The anti-inflammatory activity of licorice, a widely used Chinese herb

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ABSTRACT

Context: Increasing incidence and impact of inflammatory diseases have encouraged the search of new pharmacological strategies to face them. Licorice has been used to treat inflammatory diseases since ancient times in China.

Objective: To summarize the current knowledge on anti-inflammatory properties and mechanisms of compounds isolated from licorice, to introduce the traditional use, modern clinical trials and officially approved drugs, to evaluate the safety and to obtain new insights for further research of licorice.

Methods: PubMed, Web of Science, Science Direct and ResearchGate were information sources for the search terms 'licorice', 'licorice metabolites', 'anti-inflammatory', 'triterpenoids', 'flavonoids' and their combinations, mainly from year 2010 to 2016 without language restriction. Studies were selected from Science Citation Index journals, in vitro studies with Jadad score less than 2 points and in vivo and clinical studies with experimental flaws were excluded.

Results: Two hundred and ninety-five papers were searched and 93 papers were reviewed. Licorice extract, 3 triterpenes and 13 flavonoids exhibit evident anti-inflammatory properties mainly by decreasing TNF, MMPs, PGE2 and free radicals, which also explained its traditional applications in stimulating digestive system functions, eliminating phlegm, relieving coughing, nourishing qi and alleviating pain in TCM. Five hundred and fifty-four drugs containing licorice have been approved by CFDA. The side effect may due to the cortical hormone like action.

Conclusion: Licorice and its natural compounds have demonstrated anti-inflammatory activities. More pharmacokinetic studies using different models with different dosages should be carried out, and the maximum tolerated dose is also critical for clinical use of licorice extract and purified compounds.

Introduction

The applications of natural compounds and medicinal plants to diseases are novel trends in clinical medicine research. Licorice is a very famous ancient herb, which is most frequently used in traditional Chinese medicine (TCM). In Chinese Pharmacopoeia, three original plants from the family Leguminosae, Glycyrrhiza uralensis Fisch., G. inflata Bat. and G. glabra L. are prescribed as licorice. The licorice cuts from the dry roots and rhizomes of licorice are widely used in clinical prescriptions (Figure 1). The pharmaceutical importance of licorice lies in their capacity to produce a great variety of secondary metabolites. Depending on the modern studies, the most important bioactive compounds in licorice are triterpenes, flavonoids and polysaccharides (Seki et al. 2011; Zhu et al. 2016). They have been reported with antitumor (Wang KL et al. 2013; Li et al. 2014), antimicrobial (Ahn et al. 2012; Long et al. 2013), antiviral (Kwon et al. 2010; Feng et al. 2013), anti-inflammatory (Chandrasekaran et al. 2011; Wu et al. 2011), antidiabetic (Mae et al. 2003; Li et al. 2010), immunoregulatory (Hong et al. 2009; Li et al. 2012), hepatoprotective (Abe et al. 2008; Sharifzadeh et al. 2008), neuro-protective activities (Zhao et al. 2008; Michel et al. 2013) and adrenal cortical hormone kind functions (Kageyama et al. 2008; Raikkonen et al. 2010).

In recent years, inflammation responses with Celsus (Fullerton & Gilroy 2016). Inflammation responses play an important role in multiple diseases with a high prevalence among population, such as hepatitis (Matsuzaki et al. 2007), lung disease (Yang H et al. 2013) and Alzheimer’s disease (Jayaraman et al. 2011). And, they are also centrally related to the pathogenesis of a large number of acute and chronic diseases, such as rheumatoid arthritis (Yang CLH et al. 2013), colonic inflammatory response (Takhshid et al. 2012) and periodontitis (Farhad et al. 2013). However, the conventional therapies for inflammation, including steroids and nonsteroid anti-inflammatory drugs (NSAID) (Sostres et al. 2010; Parikh & Scadding 2014; Carrasco-Pozo et al. 2016), have shown many side effects and deficiencies. Considering this, licorice is an excellent alternative choice, due to the fact that it causes minimal disorders in the physiological functions of organism, has a nonspecific action and exerts a therapeutic action regardless of the direction of the pathological state. Furthermore, it is especially suitable for children, since glycyrrhizin (GC), a compound isolated from licorice, is 50 times sweeter than sugar that makes it much easier for children to accept (Liu et al. 2011).

The present review aims to summarize the anti-inflammatory properties and mechanisms of licorice and its natural compounds, introduce the related clinical drugs, evaluate the safety and obtain new insights for further research of licorice.
Literature search

The present review is intended to discuss past and current research on the anti-inflammatory activities of licorice and its natural products. With this objective, an extensive collection of scientific literature was examined by considering all highlighted research articles and reviews on the issue. Four main databases, PubMed, Web of Science, Science Direct and ResearchGate were used as information sources by the inclusion of the search terms ‘licorice’, ‘licorice metabolites’, ‘anti-inflammatory’, ‘triterpenoids’, ‘flavonoids’ and their combinations, mainly from the years 2010 to 2016 without language restriction. All the references were selected from Science Citation Index journals, in vitro studies with the Jadad score less than 2 points and in vivo and clinical studies with experimental flaws were excluded. As a result, we searched 295 papers and a total of 93 references were included in the present work.

Licorice applications in TCM therapeutics to treat inflammation

In TCM therapeutics, licorice has been used to strengthen the function of digestive system, eliminate phlegm, relieve coughing and alleviate pain since ancient times (Guo et al. 2014). Licorice is honoured as the 'excellent coordinator' for harmonizing different ingredients, and regarded as 'guide drug' for helping the rapid absorption into bloodstream, organs and target cells (Wang X et al. 2013). In authoritative medical formulation in ancient China, it has been applied to treat respiratory, gastric and liver diseases, and also used to alleviate the toxicity of other drugs.

