



Anti-inflammatory activity of traditional Chinese medicinal herbs

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Abstract

Accumulating epidemiological and clinical evidence shows that inflammation is an important risk factor for various human diseases. Thus, suppressing chronic inflammation has the potential to delay, prevent, and control various chronic diseases, including cerebrovascular, cardiovascular, joint, skin, pulmonary, blood, lymph, liver, pancreatic, and intestinal diseases. Various natural products from traditional Chinese medicine (TCM) have been shown to safely suppress proinflammatory pathways and control inflammation-associated disease. *In vivo* and/or *in vitro* studies have demonstrated that anti-inflammatory effects of TCM occur by inhibition of the expression of master transcription factors (for example, nuclear factor- κ B (NF- κ B)), pro-inflammatory cytokines (for example, tumor necrosis factor- α (TNF- α), chemokines (for example, chemokine (C-C motif) ligand (CCL)-24), intercellular adhesion molecule expression and pro-inflammatory mediators (for example, inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2)). However, a handful of review articles have focused on the anti-inflammatory activities of TCM and explore their possible mechanisms of action. In this review, we summarize recent research attempting to identify the anti-inflammatory constituents of TCM and their molecular targets that may create new opportunities for innovation in modern pharmacology.

Key words: Anti-inflammatory activity, Traditional Chinese medicinal herbs, Pro-inflammatory cytokines

Inflammation and chronic disease

Inflammation is known to contribute to physiological and pathological processes by the activation of the immune system, local vascular system, and various cells within the damaged tissue (Coussens and Werb, 2002). Prolonged inflammation, known as chronic inflammation, is caused by a variety of factors, including microbial pathogen infection, physical, chemical, and surgical irritation, and/or wounding. The classical characteristics of inflammation are pain, swelling, edema, redness and heat (Mantovani, 2010).

There is now growing evidence supporting the concept that chronic inflammation may affect many organ systems including skin, brain, colon, blood vessels, pancreas, joints, lung, and heart (Khatami, 2009).

Epidemiological studies have also revealed that chronic inflammation is causally linked to various human diseases, including cerebrovascular, cardiovascular, joint, cutaneous, pulmonary, blood, liver, and intestinal diseases as well as diabetes (Figure1). The inflammatory process leads to the up-regulation of a series of pro-inflammatory enzymes, cytokines, reactive oxygen/nitrogen species (RO/NS) and signaling

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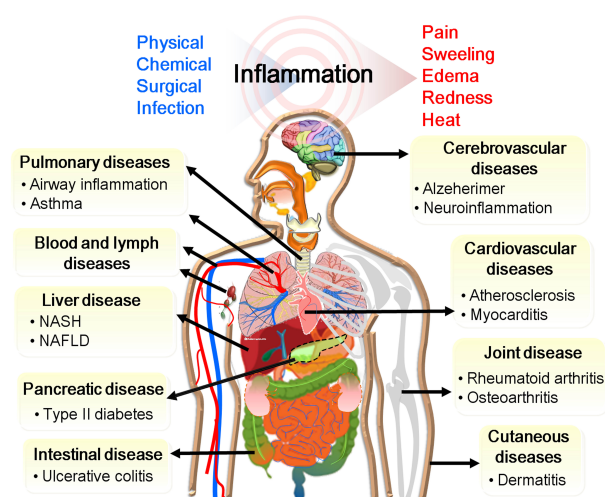


Figure 1. Human diseases linked with chronic inflammation

proteins in infected tissues and cells. Elevation in both the tissue and the serum levels of pro-inflammatory mediators predict an increased health risk at all stages of these diseases (Forrester and Bick-Forrester, 2005). Thus, blocking of inflammatory signaling is usually recognized as a potential therapeutic modality for chemoprevention.

TCM herbs as promising anti-inflammatory agents

TCM has evolved over the past 5,000 years to prevent and manage human disease. The clinical recognition and diagnosis of disease in TCM are mainly based on the yin-yang and five elements theories (Lu et al., 2009a). Traditionally, the two most common methods of applying herb treatments are to make a decoction (a strong tea that must be simmered for an hour or more) and to make large pills containing honey as a binding agent. However, modern herbs, developed to replace the standard Chinese preparations, come in two popular forms, namely, extract powders (or granules) and smooth (Wang et al., 2009). Herbs used in TCM and their active components have been demonstrated in many animal or cell culture models to inhibit inflammatory responses in different organs including the lung, esophagus, cerebrum, colon, skin, prostate, mammary glands, liver, pancreas, and lung (Pan et al., 2011; Ichikawa et al., 2003; Yarosh et al., 2006). Table 1 summarizes the various natural products derived from TCM herbs, which have been shown to safely suppress proinflammatory signaling pathways and to control inflammation-associated disease.

Anti-inflammatory properties in chronic diseases and its possible mechanisms

Blood and lymph diseases

The human's immune system is composed of organs such as the spleen and thymus along with lymph nodes and bone marrow that also contribute to the prevention of infection and disease by producing and storing specific immune cells (Schmid-Hempel, 2005). Indeed, inflammation is an integral part of the immune system, but sometimes chronic inflammation becomes a pathophysiological process leading to disease development and progression (Handschin and Spiegelman, 2008).

Macrophages play a central role in chronic inflammation by mechanisms such as the overproduction of pro-inflammatory cytokines (tumor necrosis factor- α (TNF- α and interleukins (IL-6 and IL-1 β) and generation of inflammatory mediators in response to microbial products (LPS, lipopolysaccharide), such as reactive oxygen species (ROS), prostaglandin E₂ (PGE₂), nitric oxide (NO) and interferon- γ (IFN- γ). These mediators are potent activators of components of the pro-inflammatory signal transduction cascade, including NF- κ B-inducing kinase, mitogen-activated protein kinase (MAPK), and protein kinase C (PKC) (Pan et al., 2009a). 6-gingerol, 6-shogaol, andrograpanin, phylligenin, tectorigenin, rhein, baicalin, berberine, naringenin, cimicifugine A, ligustilide and schisantherin A are bioactive substances in medicinal plants that have been reported to decrease LPS and/or IFN- γ -induced production of pro-inflammatory cytokines and mediators in macrophages and primary mouse splenocytes by down-regulation of MAPK and inhibition of PKC-mediated activation of downstream transcription factors NF- κ B and activator protein 1 (AP-1) (Lee et al., 2009c; Lim et al., 2008; Dugasani et al., 2010; Liu et al., 2008a; Ling et al., 2010; Zhang et al., 2010a; Pan et al., 2008; Luo et al., 2009; Li et al., 2011b; Lin et al., 2008; Ho and Lin, 2008; Lin and Lin, 2011; Hwang et al., 2011; Yang et al., 2009; Su et al., 2011). Recently, evodiamine extracted from *Evodia Fructus* (吴茱萸 *wú zhū yú*; the fruits of *Evodia rutaecarpa*), was also demonstrated to be effective in inhibiting the production of COX-2-mediated PGE₂ and expression of iNOS through inhibition of PI3K/Akt/p70S6K signaling and inhibition of hypoxia-inducible factor-1 α (HIF-1 α) accumulation in hypoxia-stimulated RAW 264.7 macrophages (Liu et al., 2009b).

