Overview of Contraindicated Chinese Medicines for Pregnancy

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Abstract

Chinese medicines should be classified into drugs, which have both beneficial and harmful effects. For centuries, Chinese medicines have been widely used to relieve many symptoms and to treat complications during pregnancy. It is not clear how safe the Chinese medicines are being used during pregnancy and if there is any adverse effects to embryofetal development and prenatal and postnatal growth. Some Chinese medicines are indicated that they cannot be used in pregnancy. In this chapter, we will conduct a systematic review to summarize and characterize in details the Chinese medicines classified as contraindicated, not recommended and cautiously used for pregnancy in most updated version of Pharmacopeia of the People’s Republic of China. Clinical reports including clinical trials, case reports, case series and animal studies including short-term and long-term toxicity, specific organ toxicity and different species of the Chinese medicines will be studied. Unlike those pharmaceutical drugs not recommend for use during pregnancy because of known or suspected adverse or teratogenic effects evident by animal studies and/or clinical trials, most of the Chinese medicines were utilized for long history in culture which, however, has very limited scientific data regarding the adverse pregnant outcomes.

Keywords: Chinese medicines, pregnancy, safety, review

1. Introduction

1.1. Chinese medicines for pregnancy

1.1.1. Application in China

Chinese medicines have become very popular and are widely applied to different kinds of medical conditions during pregnancy [1]. It promotes both mothers’ and fetuses’ health,
relieves and cures common disorders in women [1]. It has been used as a main stream medicine in China with a longer history than Western medicines.

The first record of Chinese medicines treatment related to reproductive was first explained in A Chinese Bestiary 3000 years ago during Xia, Shang and Zhou era [2, 3]. Since then, Gu Rong was commonly used for contraception [2, 3]. In the following centuries, considerable progress was achieved in both clinical theory and practice while lots of milestones have been developed in Obstetrics and Gynecology. Due to historical factors of the late Qing Dynasty, and the influence of Western Medicine under the Renaissance, development of Chinese Medicine was less prominent [4]. After the establishment of People’s Republic of China, with the great efforts of lots of Chinese Medicine practitioners and researchers, 6th edition of the textbook “Traditional Chinese Medicine in Obstetrics and Gynecology” [4] and lots of reference books and monographs have been published and used for daily teaching, training and self-learning. Apart from medical educations in Chinese Medicine, researches in collaborations with Chinese medicines and Western medicines have been raised to a new level and lots of meaningful conclusions have been drawn. For example, it was reported that combined Chinese medicines and Western medicines for ectopic pregnancy were more effective than conventional treatment [5, 6], and the method of combined medicines has been well studied and applied widely since then.

1.1.2. Development in foreign countries

Chinese Medicine in China has a long history, but its development for pregnant women in other countries is just within recent centuries. In foreign nations, the most common treatments are Acupuncture and Chinese herbal medicines (CHMs). Other therapies of Chinese Medicine, which could be used during pregnancy, began to spread to the world in very late twentieth century, such as Tui Na Massage and Die Da [4].

Chinese herbal medicines (CHMs) spread to the world earlier than acupuncture but only widely applied lately, due to the early advancement and modernization of Western medicines in foreign countries [7]. For instance, the “European Pharmacopoeia” had been locally well-developed, and Chinese herbs as medicines were not attractive to the practitioners and patients. With the advantages of Chinese medicines, including less side effects and greater effectiveness in some chronic diseases (such as infertility and irregular menstruation) than Western medicines, it was gradually accepted by foreigners and now has been spread to over 160 countries [3]. More and more foreign researchers and clinical doctors seriously have interests in it and come to China for further study.

1.1.3. Effectiveness and efficacy

With a long history of application of Chinese medicines to treat pregnant disorders, large amounts of case reports and clinical trials have been reported [8]. However, until now, limited data are available to overview Chinese medicines for pregnancy. Our team has reported in a systematic review [9] about the general applications, including common formulae, common individual CHMs, dosage and dosing, frequency, therapeutic efficacy, clinical indications and so on.
Chinese medicines are prescribed in formulae, and the Chinese medicine practitioners decide the formula according to the clinical presentation. Based on medical knowledge and personal experience, some use original or traditional formula, the others have individual prescription as personalized medicine. The prescribed formulae vary a lot, some formulae even lack unified theory and scientific evidence. Therefore, under a long-term collaboration with Cochrane Review Pregnancy and Childbirth Group, our team has conducted two systematic reviews with meta-analyses to study the claimed efficacy of Chinese herbal medicines for pregnancy-related disorders [10, 11]. The results showed that combined Chinese herbal medicines and other pharmaceuticals are more beneficial than other pharmaceuticals alone for threatened miscarriage [10] and unexplained recurrent miscarriage [11], but the evidence on the effectiveness and safety of Chinese herbal medicines alone as treatment is still insufficient, due to the poor qualities of the included clinical trials.

1.1.4. Safety

Safety is always the biggest issue in daily medical practice, and the issue is also a major concern to pregnant women. Chinese herbal medicines have been used to treat diseases and complications during pregnancy, and it is apparently well accepted as with fewer side effects.

There are 31 Chinese herbal medicines that were classified as toxic and contraindicated during pregnancy, which have been listed in many textbooks. The website of Chinese Medicine Council of Hong Kong (CMCHK) recently released another five CHMs, which contain aristolochic acid, which could induce abortion, kidney damage and cancer. Further studies of these Chinese herbal medicines have been carried out in the last 20 years and have demonstrated their adverse effects on both/either mothers and/or newborns. For example, Kansui Root (Radix Kansui, Gan Sui) is prohibited in pregnancy because it can poison the fetus and stimulate uterine contraction [12].

On the other hand, numbers of clinical trials have also been carried out to assess the safety of some Chinese herbal medicines in pregnancy and associated conditions, or to compare the adverse effects of Chinese herbal medicines with other medicines. Among the commonly used Chinese medicines, there are not too many studies of their potential harmful effects however. Our team has carried out a systematic review [13, 14] with meta-analyses to record the potential adverse effects and safety issues of CHMs as treatment for threatened miscarriage, but conclusive results remain elusive, as studies varied considerably in design, interventions and outcome measures. In the absence of placebo-controlled trials, the safety of Chinese medicines for the treatment of threatened miscarriage is unknown. Rigorous scientific and clinical studies to assess the possible risks of Chinese medicines are needed.

In conclusion, it is not clear how safe the Chinese medicines are being used during pregnancy and if there is any adverse effects to embryo-fetal development and prenatal and postnatal growth.

1.2. Chinese pharmacopeia

Unlike those pharmaceutical drugs not recommend for use during pregnancy because of known or suspected adverse or teratogenic effects evident by animal studies and/or clinical
trials, most of the Chinese medicines were utilized for long history in culture which, however, has very limited scientific data regarding the adverse pregnant outcomes.

“Chinese Pharmacopeia”, acknowledged by World Health Organization (WHO) as the official pharmacopeia for Chinese medicines, records 1146 different Chinese medicines [15]. It provides information on the herbs with their characteristics, identity, impurity, contents, extractum, analysis, property and channel, therapeutic action, pharmacological data, dose and dosing, precautions, storage, authentication methods and so on.

Among all this valuable information, we will obtain the most specific safety information for pregnancy from the Chinese Pharmacopeia and provide to the doctors, scholars and patients as scientific evidence on the safe application of Chinese medicines during pregnancy.

2. Objective

In this chapter, we will conduct a systematic review to summarize and characterize in details the Chinese medicines classified as contraindicated, not recommended and cautiously used for pregnancy in the most updated version of Chinese Pharmacopeia. Clinical reports including clinical trials, case series, case reports and animal studies including short-term and long-term toxicity, specific organ toxicity and different species of Chinese medicines will be studied.

3. Method

3.1. Search in Chinese pharmacopeia

Two review assessors carried out the word-by-word study in Chinese Pharmacopeia to identify the study medicines. First, they read all the recorded individual Chinese medicines and the formulae one by one and recorded in a list of the medicines remarked with application in pregnancy. Second, they checked the details of pharmaceutical effects and clinical functions and indications of these list-out medicines. If any adverse effects related to pregnancy were reported, the reference study would be traced and more details of the adverse outcomes were recorded, for further summaries and analyses. Third, they carried out the same rules to expand the search in different online databases, if the details of the adverse outcomes could not be accessed from the Chinese Pharmacopeia or the reference study. Finally, they extracted and summarized the specific safety information on three classifications of these Chinese medicines.

3.2. Search in other databases

To further supplement the pharmacological and toxicology data of the Chinese medicines, several online national and public resources on World Wide Web were also referred. It included Center for Food Safety and Applied Nutrition (CFSAN) from US Food and Drug Administration (FDA, (http://vm.cfsan.fda.gov/~dms/supplmnt.html), National Center
for Complementary and Alternative Medicine (NCCAM) from US National Institute of Health (NIH, http://nccam.nih.gov), Agricultural Research Service (ARS) from US Department of Agriculture (USDA, http://www.ars-grin.gov/duke), Medical Dictionary for Regulatory Activities (MedDRA) from International Federation of Pharmaceutical Manufacturers and Associations (IFPMA, http://www.meddramsso.com), National Council Against Health Fraud (NCAHF) from a private health agency (http://www.ncahf.org), Quackwatch from an American non-profit organization (http://www.quackwatch.com), HerbMed from Alternative Medicine Foundation (http://www.herbmed.org) and ConsumerLab from an independent laboratory (http://www.consumerlab.com), accessibility verified until 1 September 2016.

3.2.1. Search strategies for online databases

Search by subject heading/keyword/abstract/full text with:

1. Traditional Chinese medicines
2. Pregnancy
3. Western medicines
4. Comparisons studies
5. Safety
6. Toxicity

Or could be included or replaced by similar words:

1. Herbal medicines
2. Pharmaceuticals
3. Obstetric disorders
4. Pregnancy diseases
5. Therapy

Only clinical trials, which assessed the adverse pregnant outcomes of the Chinese medicines, were further selected for meta-analysis.

3.3. Study criteria

3.3.1. Types of studies

All published studies (list in Chinese Pharmacopeia and reference and reference of reference) that evaluated the safety of Chinese medicines for pregnancy were included. Studies of Chinese medicines for other clinical applications and in animal, chemical and basic research were included. (Non)/Randomized control trials, case controlled studies, case series, case reports, commentary articles and non-systematic reviews were excluded. Studies with no evaluation or incomplete records of adverse pregnancy outcome were also included.
Language of the publications was restricted to English and Chinese. Literature with either English or Chinese abstract should be available for initial search. No translation was required for Chinese articles as all review assessors can read Chinese and understand Traditional Chinese Medicine and Chinese medicines thoroughly. Translations were only sought from the language facilities of the university for articles written in English and Chinese.