Sanmao decoction, which consists of licorice, ephedra (the stem of Ephedra sinica Stapf, Mahuang in Chinese) and apricot seeds (the seeds of Prunus armeniaca L. var. ansu Maxim, Xingren in Chinese), and Jieging decoction, which consists of licorice and Platycodon grandiflorum (the roots of Platycodon grandiflorum (Jacq.) A. DC, Jieging in Chinese), are always combined with peony (the roots of Paeonia lactiflora Pall., Shaoyao in Chinese) for harmo-

Table 1. The anti-inflammatory activities of licorice extracts.

| Species         | Solvent | Inflammation tissue/disease | Model formation          | Extract concentration | Inhibition rate | Toxic signs/ mortality | Reference               |
|-----------------|---------|-----------------------------|--------------------------|-----------------------|-----------------|------------------------|-------------------------|
| *G. glabra*     | Acetone | LPS (0.1 μg·mL⁻¹) - induced | Stimulation with LPS (0.1 μg·mL⁻¹) | 20–40 μg·mL⁻¹ | Dose-dependently inhibit IL-1β, up to 47.8% | (Thiyagarajan et al. 2011) |
| *G. uralensis*  | Ethanol | The murine RAW264.7 macrophage cells | Stimulation with LPS (1 μg·mL⁻¹) | 25 μg·mL⁻¹ | Inhibit LPS-induced NO production (p<0.001) by 48% | (Wu et al. 2011) |
| *G. uralensis*  | Ethanol | Human colon cancer cells HT-29 (HT-29-N9) | Stimulation with LPS (1 μg·mL⁻¹) | 25 μg·mL⁻¹ | Suppress the LPS-induced NF-κB luciferase activity (p<0.05) | (Wu et al. 2011) |
| *G. uralensis*  | Ethanol | Human hepatoma HepG2 cell (HepG2-C8) | Stimulation with LPS (1 μg·mL⁻¹) | 25 μg·mL⁻¹ | Induce the luciferase activity in HepG2C8 cells by fourfolds (p<0.001) | (Wu et al. 2011) |

Anti-inflammatory activities of licorice extracts

Thus far, reports about the anti-inflammatory activity of licorice extracts concentrated mainly on *G. glabra* and *G. uralensis* (Table 1). Glycyrrhiza glabra has been used to treat gastric ulcer, oral ulcer (Liu et al. 2011) and ulcerative colitis (Samadnejad et al. 2012). Glycyrrhiza glabra reduced the ulcer zone, and is a good choice for children who do not like taking bitter medicines.
It attenuated macroscopic damage, improved the microscopic structure of the colonic mucosa, and effectively increased superoxide dismutase (SOD) enzymatic defence system to treat acetic acid-induced ulcerative colitis. Furthermore, TNF-α, NO and IL-6 levels were also diminished dose-dependently ($p < 0.05$) (Samadnejad et al. 2012).

*Glycyrrhiza uralensis* has been applied to lipopolysaccharide (LPS)-treated Raw264.7 macrophages and mouse skin treated with 12-O-tetradecanoylphorbol-13-acetate (TPA) *in vitro*. In LPS-treated Raw264.7 macrophages model, *G. uralensis* reduced NO and prostaglandin E2 (PGE2) release, the secretion and mRNA levels of TNF-α, IL-6, cyclooxygenase-2 (COX-2) and IL-1β, the protein expression and transcriptional activity of inducible nitric oxide synthase (iNOS) and phospholipase A2 (PLA2) (Wu et al. 2011). It also prevented the inhibitor of NF-κB (IκB) degradation and p65 nuclear translocations. In the mouse inflammation model, it suppressed skin swelling and the expression of iNOS and COX-2 (Cho HJ et al. 2010).

### Anti-inflammatory active compounds of licorice

The three original plants of licorice are *G. uralensis*, *G. inflata* and *G. glabra*. They contain many natural active compounds, including more than 20 triterpenes and 300 flavonoids. Seventy-three bioactive compounds and 91 potential targets are identified for this medicinal herb (Li et al. 2011; Liu et al. 2013). Among them, 3 triterpenes, 18β-GC, 18α-GC and 18β-glycyrrhetinic acid (18β-GA), and 13 flavonoids, licochalcone A (LCA), licochalcone B (LCB), licochalcone C (LCC), licochalcone D (LCD), licochalcone E (LCE), isoliquiritigenin (ISL), echinatin (EC), glabridin (GLD), isoangustone A (ISOA), licoricidin (LID), licorisoflavan A (LIA), dehydroglyasperin C (DGC) as well as dehydroglyasperin D (DGD), all have been reported to possess anti-inflammatory activity. The large number of metabolites indicated that licorice was an ideal option for obtaining anti-inflammation compounds. The chemical structure formulas of the above compounds are shown in Figure 2. Furthermore, in order to have a full appreciation of these active compounds, all available data related to *in vitro* anti-inflammatory activities referring to 16 compounds in 52 assays are shown in Table 2. Similarly, in Table 3, we focussed on the anti-inflammatory activities of these natural compounds *in vivo*, thus, recent investigations of 6 compounds and 10 assays have been collected. The inflammation tissues, cell lines and animal models, dosage of drugs, inhibition rates, detective methods and the toxic signs are all listed in detail.

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**Figure 2.** The chemical structure formulas of compounds with anti-inflammatory activity in licorice.
Triterpenes and related possible mechanisms for inflammation prevention

More than 20 triterpenes have been isolated from the roots of licorice, but only 18β-GC, 18α-GC and 18β-GA, have been reported to possess the anti-inflammatory activity. The possible mechanisms for the inflammation prevention of the three triterpenes and the inflammatory types were investigated as follows.

18β-Glycyrrhinizin

18β-GC is regarded as the marker compound in licorice. It has been demonstrated that 18β-GC suppressed MPO activity (Ni et al. 2011) and phosphorylation and secretion of high mobility group protein 1 (Kim SW et al. 2012). It also decreased the levels of cholesterol of lipid rafts, the translocation of toll-like receptor 4 to lipid rafts and the interferon regulating factor 3 activation (Fu et al. 2014). Furthermore, it attenuated the production of PGE2, intracellular reactive oxygen species (ROS), TNF-α, COX-2 and iNOS (Luo et al. 2013). Moreover, 18β-GC also activated ATP-binding cassette transporter A1, which induced cholesterol efflux from lipid rafts (Fu et al. 2014).