Cerebrovascular diseases

Recent studies have shown that the severity of cerebrovascular disease, including Alzheimer's disease, Parkinson's disease and cerebral ischemia, correlates with inflammation-mediated responses in neural cells (Britschgi and Wyss-Coray, 2007). Inflammation of the brain and central nervous system (CNS) are also mediated by the generation of various pro-inflammatory cytokines, including TNF- α , IL-1 β and IL-6 in microglia, astrocytes, ependymal cells, macrophages and mast cells (Rivest, 2009). Moreover, microglia activation is one of the causative factors in neuroinflammation, which results in brain damage during neurodegenerative disease. Previous studies have shown that luteolin, senkyunolide A, Z-ligustilide and Agrimoniae Herba possess anti-inflammatory properties by decreasing LPS-induced NO and PGE₂ production, by suppressing TNF- α , IL-1 β , iNOS and COX-2 expression, and by blocking NF- κ B activation in murine BV-2 microglial cells (Zhu *et al.*, 2011b; Or *et al.*, 2011b; Bae *et al.*, 2010). *In vivo* studies have shown that cholic acid, hyodeoxycholic acid and total glucosides of peony (TGP) can prevent cerebral ischemia and Alzheimer's disease by inhibiting inflammatory cytokine (TNF- α , IL-1 β and IL-6) production and down-regulating c-Jun N-terminal kinases (JNK), p-38 and MAPK extracellular signal-regulated kinases (ERK) kinase3/6 (MEK3/6) phosphorylation (Huang *et al.*, 2011; Hua *et al.*, 2009).

Cardiovascular diseases

Recent studies have demonstrated that inflammatory responses may cause myocardial damage and atherosclerosis, leading causes of cardiovascular disease (CVD) (Libby, 2006).

Tanshinone IIA and curcumin, substances with strong anti-inflammatory activity, have been shown to be effective in protecting against cardiac inflammation in *in vitro* and *in vivo* models (Ren *et al.*, 2010; Pari *et al.*, 2008). Mito *et al.* (Mito, 2011) reported that the cardioprotective effects of curcumin are elicited through the inhibition of IL-11, TNF- α , GATA-4 and NF- κ B expression and may provide a novel therapeutic strategy for the treatment of autoimmune myocarditis. In addition, *Salvia miltiorrhiza* Radix (丹参 *dān shēn*; the roots of *Salvia miltiorrhiza* Bunge) preparations rich in tanshinone IIA were shown to reduce infarct size and improve cardiac apoptosis and inflammation by significantly enhancing Akt phosphorylation and suppressing NF- κ B phosphorylation, myeloperoxidase

(MPO) activity and production of inflammatory cytokines, such as TNF- α , and IL-6 (Zhang *et al.*, 2010b). Clinical studies have shown that vascular inflammation is the earliest event in the development of atherosclerosis (Izumimoto and Kawakami, 2011). The process involves stimulation of cholesterol and oxidized low density lipoprotein (ox-LDL) accumulation within the vessel wall and generation of oxidative free radicals, which activate vascular endothelial cells and enhance the adhesion of monocytes to them by promoting expression of endothelial adhesion molecules, including selectins, vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1) (Libby and Theroux, 2005). Once monocytes firmly attach to the surface of the endothelium under the influence of chemoattractants such as monocyte chemoattractant protein-1 (MCP-1), they transmigrate into the arterial intima and differentiate into macrophages. These macrophages proliferate and amplify the inflammatory response through the secretion of numerous growth factors, adhesion molecules, pro-inflammatory cytokines (IL-6, IL-1 β and TNF- α) and matrix metalloproteinases (MMPs) (Packard and Libby, 2008). In addition, the toll-like receptors (TLRs) TLR-2 and TLR-4 also play an important role in innate immune and inflammatory responses, and several reports have demonstrated the expression of TLR-2 and TLR-4 in atherosclerotic lesions (Schoneveld *et al.*, 2008). TGP, ginsenoside, ginkgolide B, monacolin K and glycyrrhetic acid have been shown in experimental animal studies and *in vitro* studies of human umbilical vein endothelial cells (HUVEC) to significantly attenuate the development of atherosclerotic disease by decreasing ROS generation, reducing expression of adhesion molecules, MMP-2 and pro-inflammatory mediators and increasing macrophage migration inhibitory factor (MIF) levels (Li *et al.*, 2009; Chang *et al.*, 2010; Xie *et al.*, 2011; Li *et al.*, 2008; Li *et al.*, 2011a; Liu *et al.*, 2008b; Liu *et al.*, 2010b).

Pancreatic disease

Mounting evidence suggests that oxidative stress and chronic inflammation play an important role in obesity-related metabolic disorders such as type 2 diabetes (Hotamisligil, 2006). However, type 1 diabetes, one of the most common autoimmune diseases, is caused by T cell-mediated destruction of pancreatic beta cells (Kalousova *et al.*, 2004). More and more evidence indicates that the anti-inflammatory effects of TCM may contribute to their antidiabetic action (Xie and Du, 2011).

Recent studies have shown that berberine can ameliorate type 1 diabetes and decrease the expression of Th17 cytokines in nonobese diabetic (NOD) mice via suppression of Th17 and Th1 differentiation. Berberine inhibited Th1 differentiation by decreasing the activity of STAT1 and STAT4 through suppression of p38 MAPK/JNK activity, but down-regulated Th17 differentiation through activation of ERK1/2 and reduction in the levels of STAT3 phosphorylation and retinoic acid-related orphan receptor γ t (ROR γ t) expression (Cui *et al.*, 2009).