3.3.2. Types of participants

There was no strict for types of participants, as we collected all safety information then further extracted for the summary table (Table 1).

3.3.3. Types of interventions

Since Chinese medicines are crude drugs of plant, animal and mineral origins, not only those Chinese medicines originated from plants or herbs but also those from animals and minerals were included. All types of Chinese medicine in either standard or combined formulas used during pregnancy or on pregnancy model animals regardless of the dose or duration of administration.

3.3.4. Types of outcome measures

General and specific adverse effects of the study Chinese medicines were recorded. Adverse reproductive outcomes in both mothers and fetuses/infants (both human and animals) will be recorded. Maternal outcomes included (1) toxicity (e.g. renal failure, liver failure, neurological impairment and death); (2) side-effects (e.g. anaphylaxis, gastrointestinal disturbance, hypertension/hypotension, cardiac arrhythmia, gestational diabetes and so on); (3) pregnancy loss (e.g. late abortion, intrauterine death and still birth) and (4) pregnancy complications (e.g. preterm/postdate labor, placenta previa, placenta abruption and so on). Fetal outcomes included (5) perinatal mortality (including prenatal and postnatal death); (6) toxicity (e.g. fetal compromise, neurological consequences, hydrops fetalis and so on); (7) congenital malformations and (8) neonatal complications (e.g. jaundice, infection, hypoglycemia and so on). Both long- and short-term adverse outcomes were reported and summarized.