Thus far, 18β-GC has been applied to LPS-stimulated macrophage models (Wang et al. 2011), mouse mammary epithelial cells (Fu et al. 2014) and Leishmania donovani-infected macrophages (Bhattacharjee et al. 2012) in vitro, and been applied to the postischaemic brain rats models (Kim SW et al. 2012; Luo et al. 2013), LPS-induced mastitis rat models (Fu et al. 2014) and LPS-induced acute lung injury (ALI) rat models in vivo. It can also suppress microglia activation, the mammary gland histopathological changes and LPS-induced alveolar haemorrhage (Ni et al. 2011).

18α-Glycyrrhinizin

18α-GC and 18β-GC is a pair of epimers, differed only in the C18-H. The anti-inflammatory activities of 18α-GC have been affirmed. It suppressed PLA2/arachidonic acid metabolites, such as PGE 2, prostacyclin 2, thromboxane 2 and leukotrienes B4 (Xie et al. 2015). It significantly reduced the content of intercellular adhesion moledule-1 and MMP-9 (Xiao et al. 2014). What’s more, it increased the activities of SOD and GSH-Px, and the expression of p-Akt and p-ERK (Huang et al. 2014).

It has been reported that the protective and anti-inflammatory effects of 18α-GC were better than 18β-GC (Zeng et al. 2006). It has been applied to RAW264.7 macrophages (Xie et al. 2015), human ischaemia/reperfusion injury hepatic L02 cells
| Compounds | Inflammation tissue/disease | Cell | Concentration | Inhibition rate | Method | Toxic signs/mortality | Reference |
|-----------|----------------------------|------|---------------|----------------|--------|----------------------|-----------|
| 18β-GC   | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | RAW 264.7 cells | 75 μM | 51% reduction in NO | ELISA | Do not affect the viability of the RAW 264.7 cells at the concentration lower than 200 μM | (Wang et al. 2011) |
| 18β-GC   | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | RAW 264.7 cells | 75 μM | 49% reduction in PGE₂ | ELISA | | (Wang et al. 2011) |
| 18β-GC   | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | RAW 264.7 cells | 75 μM | 46% reduction in TNF-α | ELISA | | (Wang et al. 2011) |
| 18β-GC   | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | RAW 264.7 cells | 75 μM | 42% reduction in IL-6. | ELISA | | (Wang et al. 2011) |
| 18β-GC   | Leishmania donovani-infected macrophages | Peritoneal macrophages of Leishmania donovani-infected BALB/c mice (4–6 weeks old) | 50 mg·mL⁻¹ | 90.94% reduction in the parasite load | ELISA | Optimal viability at mg·mL⁻¹ showing 88% survival | (Bhattacharjee et al. 2012) |
| 18β-GC   | Ischaemia/reperfusion in L02 cells | The human hepatic L02 cell line | 10 mg·mL⁻¹ | Increase the activities of SOD and GSH-Px | SOD and GSH-Px Detection Kits | | (Huang et al. 2014) |
| 18β-GC   | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | RAW264.7 macrophages | 0.5 mg·mL⁻¹ or 1 mg·mL⁻¹ | Inhibit in a dose-depend- | EMSA | | (Chida et al. 2013) |
| 18β-GA   | Complex compound of 18β-GA and hydroxypropyl-γ-cyclodextrin | Reduce mRNA expressions of TNF-α, IL-1β and IL-6 | | | | | |
| 18β-GA   | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | RAW 264.7 cells | 75 μM | 34% reduction in NO | ELISA | Do not affect the viability of the RAW 264.7 cells at the concentration lower than 150 μM | (Wang et al. 2011) |
| 18β-GA   | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | NIH-3T3 cells | 75 μM | 58% reduction in PEG2 | ELISA | | (Wang et al. 2011) |
| 18β-GA   | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | NIH-3T3 cells | 75 μM | 34% reduction in TNF-α | ELISA | | (Wang et al. 2011) |
| 18β-GA   | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | NIH-3T3 cells | 75 μM | 35% reduction in IL-6 | ELISA | | (Wang et al. 2011) |
| LCA      | TNF-α (10 ng·mL⁻¹)-induced NF-κB activation | NIH-3T3 cells | 10/20/30 μM | Inhibit in a dose-depend- | EMSA | | (Funakoshi-Tago et al. 2010) |
| LCA      | LPS (1 μg·mL⁻¹)-induced mouse peritoneal macrophage cells | Mouse peritoneal macrophage cells | 0.1/0.5/1 μg·mL⁻¹ | Decrease PGE₂ by 31.1, 58.3 and 80.3% | PGE₂ kit | | (Cui et al. 2008) |
| LCA      | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | RAW 264.7 cells | 10 μM | The PGE₂ inhibition rates exceed 80% | DCFH-DA fluorometric assay | | (Fu et al. 2013) |
| LCA      | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | RAW 264.7 cells | 12.8±1.45 μM | The effective concentration of ABTS⁺ radicals are scavenged by 50% Inhibitory activity on lipid peroxidation EC50 | ABTS⁺ + radical scavenging capacity assay | | (Fu et al. 2013) |
| LCA      | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | RAW 264.7 cells | 11.6±1.8 μM | Inhibitory activity on lipid peroxidation EC50 | Fe²⁺-ascorbic acid system | | (Fu et al. 2013) |
| LCB      | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | RAW 264.7 cells | 1 μM | The inhibition rate of NO exceeds 50% | DCFH-DA fluorometric assay | | (Fu et al. 2013) |
| LCB      | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | RAW 264.7 cells | 3.68±0.09 μM | The concentration of ABTS⁺ radicals are scavenged by 50% | ABTS⁺ radical scavenging capacity assay | | (Fu et al. 2013) |
| LCB      | LPS (1 μg·mL⁻¹)-induced murine RAW 264.7 cells | RAW 264.7 cells | 3.92±0.12 μM | Inhibitory activity on lipid peroxidation EC50 | Fe²⁺-ascorbic acid system | | (Fu et al. 2013) |
| LCC      | RBL-2H3 cells sensitized with anti-DNP IgE (100 ng·mL⁻¹) | RBL-2H3 cells | 24 μM | Inhibition of β-hexosaminidase release | β-hexosaminidase release assay and trypan blue exclusion assay | 30% cytotoxicity: > 30 μM | (Tanifuji et al. 2010) |

