai hu li jie 白虎历节, disease name ‘white tiger joint disease’

Bai shao yao 白芍药 *Paeonia lactiflora* Pall. [radix] (see Table 3)

Bai zhu 白术, *Atractylodes macrocephala* Koidz [rhizome] (see Table 3)

Bai zhi 白芷, *Angelica dahurica* Fisch. ex Hoffm.Benth.et Hook.f [root] (see Table 3)

bi 痾, disease name ‘arthritis’ ‘painful obstruction’

Cao wu 草乌, *Aconitum kusnezoffii* Reichb. [root] (see Table 3)

Chuan niu xi 川牛膝, *Cyathula officinalis* Kuan [root] (see Table 3)

Chuan wu 川乌, *Aconitum carmichaelii* Debx [mother root]

Cang zhu 苍术, *Atractylodes lancea* Thunb.DC [rhizome] (see Table 3)

Chen pi 陈皮, *Citrus reticulata* Blanco [skin, peel] (see Table 3)

Chi fu ling 赤茯苓, *Poria cocos* (Schw.) Wolf [sclerotium] (see Table 3)

Chi shao yao 赤芍药 *Paeonia lactiflora* Pall. [radix] (see Table 3)

Chuan xiong 川芎, *Ligusticum wallichii* Franch [root] (see Table 3)

Dang gui 当归, *Angelica sinensis* Oliv. Diels [root] (see Table 3)

Dan dou chi 淡豆豉, *Glycine max* L. Merr [seed]

Da qiang huo tang 大羌活汤: formula name (see Table 2)

Da qin jiao tang 大秦艽汤: formula name (see Table 4)

Dang gui nian tong tang 当归拈痛汤: formula name (see Table 4)

Da zao 大枣, *Ziziphus jujuba* Mill [fruit]
Di huang, Rehmannia glutinosa Libosch. [root] (see Table 3)

Du huo ji sheng tang 独活寄生汤: formula name (see Table 4)

Du huo 独活, Angelica pubescens Maxim. f. biserrata Shan et Yuan [root] (see Table 3)

Da fu zi 大附子, Aconitum carmichaelii Debx. [root] (see Table 3)

Er miao san 二妙散: formula name (see Table 4)

Er chen tang 二陈汤: formula name (see Table 4)

Fu zi 附子, Aconitum carmichaelii Debx [processed root] (see Table 3)

Fang feng 防风, Saposhnikovia divaricata Turcz. Schischk [root] (see Table 3)

Fang ji huang qi tang 防己黄芪汤: formula name (see Table 2)

Fang ji 防已, Stephania tetrandra S. Moore [caulis] (see Table 3)

Fu shen 茯神, Poria cocos (Schw.) Wolf, [sclerotium] (see Table 3)

Fu ling 茯苓, Poria cocos Schw.Wolf [sclerotium] (see Table 3)

Fu zi ba wu tang 附子八物汤: formula name (see Table 2)

Gui pi tang 归脾汤: formula name (see Table 4)

Gan cao 甘草, Glycyrrhiza uralensis Fisch [root] (see Table 3)

Gan cao fu zi tang 甘草附子汤: formula name (see Table 2)

Gan di huang 干地黄, Rehmannia glutinosa Libosch. [root] (see Table 3)

Gan jiang 干姜, Zingiber officinale Rosc [rhizome]

Ge Zhi Yu Lun 格致余论 (c.1347) book name

Gu chui feng 鼓槌风, disease name ‘drum stick wind’

Gui zhi 桂枝, Cinnamomum cassia Presl [twig] (see Table 3)

Gui xin 桂心, Cinnamomum cassia Presl [bark]

Gui zhi shao yao zhi mu tang 桂枝芍药知母汤: formula name (see Table 2)

He xue san tong tang 和血散痛汤: formula name
Han fang ji 汉防己, *Stephania tetrandra* S. Moore [caulis] (see Table 3)

Huai niu xi 怀牛膝, *Achyranthes bidentata* Bl [root] (see Table 3)

Huang qi gui zhi wu wu tang 黄芪桂枝五物汤: formula name (see Table 4)

Hou pu 厚朴, *Magnolia officinalis* Rehd. et Wils; *M. officinalis* Rehd. et Wils. var. *biloba* Rehd. et Wils [Cortex]

Huang qi 黄芪, *Astragalus membranaceus* Fisch. *Bge. var. mongholicus* Bge.Hsiao [root] (see Table 3)

Huang bai 黄柏, *Phellodendron chinense* Schneid [cortex] (see Table 3)

Huang qin 黄芩, *Scutellaria baicalensis* Georgi [root] (see Table 3)

Jiang 姜, *Zingiber officinale* Rosc. [rhizome] (see Table 3)

Jin Gui Yao Lue Fang Lun 金匮要略方论 (c. 206) book name

Jie geng 桔梗, *Platycodon grandiflorum* Jacq. A. DC [root]

ji zhua feng 鸡爪风, disease name ‘chicken’s claw wind’