3.3.5. Data collection and analysis

For each reference study to be involved in this review, all review assessors first screened the titles, abstract sections and keywords of every record to exclude the duplicates and obvious false positive. Second, full text of eligible studies was assessed for further inclusion or exclusion. If there was sufficient information and it met the inclusion criteria, the study was included in the analyses and summaries. Two review assessors assessed the studies for inclusion independently; any disagreement was resolved by discussion among all the review authors. The study authors were contacted for clarification if there were doubts about the eligibility of the study and the disagreement could not be resolved. The review authors were not blinded to the journal of origin or institution.
| CHM (English) | CHM (Biological name) | CHM (Chinese) | Dose | Actions and clinical indications | Classification in pregnancy |
|--------------|-----------------------|---------------|------|----------------------------------|-----------------------------|
| 1 Aconiti kusnezoffii radix | Aconitum kusnezoffii Reichb. | 草乌 (Cao Wu) | After preparation | To restore yang, to improve fire, and to disperse cold. Being used in: sweating profusely with body temperature dropping; muscle spasm in cholera; instant sweating, afraid of cold in cases of yangxu (yang deficient); pain and cold in chest and abdomen, chronic diarrhea due to pixu (spleen deficient), chronic muscle or joint pain due to wind cold dampness, tightness and pain in joints and muscles; edema and coldness in the lower legs due to shenyangxu (kidney yang deficient) | Contraindicated |
| 2 Aconiti radix | Aconitum carmichaelii Debx. | 川乌 (Chuan Wu) | After preparation | To restore yang, to improve fire, and to disperse cold. Being used in: sweating profusely with body temperature dropping; muscle spasm in cholera; instant sweating, afraid of cold in cases of yangxu (yang deficient); pain and cold in chest and abdomen, chronic diarrhea due to pixu (spleen deficient), chronic muscle or joint pain due to wind cold dampness, tightness and pain in joints and muscles; edema and coldness in the lower legs due to shenyangxu (kidney yang deficient) | Contraindicated |
| 3 Anemones raddeanae rhizoma | Anemone raddeana Regel | 两头尖 (Liang Toujian) | 1–3 | Rheumatism | Contraindicated |
| 4 Aristolochiae fructus | Aristolochia debilis Sieb.et Zucc | 马兜铃 (Ma Douling) | 3–9 | In coughs, phlegm, wheezing, blood in phlegm, with lung heat; hypertension, dizziness, with red face due to yinxu and liver yang ascending (gan yang ascending) condition; bleeding hemorrhoids and swelling in the anus | Contraindicated |
| 5 Aristolochiae herba | Aristolochia debilis Sieb.et Zucc; Aristolochia contorta Bge. | 天仙藤 (Tian Xianteng) | 3–6 | Same as 4 | Contraindicated |
| 6 Calomel | Calomelas | 轻粉 (Qing Fen) | 0.1–0.2 | Use externally to kill parasites; for ringworms, boils and syphilis. Take internally to promote urination and bowel movements. Usually use with other water-removing herbs in difficulty in urination and defection | Contraindicated |
| 7 Cinnabaris | Mercury sulfide | 朱砂 (Zhu Sha) | 0.1–0.5 | Insomnia | Contraindicated |
| CHM (English) | CHM (Biological name) | CHM (Chinese) | Dose | Actions and clinical indications                                                                                                                                                                                                                                                                                                                                 | Classification in pregnancy |
|---------------|------------------------|---------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| 8  | Crotonis fructus | Croton tiglium L. | 巴豆 (Ba Dou) | Proper dose | As laxative for constipation, distention, abdominal fullness and pain, caused by extreme coldness of bowels; for ascites; for clogged phlegm; for topical uses for abscesses and ulcers, to speed up ulceration of abscesses | Contraindicated |
| 9  | Crotonis semen pulveratum | Croton tiglium L. | 巴豆霜 (Ba Doushaung) | 0.1–0.3 | Same as 8 | Contraindicated |
| 10 | Curcumae rhizoma | Curcuma phaeoaulis Val. | 茜术 (E Zhu) | 6–9 | Promotes qi flow and rids of blood stasis, amenorrhea due to blood stasis; distention and pain due to stagnation of undigested food; early stages of cancer in the cervix uteri (neck of uterus) | Contraindicated |
| 11 | Daturaе flos | Datura metel L. | 洋金花 (Yang Jinhua) | 0.3–0.6 | The flowers are being used in anesthesia, as sedative and for inducing sleep. The leaves are being used in rheumatoid arthritis. The seeds are being used in promoting blood circulation and in ridding of pain | Contraindicated |
| 12 | Erycibe schmidtii | Erycibe obtusifolia Benth. | 丁公藤 (Ding Gongteng) | 3–6 | Rheumatism | Contraindicated |
| 13 | Euphorbiae pekinensis radix | Euphorbia pekinensis Rupr. | 京大戟 (Jing Daji) | 1.5–3 | For edema, ascites, retention of phlegm, tuberculosis of lymph nodes. Can be taken internally or applied externally | Contraindicated |
| 14 | Euphorbiae semen | Euphorbia lathyris L. | 千金子 (Qian Jinzi) | 1–2 | Dermatomycosis | Contraindicated |
| 15 | Euphorbiae semen pulveratum | Euphorbia lathyris L. | 千金子霜 (Qian Jinzhiaung) | 0.5–1 | Dermatomycosis | Contraindicated |
| 16 | Eupolyphaga steleopha | Eupolyphaga sinensis Walker | 土鳖虫 (Tu Biechong) | 3–10 | For blood stasis, amenorrhea, injuries of bones and muscles from impact, sprain in loin area | Contraindicated |
| 17 | Ferulae resina | Ferula sinkiangensis K.M. Shen; Ferula fukanensis K.M. Shen | 阿魏 (A Wei) | 1–1.5 | Being used in ridding of parasites, improving meat digesting, treating purpura, epilepsy, enlarged liver | Contraindicated |
| 18 | Genkwa flos | Daphne genkwa Sieb. et Zucc. | 芫花 (Yuan Hua) | 1.5–3 | For edema, ascites. For worm parasite: vinegar processed yuan hua, xiong huang. Make into powder. Take internally. For head fungal or ringworm: mix with lard and apply topically | Contraindicated |
| CHM (English) | CHM (Biological name) | CHM (Chinese) | Dose | Actions and clinical indications | Classification in pregnancy |
|--------------|-----------------------|---------------|------|----------------------------------|-----------------------------|
| 19 Gleditsiae fructus abnormalis | Gleditsia sinensis Lam. | 猪牙皂 (Zhu Yazao) | 1–1.5 | Oral: for sequelae of strokes, losing consciousness, epilepsy with abundance of phlegm, difficulty in expelling phlegm, constipation. External usage: boils; breast engorgement in new mothers: wrap a peanut size powdered Zhu ya zao in clean gauze. Dip it in 75% alcohol to wet the outer layer. Stuff it in the nostril (same side as the engorgement is) for 12 hours. If necessary repeat treatment after rested for 8 hours. | Contraindicated |
| 20 Ground beetle | Eupolyphaga sinensis Walker | 蚷虫 (Zhe Chong) | 3–10 | For blood stasis, amenorrhea, injuries of bones and muscles from impact, sprain in loin area. | Contraindicated |
| 21 Hirudo | Hirudo nipponica Whitman | 水蛭 (Shui Zhi) | 1–3 | For treatment of blood stasis, asthma, amenorrhea, physical injuries, unable to conceive, also used in abortion. Live shui zhi used externally in treating tumors, rid of swelling in boils, local blood clots (bruises) | Contraindicated |
| 22 Hydargyri oxydum rubrum | Hydargyri Oxydum Rubrum | 红粉 (Hong Fen) | Proper dose | Suppurative infection | Contraindicated |
| 23 Hyoscyami semen | Hyoscyamus niger L. | 天仙子 (Tian Xianzi) | 0.06–0.6 | Relieving spasm | Contraindicated |
| 24 Kansui radix | Euphorbia kansui T.N. Liou ex T.P. Wang | 甘遂 (Gan Sui) | 0.5–1.5 | Anti-inflammation | Contraindicated |
| 25 Moschus | Moschus berezovskii Flerov | 麝香 (She Xiang) | 0.03–0.1 | For coma due to stroke, angina, tumors and carbuncles, hastens delivery and facilitate the passage of stillborns. Seizures | Contraindicated |
| 26 Mylabris | Mylabris phalerata Pallas | 斑蝥 (Ban Mao) | 0.03–0.06 | For cancer, skin fungus infection, cancer of the lymphatic system, boils cannot ripen, dead tissues | Contraindicated |
| 27 Nigellae semen | Nigella glandulifera Freyn et Sint. | 黑种草子 (Hei Zhongcaozi) | 2–6 | For treatment of: heart palpitation, insomnia, weakness, cold or flu, cough | Contraindicated |
| 28 Papaveris pericarpium | Papaver somniferum L. | 罂粟壳 (Ying Suke) | 3–6 | Pain relief | Contraindicated |
| 29 Pharbitidis semen | Pharbitis nil (L.) Choisy; Pharbitis purpurea (L.) Voigt | 牵牛子 (Qian Niuzi) | 3–6 | Edema; ascites; constipation; difficulty in urination; beri beri; flatulence; abundance of phlegm, cough, asthma; abdomen pain with parasite | Contraindicated |
| CHM (English) | CHM (Biological name) | CHM (Chinese) | Dose | Actions and clinical indications | Classification in pregnancy |
|---------------|-----------------------|---------------|------|----------------------------------|-----------------------------|
| 30 Phytolaccae radix | Phytolacca acinosa Roxb. | 商陆 (Shuang Lu) | 3–9 | Promote diuresis | Contraindicated |
| 31 Realgar | Realgar | 雄黄 (Xiong Huang) | 0.05–0.1 | Topical application for ridding of parasites: for scabies, ringworm, damp rashes, abscesses, ulcers, snake bites. Taking internally for intestinal parasites, especially effective for roundworms. Dries dampness: expels phlegm | Contraindicated |
| 32 Rhododendron mollis flos | Rhododendron molle G. Don | 阴羊花 (Nao Yanghua) | 0.6–1.5 | Alleviates pain. Being used in rheumatoid arthritis, pain in broken bones, fungal infection of the skin | Contraindicated |
| 33 Scolopendra subspinipes mutilans | Scolopendra subspinipes mutilans L. Koch | 蜈蚣 (Wu Gong) | 3–5 | Epilepsy, spasms, scrofula, sores, arthritis, hemorrhoids with pain, snake poison, scalding, leukemia, stroke | Contraindicated |
| 34 Scorpio | Buthus martensii Karschi | 全蝎 (Quan Xie) | 0.6–9 | Epilepsy, stroke, paralysis, migraine, pain in arthritis, tetanus, tuberculosis in lymph nodes, urticaria, and bunad | Contraindicated |
| 35 Sparganium rhizoma | Sparganium stoloniferum Buch. -Ham. | 三棱 (San Leng) | 5–10 | Painful menses. Postpartum complication, amenorrhea cause by qi stagnation and/or blood stasis. Cu san leng (prepared with vinegar) is stronger in pain inhibition. Fu san leng (stir fried with flour) is milder and is being used in promoting digestion | Contraindicated |
| 36 Strychni semen | Strychnos nux-vomica L. | 马钱子 (Ma Qianzi) | 0.3–0.6 | Rheumatoid arthritis, injuries, boils and swellings, sequelae from polio of children, impotence, for diseases of the gastrointestinal tract, organic and functional disorders of the heart and circulatory system, glycine encephalopathy, nervous conditions, myasthenia gravis; amyotrophic lateral sclerosis (als), cancer, depression, migraine, menopausal syndromes, facial neuralgias, raynaud’s syndromes | Contraindicated |
| 37 Strychni semen pulveratum | Strychnos nux-vomica L. | 马钱子粉 (Ma Qianzi fen) | 0.3–0.7 | Same as 36 | Contraindicated |
| 38 Toxicodendri resina | Toxicodendron vernicifluum (Stokes) F.A. Barkl | 干漆 (Gan Qi) | 2–5 | Elimination of parasite | Contraindicated |
| 39 Gleditsiae sinensis fructus | Moschus berezovskii Flerov | 大皂角 (Da Zaojiao) | 1–1.5 | 1. Dispels phlegm or coughs with abundance of phlegm; 2. Opens the orifices after strokes or epilepsies or facial paralysis due to excessive of phlegm; 3. Discharges puss when used externally for boils. Zao jiao ci uses: early stages of boils, difficulty in discharging of pus, eczema, and leprosy | Not recommended |
| CHM (Chinese) | Actions and clinical indications | Classification in pregnancy |
|---------------|---------------------------------|-----------------------------|
| **40** Saussureae involucratae herba | For hardening of blood vessels of the brain, tumor. Folk applications include rheumatoid arthritis, impotence, irregular menses, placenta not being expelled after birth | Not recommended |
| **41** Abelmoschi corolla | Promote diuresis | Cautiously used |
| **42** Achyranthis bidentatae radix | Damp cold, weakness and pain in loin and knees, tight and spastic limbs, irregular menses, postpartum pain in abdomen due to blood stasis, afterbirth not being expelled, blood in urine, physical injuries and difficulty in bending knees. Raw huai niu xi is effective for breaking blood stasis. Cooked huai niu xi is effective for strengthening muscles and bones, promoting urination and strengthening essence of the body | Cautiously used |
| **43** Aconiti kusnezoffii folium | Same as 1 | Cautiously used |
| **44** Aconiti kusnezoffii radix cocta | Same as 1 | Cautiously used |
| **45** Aconiti lateralis radix praeparata | Similar as 2 | Cautiously used |
| **46** Aconiti radix cocta | Same as 2 | Cautiously used |
| **47** Aloe | For constipation, dizziness, red eyes, and irritability due to heat buildup (yinxu (yin deficient) with heat). Kills intestinal parasites, especially roundworms. For treatment of ringworms. For burns and wounds. For treatment of liver yang over active | Cautiously used |
| **48** Arisaematis rhizoma | Being used in stroke with abundance of phlegm, paralysis, epilepsy, tetanus, tumors, arrhythmia. External use: insect and snake bites (grind with vinegar or water and apply to affected area) | Cautiously used |
| No. | CHM (English) | CHM (Biological name) | CHM (Chinese) | Dose | Actions and clinical indications | Classification in pregnancy |
|-----|---------------|------------------------|---------------|------|----------------------------------|-----------------------------|
| 49  | Arisaematis rhizoma preparatum | Arisaem erubescens (Wall.) Schott | 制天南星 (Zhi Tiannanxing) | 3–9  | Same as 48 | Cautiously used |
| 50  | Aurantii fructus | Citrus aurantium L. | 枳壳 (Zhi Qiao) | 3–10 | Indigestion due to low function; bloating in chest, abdomen and solar plexus area; constipation; diarrhea but difficult to expel, focal distention; fullness in the chest; cough with abundance of phlegm; prolapse of stomach, uterus and rectum | Cautiously used |
| 51  | Aurantii fructus | Citrus aurantium L. | 枳实 (Zhi Shi) | 3–10 | Same as 50 | Cautiously used |
| 52  | Borneolum | Cinnamomum camphora (L.) Presl | 天然冰片 (Tian Ranbingpian) / 右旋龙脑 (You Xuanlongnao) | 0.3–0.9 | For fainting due to strokes or heat, bunacle, pain in joints, ulceration of the cornea, sores in the mouth, eczema, taking internally: mainly being used in pills; seldom in decoction. External application: for washing or added in external medication | Cautiously used |
| 53  | Borneolum syntheticum | Borneol | 冰片 (Bing Pian) / 合成龙脑 (He Chenglongnao) | 0.15–0.3 | Similar as 58 | Cautiously used |
| 54  | Bovis calculus | Bos taurus domesticus Gmelin | 牛黄 (Niu Huang) | 0.15–0.35 | Anti-inflammatory, anti-fever, anti-bacterial, opens the orifices, awakens the spirit, rid of phlegm. For high fever with delirium and convulsion due to hot diseases with hot phlegm, for chronic sore throat, for abscesses that have ripen and ruptured. Clears the heart, liver, relieves toxicity, rid of wind and tremors. For convulsions with high fever due to liver heat | Cautiously used |
| 55  | Bovis calculus artifactus | Bos taurus domesticus Gmelin | 人工牛黄 (Ren Gongniuhuang) | 0.15–0.35 | Same as 54 | Cautiously used |
| 56  | Bovis calculus sativus | Bos taurus domesticus Gmelin | 体外培育牛黄 (Ti Waipelyuniuhuang) | 0.15–0.35 | Same as 54 | Cautiously used |
| CHM (English) | CHM (Biological name) | CHM (Chinese) | Dose | Actions and clinical indications | Classification in pregnancy |
|--------------|-----------------------|------------|------|--------------------------------|---------------------------|