(continued)
| Compounds | Inflammation tissue/disease | Cell | Concentration | Inhibition rate | Method | Toxic signs/mortality | Reference |
|-----------|-----------------------------|------|---------------|----------------|--------|----------------------|-----------|
| LCD       | RBL-2H3 cells sensitized with anti-DNP IgE (100 ng mL\(^{-1}\)) | RBL-2H3 cells | 21 µM | Inhibition of \(\beta\)-hexosaminidase release | \(\beta\)-hexosaminidase release assay and trypan blue exclusion assay | 30% cytotoxicity: > 30 µM | (Tanifuji et al. 2010) |
| LCE       | LPS-stimulated RAW 264.7 murine macrophage | RAW 264.7 murine macrophage | 2.5–7.5 µmol L\(^{-1}\) | Dose-dependently inhibit NO, PGE2; markedly suppress the expression of iNOS and COX-2 proteins; and the secretion of IL-6, IL-1β, and TNF-α | | | (Lee et al. 2013) |
| Echinatin | LPS (1 µg mL\(^{-1}\))-induced murine RAW 264.7 cells | RAW 264.7 cells | 2.95 ± 0.11 µM | The effective concentration of ABTS\(^{+}\) radicals are scavenged by 50% | ABTS\(^{+}\) radical scavenging capacity assay | | (Fu et al. 2013) |
| Echinatin | | | 47.2 ± 2.64 µM | Inhibitory activity on 50% lipid peroxidation | Fe\(^{2+}\)-ascorbic acid system | | (Fu et al. 2013) |
| ISL       | LPS (0.1 µg mL\(^{-1}\))-induced J774A.1 murine macrophage cell line | J774A.1 murine macrophage cell line | 2.5–10 µg mL\(^{-1}\) | NO levels with 50% inhibition attain at 7.5 µg mL\(^{-1}\) (29 µM). | ELISA | | (Thiyagarajan et al. 2011) |
| ISL       | LPS (0.1 µg mL\(^{-1}\))-induced J774A.1 murine macrophage cell line | J774A.1 murine macrophage cell line | 1.85 µg mL\(^{-1}\) | IL-1 levels with 50% inhibition | ELISA | | (Thiyagarajan et al. 2011) |
| ISL       | LPS (0.1 µg mL\(^{-1}\))-induced J774A.1 murine macrophage cell line | J774A.1 murine macrophage cell line | 1.92 µg mL\(^{-1}\) | IL-6 levels with 50% inhibition | ELISA | | (Thiyagarajan et al. 2011) |
| ISL       | PMA (50 ng mole\(^{-1}\))-exposed human umbilical vein endothelial cells | Human umbilical vein endothelial cells | 10 µM | Nearly abolish the expression of MMP-2 mRNA | MTT | Nontoxic concentrations showed up 25 ≤ µM for 24h serum-free culture experiments | (Kang et al. 2010) |
| GLD       | LPS (0.1 µg mL\(^{-1}\))-induced J774A.1 murine macrophage cell line | J774A.1 murine macrophage cell line | 10 µg mL\(^{-1}\) | 33% inhibition in NO levels | ELISA | | (Thiyagarajan et al. 2011) |
| GLD       | LPS (0.1 µg mL\(^{-1}\))-induced J774A.1 murine macrophage cell line | J774A.1 murine macrophage cell line | 10 µg mL\(^{-1}\) | IL-1 levels with 50% inhibition | ELISA | | (Thiyagarajan et al. 2011) |
| LIA       | LPS (0.1 µg mL\(^{-1}\))-induced U937 cells line | U937 cells (ATCC CRL-1593.2; human monoblastic leukemia cell line | 0.1, 0.5, 1 µg mL\(^{-1}\) | Decreased the secretion of IL-6 | | No obvious cytotoxic effects were detected at 1mg mL\(^{-1}\) with the cell viability of 85% | (La et al. 2011) |
| LIA       | LPS (0.1 µg mL\(^{-1}\))-induced U937 cells line | U937 cells (ATCC CRL-1593.2; human monoblastic leukemia cell line | 1 µg mL\(^{-1}\) | Decreased the secretion of CCL5 | | | (La et al. 2011) |
| LIA       | LPS (0.1 µg mL\(^{-1}\))-induced U937 cells line | U937 cells (ATCC CRL-1593.2; human monoblastic leukemia cell line | 0.1, 0.5, 1 µg mL\(^{-1}\) | Decreased the secretion of MMP-8 | | | (La et al. 2011) |
| LIA       | LPS (0.1 µg mL\(^{-1}\))-induced U937 cells line | U937 cells (ATCC CRL-1593.2; human monoblastic leukemia cell line | 0.5, 1 µg mL\(^{-1}\) | Decreased the secretion of MMP-7 | | | (La et al. 2011) |
| LIA       | LPS (0.1 µg mL\(^{-1}\))-induced U937 cells line | U937 cells (ATCC CRL-1593.2; human monoblastic leukemia cell line | 1 µg mL\(^{-1}\) | Decreased the secretion of MMP-9 | | | (La et al. 2011) |