Recently, the active principles in Astragali Radix (黄耆 huáng qí) (calycosin, calycosin-7- β -D-glucoside, ononin, calycosin and formononetin) that inhibit pro-inflammatory cytokine production were identified. Xu *et al.* (Xu *et al.*, 2011) have reported that calycosin can inhibit advanced glycation end products (AGEs)-induced macrophage migration and adhesion to endothelial cells; calycosin also can relieve local inflammation by reducing expression of transforming growth factor- β 1 (TGF- β 1), ICAM-1, p-ERK 1/2, p-NF- κ B and receptor for advanced glycation end products (RAGE) and by increasing expression of the estrogen receptor in HUVECs (Xu *et al.*, 2011). In another study, it was demonstrated that four natural compounds from Astragali Radix (黄耆 huáng qí) with anti-diabetic and insulin sensitizing effects can reduce the secretion of pro-inflammatory cytokines (TNF- α , IL-6 and MCP-1) and expression levels of inflammatory cell markers (CD68 and F4/80) and increase the level of agrinase I (Hoo *et al.*, 2010).

This major increase in morbidity and mortality of diabetes is due to the development of both macro- and micro-vascular complications such as are commonly found in diabetic patients with foot ulcers (Levin, 2002). Previous scientific studies reported that Rehmanniae Radix (地黄 dì huáng) was effective in promoting diabetic foot ulcer healing, angiogenesis, and tissue regeneration and in inhibiting inflammation through induction of vascular endothelial growth factor (VEGF) expression, reduction of LPS-induced NO production, stimulation of human fibroblast cell (Hs27) proliferation and promotion of HUVEC cell migration and tube formation (Lau *et al.*, 2009; Tam *et al.*, 2011).

Intestinal disease

The major forms of inflammatory bowel disease (IBD), i.e., Crohn's disease and ulcerative colitis (UC), are chronic relapsing inflammatory conditions of the gastrointestinal tract, resulting from impairment of

intestinal epithelial barrier function and subsequent defects in adaptive immunity (Tsianos and Katsanos, 2009). Increasing evidence demonstrates that infiltration and migration of innate immune cells depends on production of pro-inflammatory cytokines, chemokines and adhesion molecules (Jose *et al.*, 2006). In addition, the inflammatory reaction involves complex interactions between immune cells and endothelial cells (ECs), the monolayer between blood and tissue (Bouguen *et al.*, 2011). Therefore, restoration of the balance between pro- and anti-inflammatory cytokines may be a promising strategy for the treatment of IBD. Recent studies have shown that mollugin inhibits TNF- α -induced inflammatory responses and chemotaxis in HT-29 cells and U937 cells through inhibition of NF- κ B activation and decreased MCP-1, IL-8 and ICAM-1 expression (Kim *et al.*, 2009). In another model it has also been found that matrine, berberine, hypaconitine and skimmianine could inhibit the LPS-stimulated inflammatory reaction by improving NO-dependent vasomotion and inhibiting expression of inflammatory mediator (IL-6, IL-8, soluble ICAM-1, TNF- α LBP, and PGE $_2$) (Zhang *et al.*, 2011; Suo *et al.*, 2009). The colitis model in rats has indicated that berberine, hypaconitine, skimmianine, oxymatrine and rhubarbs can ameliorate acetic acid- and 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis and bowel pain via decreases in TNF α , LBP, IL-12, TLR-4 and NF- κ B activation and increases in the IL-10 level, resulting in an improved balance of Th1 and Th2 cells (Zhang *et al.*, 2011; Fan *et al.*, 2008; Liu *et al.*, 2009a).

Pulmonary diseases

Respiratory epithelium plays a key role in airway inflammatory disease, including asthma, acute and chronic microbial infections, and obstructive pulmonary disease by the production of numerous cytokines, chemokines, inflammatory enzymes, and adhesion molecules (Iwamoto, 2003). Importantly, balance of Th1-Th2 cytokine secretion has been suggested as necessary to maintain healthy immune homeostasis. Imbalance has been hypothesized to underlie allergic asthma through a shift in immune responses from a Th1 (IFN- γ) pattern toward a Th2 (IL-4, IL-5, and IL-13) profile, which promotes IgE production, eosinophilic inflammation, activation and survival, and enhanced airway smooth muscle contractility (Busse and Rosenwasser, 2003). Previous studies also suggest that lung epithelial cells are involved in inflammatory processes by recruiting immune cells and producing pro-

inflammatory cytokines, resulting in amplification of the inflammatory signal (Lee *et al.*, 2007). Recent studies showed that ursolic acid, triptolide and Viticis Fructus (蔓荆子 *màn jīng zǐ*; the fruits of *Vitex rotundifolia*) extract could suppress Th2 cell proliferation, eosinophil migration and neutrophilic inflammation by down-regulation of cytokines, chemokines and cell adhesion molecules (Lee *et al.*, 2007; Lee *et al.*, 2008; Hoyle *et al.*, 2010; Sohn *et al.*, 2009). We found that Visci Ramus (槲寄生 *hú jì shēng*; the dried stem, with leaf *Viscum coloratum*), Ganoderma (靈芝 *líng zhī*; *Ganoderma lucidum*), Sophorae Flavescentis Radix (苦參 *kǔ shēn*) and Glycyrrhizae Radix (甘草 *gān cǎo*) extract potently inhibited airway hyperresponsiveness (AHR) and reduced eosinophil infiltration of the lungs in ovalbumin (OVA)-sensitized mice by reducing levels of IgE, CCLs (CCL11 and CCL24) and Th2-associated cytokines (IL-5, IL-4 and IL-13), and by increasing IFN- γ secretion (Busse *et al.*, 2010; Shen *et al.*, 2011). Polyphenol rich extracts from officinal magnolia bark (厚朴 *hòu pò*) and baicalin were also shown to alleviate pneumonia by decreasing the level of NO, IL-6, TNF- α and ICAM-1 and reducing NF- κ B and Toll like receptor (TLR)-3 expression in *Pneumocystis carinii* and influenza virus A (IVA)-infected lung tissue (Wu *et al.*, 2011; Zhou and Zhou, 2009).

Joint diseases

Rheumatoid arthritis (RA) is a systemic and chronic inflammatory autoimmune disorder characterized by synovial hyperplasia, inflammatory cell infiltration and angiogenesis, which ultimately lead to cartilage erosion and articular destruction (Leff, 2006). Several inflammatory cytokines, such as TNF- α , IL-1 β , IL-6, IL-33 and rheumatoid factor (RF) not only play important roles in the chronic inflammation of human RA, but are also associated with various manifestations of inflammation-related angiogenesis (Marrelli *et al.*, 2011).

