Review Article

Lonicerae Japonicae Flos and Lonicerae Flos: A Systematic Pharmacology Review

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Received 1 April 2015; Accepted 23 June 2015

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Lonicerae japonicae flos, a widely used traditional Chinese medicine (TCM), has been used for several thousand years in China. Chinese Pharmacopeia once included Lonicerae japonicae flos of Caprifoliaceae family and plants of the same species named Lonicerae flos in general in the same group. Chinese Pharmacopeia (2005 Edition) lists Lonicerae japonicae flos and Lonicerae flos under different categories, although they have the similar history of efficacy. In this study, we research ancient books of TCM, 4 main databases of Chinese academic journals, and MEDLINE/PubMed to verify the origins and effects of Lonicerae japonicae flos and Lonicerae flos in traditional medicine and systematically summarized the research data in light of modern pharmacology and toxicology. Our results show that Lonicerae japonicae flos and Lonicerae flos are similar pharmacologically, but they also differ significantly in certain aspects. A comprehensive systematic review and a standard comparative pharmacological study of Lonicerae japonicae flos and Lonicerae flos as well as other species of Lonicerae flos support their clinical safety and application. Our study provides evidence supporting separate listing of Lonicerae japonicae flos and Lonicerae flos in Chinese Pharmacopeia as well as references for revision of relevant pharmacopeial records dealing with traditional efficacy of Lonicerae japonicae flos and Lonicerae flos.

1. Introduction

Lonicerae japonicae flos (also Jinyinhua in Chinese), a plant species in traditional Chinese medicine (TCM), has been widely used as a drug for several millennia with confirmed curative effects. It has been recorded in the Chinese Pharmacopeia (1963 Edition), limiting the therapeutic use of Lonicerae japonicae flos to the dried flower buds of Lonicera japonica Thunb., which belongs to Caprifoliaceae. In the 1977, 1985, 1990, 1995, and 2000 Editions of Chinese Pharmacopeia, three other plant sources were also listed in the category of Lonicerae japonicae flos including the dried flower buds or initial flowers of Lonicera hypoglauca Miq., Lonicera confusa DC., and Lonicera dasystyla Rehd. Chinese Pharmacopeia (2005 Edition) lists Lonicerae japonicae flos and Lonicerae flos as independent items based on differences in medicinal history, plant morphology, medicinal properties, and chemical constituents, and the only plant source of Lonicerae japonicae flos is again limited to Lonicera japonica Thunb. Lonicerae flos has three sources of germplasm including Lonicera macranthoides Hand.-Mazz., Lonicera hypoglauca Miq., and Lonicera confusa DC. Chinese Pharmacopeia (2010 Edition) adds Lonicera fulvotomentosa Hsu et S. C. Cheng to Lonicerae flos following the 2005 Edition, making the afore-mentioned 4 plant species legal for Lonicerae flos. However, the descriptions of flavor, meridian tropism (MT), functions, and indications are not different between Lonicerae japonicae flos and Lonicerae flos in Chinese Pharmacopeia although they have different sources.

In order to comprehensively review the pharmacological studies, we investigate the efficacy of Lonicerae japonicae flos and Lonicerae flos in ancient books of TCM and
searched for the literatures both at home and abroad from the China Academic Journal Network Publishing Database of the China National Knowledge Infrastructure, Wanfang Database, China Biomedical Database, and MEDLINE/PubMed. A total of 2864 papers relevant to Lonicerae japonicae flos and Lonicerae flos are retrieved before August 2014, of which 514 dealt with pharmacological effects of main ingredients of Lonicerae japonicae flos and Lonicerae flos. The literatures are further collated to summarize the studies with clear information of the origin of species. Pharmacological advances are also systematically reviewed to provide references for scientific appreciation of Lonicerae japonicae flos and Lonicerae flos.

2. Traditional Records of Lonicerae Japonicae Flos [1]

Lonicerae japonicae flos is termed “Rendong” in ancient books of TCM. The Collective Notes to Canon of Materia Medica (around 480–498 AD) writes: “It grows everywhere and is classified into liane. It does not fade over winter and thus be named as Rendong.” Since then only the name “Rendong” has been recorded in all the medical books until Tang Dynasty. Subsequently in Song Dynasty, The Prescriptions of Su and Shen (960–1127 AD) and Lychanyan Materia Medica (1220 AD) used the term “Lonicerae japonicae flos” as a herb also named as Rendong.

Before Ming Dynasty, the Collective Notes to Canon of Materia Medica, Annotation of Materia Medica, and The Prescriptions of Su and Shen only provided a brief description of Rendong and the recorded characteristics of the original plant including liane, opposite leaf, and leaf shape consistent with those of Caprifoliaceae. In Ming Dynasty, the Compendium of Materia Medica (1578 AD) offered the most detailed description of Lonicera flower that “it blossoms in March and April with the length of flower over 3 decimeters. One pedicel contains 2 flowers and each flower has 2 petals either large or narrow with half-edge structure. It has stamens and pistils. The early flower has white stamens, pistils, and petals that turn yellow in 2 to 3 days.” In the ancient Materia Medica, An Illustrated Book of Plants authored by Wu Qijun in Qing Dynasty included the ink drawings of Lonicerae japonicae flos with accurate proportion and precise morphology. In addition, the Collected Essentials of Species of Materia Medica written in Ming Dynasty also contains representative colored illustrations of Lonicerae japonicae flos, and the archives show clearly the typical morphological characteristics of Caprifoliaceae including liane, 1 pedicel containing 2 flowers, lip-like and white flowers, opposite leaf, ovate shape, and lobate and ovate shape.

In summary, the original plant morphology of Lonicerae japonicae flos is basically similar in the studies before Qing Dynasty. No records of the medicinal use of Lonicerae flos have been found in ancient books. Based on comparative plant morphology, only Lonicera japonica Thunb., among 21 varieties of Lonicera, is consistent with the morphological characteristics of traditional medicinal Lonicerae japonicae flos while the other 4 species in Chinese Pharmacopeia (2010 Edition) were markedly different in origin.

According to Chinese Pharmacopeia (2005 and 2010 Editions), both Lonicerae japonicae flos and Lonicerae flos are sweet in flavor and cold in nature, attributed to lung, heart, and stomach meridians. They clear heat, toxins, and certain external ailments. They are indicated for carbuncles and pyocutaneous disease, pharyngitis, erysipelas, heat toxins, blood dysentery, exogenous hot ailments, and febrile diseases.