(cont.)
| Compounds | Inflammation tissue/disease | Cell | Concentration | Inhibition rate | Method | Toxic signs/mortality | Reference |
|-----------|-----------------------------|------|---------------|----------------|--------|-----------------------|-----------|
| LID       | LPS (0.1 µg·mL⁻¹)-induced U937 cells line | U937 cells (ATCC CRL-1593.2; human monoblastic leukemia cell line) | 0.1, 0.5, 1 µg·mL⁻¹ | Decreased the secretion of IL-6 | Ferric reducing antioxidant power assay | No obvious cytotoxic effects were detected at 1mg·mL⁻¹ with the cell viability of 85% | (La et al. 2011) |
| LID       | LPS (0.1 µg·mL⁻¹)-induced U937 cells line | U937 cells (ATCC CRL-1593.2; human monoblastic leukemia cell line) | 0.1, 0.5, 1 µg·mL⁻¹ | Decreased the secretion of MMP-7 and MMP-8 | Ferric reducing antioxidant power assay | | (La et al. 2011) |
| LID       | LPS (0.1 µg·mL⁻¹)-induced U937 cells line | U937 cells (ATCC CRL-1593.2; human monoblastic leukemia cell line) | 0.5, 1 µg·mL⁻¹ | Decreased the secretion of MMP-9 | Ferric reducing antioxidant power assay | | (La et al. 2011) |
| DGC       | Ferric reducing antioxidant power 855.07 ± 84.14 µmole·L⁻¹ | Ferric reducing antioxidant power assay | | | | (Kim HJ et al. 2012b) |
| DGC       | 0.205 ± 0.005 mM IC₅₀ for DPPH | DPPH radical scavenging assay | | | | (Kim HJ et al. 2012b) |
| DGC       | 0.465 ± 0.081 mM IC₅₀ value for ABTS⁺ | ABTS⁺ radical cation-decolourization assay | | | | (Kim HJ et al. 2012b) |
| DGC       | 2 µM Dose-dependently inhibit ROS production | 2,7-dichlorofluorescein (DCF) assay and western-blot | | | | (Kim HJ et al. 2012a) |
| DGC       | 0.5 mM Ferric reducing antioxidant power 812.04 ± 40.35 µmole·L⁻¹ | Ferric reducing antioxidant power assay | | | | (Kim HJ et al. 2012b) |
| DGD       | 0.309 ± 0.002 mM IC₅₀ for DPPH | DPPH radical scavenging assay | | | | (Kim HJ et al. 2012b) |
| DGD       | 0.635 ± 0.035 mM IC₅₀ value for ABTS⁺ | ABTS⁺ radical cation-decolourization assay | | | | (Kim HJ et al. 2012b) |
| ISOA      | 0.5 mM Ferric reducing antioxidant power 231.57 ± 24.44 µmole·L⁻¹ | Ferric reducing antioxidant power assay | | | | (Kim HJ et al. 2012b) |
| ISOA      | 0.418 ± 0.015 mM IC₅₀ for DPPH | DPPH radical scavenging assay | | | | (Kim HJ et al. 2012b) |
| ISOA      | 0.655 ± 0.042 mM IC₅₀ value for ABTS⁺ | ABTS⁺ radical cation-decolourization assay | | | | (Kim HJ et al. 2012b) |
18β-Glycyrrhetinic acid

18β-GA is a hydrolyzed metabolite of 18β-GC. Since 18β-GC can generate 18β-GA through metabolic processes in the human body, the pharmacological effects of 18β-GA are essentially the same as 18β-GC. 18β-GA exerted its anti-inflammatory activities via inducing antioxidant defence systems, decreasing lipid peroxidations, ameliorated oxidative and histological damage. It also significantly reduced the generation of excessive NO, PGE2 and ROS, inhibited the protein and mRNA levels of iNOS and COX-2 and suppressed the release of LPS-induced TNF-α, IL-6 and IL-1β in a dose-dependent manner (Wang et al. 2011; Ishida et al. 2013). It has been studied in indomethacin-induced small intestinal damage (Ishida et al. 2013), LPS-induced macrophages (Wang et al. 2011) in vitro and neuronal damage caused by global cerebral ischaemia/reperfusion in C57BL/6 mice models (Oztanir et al. 2014) in vivo, and the anti-inflammatory actions were significantly affirmed.

Flavonoids and related mechanisms for inflammation prevention

About 300 polyphenols have been isolated from licorice, including phenolic acids, flavonoids, flavans, chalcones, isoflavon and isoflavonoids. Thus far, the main anti-inflammatory active polyphenols in licorice are chalcones, isoflavon and isoflavonoids. Among them, chalcones, such as LCA, LCB, LCC, LCD, LCE, ISL and EC, isoflavonoids, such as ISOA, and isoflavan, such as GLD, LID, LIA, DGC and DGD have shown the potential as anti-inflammatory drugs.

Chalcones

Chalcones include LCA, LCB, LCC, LCD, LCE, ISL and EC. The special scaffold of chalcones was regarded as the key factor for their broad biological activities (Karthikeyan et al. 2015). It is believed that the fixed structure of LCA is necessary for its anti-inflammatory activity, since 4,8-unaturated ketone reduced LCA, which lacks a double bond, failed to inhibit TNF-α-induced NF-kB activation. Furthermore, LCA markedly inhibited acute carrageenan-induced paw oedema in mice while the reduced LCA failed (Funakoshi-Tago et al. 2009, 2010).

The mechanisms for the anti-inflammatory activities of chalcones have been fully investigated. LCA, LCB, ISL and EC all inhibited the production of NO, IL-6 and PGE2, while LCA, LCD and EC all exhibited potent inhibition of lipid peroxidation (Haraguchi et al. 1998; Thiyagarajan et al. 2011; Fu et al. 2013; Honda et al. 2014). LCD and EC both showed strong scavenging activity towards the 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulphonate) (ABTS) (+) radical. LCD and EC both strongly inhibited superoxide anion production in the xanthine oxidase system, showed potent scavenging activity on DPPH radical and

Huang et al. 2014 in vitro, and paraquat poisoning-induced lung injury rat models (Xiao et al. 2014) in vivo.