In the rat model of arthritis, the extract of Arisaematis Rhizoma (天南星 *tiān nán xīng*; the root of *Arisaema rhizomatum*), scopolin and kirenol inhibited paw and joint swelling by suppressing inflammatory cytokines and NO production, inhibiting VEGF and fibroblast growth factor (FGF-2) expression and up-regulating Annexin-1 which interacts with NF- κ B to inhibit NF- κ B activity (Chunxia *et al.*, 2011; Wang *et al.*, 2011; Pan *et al.*, 2009b). Liu *et al.* (Liu *et al.*, 2010a) also demonstrated that icariin can protect chondrocytes from LPS-induced inflammation and extracellular matrix

degradation through inhibition of NO, MMP, iNOS and COX-2 expression. The direct anti-inflammatory and analgesic effects of TCM were observed in animal models of both acute and subacute inflammation, such as formalin-induced paw licking, carrageenan-induced paw edema, cotton pellet-induced granuloma, acetic acid-induced permeability, xylene-induced ear edema, collagen-induced arthritis, complete Freund's adjuvant (CFA)-induced joint inflammation and thermally induced pain.

Skin diseases

As the primary interface between the body and the external environment, the skin provides the first line of defense against traumatic injury and infection by microbial pathogens. Besides its properties as a physical barrier, the skin has many active defense mechanisms and regulation of these mechanisms is important because inappropriate or misdirected immune activity is implicated in the pathogenesis of a large variety of inflammatory skin diseases. High levels of pro-inflammatory cytokines and ROS are proposed to contribute to the pathophysiological mechanisms (Numerof *et al.*, 2005). Lee *et al.* (Lee *et al.*, 2009a; Lee *et al.*, 2009b) found anti-inflammatory effects of the extract of wild chrysanthemum (野菊 *yě jú*; *Chrysanthemum indicum*, CIE) and Asparagi Radix (天門冬 *tiān mén dōng*; *Asparagus cochinchinensis* Merrill, ACE) in 12-O-tetradecanoyl-phorbol-13-acetate (TPA)-induced mouse ear edema and acetic acid-induced vascular permeability models. CIE and ACE showed potent inhibitory activity against topical edema of the mouse ear, leading to substantial reductions in skin thickness and tissue weight, inflammatory cytokine production (TNF- α and IL-1 β , neutrophil-mediated MPO activity, and various histopathological indicators.

Liver disease

Most acute and chronic liver diseases are characterized by the presence of inflammatory and oxidative stress processes with enhanced expression of various pro-inflammatory cytokines and lipid mediators (Ferre and Claria, 2006; Tilg *et al.*, 2006). In the non-alcoholic steatohepatitis (NASH) model, keishibukuryo-gan and Qu Yu Hua Tan Tong Luo decoctions have been found to relieve lipid peroxidation and inflammation of the liver by down-regulation of TNF- α , IL-8, cholesterol, triglycerides (TGs) and MDA levels and up-regulation of superoxide dismutase (SOD) activity (Fujimoto *et al.*, 2010; Zhang *et al.*, 2008).

Conclusion

Strong direct evidence suggests that chronic inflammation promotes development of numerous human diseases such as Alzheimer's, atherosclerosis, arthritis, asthma, diabetes and IBD. The Chinese herbs investigated are mostly qi supplementation (補氣 *bǔ qì*), heat-clearing (清熱 *qīng rè*) and toxin-resolving (解毒 *jiě dú*) drugs, as described previously in the theory of TCM (Xie and Du, 2011). TCM has a long history of human use, and the main active components recorded and identified, in heat-clearing and detoxifying Chinese herbs usually have widespread pharmacological effects including anti-inflammatory actions (Ren *et al.*, 1994). Clinical trials have also demonstrated the effectiveness of TCM for the prevention and therapy of many chronic inflammatory diseases, and the related mechanisms have also been identified. Therefore, in this article, we systemically reviewed the evidence for the efficacy of anti-inflammatory products used in TCM in the treatment of inflammatory processes associated with various chronic diseases and shared their known mechanisms of action.

It is clear that natural bioactive compounds from herbs used in TCM can interfere with multiple cell signaling pathways and have multiple targets within the cells. These mechanisms include (a) modulation of inflammatory signal transduction pathways linked to NF- κ B, AP-1, PI3K/Akt, MAPKs, STATs, and TLRs,

(b) induction of antioxidant enzymes such as SOD, glutathione peroxidase (GPx) and glutathione reductase (GRx), (c) reduction of inflammatory molecule production including iNOS, COX-2, NO and PGE₂ (d) diminished recruitment and activation of inflammatory cells, (e) altered regulation of cellular functions and (f) changes in the balance of Th1 and Th2 cell-derived cytokines (Figure 1). Besides their influence on the regulation of intracellular signaling pathways, the active components from TCM may also inhibit expression of growth factors (VEGF, FGF-2 and TGF- β 1) and MMPs, which are important cofactors for angiogenesis, wound repair and tissue regeneration.

This information adds to the body of evidence indicating that the products of TCM, because of their safety and anti-inflammatory efficacy, may have a potential role in the prevention and treatment of chronic inflammatory disease (Figure 2). Furthermore, extensive research is needed concerning the influence of active herbal products on the pathological, immunological, biochemical and molecular biology-related aspects of disease processes, which may ultimately lead to enhanced formulations for chemoprevention.