3. Modern Pharmacological Studies on Lonicerae Japonicae Flos and Lonicerae Flos

Lonicerae japonicae flos grows mainly in Shandong, Shaanxi, Henan, and Hebei Provinces in China, among which the Pingyi County, Linyi City, Shandong Province, is the main area with the largest production. Lonicerae flos is mainly grown in the provinces located at the southern regions of Yangtze River such as Hunan Province, Sichuan Province, Guangdong Province, Guizhou Province, and Guangxi Province. Recent studies have been focused on the pharmacological effects of Lonicerae japonicae flos. In contrast, the studies of Lonicerae flos are comparatively limited and most studies focus on Lonicera macranthoides Hand.-Mazz., which exhibits basically similar pharmacological effects as those of Lonicerae japonicae flos.

3.1. Antibacterial Effects

3.1.1. Lonicerae Japonicae Flos. Many pharmacologic studies have clearly confirmed the bacteriostatic and antibacterial effects of Lonicerae japonicae flos both in vivo and in vitro. Compared with other commonly seen antibacterial drugs, Lonicerae japonicae flos exhibits a broader antimicrobial spectrum, more powerful antibacterial activity, and inhibition of drug-resistant bacteria. The antibacterial activities of Lonicerae japonicae flos were detailed in Table 1.

Components of Lonicerae japonicae flos including water extract, alcohol extract, polysaccharide, and volatile oil can extensively inhibit Gram-negative bacteria and Gram-positive bacteria including Streptococcus haemolyticus, Staphylococcus aureus, Salmonella Typhi, Klebsiella pneumoniae, Salmonella paratyphi, Vibrio cholerae, oral pathogens, Diplococcus intracellularis, Streptococcus pneumoniae, Mycobacterium tuberculosis, and Pseudomonas aeruginosa. In particular, the water extracts of Lonicerae japonicae flos strongly inhibit Escherichia coli and Staphylococcus aureus but are comparatively weak against Pseudomonas aeruginosa and Shigella flexneri [2–12]. Based on in vivo antimicrobial tests, Lonicerae japonicae flos is fairly inhibitory to Staphylococcus aureus and Diplococcus pneumoniae but minimally active against other pathogens [13, 14]. A study reports that 10% Lonicerae japonicae flos extract has antibacterial effect against Escherichia coli and Staphylococcus aureus, which is equivalent to that of penicillin 100 μmol/mL [15], indicating characteristic high antibacterial activity similar to that of antibiotics.

The components of Lonicerae japonicae flos including water-soluble polysaccharides have remarkable inhibitory
| Variety | Part/compound | Antibacterial spectrum | Detection methods | References |
|---------|--------------|------------------------|-------------------|------------|
| **Lonicera japonicae flos**<br>Water extract | Gram-positive bacteria | *Streptococcus mutans, Actinomyces viscosus, Staphylococcus aureus, Bacillus subtilis*, pathogenic *Streptococcus* of recurrent aphthous ulcer | Dilution-plate method (for minimum inhibitory concentration [MIC]); filter paper method; agar diffusion method | [147–149] |
| | Gram-negative bacteria | Black-pigmented bacteria, *Pseudomonas aeruginosa* P29, *Pseudomonas aeruginosa, Escherichia coli* | Dilution-plate method (for MIC); replica plating method, elimination experiment; in vivo test; tube dilution method (for MIC); filter paper method | [19, 147, 148, 150] |
| Fungi | Penicillium, *Aspergillus flavus, Aspergillus niger, Epidermophyton floccosum, Trichophyton violaceum, Trichophyton schoenleinitii, Ashland's Grubyella variant Mongolia, Concentric endodermophyton, Trichophyton interdigitalis, ToéTrichophyton, dog Microsporum, Ferruginous microsporum, Nocardia asteroides* | Filter paper method; fungal inhibition test | [18, 148] |
| **Lonicera japonicae flos**<br>Water extracting-alcohol precipitating solution | Drug-resistant bacteria | MRSA, MRSH, MRSE, HILAR | Dilution-plate method (for MIC) | [22] |
| | Gram-positive bacteria | *Staphylococcus aureus* | Microdilution checkerboard method | [151] |
| | Gram-negative bacteria | *Salmonella, Escherichia coli* | Microdilution checkerboard method | [151] |
| **Lonicera japonicae flos**<br>Water extract and alcohol extract | Gram-positive bacteria | *Streptococcus suis* type 2 | Microtubule-plate method | [152] |
| | Gram-negative bacteria | *Bacillus subtilis, Staphylococcus aureus* | Circular paper method and MIC detection | [16] |
| | Gram-negative bacteria | *Escherichia coli, Proteus vulgaris* | Circular paper method and MIC detection | [16] |
| **Lonicera japonicae flos**<br>Water-soluble polysaccharide | Fungi | *Saccharomyces cerevisiae, Penicillium citrinum, Aspergillus niger Staphylococcus aureus, Bacillus subtilis, Staphylococcus albus* | Circular paper method and MIC detection | [16] |
| **Lonicera japonicae flos**<br>Supercritical carbon dioxide extract | Gram-positive bacteria | *Escherichia coli, Pseudomonas aeruginosa, Salmonella Typhimurium* | Agar diffusion method and tube dilution method (for MIC) | [14] |
| **Lonicera japonicae flos**<br>Total isochlorogenic acid, total chlorogenic acid, total flavone, total iridoid glycoside | Gram-negative bacteria | *Escherichia coli* | Microcalorimetric method | [153] |
| **Lonicera japonicae flos**<br>Chlorogenic acid | Gram-positive bacteria | *Sarcina lutea, Bacillus subtilis* | Dilution method (for MIC) | [154] |
| Variety                   | Part/compound                                                                 | Antibacterial spectrum                                                                 | Detection methods                                      | References |
|---------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------|------------|
| *Lonicera hypoglauca* Miq| alcohol extract 70%                                                            | Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa                        | Agar dilution method (for MIC)                         | [23]       |
|                           | Water extracting-alcohol precipitating solution of *Lonicera macranthoides*    | Staphylococcus aureus, Sarcina, Bacillus subtilis                                       | Disk agar diffusion method                             |            |
|                           | Hand.-Mazz.                                                                    | Escherichia coli, Pseudomonas aeruginosa, Salmonella Typhi                              |                                                        |            |
|                           | Glove extract of *Lonicera macranthoides* Hand.-Mazz. plumule                  | Staphylococcus aureus, Sarcina micrococcus, Bacillus subtilis                          |                                                        |            |
| *Lonicerae flos*          | Gram-positive bacteria                                                          | Escherichia coli, Pseudomonas aeruginosa, Salmonella Typhi                              |                                                        |            |
|                           | Gram-negative bacteria                                                         |                                                                                       |                                                        |            |
| *Lonicera macranthoides* Hand.-Mazz. components: phenolic acid (total chlorogenic acid), glycoside, flavonoid (total flavone), and volatile oil | Gram-positive bacteria                                                              | Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa                          | [29]       |
|                           | Gram-negative bacteria                                                         |                                                                                       |                                                        |            |
|                           | Water extract of *Lonicera hypoglauca* Miq.                                   | Staphylococcus aureus, Streptococcus haemolyticus, Streptococcus pneumoniae            | Punch method                                           | [28]       |
|                           | Gram-positive bacteria                                                          | Escherichia coli, Shigella flexneri, Salmonella Typhimurium                            |                                                        |            |
|                           | Gram-negative bacteria                                                         |                                                                                       |                                                        |            |
activities against fungi such as dermatophytes, *Saccharomyces cerevisiae*, *Penicillium citrinum*, *Aspergillus niger*, *Cryptococcus neoformans*, *Fusarium moniliforme*, *Candida albicans*, and *Aspergillus* sp. In addition, the volatile oil of Lonicerae japonicae flos has proven to have antifungal activities [16–18].