Table 3. The anti-inflammatory properties of licorice compounds in vivo.

| Compounds | Inflammation tissue/disease | Models | Treatment | Outcomes | Reference |
|-----------|-----------------------------|--------|-----------|----------|-----------|
| 18β-GC    | An intratracheal instillation of LPS (1 mg kg⁻¹) | Male BALB/C mice weighing 20–25 g | Intraperitoneal injection of 10, 25 and 50 mg kg⁻¹ | Markedly decrease the MPO activity and NO concentrations | (Ni et al. 2011) |
|           | Injection of 0.94 nmole (0.2 μg) of kaic acid (KA)-induced neuronal death model | Male BALB/c mice (25-30 g) | Intraperitoneal injection of 10 or 50 mg kg⁻¹ | Iβ-1-positive cells are almost completely suppressed by 50 mg kg⁻¹ 18β-GC | (Luo et al. 2013) |
| 18α-GC    | 20% paraquat poisoning solution at 15 mg kg⁻¹ dose | 30 male Sprague Dawley rats from 180 g to 200 g | Intraperitoneal injection of 30 mg kg⁻¹ | Significantly decrease inter-cellular adhesion molecule-1 (ICAM-1) and matrix metalloproteinase-9 (MMP-9) | (Xiao et al. 2014) |
| LCA       | Noninfectious mouse model of asthma | BALB/c mice | 50 mg kg⁻¹ | Inhibit the increase in T-helper type 2 cytokines, reduce serum levels of ovalbumin-specific IgE and IgG | (Chu et al. 2013) |
|           | Topical inflammation was instantly induced on the posterior surface of the same ear by the application of xylene (0.05 mL) | Kunming mice 20–25 g and Wistar rats (150–200 g) | 5 mg kg⁻¹ | Decrease the ear oedema rate by 30.3% | (Cui et al. 2008) |
|           | 0.1 mL freshly prepared carrageenan was injected into the right hind paw | Kunming mice 20–25 g and Wistar rats (150–200 g) | 2.5, 5 and 10 mg kg⁻¹ | Dose-dependently reduce the paw oedema rate by 41.3, 39.7 and 30.7%, respectively | (Cui et al. 2008) |
| LCE       | 5 nmole of TPA 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced mouse ear oedema | ICR mice | 0.5–2 mg | Dose-dependently reduce the TPA-induced increase in ear weight and ear thickness | (Lee et al. 2013) |
| ISL       | Male, 5-week-old C57BL/6 mice were fed a HFD containing 60% fat | C57BL/6 mice | 10 μM | Inhibit HFD-induced IL-1 and caspase-1 production | (Honda et al. 2014) |
| GLD       | 5% dextran sulphate sodium-induced BALB/c mice | BALB/c mice | 10 or 50 mg kg⁻¹ | Attenuate mortality, loss of body weight, shortening of the colon and severe clinical symptoms. | (Kwon et al. 2008) |
inhibited phosphorylation of NF-κB p65 (Haraguchi et al. 1998; Furusawa et al. 2009). Furthermore, LCA significantly inhibited the release of cytokines, such as IL-4, IL-5 and IL-13, and serum levels of ovalbumin-specific immunoglobulin E (IgE), IgG. It also reduced the mRNA expression of acidic mammalian chitinase, chitinase 3-like protein 4, E-selectin, Muc5ac, CCl11 and CCR3 in reduced the mRNA expression of acidic mammalian chitinase, chitinase 3-like protein 4, E-selectin, Muc5ac, CCl11 and CCR3 in lung tissues (Chu et al. 2013). LCA, LCB, LCD, LCE and EC has been applied to LPS-induced J774A.1 murine macrophage cell models and rat liver microsomes (Cui et al. 2008; Fu et al. 2013). LCD has been studied in rat baso-leukaemia (RBL)-2H3 cells, and ISL has been applied to LPS-induced RAW264.7 mouse macrophage cell models and human umbilical vein endothelial cells (Kang et al. 2010; Thiyagarajan et al. 2011).

For studies in vitro, LCA, LCB, LCC, LCD, LCE and EC has been applied to LPS-induced RAW264.7 mouse macrophage cell models and rat liver microsomes (Cui et al. 2008; Fu et al. 2013). LCD has been studied in rat baso-leukaemia (RBL)-2H3 cells, and ISL has been applied to LPS-induced J774A.1 murine macrophages cells models and human umbilical vein endothelial cells (Kang et al. 2010; Thiyagarajan et al. 2011).

For studies in vivo, LCA attenuated allergic airway inflammation in a murine model of asthma (Chu et al. 2013), inhibited xylene-induced mice ear oedema and carrageenan-induced paw oedema (Cui et al. 2008). LCE has been studied in TPA-induced mouse ear oedema models and oxazolone-induced chronic allergic contact dermatitis mouse skin models (Cho YC et al. 2010; Lee et al. 2013). In vivo analyses also revealed that ISL potently attenuated high-fat-diet-induced obesity, hypercholesterolaemia and insulin resistance, which indicated that ISL could be useful...
for the treatment of NLRP3 inflammasome-associated diseases (Honda et al. 2014).

Depending on some clinical studies, LCA had a similar effect to moderate childhood atopic dermatitis in comparison with 1% hydrocortisone. The transepidermal water loss was significantly lower than baseline, and the use of LCA for four weeks could maintain clinical improvement (Wanankanul et al. 2013).