Juan bi tang 瘠痹汤: formula name (see Table 4)

Jing Shi Zheng Lei Da Guan Ben Cao 经史证类大观本草 (c. 1108) book name

Lei feng shi guan jie yan 类风湿关节炎: rheumatoid arthritis

Lei Zheng Zhi Cai 类证治裁 (c.1839) book name

Lei gong teng 雷公藤, *Tripterygium wilfordii* Hook F [all parts]

li jie (bing) 历节(病), disease name ‘joint disease’

li jie feng 历节风, disease name ‘joint wind’, ‘articular wind’

Long dan 龙胆, *Gentiana manshurica* Kitage; *G. scabra* Bge; *G. triflora* Pall; *G. rigescens* Franch [rhizome]

Ma huang 麻黄, *Ephedra sinica* Stapf; *E. equisetina* Bge; *E. intermedia* Schrenk et C.A. Mey [aerial parts] (see Table 3)

Mi Zhan Zheng Zhi Yao Jue Ji Lei Fang 秘传证治要诀及类方 (c.1443) book name

Ma huang fu zi xi xin tang 麻黄附子细辛汤: formula name (see Table 4)
Mu fang ji 木防己, *Cocculus orbiculatus* (L.) DC. [root]

Niu bang zi san 牛蒡子散: formula name (see Table 2)

Niu xi 牛膝, *Achyranthes bidentata* Bl [root] (see Table 3)

Niu bang zi 牛蒡子, *Arctium lappa* L [fructus] (see Table 3)

Pao jiang 炮姜, *Zingiber officinale* Rosc. [processed rhizome] (see Table 3)

Pao tian xiong 炮天雄, *Aconitum carmichaelii* Debx [processed root] (see Table 3)

*Pu Ji Fang* 普济方 (c.1406) book name: ‘Prescriptions for Universal Relief’

Qin jiao tang 秦艽汤: formula name (see Table 4)

Qiang huo sheng shi tang 羌活胜湿汤: formula name (see Table 4)

Quan xie 全蝎, *Buthus martensii* Karsch [scorpion]

Qiang huo 羌活, *Notopterygium incisum* Ting [root and rhizome] (see Table 3)

Qing feng teng 青风藤, *Sinomenium acutum* (Thunb.) Rehd. et Wils [caulis] (see Table 3)

Qin jiao 秦艽, *Gentiana macrophylla* Pall; *G. straminea* Maxim; *G. crassicaulis* Duthie ex Burk; *G. dahurica* Fisch [root] (see Table 3)

Ren shen 人参, *Panax ginseng* C. A. Mey [root] (see Table 3)

Rou gui 肉桂, *Cinnamomum cassia* Presl [cortex] (see Table 3)

San bi tang 三痹汤: formula name (see Table 4)

Sheng di huang 生地黄, *Rehmannia glutinosa* Libosch. [root] (see Table 3)

Sheng fu zi 生附子, *Aconitum carmichaelii* Debx [root] (see Table 3)

Sheng gan cao 生甘草, *Glycyrrhiza uralensis* Fisch [root] (see Table 3)

Shu di huang 熟地黄, *Rehmannia glutinosa* Libosch. [processed root] (see Table 3)

Shu fu zi 熟附子, *Aconitum carmichaelii* Debx [processed root] (see Table 3)

Si shen jian 四神煎: formula name (see Table 4)

Shen tong zhu yu tang 身痛逐瘀汤: formula name (see Table 4)

Shi quan da bu tang 十全大补汤: formula name (see Table 4)
Shi Zheng Lei Da Guan Ben Cao 经史证类大観本草 (ca. 1108) book name
Shao yao 芍药, *Paeonia lactiflora* Pall [root] (see Table 3)
Sheng jiang 生姜, *Zingiber officinale* Rosc [rhizome] (see Table 3)
Si wu tang 四物汤: formula name (see Table 2)
Sheng di huang 生地黄, *Rehmannia glutinosa* Libosch [radix] (see Table 3)
Sheng jiang 生姜, *Zingiber officinale* Rosc. [rhizome] (see Table 3)
Shuang he tang 双合汤: formula name (see Table 4)
Tai qiong 台芎, *Ligusticum wallichii* Franch [root] (see Table 3)
Tao hong yin 桃红饮: formula name (see Table 4)
Tao ren 桃仁, *Prunus persica* L. Batsch [seed] (see Table 3)
tong feng 痛风, disease name ‘painful wind’
wang 尖, disease name ‘lameness’
Wu tou 乌头, *Aconitum carmichaelii* Debx; *A. kusnezoffii* Reichb. [radix] (see Table 3)
Wu tou tang 乌头汤: formula name (see Table 2)
Wu ji san 五积散: formula name (see Table 2)
Wei ling xian 威灵仙, *Clematis chinensis* Osbeck; *C. hexapetala* Pall; *C. manshurica* Rupr [rhizome] (see Table 3)
Xiong qiong 芎穹, *Ligusticum wallichii* Franch [root] (see Table 3)
Xuan bi tang 宣痹汤: formula name (see Table 4)