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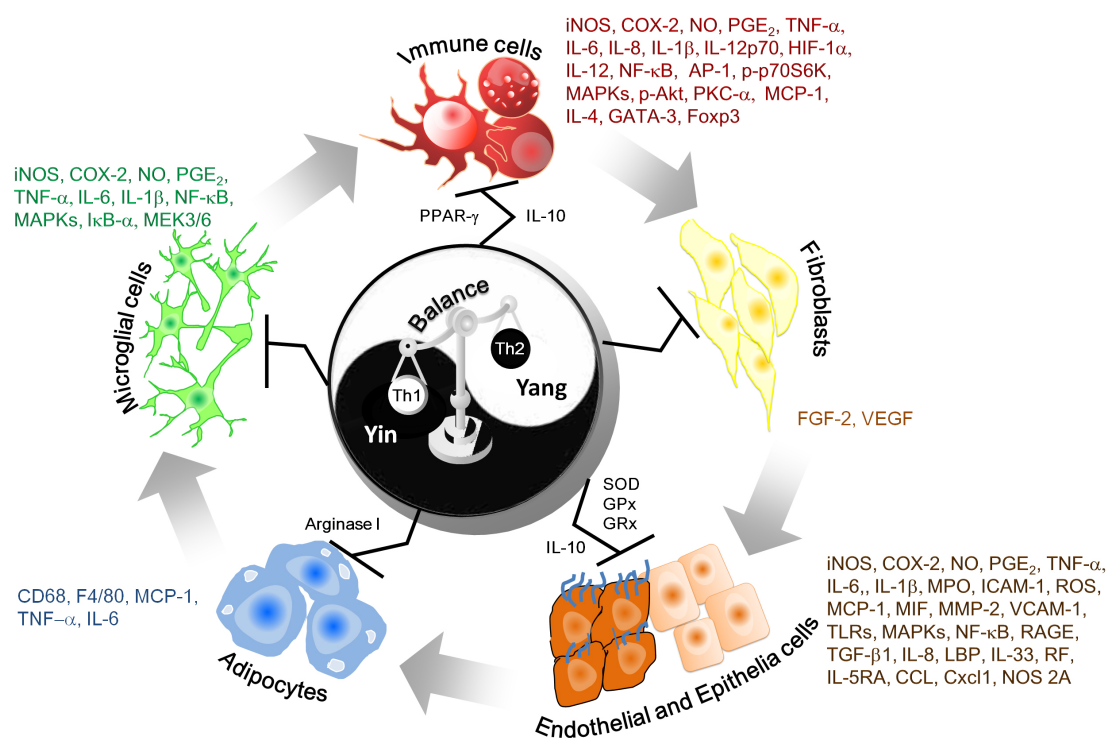
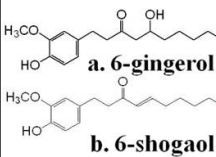
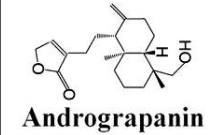
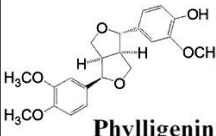
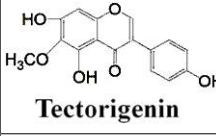
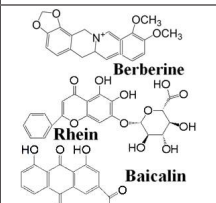
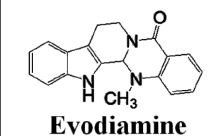
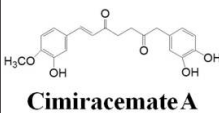
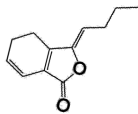
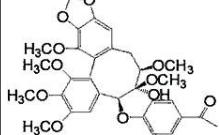
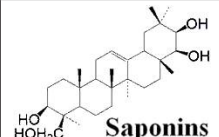
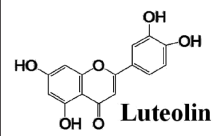
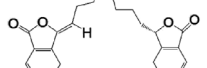
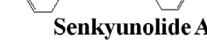
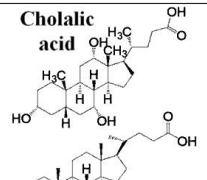
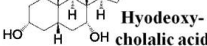
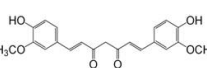
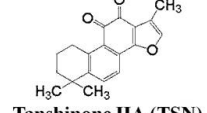
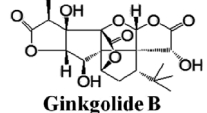
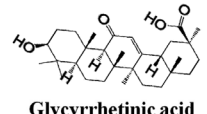
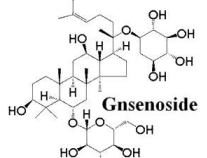


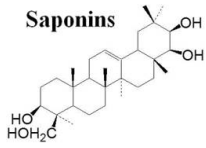
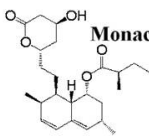
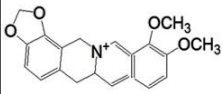
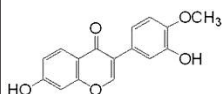
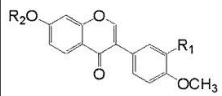
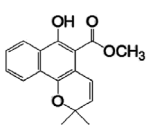
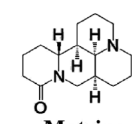
Figure 2. Effects of traditional Chinese medicine (TCM) mediated by the molecular mechanisms of anti-inflammatory action

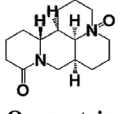
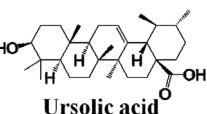
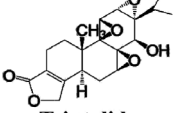
Table 1. Anti-inflammatory effects of the active components from TCM herbs