Current clinical antimicrobial treatments are associated with a high frequency of multidrug resistance and widespread plasmid resistance. Studies suggest that Lonicerae japonicae flos extracts not only potently inhibit common pathogens but also significantly suppress drug-resistant bacteria. In addition, the water decoction effectively inhibits drug-resistant *Pseudomonas aeruginosa* and sensitizes *Pseudomonas aeruginosa* to single antibiotic. Mice administered with extracts of Lonicerae japonicae flos show improved multiantibiotic sensitivities [19–21]. Lonicerae japonicae flos kills several clinically common drug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus haemolyticus* (MRSH), methicillin-resistant *Staphylococcus epidermidis* (MRSE), and high-level aminoglycoside resistant (HLAR) bacteria to varying degrees, and the antibiotic effects are positively correlated with drug concentration [22]. These experimental results further enrich our understanding of the antibacterial activity of Lonicerae japonicae flos and provide scientific data of therapeutic efficacy against drug-resistant pathogens.

### 3.1.2. Lonicerae Flos

Reports of efficacy and pharmacology of Lonicerae flos suggest several effective antifungal and antibacterial extracts (see Table 1).

The ethanol extracts, water extracting-alcohol precipitating solution, and water extracts of Lonicerae flos are strongly inhibitory against multiple pathogens such as *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus*, *Candida albicans*, *Escherichia coli*, *Salmonella Typhi*, *Shigella dysenteriae*, and *Pseudomonas aeruginosa* [23–25] and effectively protected *Staphylococcus aureus*-infected mice [26].

Lonicerae flos shows various antibacterial activities. The water extracts of *Lonicera macranthoides* Hand.-Mazz. are the most effective against *Staphylococcus aureus* and group B *Streptococcus* and effective against *Salmonella Typhi*, *Escherichia coli*, and *Shigella dysenteriae* but poorly effective against *Proteus vulgaris* [27]. Lonicerae flos (*Lonicera macranthoides* Hand.-Mazz., *Lonicera hypoglaucu* Miq.) from Sichuan has inhibitory effects against *Staphylococcus aureus*, *Streptococcus haemolyticus*, *Escherichia coli*, *Shigella flexneri*, *Salmonella Typhimurium*, and *Streptococcus pneumoniae*, but not against *Streptococcus haemolyticus* and *Salmonella Typhimurium* [28]. Although reports of antibacterial activity of Lonicerae flos vary, they still clearly indicate that the antibacterial pharmacologic activity of Lonicerae flos is markedly different depending on bacteriostatic effect.

The antibacterial effects of Lonicerae flos extracts vary with the different types and methods of preparation. For example, *Lonicera macranthoides* Hand.-Mazz. contains phenolic acids (total chlorogenic acids), glycosides, flavonoids (total flavones), and volatile oil that inhibit *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* to different degrees, with greater inhibition of *Staphylococcus aureus* than *Escherichia coli*. Further, phenolic acids have significantly better antibacterial effects than others [29].

### 3.2. Antiviral Effects

#### 3.2.1. Lonicerae Japonicae Flos

Lonicerae japonicae flos extracts and its active components including chlorogenic acid, flavonoid, caffeoylquinic acid, and iridoid glycoside can inhibit herpes simplex keratitis [30], influenza virus pneumonia [31], influenza A virus [31–33], porcine reproductive and respiratory syndrome virus [34], Newcastle disease virus [35], respiratory syncytial virus [36–38], influenza virus [39], human cytomegalovirus [40], and so on. In addition, the extracts can significantly inhibit and inactivate cytomegalovirus in guinea pigs [41], pseudorabies virus strain Min-A [42], influenza virus variant FMI [31], Coxsackie B virus [36, 43], enteric cytopathic human orphan 19 virus [43], and so forth. The mechanism of action entails enhancing the binding of drug with ceramidase [44] and increases cellular antiviral potency [45] and organ protection in influenza [46].

#### 3.2.2. Lonicerae Flos

The water extracts of *Lonicera macranthoides* Hand.-Mazz. significantly inhibit the infectivity of 293 cells by defective adenovirus (Ad-laCZ) [45, 46]. The alcohol-soluble component of *Lonicera hypoglaucu* Miq. named pheophytin is a hepatitis C virus (HCV) NS3 inhibitor (IC\_50 0.89 \(\mu\)M), which decreases the expression of HCV viral proteins and ribonucleic acids with dose-dependent effect [47].

The flavone extracts of Lonicerae flos (Lonicerae macranthoides Hand.-Mazz.) significantly inhibit and inactivate pseudorabies virus (PRV) infection of Vero cells [42]. The active components called chlorogenic acids significantly suppress the Newcastle disease virus (NDV) infection in Vero cells [48] and chlorogenic acids significantly inhibit the proliferation of NDV in Vero cells [49].

### 3.3. Anti-Inflammatory Effects

#### 3.3.1. Lonicerae Japonicae Flos

The water extracts of Lonicerae japonicae flos have significant anti-inflammatory effects on classical inflammatory models such as carrageenan/formaldehyde-induced rat paw swelling [50], mouse ear edema [13, 51], cotton ball granulomatous hyperplasia, mouse cutaneous vascular hyperpermeability [52], and egg white-induced localized acute inflammation [53]. Furthermore, it also exhibits anti-inflammatory effect in rat cervicitis model [54, 55], *Escherichia coli*-infected mouse model [56], excision wound model of infected rat [57], and ovalbumin-induced rat asthma model [58]. The mechanisms include inhibition of inflammatory factor synthesis/release, decreased expression of immune related molecules, and enzyme activities of matrix metalloproteinase.