| 57 | Buonis venenum | 蟾酥 (Chan Chu) | 0.015-0.03 | For food poisoning with stomach pain and bloating, vomiting with diarrhoea, even fainting. Usually combine with she xiang, ding xiang, cang zhu, like formula called chan su wan. For bunades, sofula, painful and swollen throat and various kinds of toothache combine with xiong huang, ku fan, zhu sha, etc. Make into pills the sizes of mung beans. Take five pills each time with decoction of white portions of green onion. For scarlet fever usually combine with niu huang, xiong huang, bing pian, like liu shen wan. Being used in various types of cancer, like liver cancer, intestine cancer, leukemia, skin cancer, etc. Taking orally or external application has been successful to certain degree, according to some reports. Being used in respiratory and in circulatory exhaustion. It possesses the effect of raising blood pressure for long time. It also possesses respiratory stimulating effect. | Cautiously used |
| 58 | Campsis flos | 凌霄花 (Ling Xiaohua) | 5–9 | Flower: for irregular menses, amenorrhea, tumors of the uterus, ovaries, endometriosis, mammary glands hyperplasia, chronic inflammation of the pelvic area, postpartum breast swelling, rubella, erysipelas, itchy skin, rosacea, acne. Roots: for rheumatoid arthritis, injuries from impact, broken bones, dislocations, acute infection of the digestive tract | Cautiously used |
| 59 | Carthami flos | 红花 (Hong Hua) | 3–10 | Actions and indications: 1. Being used in lumps in intestines and bowels, sores and carbuncles, pain from impact injuries, rheumatoid arthritis, invigorates circulation, breaks up blood stasis condition, and promotes menstruation: injuries from impact, swollen boils, irregular menses, pain in stopping of menses, pain from blood stasis after birth. Small amount can invigorate circulation and large amount can get rid of blood clot. It is an important herb in blood stasis therapy and often is prescribed with tao ren. To invigorate circulation, it is often used with dang gui, chuan xiong, shao yao. To rid of blood stasis, it is used with san leng, e zhu, and da huang; 2. Measles with blood stasis, color not lively red: use hong hua, dang gui, zi cao, da qing ye; 3. Angina of coronary diseases: use hong hua, dan shen, chuan xiong, chi shao; 4. Thromboangitis obliterans: use hong hua, dang gui, tao ren, chi shao, ru xiang; 5. For treatment of enlargement of the liver and spleen; 6. For physical injuries with blood stasis and pain: broken bones, dislocated joints, sprains, and impact | Cautiously used |
| CHM (English) | CHM (Biological name) | CHM (Chinese) | Dose | Actions and clinical indications | Classification in pregnancy |
|--------------|----------------------|---------------|------|----------------------------------|-----------------------------|
| ****60       | Cinnamomi cortex     | Cinnamomum cassia Presl | 肉桂 (Rui Gui) | 1–5 | Tonic for stomach, rid of wind, to promote sweating, for headache, anemia, cold limbs, to promote urination. To promote lung qi, in chill and fever, cold phlegm, diarrhea, muscle spasm, headache, back pain, sweating, to stop easily being annoyed, strengthening muscles and bones, promote circulation. Use in impotence due toshen yang xu (kidney yang deficient) | Cautiously used |
| 61           | Cinnamomi ramulus    | Cinnamomum cassia Presl | 桂枝 (Gui Zhi) | 3–10 | Same as 60 | Cautiously used |
| 62           | Coicis semen         | Coix lacryma-jobi L. var.ma-yuen (Roman.) Staph | 薏苡仁 (Yi Yiren) | 9–30 | For improving digestion, enhancing the lung function, ridding of bacterial or fungal infection, arresting pain and itchiness. For treatment of spastic muscles, arthritis pain in joints and muscular rigidity. Beri-beri and edema, vagina yeast infection, stones in the urinary tract, neuralgia, difficulty in urination, lung abscess, gonorrhea, restless leg syndrome. Use raw yi yi ren for infection. Use stir fried yi yi ren for improving digestion | Cautiously used |
| 63           | Croci stigma         | Crocus sativus L. | 西红花 (Xi Honghua) | 1–3 | Similar as 59 | Cautiously used |
| 64           | Cyathulae radix      | Cyathula officinalis Kuan | 川牛膝 (Chuan Niu xi) | 5–10 | Rheumatism, hematuria, amenorhea, abdominal mass (fibroids of the uterus, ovarian cysts, endometriosis, pelvic inflammation, blood retention due to gynatresia, extra-uterine pregnancy, bleeding in the uterus, and other pelvic masses) | Cautiously used |
| 65           | Dianthi herba        | Dianthus superbus L. | 翟麦 (Qu Mai) | 9–15 | Gonorrhea, edema, urinary tract inflammation, difficulty in urination, irregular menses, amenorhea, dystocia, carbuncle | Cautiously used |
| 66           | Dichroae radix       | Dichroa febrifuga Lour. | 常山 (Chang Shan) | 5–9 | Vomitting, malaria | Cautiously used |
| 67           | Echinopsis radix     | Echinops latifolius Tausch.; Echinops grijsii Hance | 禹州漏芦 (Yu Zhouroulu) | 5–10 | For boils, carbuncles, acute mastitis, unable to discharge milk | Cautiously used |
| 68           | Euphorbiae hirtae herba | Euphorbia hirta L. | 飞扬草 (Fei Yang cao) | 6–9 | Relieve itching, lactogenesis | Cautiously used |
| 69           | Ferrous sulfate      | Melanterite | 绿矾 (Lv Fan) | 0.8–1.6 | Killing parasites | Cautiously used |
| CHM (English) | CHM (Biological name) | CHM (Chinese) | Dose | Actions and clinical indications | Classification in pregnancy |
|---------------|-----------------------|---------------|------|---------------------------------|-----------------------------|
| 70 Gendarussae herba | Gendarussa vulgaris Nees | 小驳骨 (Xiao Bogu) | 9–15 | Functure | Cautiously used |
| 71 Haematitum | Haematitum | 赭石 (Zhe Shi) | 9–30 | Liver yang over active, blurry vision and dizziness. Vomiting, hiccups, asthma; bleeding due to heat in the blood, excessive bleeding during menopause; chronic diarrhea; vagina yeast and bacterial infection; gastric neurosis | Cautiously used |
| 72 I-borneolum/l-borneolum | Blumea balsamifera (L.) DC. | 艾片 (Ai Pian)/左旋龙脑 (Zuo Xuanlongnao) | 0.15–0.3 | For fainting due to strokes or heat, bunacle, pain in joints, ulceration of the cornea, sores in the mouth, eczema, taking internally: mainly being used in pills; seldom in decoction. External application: for washing or added in external medication | Cautiously used |
| 73 Impatientis semen | Impatiens balsamina L. | 急性子 (Ji Xingzi) | 3–5 | As astringent, invigorate blood flow, promotes urination and rids of edema, rids of blood stasis, regulate menses, for premenstrual abdominal pain, infertility, post partum abdominal pain with lochioschesis (discharge in post delivery) | Cautiously used |
| 74 Leonuri herba | Leonurus japonicus Houtt. | 益母草 (Yi Mucao) | 9–40 | As astringent, invigorate blood flow, promotes urination and rids of edema, rids of blood stasis, regulate menses, for premenstrual abdominal pain, infertility, post partum abdominal pain with lochioschesis (discharge in post delivery) | Cautiously used |
| 75 Limonitum | Limonite | 禹余粮 (Yu Yuliang) | 9–15 | Chronic diarrhea, bleeding not during menses, vagina discharge, hemorrhoids and hemorrhoids with bleeding or with pus | Cautiously used |
| 76 Manis squama | Manis pentadactyla Linnaeus | 穿山甲 (Chuan Shanjia) | 5–10 | Promote lactation, hastens boils to be ripen, expels pus, stop pain, pain in the joints of lower limbs, chronic malaria, rid of parasites. Unblocks menstruation, undo yu (blood stasis), acute mastitis, ridding of wind dampness bi | Cautiously used |
| 77 Melanteritum | Ferrous sulfate heptahydrate | 皂矾 (Zao Fan) | 0.8–1.6 | Rid of toxins and dampness: being used externally on boils, skin ulcers, skin fungal infection. As tonic and rid of parasites: being used in edema due to deficiency; parasites and pain in the abdomen | Cautiously used |
| CHM (English) | CHM (Biological name) | CHM (Chinese) | Dose | Actions and clinical indications | Classification in pregnancy |
|--------------|-----------------------|--------------|------|-------------------------------|---------------------------|
| 78 Meliae cortex | Melia toosendan Sieb. et Zucc.; Melia azedarach L. | 苦楝皮 (Ku Lianpi) | 3–6 | Promote qi flow, rid of dampness-heat, clear liver fire, rid of pain, promote urination, regulates qi, kills parasites. Also used externally for fungus infections of scalp. Ku lian pi should be cooked longer than other herbs in the formula, because the active ingredients are more difficult to dissolve in water. | Cautiously used |
| 79 Momordicae semen | Momordica cochinensis (Lour.) Spreng. | 木鳖子 (Mu Biezi) | 0.9–12 | Similar as 36 | Cautiously used |
| 80 Moutan cortex | Paeonia suffruticosa Andr. | 牡丹皮 (Mu Danpi) | 6–12 | Clears heat and cools the blood, clears fire of yin deficiency, clear blood stasis and rid of clots, drain pus and reduces swelling due to blood stasis | Cautiously used |
| 81 Myrrha | Commiphora myrrha Engl.; Commiphora molmol Engl. | 没药 (Mo Yao) | 3–5 | For pain due to injuries, bruises, rheumatoid arthritis, tumors in the uterus, hemorrhoid, cataract, amenorrhea, bone and muscle ache, angina pectoris. External use on inflammation of the mouth cavity, periodontitis, wounds from cut not healing, and pharyngitis | Cautiously used |
| 82 Natrii sulfas | Mirabilitum | 芒硝 (Mang Xiao) | 6–12 | 1. Constipation with dark urine, fullness and pain in abdomen; 2. Conjunctivitis; 3. Boils in mouth and tongue; 4. Swollen and painful throat area; 5. Tumor of the breast; 6. Stopping lactation; 7. Worm parasites of small children; 8. Red, swollen boils, before breakage | Cautiously used |
| 83 Natrii sulfas exsiccatus | Natrii Sulfas Exsiccatus | 玄明粉 (Xuan Mingfen) | 3–9 | Similar as 82 | Cautiously used |
| 84 Notoginseng radix et rhizoma | Radix Notoginseng | 三七 (San Qi) | 1–9 | Raw san qi can stop bleeding and can transform blood stasis. It can stop bleeding without causing blood clots. It is widely used in injury medicine as in broken bones, swelling, impact injuries. Cooked san qi can be used as tonic | Cautiously used |
| 85 Olibanum | Boswellia Carterii Birdw.; Boswellia Bha-Dajiana Birdw. | 乳香 (Ru Xiang) | 3–5 | Improves circulation, repairs muscle, as resolvent. Being used in: pain due to blood clots, spastic muscle, carbuncles, gum bleeding, gingivitis, rheumatoid arthritis, cirrhosis of liver, amenorrhea, physical injuries, ulcerated wounds not healing | Cautiously used |
| 86 Persicae semen | Prunus persica (L.) Batsch | 桃仁 (Tao Ren) | 5–10 | Breaks up blood stasis for constipation due to dry intestines for early stage of liver cirrhosis inhibits epstein-barr virus anti-tumor | Cautiously used |
| CHM (English) | CHM (Biological name) | CHM (Chinese) | Dose | Actions and clinical indications | Classification in pregnancy |
|--------------|-----------------------|--------------|------|---------------------------------|-----------------------------|
| 87 | Physochlainae radix | 华山参 (Hua Shanshen) | 0.1–0.2 | Relieve cough, resolving phlegm | Cautiously used |
| 88 | Polygoni cuspidati rhizoma et radix | 虎杖 (Hu Zhang) | 9–15 | For jaundice, gall bladder stones, blood stasis with menses stoppage, yeast infection, rheumatoid arthritis, physical injuries from impacts, inflammation of the bronchi, lobar pneumonia, poisonous snake bites, scalding injuries, acute hepatitis, urinary tract infection, boils, stoppage of menses due to heat in the blood, breast cancer, menopausal bleeding disorder | Cautiously used |
| 89 | Pruni semen | 郁李仁 (Yu Liren) | 6–10 | Coprostasis | Cautiously used |
| 90 | Psammosilenes radix | 金铁锁 (Jin Tiesuo) | 0.1–0.3 | Pain control | Cautiously used |
| 91 | Rhapontici radix | 漏芦 (Lou Lu) | 5–9 | Similar as 67 | Cautiously used |
| 92 | Rhei radix et rhizoma | 大黄 (Da Huang) | 3–15 | Lack of bowel movement, dysentery, blood clots, tumor, red and painful eyes, abdominal distention and/or pain, blood in stool, hemorrhoidal bleeding, urination burning sensation, nose bleeding, coughing up blood, sore extremities, edema, jaundice, lesions, burns and scalding (external application), absence of menses. Note: cooking for more than 10 minutes will reduce its purgative effect. For purgative effect use raw da huang. For blood invigorating action use wine or vinegar treated da huang. To stop bleeding use charred da huang | Cautiously used |
| 93 | Sappan lignum | 苏木 (Su Mu) | 3–9 | For vomiting, hicups, burping, indigestion, and flatulence due to pixu (spleen deficient) or fungal infection; and for difficulty in expelling phlegm; chronic bronchitis; injuries from impact, dysentery, tetanus | Cautiously used |
| CHM (English) | CHM (Biological name) | CHM (Chinese) | Dose | Actions and clinical indications | Classification in pregnancy |
|--------------|-----------------------|---------------|------|----------------------------------|-----------------------------|
| 94           | Selaginellae herba    | 卷柏 (Juan Bai) | 5–10 | Improves circulation             | Cautiously used |
| 95           | Sennae folium         | 蕲叶 (Fan Xieye) | 2–6  | Coprostasis                      | Cautiously used |
| 96           | Sulfur                | 硫黄 (Liu Huang) | 1.5–3| Coprostasis, killing parasite    | Cautiously used |
| 97           | Tetrapanax medulla    | 通草 (Tong Cao) | 3–5  | Being used in typhoid, paratyphoid with dark urine, pain in gonorrhea, edema scanty urine, and lack of mother’s milk | Cautiously used |
| 98           | Trichosanthis radix   | 天花粉 (Tian Huafen) | 10–15| Clears lung heat, dissolves phlegm, for cough with thick phlegm, rid of toxicity, expels pus; for treatment of chlorion epithelioma, hydatidiform mole | Cautiously used |
| 99           | Typhae pollen         | 蒲黄 (Pu Huang) | 5–10 | Hei pu huang is pu huang that has been stir fried till dark color. It is being used in stopping bleeding. Raw pu huang possesses double effects of stopping bleeding and promoting circulation. For treatment of: angina: blood clot in the brain, high blood lipids, inflammation of the intestine and difficulty in urination: pu huang 50 g, xiong huang 10 g, bing pian 3 g, fresh white part of green onion 200 g,(wash the part of green onion and boil in water for 3 minutes. Smash all herb past it to the lower abdomen while still warm. Bleeding and abdomen ache due to chronic colitis: pu huang 3 g, wu ling zhi 3 g (wrap in cloth), baked ge gen 10 g, baked rou dou kou 3 g. Make into decoction and use as tea. External injury of the head with swelling: use raw pu huang and apply to the injury, 3 times a day. Bleeding in external injuries, hemorrhoids, boils, inflammation of the rib cartilage (without pus), rash in babies | Cautiously used |
| 100          | Typhonii rhizoma      | 白附子 (Bai Fuzi) | 3–6  | Similar as 2                     | Cautiously used |
| 101          | Vaccariae semen       | 王不留行 (Wang Bulixing) | 5–10 | Promote diuresis                 | Cautiously used |
| CHM (English) | CHM (Biological name) | CHM (Chinese) | Dose | Actions and clinical indications | Classification in pregnancy |
|--------------|-----------------------|--------------|------|---------------------------------|----------------------------|
| 102 Wenyujin rhizoma concisum | Curcuma wenyujin Y.H. Chen et C. Ling | 片姜黄 (Pian Jianghuang) | 3–9 | Actions and indications: improves circulation of blood and qi, promotes flow of menses and relieves pain. For wind chill induced shoulder pain, mood fluctuations, schizophrenia, fever with dizziness, vomiting blood, nose bleeding, blood in urine, bleeding not during menses, jaundice, lower back pain, chest and abdomen pain caused by blood stasis, flatulence, pain during period of menses, injuries, bruises and swelling. Angina, treatment of pain in the rib area, gallbladder stones, postpartum pain. Today’s application: high lipids, angina pectoris, rheumatoid arthritis, inflammation after surgery, periodontitis, tumor, acid dyspepsia, flatulent dyspepsia, atonic dyspepsia, shingles/herpes zoster, herpes simplex, coronary atherosclerosis, for inhibiting building up of β-amyloid, leukemia | Cautiously used |