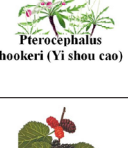
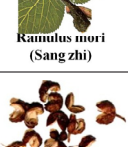
Group of diseases (target organ)	Chinese herbs		Experimental models Studied type (Dose)	Mechanism(s) of action (refs)
Blood and lymph diseases	Origin (pinyin)	Effective ingredient/ Decoction		
	 Zingiber officinale Roscoe (Sheng jiang)	 a. 6-gingerol b. 6-shogaol	a. LPS-stimulated macrophage cells (RAW264.7) (20-80 μ M) b. LPS-induced RAW 264.7 cells (1-6 μ M)	a. Decreases inducible nitric oxide synthase (iNOS) and tumor necrosis factor- α (TNF- α) expression by blocking nuclear factor- κ B (NF- κ B) and protein kinase C- α (PKC- α) signaling (Lee et al., 2009c) b. Reduces prostaglandin E ₂ (PGE ₂) and nitric oxide (NO) production (Dugasani et al., 2010)
	 Andrographis paniculata (Chuanxinlian)	 Andrograpanin	LPS-stimulated bone marrow-derived murine macrophage cells (1.5-90 μ M)	Inhibits iNOS, TNF- α interleukin (IL)-6 and IL-12p70 expression and NO production by down-regulation of p38 mitogen-activated protein kinase (MAPKs) signaling pathways (Liu et al., 2008a)
	 Forsythia koreana (Nakai)	 Phylligenin	a. LPS-stimulated RAW264.7 cells (1-100 μ M) b. λ -Carrageenan-induced paw edema in mice (12.5-100 mg/kg)	a. Inhibits cyclooxygenase-2 (COX-2)-mediated PGE ₂ and iNOS-mediated NO synthesis by down-regulation of NF- κ B signaling pathways b. Suppresses mouse carrageenan-induced paw edema (Lim et al., 2008)
	 Rasmulus mori (Sangzhi)	Mori Ramulus was extracted by EtOAc, n-BuOH and chloroform	LPS/Interferon-gamma (IFN- γ) stimulated macrophage cells	EtOAc and n-BuOH extractions: inhibits NO production (Ling et al., 2010)
	 Belamcanea chinensis (Shegan)	 Tectorigenin	LPS/ IFN- γ stimulated RAW264.7 cells (50-100 μ M)	Decreases NO, IL-1 β and PGE ₂ production, and iNOS and COX-2 protein expression by blocking of NF- κ B activation (Pan et al., 2008)
	 Anisomeles indica (Luo Ma Yi)	One cembrane-type diterpenoid Two benzenoids Five flavonoids Six phenyl propanoids	LPS/ IFN- γ stimulated peritoneal excluded macrophage cells (2-40 μ M)	Decreases NO, TNF- α and IL-12 production (Rao et al., 2009)
	 Ganoderma lucidum (Lingzhi)	Triterpenes and polysaccharides were extracted by 95% EtOH from <i>G. lucidum</i> (GLT)	a. LPS-induced RAW264.7 cells (3-50 (μ g/mL) b. LPS-induced endotoxemic mice (12 mg/kg)	a. Reduces TNF- α , IL-6, PGE ₂ and NO production, and protein expressions of iNOS and COX-2 by inhibiting ERK and JNK-mediated b. NF- κ B and AP-1 activation. Inhibits the production of TNF- α and IL-6 (Dudhgaonkar et al., 2009)
	 Xixin Decoction (Xie xin tang) Radix et Rhizoma Rhei Rhizoma Coptidis Radix Scutellaria	 Berberine Rhein Baicalin	a. LPS-stimulated RAW264.7 cells (0.3-10 μ M) b. Intraperitoneal-injection of LPS (3.2 mg/kg) in male SD rats (oral administration, 3.34 g/kg)	Decreases NO production <i>in vitro</i> and <i>in vivo</i> (Xu, 2006)
	 Evodia rufescarpa (Wu zhu yu)	 Evodiamine	Hypoxia (1% O ₂)-induced RAW264.7 cells (0.3-3 μ M)	Represses hypoxia-induced COX-2-mediated PGE ₂ production and iNOS expression by down-regulation of p-Akt and p-p70S6K-mediated HIF-1 α translational process (Liu et al., 2009b)
	 Berberis aristata (Yin du xiao bi) Citrus paradise (Putao you)	 Berberine Naringenin	LPS-stimulated primary mouse splenocytes (Berberine: 0.8-3.3 μ M) (Naringenin: 18-70 μ M)	Inhibits IL-6/IL-10 or TNF- α /IL-10 ratios (Lin and Lin, 2011)

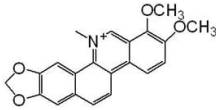
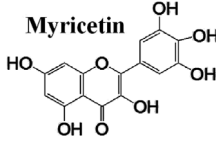
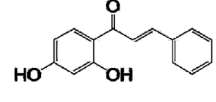
Group of diseases (target organ)	Chinese herbs	Experimental models Studied type (Dose)	Mechanism(s) of action (refs)	
	 Houttuynia cordata thunb (Yuxingcao)	<i>Houttuynia cordata</i> Thunb. (HC) essential oil were extracted by steam distillation	LPS-induced mouse peritoneal macrophages (0.01-100 µg/mL)	Decreases PGE ₂ production, COX-2 activity, and COX-2 gene and protein expression (Li et al., 2011b)
	 Cimicifuga rhizome (Sheng ma)	 Cimicifugate A	LPS-induced human primary blood macrophages (140 µM)	Inhibits TNF-α production by down-regulation of ERK and NF-κB activities (Yang et al., 2009)
	 Acanthopanax senticosus (Ci wu jia)	<i>Acanthopanax senticosus</i> extract (ASE)	LPS/ IFN-γ-stimulated RAW264.7 cells (100-1000 µg/mL)	Suppresses iNOS and NO production through the inhibition of intracellular peroxides levels and NF-κB activity (Lin et al., 2008)
	 Sargassum hemiphyllum	<i>S. hemiphyllum</i> sulfated polysaccharide extract (SHSP)	LPS-stimulated RAW264.7 cells (1-5 mg/mL)	Reduces TNF-T, IL-6, IL-1β and NO production, and RNA expressions of IL-1β, iNOS and COX-2 by down-regulation of NF-κB translocation (Hwang et al., 2011)
	 Citrus reticulata (Chen pi)	Citrus fruit peels were extracted by heat treatment (naringin, hesperidin, nobiletin and tangeretin)	LPS-stimulated RAW264.7 cells (0.5-4 mg/mL)	Inhibits NO production, and iNOS gene expression (Ho and Lin, 2008)
	 Angelica sinensis (Danggui)	Ligustilide 	LPS-stimulated RAW264.7 cells (5-250 µM)	Suppresses NO, PGE ₂ and TNF-α production by blocking the activation of p38MAPK, extracellular signal-regulated kinase (ERK1/2), c-Jun N-terminal kinase (JNK) and the downstream transcription factors AP-1 and NF-κB (Zhu et al., 2011b)
	 Schisandra sphenanthera (Wu wei zi)	Schisantherin A 	LPS-stimulated RAW264.7 cells (0.5-25 mg/mL)	Reduces TNF-α, IL-6, PGE ₂ and NO production, and protein expressions of iNOS, and COX-2 by blocking NF-κB and MAPKs (JNK, p-38 and ERK) signaling (Ci et al., 2010)
	 Semen nigellae (Heizhongcaizi)	 Saponins	LPS/ IFN-γ-stimulated RAW264.7 cells	Suppresses NO production, iNOS, COX-2, IL-1β, IL-6 levels and increases peroxisome proliferator-activated receptor gamma (PPAR-γ) expression through ERK/ pathway (Zhang et al., 2010a)
	 Radix linderae (Wuyao)	Total alkaloids from Radix Linderae (TARL)	LPS-stimulated RAW264.7 cells (10-100 mg/mL)	Prevents NO, IL-1β and TNF-α production, and mRNA expressions of iNOS, IL-1β and TNF-α by blocking MAPKs (p-38 and ERK) and NF-κB p65 protein phosphorylation (Luo et al., 2009)
Cerebrovascular diseases (brain and neuron)				
Neuroinflammation	 Peanut shell (HuaSheng Ke)	 Luteolin	LPS-stimulated murine BV2 microglia (10-50 µM)	Suppresses NO and PGE ₂ production, and TNF-TTTiNOS, COX-2 and IL-1β expression by blocking the activation of NF-κB signaling (Zhu et al., 2011a)
Alzheimer's disease	 Valeriana amurensis Smitt. ex Kom. (Xie Cao)	Valeriana amurensis was extracted by 50% EtOH	Alzheimer's disease model rats' brain	Reduces iNOS, COX-2 and IκB-α levels (Zhang et al., 2010c)