The water extracts of Lonicerae japonicae flos inhibit the production of histamine and the expression of L-histamine decarboxylase by cultured human keratinocytes [59]. Further, it inhibits the production of nitric oxide and secretion of tumor necrosis factor-alpha (TNF-a) by Raw264.7 cells with dose-dependent effects [60] and prevents the trypsin-induced mast cell activation by suppressing the extracellular
Table 2: Anti-inflammatory effects of Lonicerae japonicae flos and Lonicerae flos.

| Species            | Part/compound                  | Detection methods                                                                 | References                  |
|--------------------|--------------------------------|-----------------------------------------------------------------------------------|-----------------------------|
| Lonicerae japonicae | Water extract                  | Carrageenan-induced paw swelling model, dimethylbenzene/formalin-induced inflammatory model, cotton ball granulomatous hyperplasia model, cervicitis model, *Escherichia coli* infection model, Raw264.7 cell activation model, trypsin-induced mast cell activation model, human keratinocyte three-dimensional culture inflammatory activation model | [50, 52, 54, 56, 59–61]    |
|                    | Alcohol extract 30%            | Croton oil-induced inflammatory model                                               | [55]                        |
|                    | Alcohol extract 57%            | Egg white-induced paw swelling model, dimethylbenzene-induced inflammatory model     | [51, 53]                    |
|                    | Alcohol extract 70%            | LPS-induced Raw264.7 cell activation model                                          | [62]                        |
|                    | Alcohol extract 95%            | Resection wound model, H1N1-infected human bronchial epithelial cell line A549 model | [57, 156]                   |
|                    | Alcohol extract               | Ovalbumin-induced asthma model                                                     | [58]                        |
|                    | Supercritical carbon dioxide extract | Dimethylbenzene-induced inflammatory model                                      | [31]                        |
| Lonicerae flos      | Water extract of *Loniceracranthoides* Hand.-Mazz. | Formalin pain model, acetic acid-writhing model, xylene-induced inflammation model, carrageenan-induced paw swelling model, yeast thermal model | [85]                        |
|                    | Water extract of *Loniceracranthoides* Hand.-Mazz. flower | Acetic acid-induced capillary permeability increase model, paw swelling model, cotton ball granulomatous hyperplasia model | [102]                       |
|                    | Supercritical carbon dioxide extract of *Loniceracranthoides* Hand.-Mazz. | Acetic acid-induced abdominal capillary permeability increase model, carrageenan-induced paw swelling model, pleuritis model, cotton ball granulomatous hyperplasia model | [65, 66]                    |
|                    | Water extract 50% and alcohol extract 95% of *Lonicerahypoglauca* Miq. | Dimethylbenzene-induced inflammation model, carrageenan-induced paw swelling model, cotton ball granulomatous hyperplasia model | [64]                        |

signal-regulated kinase (ERK) phosphorylation [61]. The polyphenols of *Lonicera japonica* Thunb. downregulate proinflammatory mediators and counter the lipopolysaccharides-induced inflammatory response of Raw264.7 cells by inhibiting NF-κB p65 nuclear translocation and p38 MAPK phosphorylation [62].

According to the Min Jiang research, it is clear that the anti-inflammatory activity of Flos Lonicerae Japonicae (FLJ) has profound material basis. By using UPLC-Q/TOF-MS and dual luciferase reporter gene assay, they revealed the potent NF-κB inhibition influence of the extract from FLJ, which could be classified into 2 types: chlorogenic acid and iridoid glycosides, including swertiamarin. More importantly, as reported in this study, the anti-inflammatory activity decreased during the flowering phases progression. This result suggested that the intensity of anti-inflammatory efficacy of FLJ is dynamically changed in distinct flowering phases, indicating that the effective components temporally affect the clinical application. Taken together, the molecular based quality control (including chlorogenic acid, swertiamarin, and sweroside) and the optimized pharmacological practice are extremely needed and urgent for FLJ [63].

### 3.3.2. Lonicerae Flos

Water and alcohol extracts of the leaves and flowers of Lonicerae flos have anti-inflammatory effects on dimethylbenzene-induced mouse ear edema, carrageenan-induced rat swelling, and cotton ball granulomatous hyperplasia model [23, 64]. The volatile organic compounds of Lonicerae flos (*Loniceracranthoides* Hand.-Mazz.) have some inhibitory effects on acetic acid-induced abdominal capillary permeability increase in mice, mouse ear edema, rat pleuritis, and cotton ball granulomatous hyperplasia, significantly lower the concentrations of prostaglandin E$_2$ (PGE$_2$) and malondialdehyde of the carrageenan-induced paw swelling in norepinephrine animals, and decrease the contents of PGE$_2$ and NO in acute pleural effusion of rat [23, 65, 66]. Moreover, the water extracts of Lonicerae flos (*Loniceracranthoides* Hand.-Mazz.) have significant anti-inflammatory effects by inhibiting the increased capillary permeability in mice, rat paw swelling, and cotton ball granulomatous hyperplasia [25]. The anti-inflammatory effects of both Lonicerae japonicae and Lonicerae flos were listed in Table 2.

### 3.4. Antioxidative Effects

#### 3.4.1. Lonicerae Japonicae Flos

The major antioxidants in Lonicerae japonicae flos include neochlorogenic acid, chlorogenic acid, 4-dicaffeoylquinic acid, caffeic acid, isochlorogenic acid A, isochlorogenic acid B, isochlorogenic acid C, rutin, xylostein, isouqueritrin, luteolin-7-O-glucoside, and luteolin [67, 68].

The alcohol extracts of Lonicerae japonicae flos have antioxidative effects on edible rapeseed oil, peanut oil, ghee,
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...of Lonicerae japonicae flos to the mouse model of acute liver injury induced by intraperitoneal injection of carbon tetrachloride (CCL₄) [88].