Similar: the clinical application and or the therapeutical effects of these CHMs are similar.
Same: (1) The CHMs are origin from different parts of a same plant or animal. (2) The CHMs are origin from the same part of the same plant or animal, but prepared in a different way for clinical medications.

Table 1. Summary of 105 CHMs for pregnancy [15, 16].
3.3.6. Data extraction, evaluation and management

Extraction form was designed and used to extract data. For eligible studies, two review authors extracted the data, any discrepancy was resolved through discussion or the third person was consulted. For each selected literature, publication year, study population, participant numbers, maternal age, gestation age, symptoms and signs, clinical diagnosis, examination and laboratory results, disease course, study intervention, standard or modified Chinese medicine formulas, individual medicine, immediate and follow-up outcomes were recorded. But only the data related to the safety classification and adverse outcomes would be reported in this review.

4. Results

4.1. Chinese pharmacopeia and literature study

There were 105 CHMs in Chinese pharmacopeia remarked with potential toxicity classification for pregnant women, of which 38 were “contraindicated”, 2 were “not recommended” and 65 were “cautiously used” during pregnancy. Three of them were repeated under different common names, so we studied and collected information of 102 CHMs (Table 1) [15]. Some of the CHMs were origin from the same part of a plant, but they were prepared and applied in different format. Although their properties and safety outcomes were similar, we kept them separately list in the summary table.

An extension search on the cited references was carried out, and data of around another 600 studies were further extracted [15, 16]. A summary included the common name (English name), the biological name (Latin name), the original name (Chinese name), the recommended dose range in Chinese Pharmacopeia, clinical effects/indications and the safety classification in pregnancy of these 102 CHMs was reported in Table 1.

4.2. Adverse outcomes

4.2.1. General adverse effects and lethal effects

Among these 102 CHMs for pregnancy, around 80% were reported with their safety in clinical trials and or animal studies.