Group of diseases (target organ)	Chinese herbs	Experimental models Studied type (Dose)	Mechanism(s) of action (refs)	
Alzheimer's disease	 Paeony (Mudan)	Total glucosides of paeony (TGP)	Fibrillar Abeta42 induced Alzheimer's disease (AD)	Decreases IL-1β, IL-6, p-p38, p-c-Jun N-terminal kinases (JNK) and MAP kinase kinase3/6 (MEK3/6) protein expressions (Huang et al., 2011)
Brain inflammation	 Agrimoniae herba (Xian he cao)		LPS-induced BV2 microglial cells (0.01-1mg/mL)	Suppresses TNF-α IL-1β, IL-6 production and iNOS expression (Bae et al., 2010)
Neuroinflammation	 Ligusticum chuanxiong (Chuanxiong)	Z-ligustilide  Senkyunolide A 	LPS-stimulated murine BV-2 microglial cells and human peripheral blood monocyte derived macrophages (25-50 μg/mL)	Increases the degradation of TNF-α and iNOS mRNA expressions and reduce TNF-α half life (Or et al., 2011a)
Focal Cerebral Ischemia	 Qing Kai Ling	Cholalic acid  Hydoxy-cholalic acid 	Cerebral ischemia model in rat brain (21 mg/kg)	Decreases TNF-α and IL-1β levels (Hua et al., 2009)
Cardiovascular diseases (heart)				
Autoimmune myocarditis	 Curcuma longa (Jianghuang)	 Curcumin	Cardiac myosin-induced experimental autoimmune myocarditis (EAM) (50 mg/kg/d)	Against cardiac inflammation through suppression of IL-1β, TNF-α, GATA-4 and NF-κB expresses (Mito, 2011)
Cardiac inflammation	 Salvia miltiorrhiza Bunge (Danshen)	 Tanshinone IIA (TSN)	1. Myocardial ischaemia /reperfusion (I/R) injury in diabetic rats (5 mg/kg)	Decreases cardiac inflammation by enhancing PI3K/Akt pathway, suppressing NF-κB p65 protein phosphorylation and reducing of myeloperoxidase (MPO) activity and cytokines production including TNF-α and IL-6 (Zhang et al., 2010b)
Atherosclerosis	 Rhubarb (Dahuang)	Rhubarb were extracted by water	Atherosclerotic animal model (50 mg/kg/day)	Inhibits toll-like receptor (TLR)-2, TLR-4 and NF-κB mRNA and protein expressions (Liu et al., 2008b)
Atherosclerosis	 Paeonia lactiflora Pall (Bai shao)	Total glucosides of paeony (TGP) capsules: paeoniflorin (40 %),hydroxy-paeoniflorin (10 %) and other (50 %)	Vitamin D and cholesterol induced atherosclerosis model in rats (120 or 240 mg/kg)	Inhibits the serum level of inflammatory cytokines (IL-6, and TNF-α) (Li et al., 2011a)
Chronic vascular inflammation	 Ginkgo biloba (Yin xing)	 Ginkgolide B	Oxidized low-density lipoprotein (ox-LDL) stimulated human umbilical vein endothelial cells (HUVECs) (0.1-0.3 mg/mL)	Reduces intercellular adhesion molecule-1 (ICAM-1) expression, NF-κB signaling and inhibiting reactive oxygen species (ROS) generation (Li et al., 2009)
Atherosclerosis	 Glycyrrhizae glabra (Gan cao)	 Glycyrrhetic acid	TNF-T-activated human umbilical vein endothelial cells (HUVEC) (50 μM)	Inhibits ICAM-1 expression, leading to a decrease in adherent monocytes (THP-1) to HUVEC by inhibition of TNF-α-activated JNK/c-Jun and NF-κB signaling pathways (Chang et al., 2010)
Vascular endothelial lesion	 Ginseng (Ren shen)	 Gnsenoside	L-methionine (3%) induced SD male rats (0.8 mg/kg/day)	Decreases iNOS and COX-2 expression (Li et al., 2008)