3.6.2. Lonicerae Flos. Two species of Lonicerae flos (Lonicera fulvotomentosa Hsu et S. C. Cheng and Lonicera macranthoides Hand.-Mazz.) confer different degrees of protection against rat/mouse liver injuries induced by CCL₄, D-galactosamine (D-Gal), and acetaminophen (AAP) [89]. Saponins of Lonicera fulvotomentosa Hsu et S. C. Cheng resolve AAP-induced liver injuries by lowering the cytochrome P450 concentration in liver cells of mouse [90–92]. The total saponins of Lonicera fulvotomentosa Hsu et S. C. Cheng significantly alleviate CCL₄-induced liver injuries, reduce liver injuries of the patient, and effectively lower the incidence of liver necrotizing changes and the total amount of spotty necrosis. Chlorogenic acid has potent choleric action that not only significantly increases bile secretion volume but also alleviates chromium-induced liver injuries [93, 94].

3.7. Immunoregulation

3.7.1. Lonicerae Japonicae Flos. Lonicerae japonicae flos decoction effectively improves human immunity, increases macrophage count, elevates phagocytic ratio and lymphocyte transformation rate [82], and enhances the secretion function of Th1 cells [95]. Lonicerae japonicae flos also promotes the phagocytic function of leucocytes. It decreases T-cell α-naphthyl acetate percentage of guinea pig and in vitro secretion of neutrophils and remarkably increases the production of IL-2 [96]. The water extracting-alcohol precipitating solution or the flavones of Lonicerae japonicae flos significantly elevate the organ index of immunosuppressed mice [97]. Lonicerae japonicae flos polysaccharides improve mouse splenocyte proliferation [98], markedly enhance immunity, and resolve delayed-type hypersensitivity. Serum hemolysin test shows that Lonicerae japonicae flos polysaccharides enhance humoral immune activities and raise the organ index of immunocompromised animal models, correlated with dosage [99]. Moreover, the water extracts of Lonicerae japonicae flos have significantly regulated immune response in scald-induced immunosuppressive model [100].

The water extracts of Lonicerae japonicae flos effectively substitute the highly toxic immunosuppressants such as cyclosporin A for the induction of immune tolerance. Lonicerae japonicae flos extracts combined with Con A significantly reduce the active degree of T lymphocytes [101] and avoided acute immunological rejection, hence effective in treating graft rejection.

3.7.2. Lonicerae Flos. The water extracting-alcohol precipitating solution of Lonicerae macranthoides Hand.-Mazz. significantly enhances thymus index, spleen index, carbon clearance, and macrophage phagocytic index in cyclophosphamide-induced immunocompromised mice and improves the proliferation of abdominal macrophages and splenic lymphocytes, with remarkable immunoregulatory effects [91, 102].
3.8. Antitumor Effects

3.8.1. Lonicerae Japonicae Flos. Intraperitoneal injection of Lonicerae japonicae flos polysaccharides 30 mg/kg and 90 mg/kg inhibited 23.95% and 30.02% of sarcoma S180, respectively, upregulated the expression level of Bax protein in mouse sarcoma S180, and increased Bax/Bcl-2 ratio and serum TNF-α concentration of tumor-bearing mice, indicating an antitumor effect that does not affect the normal growth and immune functions of tumor-bearing mice [103]. The polyphenolic extracts of Lonicerae japonicae flos inhibit proliferation of human hepatoma HepG2 cell line in a dose-dependent manner, decrease the expression of CDK1, CDC25C, cyclin B1, procaspases 3 and 8, and PARP, and promote the phosphorylation of ERK1/2, JNK, and MAPKs and the dephosphorylation of Akt, resulting in G2/M arrest and apoptosis [104].

3.8.2. Lonicerae Flos. The prosapogenin B of Lonicera macranthoides Hand.-Mazz. has relatively strong growth inhibition against several types of tumor cells especially HL-60, with a dose of 1.25–5 mg/kg corresponding to a 27.41–54.57% tumor inhibition rate in Lewis tumors. Genechip detection reveals that Lonicera macranthoides Hand.-Mazz. induces differential expression of 20 out of 84 tumor-associated genes in HL-60 cells, mainly via cell-cycle arrest and inhibition of cellular invasion and metastasis [105, 106]. The macranthoide B of Lonicera macranthoides Hand.-Mazz. inhibit the growth of 6 types of tumor cells, especially HL-60 cells with an IC50 of 3.8 μM by activating apoptosis [107]. Studies using high-throughput screening models indicate that the ethyl acetate extracts of Lonicera macranthoides Hand.-Mazz. suppress epidermal growth factor receptor (EGFR) kinase, with IC50 of 2.027 μg/mL. In addition, the phenolic acids and flavones in the extract may play a major role in inhibiting EGFR kinase [108].

3.9. Effects on Glucose and Lipid Metabolism. The water extracts of Lonicerae japonicae flos inhibit the alloxan-induced blood glucose elevation in mice [109]. The results of iodine-starch colorimetry and p-nitrophenyl α-D-glucopyranoside (PNPG) assay show that the water extracts dose dependently inhibit activities of α-amylase and α-glycosidase [110]. Another study indicates that Lonicerae japonicae flos extracts lower the triglyceride levels in serum and liver tissues of hyperlipidemia animal model without significantly affecting serum cholesterol, low-density lipoprotein, high-density lipoprotein, and liver tissue cholesterol [111].

3.10. Antiatherosclerotic (As) Effects. The intragastric administration of Lonicera macranthoides Hand.-Mazz. decreases the area of atherosclerotic plaque and plaque-to-wall area ratio and alleviates atherosclerotic changes in apolipoprotein E (ApoE) gene knockout mice and reduces lipid droplets and cholesterol concentrations of lipid-loaded THP-1 macrophages [112].

3.11. Antiallergic Effects

3.11.1. Lonicerae Japonicae Flos. The caudal vein of egg white lysozyme-sensitized mice with increased blood supply is reduced by 35% alcohol extracts of Lonicerae japonicae flos. This phenomenon indicates that 35% alcohol extracts have antiallergic effects, and the effective components include chlorogenic acid, iridoid, loganin, and sweroside [113].

3.11.2. Lonicerae Flos. The water extracts of Lonicera fulvotomentosa Hsu et S. C. Cheng are used to treat the bowel inflammation and ovalbumin- (OVA-) mediated type I hypersensitivity in mice. It also decreases the serum OVA-specific Ig E level of sensitized mice, relieves focal necrosis and abscession of small intestinal villi epithelial cells in mice, reduces the IgA+ plasma cell count of small intestinal lamina propria (LP), smlgA+ lymphocyte count of Peyer's patches (PP), and mRNA expression of IL-4 of small intestinal LP and PP, increases TGF-β mRNA of intestinal mucosa, and decreases the mRNA expression of small intestinal TNF-α with dose-dependent effects [114, 115]. Subcutaneous injection of Lonicerae flos total saponins alleviates diarrhea in mice to varying degrees, decreases mast cell aggregation and degranulation, lowers OVA-specific Ig E level, relieves OVA-mediated footpad edema, and reduces small intestinal villi inflammation, indicating that total saponins attenuate mouse Ig E- and immunocyte-mediated hypersensitive response [116, 117]. The volatile organic compounds of Lonicera macranthoides Hand.-Mazz. also inhibit heterologous passive cutaneous anaphylaxis of ear and dextran-induced pruritus in mice [118].