**Other flavonoids**

Besides chalcones, other flavonoids in licorice, including DGC, DGD, ISOA, GLD, LID and LIA, also showed excellent anti-inflammatory activities. DGC, DGD and ISOA all showed strong ferric reducing activities and effectively scavenged DPPH, ABTS+ and singlet oxygen radicals (Kim HJ et al. 2012b). Furthermore, DGC increased the expression of haemeoxygenase-1 and MAPK phosphatase-1, suppressed the inflammation-mediated neurodegeneration, production of TNF-α, NO, ROS, NF-κB and phosphorylation of p38 MAPKs, ERK1/2, IκB and p65 (Kim HJ et al., 2012a; Kim et al. 2013). GLD significantly inhibited NO and IL-1β release (Thiyagarajan et al. 2011), attenuated colonic inflammation in mice with dextran sulphate sodium-induced colitis (Kwon et al. 2008), and decreased the iNOS mRNA expression under high-glucose levels, which indicated that GLD could be applied to diabetes-related vascular dysfunction (Yehuda et al. 2015). LID and LIA inhibited the secretion of IL-6, chemokine (C-C motif) ligand 5, MMP-7, -8 and -9. The suppression of cytokine and MMP secretion by LID and LIA was associated with the reduced activation of NF-κB p65 in peri-odontitis treatment (La et al. 2011).

*In vitro*, the anti-inflammatory activities of DGC, DGD and ISOA have been demonstrated in glutamate-induced mouse hippocampal HT22 cells models (Kim HJ et al. 2012a). DGC, GLD, LID and LIA have been used in LPS-treated Raw264.7 macrophages models (La et al. 2011; Thiyagarajan et al. 2011). DGC has also been applied to LPS-stimulated BV-2 microglia models (Kim et al. 2013). And GLD has been applied in macrophage-like cells models under chronic glucose stress (Yehuda et al. 2015). *In vivo*, GLD has been used in dextran sulphate sodium-induced colitis mice models (Kwon et al. 2008).

**The summary of main anti-inflammatory mechanisms of licorice**

Depending on previous studies, we found that decreasing the inflammatory factors was the key strategy for licorice to treat inflammation-related disease, such as rheumatoid arthritis (Yang et al. 2013), liver oxidative injury (Huo et al. 2011), colonic inflammatory response (Takhshid et al. 2012) and periodontitis (Farhad et al. 2013). Tumour necrosis factor, MMPs, PGE2 and free radicals are four main factors most widely reported among numerous studies related to licorice’s anti-inflammatory mechanisms.

**Tumour necrosis factor**

The role of TNF-α played in the progress of inflammation has been explored deeply. TNF-α is an autocrine stimulator as well as a potent paracrine inducer of pro-inflammatory mediators including IL-1, IL-6, IL-8 (Suzuki et al. 2000) and granulocyte-macrophage colony-stimulating factor (Haworth et al. 1991). Additionally, TNF-α stimulates chondrocytes to release MMPs in rheumatoid arthritis and periodontitis patients (Sorsa et al. 2006). Furthermore, TNF-α also induces NO production and releases PGE2 by synovial cells, which in turn causes tissue destruction (Nagy et al. 2008). Recently, treatment of ulcerative colitis with TNF-α antibody has achieved encouraging results in the clinic (Takhshid et al. 2002). In the progressive accumulation of liver fibrosis, the progress is triggered by a series of chemical mediators, with a prominent role played by the TNF-β (Poli 2000). Depending on the findings of licorice and its isolated pure compounds, *G. glabra* extracts (Samadnejad et al. 2012) inhibited the formation of TNF in acetic acid-induced ulcerative colitis animal model, 18β-GA (Ishida. 2013) exerted the activity in indomethacin-induced small intestinal damage, *G. uralensis* extracts (Wu et al. 2011), 18β-GC (Wang et al. 2011), LCE (Lee et al. 2013) and DGC (Kim HJ et al. 2012a) inhibited the formation of TNF in LPS-treated Raw264.7.

**MMPs**

The pathogenetic MMPs may lead to joint destruction. In the process of liver fibrosis, the expressions of MMPs are activated by reactive oxygen species and lipid peroxidation products (Poli 2000). In periodontal inflammation, MMPs form a family of enzymes that mediate multiple functions both in the tissue destruction and immune responses. The expression and activity of MMPs in noninflamed periodontium is low but is drastically enhanced to pathologically elevated levels due to the dental plaque and infection-induced periodontal inflammation (Sorsa et al. 2006). 18α-GC, ISL, LID and LIA all showed up inhibition activities towards MMPs in paraquat poisoning-induced lung injury rat models (Xiao et al. 2014), PMA-exposed human umbilical vein endothelial cells (Kang et al. 2010) and LPS-treated U937 cells line (La et al. 2011) separately.

**PGE2**

Prostaglandins are potent eicosanoid lipid mediators derived from phospholipase-released arachidonic acid that are involved in numerous homeostatic biological functions and inflammation. They are generated by cyclooxygenase isozymes. The prime mode of prostaglandin is through specific G protein-coupled receptors (Funk 2001). In TCM therapeutics, licorice has been used to strengthen the function of digestive system and alleviate pain for thousands of years. The inhibition of PGE2 could induce fever (Ferreira 1972). The inhibition of PGE2 could explain licorice’s ancient characteristics of alleviating pain.

**Free radicals**

Free radicals, including reactive oxygen species, such as the hydroxyl radical, superoxide anion, and hydrogen peroxide, and reactive nitrogen species, such as NO, are all associated with pathology and cell damage, which have been reported to attack nucleic acids and proteins, as well as unsaturated fatty acids in the cell membrane (Fernández-Moriano et al. 2016). In the rheumatoid arthritis, NO has been reported to be an important mediator in the progression of cartilage and bone destruction.
and induce the production of pathogenic cytokines and chemokines. In liver models, involvement of reactive oxygen species and lipid peroxidation products can be clearly demonstrated in other fundamental events of hepatic fibrogenesis (Poli 2000). 

**Glycyrrhiza uralensis** extract (Wu et al. 2011), 18β-GC, 18β-GA (Wang et al. 2011), LCA, LCB (Fu et al. 2013), LCC (Lee et al. 2013), ISL, EC, GLD (Thiyagarajan et al. 2011) and DGC (Kim HJ et al. 2012b), all significantly inhibited the production of free radicals in LPS-treated Raw264.7 macrophages model.

Thus, the underlying anti-inflammatory mechanisms for targeting the related pathogenic factors could explain the extraordinary inhibition properties of licorice.