In those 38 “contraindicated” CHMs, 28 (73.7%) of which reported either general adverse effects or lethal effects (Table 2). About 16 of 38 (42.1%) CHMs were recorded with general adverse outcomes such as gastrointestinal discomfort including nausea, vomiting, lethargy, abdominal pain, diarrhea; nervous system problems such as drowsiness, headache, dizziness, respiratory failure, shock, dermatitis and ulcers, damage to multi-organ/systems, and so on. About 18 of 38 (47.4%) CHMs were recorded with lethal effects in human and mammals like mice, rats and rabbits. Immediate death was reported when Realgar Tragacanth (a component of Realgar) was orally administrated to mice, but details of the dose and dosing were not reported.
| No. | CHM (English) | Adverse outcomes | Reproductive adverse outcomes |
|-----|---------------|------------------|-------------------------------|
|     |               | General adverse effects | Lethal effects | Maternal effects | Fetal effects |
| 1   | Aconiti kusnezoffii radix |               |               |               |               |
| 2   | Aconiti radix |               | Death (human, po, 2-5 mg component) |               |               |
| 3   | Anemones raddeanae rhizoma |               |               |               |               |
| 4   | Aristolochiae fructus |               | Death (rabbit, ip, other details not available) | Stimulation on uterine muscle |               |
| 5   | Aristolochiae herba |               |               |               |               |
| 6   | Calomelas | Necrosis in multiple organs: heart, kidney, liver, lung, ovary (animals) |               |               |               |
| 7   | Cinnabar | Damage to heart, liver and kidney (mice, po, component 9.5 g/kg) | Decrease of pregnancy rate (mice, po) |               |               |
| 8   | Crotonis fructus | 1. Inducing dermatitis; 2. Sore throat, abdominal pain, watery diarrhea or bloody mucus, cyanosis, shock (human and animals) | Death (human, po, 20 drops) |               |               |
| 9   | Crotonis semen pulveratum |               |               | Anti-pregnancy effect: interfere with implantation | Affect fetal growth |
| 10  | Curcumae rhizoma |               |               |               |               |
| 11  | Datura flos | Chromosome damage |               |               |               |
| 12  | Erycibe schmidtii | 1. Chronic toxicity on nervous system (mice); 2. Cardiac arrhythmias and death (rabbit, details not available) | Inhibition effects on uterus (pregnant rats) |               |               |
| 13  | Euphorbiae pekinensis radix | Dermatitis | Death | Stimulation on pregnancy uterus |               |
| 14  | Euphorbiae semen | 1. Diarrhea; 2 Persistent abdominal pain, nausea, vomiting, lethargy, drowsiness (human) | Death (human) |               |               |
| No. | CHM (English)               | General adverse effects | Lethal effects | Reproductive adverse outcomes |
|-----|-----------------------------|-------------------------|----------------|------------------------------|
| 15  | Euphorbiae semen pulveratum | 1. Diarrhea; 2. Persistent abdominal pain, nausea, vomiting, lethargy, drowsiness (human) | Death (human)  |                              |
| 16  | Eupolyphaga steleophaga     |                         |                |                              |
| 17  | Ferulae resina              |                         |                | 1. Termination of pregnancy: induce miscarriage (pregnant mice, po, component 180 mg/kg); 2. Stimulation on pregnancy uterus (rabbit and mice) |
| 18  | Genkwa flos                 |                         |                | Termination of pregnancy: 1. Induce miscarriage (pregnant monkeys, amniotic injection for 1–3 days, component 0.2–8 mg); 2. Stimulation on pregnancy uterus (rabbit) |
| 19  | Gleditsiae fructus abnormalis | 1. Hemolysis; 2. Local mucosal irritation, damage to central nervous system, respiratory failure, death (mammals) | Death (mammals) |                              |
| 20  | Ground beetle               |                         |                |                              |
| 21  | Hirudo                     |                         |                | 1. Termination on pregnancy: 1.25 g/kg; 2. Termination on pregnancy: (ih on pregnancy d1, d6, d10, bid, decoction 2.5–3 g/kg) |
| 22  | Hydrargyri oxydum rubrum   |                         | Death (component HgO₃) |                              |
| 23  | Hyoscyami semen             |                         |                | Chromosome damage            |
| 24  | Kansui radix               | Hemolysis effect on quadriceps (rabbit) | Anti-fertility effects: placenta damage, miscarriage | 1. Recorded embryotoxicity, but no malformation on fetus (rabbit, details not available); 2. Interfere with fetal circulation system |
| No. | CHM (English) | Adverse outcomes | Reproductive adverse outcomes |
|-----|--------------|------------------|------------------------------|
|     |              | General adverse   | Lethal effects               | Maternal effects | Fetal effects |
|     |              | effects           |                              |                 |              |
| 25  | Moschus      |                  | Death (mice, iv)             | 1. Stimulation on uterus, esp. Later stage of pregnancy (rabbit, guinea pig, rat); 2. Anti-early pregnancy and anti implantation |
| 26  | Mylabris     | 1. Poisoning dogs and mice were liver and kidney damage (dogs and mice); 2. Acute poisoning of digestive, kidney, nervous system symptoms, such as blisters, ulcers, nausea and vomiting, oliguria, hematuria, dysuria, dizziness, blurred vision, high fever, shock and other symptoms (human, po) | Death (human, po, 3 g) |
| 27  | Nigellae semen |                  |                              |                 |              |
| 28  | Papaveris pericarpium | 1. Headache, dizziness, nausea and vomiting, constipation, urinary urgency and dysuria, sweating, biliary colic, the risk for respiratory depression; 2. Acute poisoning as lethargy, miosis, respiratory depression; 3. Infant poisoning can occur convulsions (human) |                              |
| 29  | Pharbitidis semen | Under large dose (animals): 1. Gastrointestinal irritation symptoms such as vomiting, abdominal pain, diarrhea, bloody mucus; 2. Kidney stimulation symptoms such as severe hematuria; 3. Nervous system such as language barrier, coma | Stimulation on pregnancy uterus (rat) |
| No. | CHM (English)                              | Adverse outcomes                                                                 | Reproductive adverse outcomes |
|-----|-------------------------------------------|----------------------------------------------------------------------------------|-------------------------------|
|     |                                           | General adverse effects                                                                 | Lethal effects | Maternal effects | Fetal effects |
| 30  | Phytolaccae radix                         | Vomiting (cat, po, 2.5–10 g/kg), damage to brain (mice, po)                       |                 |                 |               |
| 31  | Realgar                                   | Immediate death (mice, po, component)                                             |                 |                 |               |
| 32  | Rhododendri mollis flos                    | Dermatitis                                                                       |                 |                 |               |
| 33  | Scolopendra                               | Death                                                                            |                 |                 |               |
| 34  | Scorpio                                   | Death (rabbit, iv, 0.5 mg/kg)                                                    | Specific toxicity: fetal malformation on bone development |
| 35  | Sparganii rhizoma                         | Death (mice, ip for 7 days)                                                      | Stimulation on uterus (pregnant rabbits) |
| 36  | Strychni semen                            | 1. Death (mice, details not available); 2. Death (human, po, 30 mg)              |                 |                 |               |
| 37  | Strychni semen pulveratum                 | 1. Death (mice, details not available); 2. Death (human, po, 30 mg)              |                 |                 |               |
| 38  | Toxidendri resina                         |                                                                                  |                 |                 |               |
| 39  | Gleditsiae sinensis fructus                | Chronic toxicity (mammal, po)                                                    | Death (human, po)                         |
| 40  | Saussureae involucratae herba             |                                                                                  |                 |                 |               |
| 41  | Abelmoschi corolla                        |                                                                                  |                 |                 |               |
| 42  | Achyranthis bidentatae radix              |                                                                                  | 1. Stimulation on non-pregnancy and early pregnancy uterus (mice); 2. Inhibition effects on both non-pregnancy and early pregnancy uterus (guinea pig); 3. Anti-fertility effect on pregnancy (mice) |
| 43  | Aconiti kusnezoffii folium                |                                                                                  |                 |                 |               |
| 44  | Aconiti kusnezoffii radix cocta           |                                                                                  |                 |                 |               |
| No. | CHM (English) | Adverse outcomes | Reproductive adverse outcomes |
|-----|--------------|------------------|------------------------------|
|     |              | General adverse effects | Lethal effects | Maternal effects | Fetal effects |
| 45  | Aconiti lateralis radix praeparata |  |  |  |  |
| 46  | Aconiti radix cocta |  |  |  |  |
| 47  | Aloe | 1. local muscle necrosis (dog, muscle injection, high dose of decoction); 2. abdominal pain and pelvic congestion, nephritis. |  |  |  |
| 48  | Arisaematis rhizoma | 1. Weight loss, weakness, death, the water decoction of rabbit conjunctival irritation; 2. Emetic effect (mice, po, raw herb 40 g/kg) | Death (rabbit) |  |  |
| 49  | Arisaematis rhizoma preparatum |  |  |  |  |
| 50  | Aurantii fructus |  | 1. Stimulation effects on uterus (rabbit); 2. Inhibition effects on uterus (mice) |  |  |
| 51  | Aurantii fructus immaturus | Gastrointestinal expansion and salivate phenomenon (some animals, po) | 1. Stimulation effects on uterus (rat and rabbit); 2. Inhibition effects on uterus (mice) |  |  |
| 52  | Borneolum | 1. Chronic toxicity to peripheral blood parameters and organ weight effects; 2. Liver damage (rat, po, 5 g/kg); 3. Neurotoxic effects (rat, po, 5 g/kg) | 1. Induced abortion (mice, intraperitoneal injection once, 1/4, 1/8, 1/16ld50, either in early pregnancy (7–9d), mid pregnancy (10–14d) and late pregnancy (16–18d)); 2. Induction effect in mid and late pregnancy (mice) |  |  |
| 53  | Borneolum syntheticum | 1. Chronic toxicity to peripheral blood parameters and organ weight effects; 2. Liver damage (rat, po, 5 g/kg); 3. Neurotoxic effects (rat, po, 5 g/kg) | 1. Induced abortion (mice, intraperitoneal injection once, 1/4, 1/8, 1/16ld50, either in early pregnancy (7–9d), mid pregnancy (10–14d) and late pregnancy (16–18d)); 2. Induction effect in mid and late pregnancy (mice) |  |  |
| No. | CHM (English)          | Adverse outcomes                                                                 | Reproductive adverse outcomes                                                                 |
|-----|-----------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| 54  | Bovis calculus        | Fewer activities (mice, po, 7.5 g/kg)                                            | Stimulation effects on pregnancy uterus and anesthesia uterus (rabbit, 0.9 mg component)     |
| 55  | Bovis calculus        |                                                                                  |                                                                                                |
| 56  | Bovis calculus        |                                                                                  |                                                                                                |
| 57  | Bufonis venenum       |                                                                                  |                                                                                                |
| 58  | Campsis flos          |                                                                                  | 1. Inhibition effects on mice non-pregnancy uterus (mice, 7.5 mg/ml); 2. Stimulation effects on pregnancy uterus |
| 59  | Carthami flos         | Low-spirited poisoning symptoms, reduced activity, walking difficulties (mice, intragastric and intraperitoneal injection, decoction) | Death (mice, intraperitoneal injection, component)                                             |
| 60  | Cinnamomi cortex      |                                                                                  | Stimulation effects on uterus (more obvious on pregnancy uterus than non-pregnancy one)      |
| 61  | Cinnamomi ramulus     | The toxic effects of guizhi on mice have significant differences between day and night, the daytime toxic and lethal effects were significantly enhanced at night (mice) |                                                                                                |
| 62  | Coicis semen          |                                                                                  |                                                                                                |
| 63  | Croci stigma          | Death (mammals)                                                                  | Stimulation effects on both non pregnancy and pregnancy uterus (mice, puinea pig, rabbit, god, cat) |
| 64  | Cyathulae radix       |                                                                                  | 1. Stimulation effects on pregnant uterus (rabbit and cat); 2. Miscarriage rate 100% (mice, po for 7 days, component 2.5 g/kg) |
| 65  | Dianthi herba         |                                                                                  | Stimulation on pregnancy uterine (rabbit and rat)                                             |
| No. | CHM (English) | Adverse outcomes | Reproductive adverse outcomes |
|-----|---------------|------------------|-----------------------------|
|     |               | General adverse  | Lethal effects               | Maternal effects | Fetal effects |
| 66  | Dichroae radix |                   |                            |                |              |
| 67  | Echinopsis radix |             |                            |                |              |
| 68  | Euphorbiae hirtae herba |       | Increase miscarriage rate (pregnant mice, iv, 1.2 mg/kg on d8, d12 or d16) |                |              |
| 69  | Ferrous sulfate | Vomiting, abdominal pain, diarrhea, dizziness and other adverse reactions |                |                |              |
| 70  | Gendarussae herba |                   |                            |                |              |
| 71  | Haematitum | Liver and lung damage (mice, po, 15–30% decoction) |                |                |              |
| 72  | I-borneolum | 1. Chronic toxicity to peripheral blood parameters and organ weight effects; 2. Liver damage (rat, po, 5 g/kg); 3. Neurotoxic effects (rat, po, 5 g/kg) | 1. Induced abortion (mice, intraperitoneal injection once, 1/4,1/8,1/16ld50, either in early pregnancy (7–9d), mid pregnancy (10–14d) and late pregnancy (16–18d)); 2. Induction effect in mid and late pregnancy (mice) |                |              |
| 73  | Impatientis semen |                   | 1. Anti-fertility effects (mice, po, decoction 3 g/kg); 2. Stimulation effects on uterus (mice, guinea pig and rabbit) |                |              |
| 74  | Leonuri herba | 1. Stimulation effects on uterus (mice, guinea pig, rabbit, dog, po, decoction and components); 2. Anti implantation and anti early pregnancy (mice, po, 0.1 ml for 4–5 times) |                |              |
| 75  | Limonitum | Antifeedant, pulmonary congestion, hepatomegaly (mice, iv, decoction) |                |                |              |
| 76  | Manis squama |                   |                            |                |              |
| 77  | Melanteritum |                   |                            |                |              |
| 78  | Meliae cortex | Stomach damage (rats) and inflammation (dogs) | Death (dogs, rabbits, monkeys, po, component) |                |              |
| 79  | Momordicae semen |                   |                            |                |              |
| No. | CHM (English)                          | Adverse outcomes                                                                 | Reproductive adverse outcomes |
|-----|--------------------------------------|----------------------------------------------------------------------------------|-------------------------------|
|     |                                      | General adverse effects                                                          | Lethal effects                |
| 80  | Moutan cortex                         | Some central inhibition such as temperature decreasing, reaction disappeared, reduced activity, reduced respiratory, etc. (mice, intraperitoneal injection, component) |                               |
| 81  | Myrrha                                |                                                                                  |                               |
| 82  | Natrii sulfas                         | Death (mice, intraperitoneal injection, decoction)                               | Death (mice, intraperitoneal injection, decoction) |
| 83  | Natrii sulfas exsiccatus              | Induce cancer                                                                    |                               |
| 84  | Notoginseng radix et rhizoma          | Acute and chronic toxicity reported, but details not available                    |                               |
| 85  | Olibanum                              |                                                                                  |                               |
| 86  | Persicae semen                        | Visible muscle relaxation, ataxia, piloerection and other phenomena (mice, intraperitoneal injection of 3.5 g/kg decoction) | Stimulation on pregnant uterine |
| 87  | Physsochlainae radix                  | Reduced activity, but recover on the next day (mice, intraperitoneal injection, 1 g/ml water extract) |                               |
| 88  | Polygoni cuspidati rhizoma et radix   | Different degree of peritonitis, the severity and scope and dosage showed parallel effects, 700 mg/kg dose group was administered after 6 weeks can cause white blood cell count was significantly reduced, but there were no significant changes in blood and liver and kidney function. (rats, intraperitoneal injection, component) |                               |
| No. | CHM (English) | Adverse outcomes | Reproductive adverse outcomes |
|-----|---------------|------------------|-----------------------------|
|     |               | General adverse  | Lethal effects               | Maternal effects | Fetal effects |
|     |               | effects          |                            |                |
| 89  | Pruni semen   |                  |                             |                |
| 90  | Psammosilenes radix |          |                             |                |
| 91  | Rhapontici radix |                 |                             |                |
| 92  | Rhei radix et rhizoma | 1. Long-term toxicity like cirrhosis and electrolyte metabolism (mice, po); 2. Overdose causes poisoning, nausea, vomiting, dizziness (mice, po). | | |
| 93  | Sappan lignum |                  |                             |                |
| 94  | Selaginellae herba |                |                             |                |
| 95  | Sennae folium |                  |                             |                |
| 96  | Sulfur        | 1. Antifeedant and hepatomegaly (mice, po, decoction); 2. Overdose causes sulfur, central nervous damage and death (mice, po). | Death (mice, po, overdose) | |
| 97  | Tetrapanacis medulla |                  |                             |                |
| 98  | Trichosanthis radix | 1. Allergies (human, animals); 2. General toxicity: loss of appetite, damage to heart, liver and kidney, and central nervous system, death (female dog, im, 0.2–2 mg/kg) | Death (female dog, im, 0.2–2 mg/kg) | 1. Miscarriage; 2. Stimulation effects on pregnant uterus (rabbit) |
| 99  | Typhae pollen | 1. Allergic reaction (guinea pig, intraperitoneal injection, decoction); 2. Hemolysis; 3. Reduction of red blood cells and white blood cells (mice) | 1. Stimulation effects on uterus (mice, rat, guinea pig, rabbit) 2. Induction effects (guinea pig, mice, intraperitoneal injection, 50% decoction 3–2 g/kg) 3. Induced abortion (mice, po, decoction 10–20 g/kg) | Induced fetal death (mice, po, decoction 10–21 g/kg) |
| 100 | Typhonii rhizoma | Difficulty breathing, reduced activity, individual animal death (mice, po, decoction) | Individual animal death (mice, po, decoction) | |
In 2 “not recommended for pregnancy” CHMs (Table 2), Gleditsiae Sinensis Fructus (Moschus berezovskii Flerov, DajiaoZao) was recorded with both general effects of chronic toxicity in oral administration to mammals and lethal effects when human took a higher dose. No obvious adverse effects were recorded to the other CHM, Saussureae Involucratae Herba (Saussurea involucrata (Kar.et Kir.) Sch.-Bip., TianShanXueLian). Although it has great therapeutical function of improve the immune system, due to its pharmacological effects to enhance the blood circulation and stimulate the contraction of uterus, it may induce abortion during pregnancy, so it was not recommended for pregnant women.