3.12. Antipregnancy Effects. Intraperitoneal injection of alcohol extracts of Lonicerae japonicae flos has inhibited early pregnancy in mice. Intravenous drip also shows good anti-pregnancy effects in dogs as early as days 20–22 at a dose-dependent manner [119].

3.13. Modulating Gut Microbiota. The water extracts of Lonicera fulvotomentosa Hsu et S. C. Cheng significantly improve intestinal folate deficiency and reduce Gram-negative bacterial resistance and intestinal flora imbalance in rat obstructive jaundice model [120]. The water extracts also promote the growth of bifidobacteria and lactobacilli in vitro, but they inhibit the growth at high concentration [121].

3.14. Antiultraviolet Radiation. Administration of water extracting-alcohol precipitating solution of Lonicerae japonicae flos reduces the breakage of wavy elastic fibers in the skin and the coiling degree of mouse model with ultraviolet radiation-aged skin injuries, possibly due to the antioxidant effects [122].

3.15. Antiendotoxin Effects. The water extracts 10 mg/mL of Lonicerae japonicae flos and chlorogenic acids 1 mg/mL destroy the ultrastructure of endotoxin [123].
3.16. Spasmolytic Effects. The decoction of Lonicerae japonicae flos inhibits the motility of isolated small intestine from rabbit and significantly reduces rabbit small intestinal smooth muscle contraction, electrical activity range (IC_{50}, 6.30 mg/mL), frequency, and area under curve in dose-dependent manner. Propranolol, L-NAME, and glibenclamide partly block the inhibitory effects of Lonicerae japonicae flos on rabbit small intestinal smooth muscle contraction [124]. The water extracting-alcohol precipitating solution of Lonicerae japonicae flos also inhibits the motility of rabbit isolated small intestine [125]. The decoction of Lonicerae japonicae flos significantly inhibits acetylcholine-induced intra- and extracellular calcium-mediated smooth muscle contraction [124].

3.17. Antiplatelet Effect. The water extracts of Lonicerae japonicae flos inhibited ADP-induced platelet aggregation with IC_{50} of 0.028 g/L. The IC_{50} of the organic acids in the water extracts are as follows: isomers of chlorogenic acid (4-cafeoylquinic acid, 0.0286 g/L; 5-cafeoylquinic acid, 1.707 g/L), caffeic acid (2.411 g/L), and isochlorogenic acids (3,4-dicaffeoylquinic acid, 0.026 g/L; 3,5-dicaffeoylquinic acid, 0.328 g/L; and 4,5-dicaffeoylquinic acid, 0.539 g/L), indicating relatively strong antiplatelet aggregation effects [126]. Extracts from Lonicerae japonicae flos, methyl caffeate (a polyphenol), methyl chlorogenic acid, digicitrin, and so on significantly inhibited superoxide-induced platelet activation and cellular injuries, ADP-induced platelet aggregation, and calcium ionophore A23187-triggered thromboxane synthesis in platelet microparticles [127]. Methyl caffeate, 3,4-di-O-cafeoylquinic acid, and methyl 3,4-di-O-cafeoylquininate have relatively strong inhibitory effect on platelet aggregation [128].

3.18. Neuroprotective Effect. The water extracts of Lonicerae japonicae flos have potential antiparkinsonian activities and reduce 6-hydroxydopamine-induced SH-SY5Y cytotoxicity. The protective mechanism is closely related to the inhibition of cellular apoptosis and oxidative stress and the activation of MAPKs, PI3K/Akt, and NF-κB pathways [129]. Further, the water extracts neutralize the H_{2}O_{2}-induced SH-SY5Y neuroblastoma cytotoxicity, apoptosis, and ROS production to protect the nerves, possibly via inhibition of Akt, JNK, p38 MAPK, and ERK1/2 phosphorylation [130]. The fluorescence spectrum analysis using thioflavin-T fluorescent assay and atomic force microscopy reveals that the dextran derived from Lonicerae japonicae flos inhibits Aβ_{12} deposition with dose-dependent effects and reduces the neurotoxicity of Aβ_{12} for SH-SY5Y cells, suggesting potential therapeutic value for Alzheimer's disease [131].

3.19. Toxicity and Adverse Effects. Intragastric administration of aqueous extracts of Lonicerae japonicae flos is not significantly toxic and does not affect the respiration, blood pressure, or urine volume in experimental animals. The LD_{50} of subcutaneous injection of Lonicerae japonicae flos concrete is 53 g/kg for mice [132]. The LD_{50} of oral administration of Lonicerae japonicae flos is larger than 15 g/kg and thus innocuous. The micronucleus test on bone marrow polychromat erythrocytes of mice and Ames Salmonella/microsome mutagenicity assay do not reveal any mutagenicity of Lonicerae japonicae flos. Sperm shape abnormality tests in mice reveal no genotoxicity of Lonicerae japonicae flos for germ cells of male animals. The anti-early pregnancy assay of SD rat (oral administration) indicates no adverse effects of Lonicerae japonicae flos on the reproductive function of female animals during pregnancy [133].

After intragastric administration of Lonicera macranthoides Hand.-Mazz. decoction, the mice show significantly decreased spontaneous activities and some degree of sleepiness and prone position, which were restored in 24 hours. Most death occurred in 24 hours, before any convulsions or seizure. However, subsequent anatomical observation indicates no lesions in major organs and the LD_{50} was 73.95 (69.80–78.34) g/kg [134]. The maximum dosage of Lonicera macranthoides Hand.-Mazz. buds for mice is 15 g/kg, and subacute toxicity test shows no dose-related differences in weight, hematology, blood biochemistry, or organ index with normal control group [135].

4. Comparative Pharmacology and Toxicology of Lonicerae Japonicae Flos and Lonicerae Flos

According to pharmacopoeia, Lonicerae japonicae flos and Lonicerae flos have similar efficacy, but researchers still compare the pharmacology and toxicity experimentally since the drugs have different origin and geographic distribution.