### Drugs that include compounds of licorice

Drugs came from GC have been successfully used in China and Japan for many years to treat inflammation diseases. Five hundred and fifty-four kinds of drugs containing GC have been approved by the China Food and Drug Administration (CFDA), and four generations of GC preparations have been developed so far, from GC tablets to ammonium glycyrrhizinate, diammonium glycyrrhizinate and magnesium isoglycyrrhizinate (MgIG). The dosage forms are quite abundant, such as extractum, tablet, capsule, injection, granule and oral solution, the main active compounds and preparations have been listed in Table 4. Depending on the clinical researches, MgIG, mainly containing 18α-GC, had a better lipotropy, a higher targeting and fewer adverse reactions, and was regarded as a safer and more effective drug compared with preparations mainly containing 18β-GC (Zeng et al. 2006; Xu et al. 2013).

### Safety of licorice

Although licorice is considered to be a nontoxic herb in TCM, the safety use of licorice still attached much attention. The mechanisms have been fully evaluated. Licorice was reported to be a competitive inhibitor of 11β-hydroxysteroid dehydrogenases (11β-HSDs), the most important enzymes in the systemic regulation of glucocorticoids and mineralocorticoid (Whorwood et al. 1993). There are two 11β-HSDs, 11β-HSD1 and 11β-HSD2. 11β-HSD1 is a bidirectional enzyme that preferred activation of cortisol from cortisone, expressed in liver, adipose, bone and other inflamed tissues. 11β-HSD2 converts active cortisol to inactive cortisone, expressed in the kidney, pancreas and other mineralocorticoid sensitive tissues (Ma et al. 2011). GC administration to rats in vivo (75 mg·kg⁻¹, day for 5 days) resulted in the inhibition of 11β-HSD mRNA levels and 11β-HSD activity in both predominantly mineralocorticoid (kidney and distal colon) and glucocorticoid (liver and pituitary) target tissues, and the inhibition was in a dose-dependent manner in vitro (Whorwood et al. 1993). In a study conducted in 12 healthy volunteers, the ingestion of 100 g licorice daily for 8 weeks increased the plasma atrial natriuretic peptide concentration and the mean body weight, and decreased the plasma concentrations of antidiuretic hormone, aldosterone and plasma renin activity, which reflected retention of sodium and fluid volume, and the effects were probably due to the mineralocorticoid properties of licorice (Forslund et al. 1989). In another case, a 51-year-old lady was diagnosed as acquired apparent mineralocorticoid excess and severe hypertension after eating considerable amounts of salted licorice, while her blood pressure quickly normalized after stopping the intake of the salted licorice (Ruiz-Granados et al. 2012).

All of the above reports showed that the hormonal-like effects of licorice might be the main reason for its side effects; hence the particular attention should be attached to the large doses or long-term ingestion of licorice (Wang & Nixon 2001). Furthermore, the genetic difference between individuals was also an important reason for different sensitivity, the 11β-HSD2 gene mutation led to lower 11β-HSD2 enzyme activity, and the patients with mutation would be more sensitive than the general population for licorice-induced hypertension. Therefore, the herbal medicine containing licorice may be contraindicated in patients with an 11β-HSD2 mutation (Harahap et al. 2011). Although the intake of licorice may have some side effects in humans, all of these side effects were reversible and the health benefits outweigh its side effects with proper control. Instead of raw licorice extract, the compounds isolated from licorice may reduce the GC-induced side effects and improve the therapeutic action.

### Conclusions and perspectives

Licorice has been used in TCM for thousands of years to treat inflammatory diseases. The results of this paper showed that 3 triterpenes and 13 flavonoids were mainly responsible for the anti-inflammatory activity of licorice through a variety of mechanisms, especially downregulation of mediators, such as TNF-α, MMPs, PGE2 and oxidative stress on the progression of inflammation-related diseases. In this report, we also reflected the available data on in vitro anti-inflammatory activities of licorice and purified compounds on cellular substrates and in vivo on animal models. So far, 554 drugs containing natural compounds and derivatives of licorice have been approved by CFDA. As for safety evaluation, licorice was regarded as a competitive inhibitor of 11β-HSDs, long time intake of licorice may lead to acquired apparent mineralocorticoid excess and severe hypertension, furthermore, the genetic difference between individuals was also an important reason for different sensitivity. All the above suggest that licorice could serve as a therapeutic candidate sources for the treatment of inflammatory diseases with a kind consideration of licorice’s hormonal-like effects.

A series of licorice compounds have been indicated possessing anti-inflammatory effects. So far, studies focusing on licorice extracts are rather limited, and the active compounds in the extracts are not clear. The single compound, such as 18β-GC has attracted considerably more studies. However, the studies about the interactions of different active compounds are restrained. More importantly, dosage in different models are quite different, more pharmacokinetic studies on licorice using different models should be carried out, and the maximum tolerated dose is also critical for clinical use of licorice and its purified compounds.

Our previous studies showed that the contents of triterpenes and flavonoids varied a lot among three licorice original plants, hence a quite difference will be made among their anti-inflammatory activities, which is worthy of further studies. In addition, total contents of phenols, flavonoids and tannins in licorice varied a lot at different harvest times, the samples obtained during from May and November showed the most favourable free radical scavenging and antioxidant effects, whereas the best gastroprotective effect was observed in the sample obtained during May (Cheel et al. 2013). Many compounds, especially the triterpenes, have been developed to the registered drugs of CFDA so far, the side effects of triterpenes have also been investigated for many years. While, the flavonoids of licorice has not been studied deeply, and the large sample, randomized, double-blind
and controlled chemoprevention clinical trials about flavonoids are very limited, which require more attention. We can conclude that licorice is a potential source of natural anti-inflammatory agent. However, at the same time, it still needs deeper researches for evaluating its pharmaceutical potentialities and better understanding of its pharmacological mechanisms.

Disclosure statement
All authors declare that they have no competing interests.

Funding
The paper was supported by National Science Foundation of China, 10.13039/501100001809 [81503181].

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