In 65 “cautiously used” CHMs, 33 (50.8%) of which reported either general adverse effects or lethal effects (Table 2). About 24 of 65 (36.9%) CHMs were recorded with same general adverse outcomes such as gastrointestinal discomfort, nervous system problems, skin disorders and multi-organ damage. Other adverse effects such as muscle necrosis, pelvic congestion and cancer were also recorded. A total of 9 of 38 (13.8%) CHMs were recorded with lethal effects in human and mice. One study also reported that Meliae Cortex (Melia toosendan Sieb.et Zucc.; Melia azedarach L, KuJianPi) could cause death of rabbits, dogs and monkeys after oral administration of high dose of Toosendanin (a component), and the main reason is visceral bleeding, decreased blood pressure then acute circulatory failure.

4.2.2. Maternal and fetal adverse effects

Generally speaking, more maternal adverse effects were recorded than fetal effects. But this may be due to the failure of early pregnancy of mothers.

In those 38 “contraindicated” CHMs, 2 (5.3%) of which reported adverse effects on both mothers and fetuses (Table 2). A total of 12 of 38 (31.6%) CHMs were recorded with maternal adverse outcomes such as lower pregnancy rate (mainly due to anti-implantation), miscarriage (mainly due to effects on uterus), placenta damage and so on. About 3 of 38 (7.9%) CHMs were recorded with fetal adverse effects on bone development, circulation system and malformation.

No obvious maternal and fetal adverse effects were reported in those two “not recommended for pregnancy” CHMs (Table 2).
In those 65 “cautiously used” CHMs, 1 (1.5%) of which reported adverse effects on both mothers and fetuses (Table 2). About 20 of 65 (30.8%) CHMs were recorded with same maternal adverse outcomes as the “contraindicated” CHMs, and the study animals included mice, guinea pigs, rats and rabbits. Only 1 of 65 (1.5%) CHMs, Typhae Pollen (Typha angustifolia L, PuHuang), was recorded with mouse fetal death under oral administration of a 10–21 g/kg decoction.

4.3. Animal toxicity data

In Table 3, we summarized the toxicity data of those 102 CHMs from different animal studies and provided the information of LD50, dose, doing and species [15]. About 21 of 102 (20.6%) CHMs have more than one LD50 data, by applying raw herb, main/active components, water extraction and decoction or applying different species of animals. But 35 of 102 (34.3%) CHMs did not have a LD50 record. One implied reason is the CHM is too safe to test a LD50 data. Another reason is that half of these CHMs without a LD50 data were mineral origin, and there have been no study carried out to test their LD50 so far.

| No. | CHM (English) | LD50 | Dosing | Species | Remarks |
|-----|--------------|------|--------|---------|---------|
| 1   | Aconiti kusnezoffii radix | 1.62–5780 mg/kg | po, ip | Mouse |
| 2   | Aconiti radix | 0.3–18.0 mg/kg | ig, iH | Mouse |
| 3   | Anemones raddeanae rhizoma | 4 | |
| 4   | Aristolochiae fructus | 0.02 g/kg | iv | Mouse |
| 5   | Aristolochiae herba | 410–2068 mg/kg | ig | Mouse |
| 6   | Calomelas | 1740 mg/kg | iH | Mouse |
| 7   | Cinnabaris | 12.10 g/kg | po | Rabbit |
| 8   | Crotonis fructus | 50–80 mg/kg | po | Rat |
| 9   | Crotonis fructus | 1600 mg/kg | po | Mouse |
| 10  | Curcumae rhizoma | 600 mg/kg | po | Guinea pig |
| 11  | Daturae flos | 8.2 mg/kg | po, ip | Mouse |
| 12  | Erycibe schmidtii | 6.22–8.85 mg/kg | po | Mouse |