4.1. Comparison of Antibacterial and Bacteriostatic Effects. Lonicera macranthoides Hand.-Mazz. and Lonicerae japonicae flos have similar antibacterial spectra that significantly inhibit and kill Staphylococcus aureus, Escherichia coli, Salmonella Typhi, Shigella dysenteriae, Proteus vulgaris, Streptococcus group B, Sarcina, and Bacillus subtilis, but their effects are still different. The former has more significantly inhibitory effects on Streptococcus group B [27], Escherichia coli, Staphylococcus aureus, and Pneumococcus [136] than Lonicerae japonicae flos. Only Lonicera macranthoides Hand.-Mazz. has germicidal effects on Shigella dysenteriae [137]. Compared with Lonicerae japonicae flos, it has better bactericidal effects on Shigella dysenteriae [44, 137], Sarcina, and Bacillus subtilis [44] and poorer effects on Salmonella Typhi [44] and Escherichia coli [138] while having similar effects on Pseudomonas aeruginosa [138]. Lonicera confusa DC. exhibits inhibitory effect against Staphylococcus aureus and Salmonella Typhi, equivalent to that of Lonicerae japonicae flos, but better than that of Lonicera hypoglauca Miq. Moreover, it has more significant inhibitory effects on Streptococcus haemolyticus than Lonicerae japonicae flos and Lonicera hypoglauca Miq. [139]. Lonicera macranthoides Hand.-Mazz. decoction 40 g/kg is protective in Staphylococcus aureus-infected mice, with a significantly longer survival time than Lonicerae japonicae flos [140]. In conclusion, all species of Lonicerae flos are more antibacterial and bacteriostatic.
4.2. Comparison of Antiviral Effects. The flavone extracts of Lonicera macranthoides Hand.-Mazz. and Lonicerae japonicae flos are significantly inhibitory against pseudorabies virus- (PRV-) infected Vero cells, with Lonicera macranthoides Hand.-Mazz. showing a stronger effect than Lonicerae japonicae flos, but not significantly different in blocking effects [42]. The chlorogenic acid extracts of Lonicera macranthoides Hand.-Mazz. and Lonicerae japonicae flos inhibit Newcastle disease virus that affects Vero cells without any notable differences in efficacy [48]. Lonicera macranthoides Hand.-Mazz. and the alcohol extracts of Lonicerae japonicae flos remarkably enhance the antiadenoviral ability of cells in vitro, not significantly different [45].

4.3. Comparison of Antioxidant Effects. Orthophenanthroline-Fe²⁺ colorimetry is used to compare the scavenging capacity of OH in vitro between the water extracts of Lonicera macranthoides Hand.-Mazz. and Lonicerae japonicae flos, which reveals equally strong scavenging capacity of OH (IC₅₀ of scavenging rate, Lonicera macranthoides Hand.-Mazz. versus Lonicerae japonicae flos, 6.01mg/mL versus 10.22mg/mL) [136]. Biochemiluminescence indicates that the IC₅₀ of luminescence inhibition rates of O₂⁻ and OH were 10.26mg/mL and 3.26mg/mL for the water extracts of Lonicera macranthoides Hand.-Mazz. and 16.48mg/mL and 10.79mg/mL for Lonicerae japonicae flos [141]. The total flavones of Lonicera hypoglauca Miq. inhibit lipid oxidation (according to peroxide value test). The detection results of H₂O₂-CTMAB-luminol fluorescence system show an IC₅₀ of fluorescence inhibition rate of 2.21 × 10⁻² mg/mL for the total flavones of Lonicera hypoglauca Miq. and 1.54 × 10⁻² mg/mL for Lonicerae japonicae flos, indicating different H₂O₂ scavenging capacities [142].

4.4. Comparison of Anti-Inflammatory Effects. Lonicera macranthoides Hand.-Mazz. and Lonicerae japonicae flos used at 1 and 10 g/kg significantly inhibit the abdominal capillary permeability in mice and suppress carrageenan-induced paw swelling, with no significant differences. Lonicerae japonicae flos 10 g/kg inhibits dimethylbenzene-induced ear edema in mice but Lonicera macranthoides Hand.-Mazz. only shows inhibitory trends and the comparison between them reveals significant difference [44, 138].

4.5. Comparison of Antipyretic Effects. Lonicera macranthoides Hand.-Mazz. and Lonicerae japonicae flos 20 g/kg equally inhibit the fever induced by subcutaneous injection of Saccharomyces cerevisiae in mice, although the latter is effective for a longer time [140]. Lonicera macranthoides Hand.-Mazz., 10 g/kg, shows inhibitory trend against yeast powder-induced fever in mice and the antipyretic effect is slightly weaker than Lonicerae japonicae flos at the same dose [138, 140].

4.6. Comparison of Immunoregulatory Effects. Lonicera macranthoides Hand.-Mazz. and the water extracting-alcohol precipitating concentrated concretes of Lonicerae japonicae flos (main components: total flavones and chlorogenic acid) 1g/kg and 10g/kg significantly increase spleen index, thymus index, carbon clearance index, and phagocytic index in mice, but not significantly differently [44, 138]. Lonicerae japonicae flos 10g/kg significantly elevates the white cell count in normal and immunocompromised mice unlike Lonicera macranthoides Hand.-Mazz. [138].

The water extracts of Lonicera fulvotomentosa Hsu et S. C. Cheng alleviate small intestinal villi inflammation in sensitized mice, reduce mast cell aggregation and cell degranulation, increase the whole-mast cell ratio in LP, decrease intestinal histamine release of sensitized mice, lower the levels of IL-4 and OVA-specific Ig E levels in sensitized mice, and resolved OVA-mediated delayed-type hypersensitivity of footpad in mice [143].

4.7. Comparison of Hemostatic Effects. Both Lonicerae japonicae flos and Lonicerae flos (Lonicera confusa DC. and Lonicera hypoglauca Miq.) shorten bleeding time in mice. Lonicerae japonicae flos has similar hemostatic effect equivalent to Lonicera confusa DC. Lonicerae japonicae flos and Lonicera confusa DC. are significantly more hemostatic than Lonicera hypoglauca Miq. [139].

4.8. Comparison of Toxicity and Adverse Effects. According to a comparative study, the LD₅₀ values of Lonicera macranthoides Hand.-Mazz. and Lonicerae japonicae flos are 84.14 g/kg and 72.95 g/kg, respectively, with no significant difference [27].