*Yi Fang Xuan Yao* 医方选要 (c.1495)
*Yi Xue Gang Mu* 医学纲目 (c. 1565): book name ‘Compendium of Medicine’
*Zheng Yin Mai Zhi* 症因脉治 (c.1641) book name
Zhi gan cao 炙甘草, *Glycyrrhiza uralensis* Fisch [processed root] (see Table 3)
Zhi ke 枳壳, *Citrus aurantium* L [fructus]
Zhi mu 知母, *Anemarrhena asphodeloides* Bge [rhizome]
zhong feng 中风, ‘wind stroke’

*Zhong Hua Ben Cao* 中华本草 (1999) book name

*Zhong Hua Yi Dian* 中华医典 book name: ‘Encyclopaedia of Traditional Chinese Medicine’

*Zhong Yao Da Ci Dian* 中药大辞典 book name: ‘Great Compendium of Chinese Medicines’
**TABLE SUPP 3: Traditional properties of the most frequent herbs – channel tropism, flavour, nature**

| Herb name | Channel tropism | Flavour | Nature | Ref. |
|-----------|-----------------|---------|--------|------|
|            | Heart | Liver | Spleen | Stomach | Lung | Kidney | Bladder | Gallbladder | Pericardium | Large Intestine | Sour | Bitter | Sweet | Pungent | Salty | Blanched | Neutral | Warm | Cold | Hot | Page no. |
| Gan cao    | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               | 1    | 1      | 1      | 1       | 1     | 1     | 1       | 1    | 1    | 1   | 875     |
| Sheng jiang| 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               | 1    | 1      | 1      | 1       | 1     | 1     | 1       | 1    | 1    | 1   | 229     |
| Gan jiang | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           |                |      |        |        |         |        |   1   |         |       | 230    9|
| Dang gui   | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           |                |      |        |        |         |        |   1   |         |       | 134    9|
| Bai shao3  | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 649   |         |       |        |
| Chi shao   | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 659   |         |       |        |
| Fang feng  | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 142   3|         |       |        |
| Gui zhi    | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 464   |         |       |        |
| Ma huang   | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 274   |         |       |        |
| Bai zhu    | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 189   7|         |       |        |
| Chuan xiong| 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 140   2|         |       |        |
| Fu ling    | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 189   |         |       |        |
| Huai niu xi| 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 405   |         |       |        |
| Chuan wu   | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 479   |         |       |        |
| Huang qi   | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 825   |         |       |        |
| Fang ji    | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 589   |         |       |        |
| Ren shen   | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 128   1|         |       |        |
| Cang zhu   | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 188   9|         |       |        |
| Bai zhi    | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 133   2|         |       |        |
| Fu zi      | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 587   |         |       |        |
| Du huo     | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 133   8|         |       |        |
| Huang qin  | 1     | 1     | 1      | 1      | 1    | 1      | 1       | 1           | 1           | 1               |      |        |        |         |        | 168   9|         |       |        |
|       | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 100 |
|-------|---|---|---|---|---|---|---|---|---|-----|
| Chen pi |   |   |   |   |   |   |   |   |   | 4   |
| Tao ren | 1 | 1 |   |   |   |   |   |   |   | 741 |
| Sheng di huang (gan di huang)* | 1 | 1 |   |   |   |   |   |   |   | 174 |
| Shu di huang |   |   |   |   |   |   |   |   |   | 174 |
| Rou gui | 1 | 1 | 1 |   |   |   |   |   |   | 458 |
| Qin jiao | 1 | 1 |   |   |   |   |   |   |   | 148 |
| Huang bai |   |   |   |   |   |   |   |   |   | 104 |
| Wei ling xian |   |   |   |   |   |   |   |   |   | 522 |
| Total | 12 | 15 | 18 | 8 | 13 | 10 | 7 | 3 | 1 | 4 |

Note: 1. Names are in pinyin, see glossary for scientific names; 2. Paeony is in two forms - white (bai shao) and red (chi shao); 3. Ginger is in two forms - fresh (sheng jiang) and dried (gan jiang); 4. Rehmannia is in two forms - unprocessed (sheng di huang, also called gan di huang) and steamed (shu di huang); 5. There are minor variations between sources in the channel tropism, flavour and nature of some herbs. These properties are all according to Zhong Hua Ben Cao.

**Reference**

1. State Administration of Traditional Chinese Medicine 'Chinese Materia Medica Committee', ed Zhong Hua Ben Cao: Jing Xuan Ben ‘Chinese Materia Medica: abridged version’. Shanghai: Shanghai Scientific and Technical Publishers; 1998.