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| No. | CHM (English)                      | LD50       | Dosing | Species | Remarks                                                                 |
|-----|-----------------------------------|------------|--------|---------|--------------------------------------------------------------------------|
| 14  | Euphorbiae semen                  |            |        |         |                                                                          |
| 15  | Euphorbiae semen pulveratum       |            |        |         |                                                                          |
| 16  | Eupolyphaga steleophaga           | 146.45 mg/kg | ip     | Mouse   |                                                                          |
| 17  | Ferulae resina                    |            |        |         |                                                                          |
| 18  | Genkwa flos                        | 9.25 g/kg  | ip     | Rat     |                                                                          |
| 19  | Gleditsiae fructus abnormalis     |            |        |         |                                                                          |
| 20  | Ground beetle                     | 146.45 mg/kg | ip     | Mouse   |                                                                          |
| 21  | Hirudo                            | 15.28 g/kg | iH     | Male mouse | Mouse, po, qd, decoction 500 and 1000 mg/kg, lower maternal weight, higher resorption rate, fetal malformation rate, higher neonatal mortality |
| 22  | Hydrargyri oxydum rubrum          | 22–120.98 mg/kg | ig     | Mouse   |                                                                          |
| 23  | Hyoscyami semen                   |            |        |         |                                                                          |
| 24  | Kansui radix                      | 30–346.1 mg/kg | ip     | Mouse   |                                                                          |
| 25  | Moschus                           | 152–848 mg/kg | ip, iv | Mouse   |                                                                          |
| 26  | Mylabris                          | 1.71–1037 mg/kg | ig, ip, iv | Mouse   |                                                                          |
| 27  | Nigellae semen                    |            |        |         |                                                                          |
| 28  | Papaveris pericarpium             | 64–600 mg/kg | iH, ip, po | Rat     |                                                                          |
| 29  | Pharbitidis semen                 | 37.5 mg/kg | lh     | Mouse   |                                                                          |
| 30  | Phyto lactae radix                | 11.87–486 mg/kg | ig, ip, iv | Mouse   |                                                                          |
| 31  | Realgar                           | 3.207 g/kg | ig     | Mouse   |                                                                          |
| 32  | Rhododendri mollis flos           | 0.25–5850 mg/kg | ig, po, iv, iH | Mouse   |                                                                          |
| 33  | Scolopendra                       | 22.5–9900 mg/kg | ig, ip | Mouse   |                                                                          |
| No. | CHM (English) | LD50 | Dosing | Species | Remarks |
|-----|---------------|------|--------|---------|---------|
| 34  | Scorpio       | 2.4–10.3 g/kg<sup>1,2</sup> | iv, ip | Mouse   |         |
| 35  | Sparganii rhizoma | 55.8–233.3 g/kg<sup>3</sup> | ip     | Mouse   |         |
|     |                | raw herb |        |         |         |
| 36  | Strychni semen | 1.53–301.9 mg/kg<sup>1,2,4</sup> | ig, ip | Mouse   |         |
| 37  | Strychni semen pulveratum | 301.9 mg/kg<sup>2</sup> | ig     | Mouse   |         |
| 38  | Toxicodendri resina |         |        |         |         |
| 39  | Gleditsiae sinensis fructus |         |        |         |         |
| 40  | Saussureae involucratae herba |         |        |         |         |
| 41  | Abelmochi corolla |         |        |         |         |
| 42  | Achyranthis bidentatae radix | 6.4–146.49 g/kg<sup>1</sup> | ig, ip | Mouse   |         |
| 43  | Aconiti kusnezoftii folium |         |        |         |         |
| 44  | Aconiti kusnezoftii radix cocta |         |        |         |         |
| 45  | Aconiti lateralis radix praeparata | 0.1–17400 mg/kg<sup>1,2</sup> | ig, iv, ip, Ih | Mouse |         |
| 45  | Aconiti lateralis radix praeparata (minimum lethal dose) | 0.102 mg/kg | iv | Rat |         |
| 45  | Aconiti lateralis radix praeparata | 0.075–1.65 mg/kg<sup>1</sup> | iv     | Frog    |         |
| 45  | Aconiti lateralis radix praeparata | 0.04–0.05 mg/kg<sup>1</sup> | iv     | Rabbit  |         |
| 45  | Aconiti lateralis radix praeparata | 0.06–0.12 mg/kg<sup>1</sup> | iv     | Guinea pig |         |
| 46  | Aconiti radix cocta |         |        |         |         |
| 47  | Aloe |         |        |         |         |
| 48  | Arisaematis rhizoma | 13.5–210 g/kg<sup>1,2,4</sup> | ig, ip | Mouse   |         |
| 49  | Arisaematis rhizoma preparatum |         |        |         |         |
| 50  | Aurantii fructus |         |        |         |         |
| 51  | Aurantii fructus immaturus | 71.8–267 g/kg<sup>2</sup> | iv, ip | Mouse   |         |
| 52  | Borneolum | 907–4960 mg/kg<sup>1</sup> | ig, ip | Mouse   |         |
| No. | CHM (English)               | LD50                        | Dosing       | Species | Remarks               |
|-----|----------------------------|-----------------------------|--------------|---------|-----------------------|
| 53  | Borneolum syntheticum      | 907–4960 mg/kg<sup>1</sup>  | ig, ip       | Mouse   |                       |
| 54  | Bovis calculus             | 497.5–6630 mg/kg<sup>1</sup> | ig, ip, iv   | Mouse   |                       |
| 55  | Bovis calculus artifactus  |                            |              |         |                       |
| 56  | Bovis calculus sativus      |                            |              |         |                       |
| 57  | Bufonis venenum            |                            |              |         |                       |
| 58  | Campsis flos               | 50 g/kg (raw herb, maximum tolerated dose) | ig        | Mouse   |                       |
| 59  | Carthami flos              | 2.35–20.7 g/kg<sup>1,2</sup> | ig, ig, iv   | Mouse   |                       |
| 60  | Cinnamomi cortex           | 42–46 g/kg<sup>1,2</sup>   | ip           | Mouse   |                       |
| 61  | Cinnamomi ramulus          | 624.7(daytime)–773.6(night) mg/kg<sup>2</sup> | ig        | Mouse   |                       |
| 62  | Coicis semen               | 10 ml/kg<sup>1</sup> (maximum tolerated dose) | po        | Mouse   |                       |
| 63  | Croci stigma               | 20.7 g/kg<sup>1</sup>      | po           | Mouse   |                       |
| 64  | Cyathulae radix            |                            |              |         |                       |
| 65  | Dianthi herba              |                            |              |         |                       |
| 66  | Dichroae radix             |                            |              |         |                       |
| 67  | Echinopsis radix           |                            |              |         |                       |
| 68  | Euphorbiae hirtae herba    |                            |              |         |                       |
| 69  | Ferrous sulfate            |                            |              |         |                       |
| 70  | Gendarussae herba          |                            |              |         |                       |
| 71  | Haematitum                 | 12.90 g/kg<sup>2</sup>     | iv           | Mouse   |                       |
| 72  | I-borneolum                | 907–4960 mg/kg<sup>1</sup>  | ig, ip       | Mouse   |                       |
| 73  | Impatientis semen          |                            |              |         |                       |
| 74  | Leonuri herba              | 0.572–60 g/kg<sup>1,2</sup> | iv           | Mouse   |                       |
| 75  | Limonitum                  | 8.25 g/kg<sup>2</sup>      | iv           | Mouse   |                       |
| 76  | Manis squama               |                            |              |         |                       |
| 77  | Melanteritum               |                            |              |         |                       |
| 78  | Meliae cortex              | 13.8–244.2 mg/kg<sup>1</sup> | ip, iv, iH, po | Mouse   |                       |
| 78  | Meliae cortex              | 9.8 mg/kg<sup>1</sup>      | iH           | Rat     |                       |
| 78  | Meliae cortex              | 4.2 mg/kg<sup>1</sup>      | iv           | Rabbit  |                       |
| 79  | Momordicae semen           |                            |              |         |                       |
| No. | CHM (English)                                | LD50              | Dosing          | Species    | Remarks                  |
|-----|---------------------------------------------|-------------------|-----------------|------------|--------------------------|
| 80  | Moutan cortex                               | 196–6900 mg/kg    | ig, iv, ip      | Mouse      |                          |
| 81  | Myrrha                                      |                   |                 |            |                          |
| 82  | Natrii sulfas                               | 6.738 g/kg        | ip              | Mouse      |                          |
| 83  | Natrii sulfas exsiccatus                    |                   |                 |            |                          |
| 84  | Notoginseng radix et rhizoma                | 33±5000 mg/kg     | ih, ivgtt, ip, po | Mouse      |                          |
| 84  | Notoginseng radix et rhizoma                | 498 mg/kg         | ivgtt           | Guinea-pig |                          |
| 85  | Olibanum                                    |                   |                 |            |                          |
| 86  | Persicae semen                              | 222.5 g/kg        | ip              | Mouse      |                          |
| 87  | Physochlainae radix                         | 43 g/kg           | ip              | Mouse      |                          |
| 88  | Polygoni cuspidati rhizoma et radix         | 249.5–1000 mg/kg  | ip              | Mouse      |                          |
| 89  | Pruni semen                                 |                   |                 |            |                          |
| 90  | Psammosilenes radix                         |                   |                 |            |                          |
| 91  | Rhapontici radix                            |                   |                 |            |                          |
| 92  | Rhei radix et rhizoma                       | 0.56–153.5 g/kg   | po              | Mouse      |                          |
| 93  | Sappan lignum                               | 18.9 g/kg         | ip              | Mouse      |                          |
| 94  | Selaginellae herba                          |                   |                 |            |                          |
| 95  | Sennae folium                               | 1.414 g/kg        | ip              | Mouse      |                          |
| 96  | Sulfur                                      | 0.266 g/kg        | ig              | Mouse      |                          |
| 97  | Tetrapanacis medulla                        |                   |                 |            |                          |
| 98  | Trichosanthis radix                         | 0.236–2.26 mg/each animal | iH | Mouse      |                          |
| 99  | Typhae pollen                               | 35.57 g/kg        | ip              | Mouse      |                          |
| 100 | Typhonii rhizoma                            | 29.57–32.58 g/kg  | iv              | Mouse      |                          |
| 101 | Vaccariae semen                             |                   |                 |            |                          |
| 102 | Wenyujin rhizoma concisum                   |                   |                 |            |                          |

1Main component(s).
2Herbal water extraction.
3Decoction.
4Raw herb.
ip: peritoneal injection; ig: intragastrical administration; iv: intravenous injection; iH: hypodermic injection; po: oral administration; im: intramuscular injection.

Table 3. Animal toxicity data of CHMs for pregnancy [15, 16].
5. Conclusions and recommendations

5.1. Chinese medicines are not free of risk

The active ingredients of the Chinese medicines are chemicals that are similar to prescribed drugs. Chinese medicines are not free of risk and they have the same potential to cause adverse effects.

In this overview of Chinese medicines for pregnancy with well-characterized reproductive toxicity, though these Chinese medicines are not commonly used in clinical practice, some of them could result in severe consequences when given in over dosages or even normal dosages. In the communities which use Chinese medicines, special attention should be paid and precautions should be taken to prevent mistaken overdoses of the Chinese medicines.

5.2. International guideline is necessary

It should be acknowledged that some of the studies from animals may not be comparable to human responses, both referring to Chinese medicines and Western medicines. Despite variations in clinical practice and therapeutic prescription, Chinese medication in Traditional Chinese Medicine should comply with modern pharmacological principles as in Western Medicine. Chinese medicines may be beneficial but may also adversely affect both mothers and fetuses in utero. International regulations have not been designed or specified to categorize the Chinese medicines for use in pregnancy. Until now, no detailed/well-designed reproductive toxicity and pharmacotoxicity studies are available to assess the potential risk of Chinese medicines during pregnancy, as much as true that conventional medications are not well tested in pregnancy too.

Before the detailed studies become available, here we take the initiative in gathering information about the adverse effects and potential toxicity of the Chinese medicines for pregnancy from Chinese Pharmacopeia and the extensive literature studies.

5.3. Recommendations

We hope more comprehensive and systematic experiments will be carried out. Until more reliable and scientific research data become available, clinicians should appraise both the risk and benefit before recommendations to pregnant women or women who plan to be pregnant. Both Chinese and Western physicians should explicitly elicit and document the history of the use of any Chinese medications. This is to prevent and recognize potential serious problems associated with their use and should encourage their discontinuation. More studies and clinical trials in humans with a larger sample size are obviously mandatory. We do recommend more systematic basic investigation of the safety use of Chinese medicines for pregnancy.

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