The water extracts of sun-cured Lonicera macranthoides Hand.-Mazz. are hemolytic. However, the water extracts of steaming sun-cured Lonicera macranthoides Hand.-Mazz. and Lonicerae japonicae flos show hemolytic reaction only after 3 hours [144]. Total saponins of Lonicera fulvotomentosa Hsu et S. C. Cheng also result in mild hemolysis [139].

In active systemic anaphylaxis test using crude water extracting-alcohol precipitating solution of Lonicera macranthoides Hand.-Mazz., four out of six sensitized guinea pigs show dyspnea, gait instability, and Cheyne-Stokes respiration and die in 40 s to 5 min after excitation by intravenous injection of chlorogenic acid 15 mg/kg. Two out of six guinea pigs show agitation, rapid respiration, and gait instability in 30 s. In 10 to 15 min, these symptoms disappear and the mice recover. The allergic reaction intensity is graded as strongly positive. After intravenous injection of crude extracts 15 mg/kg, the nonsensitized guinea pigs manifest agitation, gait instability, rapid respiration, spasm, urination, and defecation in 10 s to 2.5 min and recover in 20–30 min. The strength of anaphylactic reaction is strongly positive [145].

Some researchers have compared the hypersensitive and anaphylactic reactions of Lonicerae japonicae flos and Lonicerae flos. The intraperitoneal injection of the water extracts and water extracting-alcohol precipitating solution of Lonicerae japonicae flos or Lonicera macranthoides Hand.-Mazz. on alternate days for 3 times may lead to hypersensitive reaction in guinea pigs, with possible death. A further study reveals that the degranulation rate (based on β-hexosaminidase release assay) of rat basophilic leukemia
cells (RBL-2H) induced by the water extracting-alcohol precipitating solution of Lonicera macranthoides Hand.-Mazz. is significantly higher than that of Lonicerae japonicae flos (11.33% ± 0.78 versus 8.52% ± 0.44), but with similar activation and proliferation inhibition on peripheral blood mononuclear cells [146].

Therefore, compared with Lonicerae japonicae flos, Lonicerae flos may be potentially dangerous.

5. Summary

Chinese Pharmacopeia (1963 Edition) records Lonicera japonica Thunb. of Caprifoliaceae family as the only plant source of medicinal Lonicerae japonicae flos, after which a total of 5 editions of pharmacopoeias included the origin of Lonicerae japonicae flos and 4 plants of the same genus under the legal species of Lonicerae japonicae flos. In this systematic review, we confirm that the medicinal value of Lonicerae japonicae flos is limited to Lonicera japonica Thunb. of Caprifoliaceae family in traditional TCM books without any historical evidence supporting the medicinal use of Lonicerae flos-related species, thus providing a scientific basis for the independent listing of Lonicerae japonicae flos and Lonicerae flos since Chinese Pharmacopeia (2005 Edition).

The functions and indications of Lonicerae japonicae flos and Lonicerae flos are similar in Chinese Pharmacopeia 2005 and 2010 Editions. Our results confirm similar pharmacological activities of Lonicerae japonicae flos and Lonicerae flos, but the former is more widely studied pharmacologically. Lonicerae japonicae flos has glucose-lowering, anti-inflammatory, antioxidative, antiplatelet aggregation, antifertility, and neuroprotective activities that are not reported in Lonicerae flos. Lonicera macranthoides Hand.-Mazz. and Lonicerae japonicae flos have similar antibacterial, antiviral, anti-inflammatory, antioxidative, antiplatelet aggregation, heptoproctective, immunoregulatory, and antitumor activities. However, the pharmacological effects involving balancing intestinal flora and antiatherosclerotic effects have not been reported in Lonicerae japonicae flos. Antioxidation is the main pharmacological activity of Lonicera hypoglauca Miq., Lonicera confusa DC., and Lonicera fulvotomentosa Hsu et S. C. Cheng. In addition, Lonicera hypoglauca Miq. has antibacterial, anti-inflammatory, and antipyretic effects; Lonicera confusa DC. has antibacterial and hemostatic effects; Lonicera fulvotomentosa Hsu et S. C. Cheng has hepatoprotective and antiallergic effects and saponins have mild hemolytic effect.

Further analysis reveals twenty plus studies comparing the pharmacological activities between Lonicerae japonicae flos and Lonicerae flos. Lonicerae flos has certain advantages in terms of antibacterial and other effects. Some studies report better antibacterial and bacteriostatic activities with Lonicera macranthoides Hand.-Mazz. and Lonicera confusa DC. than Lonicerae japonicae flos and more antioxidant activities of Lonicera macranthoides Hand.-Mazz. than Lonicerae japonicae flos. Lonicera macranthoides Hand.-Mazz. and Lonicerae japonicae flos do not differ significantly in antiviral effects. Lonicera confusa DC. and Lonicerae japonicae flos do not differ significantly in hemostatic effect but both are better than Lonicera hypoglauca Miq. Lonicerae japonicae flos is slightly better than Lonicera macranthoides Hand.-Mazz. in anti-inflammatory, antipyretic, and immunoregulatory effects, but no significant difference in toxicity. Some studies have reported adverse events such as hypersensitive/anaphylactic and hemolytic reaction in Lonicera macranthoides Hand.-Mazz. and Lonicera fulvotomentosa Hsu et S. C. Cheng. Therefore, meticulous screening and identification of the different species are essential to avoid the risk of adverse and toxic effects during the production and clinical use.

In conclusion, modern pharmacological effects of Lonicerae japonicae flos and Lonicerae flos are similar, although a few significant differences should not be neglected. Since a systematic and standard comparative study has not been developed so far, it is difficult to scientifically evaluate their advantages/disadvantages and differences/similarities. We suggest a comprehensive systematic review and a parallel, crossover study to delineate the mechanisms underlying the comparative pharmacological activities of Lonicerae japonicae flos and Lonicerae flos and different species of Lonicerae flos. A comparative analysis of the clinical efficacy and safety of pharmacologically active ingredients/products in Lonicerae japonicae flos and Lonicerae flos is essential to fully and accurately evaluate their effects and toxic side effects. References for the revision of relevant pharmacopoeial records should be provided along with supporting clinical efficacy and safety data.

Conflict of Interests

The authors have no conflicting financial interests.

Acknowledgments

This work is supported by grants from the National Natural Science Foundation of China (30973901), International Science and Technology Cooperation Program of China (2011DFA30870), and Joint Research Project of The Twentieth Session of China-Thailand Joint Committee on Science and Technology Cooperation (20-602). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the paper.

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