Group of diseases (target organ)	Chinese herbs		Experimental models Studied type (Dose)	Mechanism(s) of action (refs)															
Atherogenesis	 Panax notoginseng (Sanqi)	Saponins 	Zymosan (10 mg/kg) high-cholesterol diet induced chronic inflammation in rabbits (120 mg/kg/day by oral gavage)	Reduces monocyte chemoattractant protein-1 (MCP)-1 and NF-κB mRNA expressions and serum level of IL-6 (Liu et al., 2010b)															
Atherosclerosis	 Monascus purpureus (Hong qu)	Monacolin K 	Angiotensin II (AngII)-induced apolipoprotein E-deficient (ApoE ^{-/-}) mice (200 mg/kg/day by oral gavage)	Increases of serum macrophage migration inhibitory factor (MIF) and reductions of serum total cholesterol, intercellular adhesion molecule- 1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), matrix metalloproteinase (MMP)-2 (Xie et al., 2011)															
Pancreas disease																			
1. Type 1 diabetes 2. Inflammatory responses and insulin resistance	 Berberis vulgaris (Fu niu hua) Rhizoma coptidis (Huang lian)	 Berberine	1. B and T cells were isolated from nonobese diabetic (NOD) mice (200 mg/kg) 2. Palmitate (PA) stimulated HepG2 cells (0.1-10 μM)	1-1. Decreases Th17 cytokine secretion and differentiation by activation of ERK1/2 and down-regulation of p-STAT3 and RORγt expression 1-2. Reduces Th1 cytokine secretion and differentiation by inhibition of p38 MAPK and JNK activation and down- regulation of STAT1 and STAT4 activities (Cui et al., 2009) 2. Inhibits IL-6, and TNF-α production, modifies of insulin receptor substrate-1 (IRS-1) and downstream Akt (Lou et al., 2010)															
Diabetic nephropathy	 Astragali radix (Huangqi)	 Calycosin	Advanced glycation end products (AGEs) -induced macrophages infiltration in HUVECs (10 ⁻⁸ M)	Reduces macrophage migration and adhesion to endothelial cells by down-regulation of transforming growth factor-β1(TGF-β1), ICAM-1 and receptor for advanced glycation end products (RAGE) expressions; increase estrogen receptor expression and inhibits p-ERK1/2 and p-NF-κB expression (Xu et al., 2011)															
Obesity-related metabolic disorders: diabetic insulin resistance hypertriglyceridemia	 Radix astragali (Huangqi)	<table border="1"><thead><tr><th>Constituent</th><th>R₁</th><th>R₂</th></tr></thead><tbody><tr><td>1 calycosin-7-β-D-glucoside</td><td>OH</td><td>β-D-Glc</td></tr><tr><td>2 ononin</td><td>H</td><td>β-D-Glc</td></tr><tr><td>3 calycosin</td><td>OH</td><td>H</td></tr><tr><td>4 formononetin</td><td>H</td><td>H</td></tr></tbody></table> 	Constituent	R ₁	R ₂	1 calycosin-7-β-D-glucoside	OH	β-D-Glc	2 ononin	H	β-D-Glc	3 calycosin	OH	H	4 formononetin	H	H	a. Human THP-1 macrophages (5-10 μg/mL) b. LPS-induced mouse RAW- Blue macrophage (10-20 μg/mL) c. C57BL/KsJ db/db diabetic mice (2g/kg/day)	a and b. Reduced the secretion of pro- inflammatory cytokines (TNF-α, IL-6 and MCP-1) c. Decreases CD68 and F4/80 mRNA expression and pro-inflammatory cytokines (MCP-1, TNF-α and IL-6), and increases arginase I in epididymal adipose tissue (Hoo et al., 2010)
Constituent	R ₁	R ₂																	
1 calycosin-7-β-D-glucoside	OH	β-D-Glc																	
2 ononin	H	β-D-Glc																	
3 calycosin	OH	H																	
4 formononetin	H	H																	
Diabetic complications : foot ulcer	 Radix rehmanniae (Di huang)	1. Radix rehmanniae (RR) extract 2. 2-herb formula (NF3) was extracted from radix astragali (RA) and RR	1-a. Streptozotocin (STZ) -induced diabetic in rats 1-b. Carrageenan-induced inflammation in rats (1.85 mg/kg) 2. Streptozotocin (STZ) -induced diabetic in rats (0.98 g/kg)	1. Enhances vascular endothelial growth factor (VEGF) expression (Lau et al., 2009) 2. Reduction of wound area and LPS-induced NO production, stimulation of human fibroblast cells (Hs27) proliferation and promotion of HUVEC cell migration and tube formation (Tam et al., 2011)															
Intestinal disease																			
Colon inflammation	 Rubia cordifolia (Qian cao)	 Mollugin	a. TNF-α-induced HT-29 human colon epithelial cells b. TNF-α-induced attachment of U937 monocytic cells to HT-29 cells (20 μM)	a. Inhibits MCP-1 and IL-8, and ICAM-1 mRNA expression by blocking NF-κB activation b. Suppress TNF-α-induced U937 monocytic cell adhesion to HT-29 colonic epithelial cells (Kim et al., 2009)															
Colon inflammation	 Sophora flavescens (Kushen)	 Matrine	LPS-stimulated second generation rat intestinal microvascular endothelial cells (RIMECs) (50 μg/mL)	Inhibits IL-6, IL-8, and soluble ICAM-1 production and improves NO-dependent vasomotion (Suo et al., 2009)															

Group of diseases (target organ)	Chinese herbs		Experimental models Studied type (Dose)	Mechanism(s) of action (refs)
Ulcerative colitis	 Fructus mume (Wumei)	Berberine, hypaconitine and skimmianine from Fructus Mume pill (FMP)	a. Trinitrobenzene-sulfonic acid induced ulcerative colitis in rats b. Xylene-induced acute edema (6-27 mg/kg/day) c. Acetic acid-induced writhing (6-27 mg/kg/day) d. LPS-stimulated HT-29 cell (5-30 µM)	a. Inhibits TNF-α, lipopolysaccharide (LPS) binding protein (LBP) production and TLR-4 and NF-κB expression b and c. Relieving acetic acid-induced bowel pain and xylene-induced acute exudative edema d. Suppresses TNF-TTLBP and PGE ₂ levels (Zhang et al., 2011)
Immunoregulatory effects and colitis	 Rheum tanguticum (Dahuang)	Rhubarbs were extracted the polysaccharides-enriched fractions	Trinitrobenzene-sulfonic acid (TNBS)-induced colitis in rats (200 mg/kg/day)	Decreases TLR-4 activation and promoted the balance of Th1 and Th2 polarization, inhibited NF-κB activity. (Liu et al., 2009a)
Immunoregulatory effects and colitis	 Sophora (Huai)	 Oxymatrine	TNBS-induced colitis in rats (63 mg/kg/day)	Regulating the unbalance of Th1 and Th2 cytokines secretion via decreases IL-2 level and increases IL-10 level and NF-κB expression (Fan et al., 2008)
Pulmonary diseases				
Chronic allergic inflammation and asthma	 Cordyceps (Dongchongcao)	Cordyceps extract	Peripheral blood mononuclear cells (PBMCs) (10-20 µg/mL)	Inhibits the proliferation and differentiation of Th2 cells and reduce IL-4 and GATA-3 expression and increasing the content of IL-10 and expression forkhead/winged-helix transcription factor-3 (Foxp3) (Sun et al., 2010)
Allergic diseases and asthma	 Vitex rotundifolia (Dan ye man jing)	<i>Vitex rotundifolia</i> was extracted by distilled water	TNF-α, IL-4 and IL-1β stimulated A549 human alveolar epithelial cells (0.1-1 µg/mL)	Suppresses eotaxin secretion, eosinophil migration and down-regulated inflammation and cell adhesion-related genes (ICAM, VCAM, IL-8, NOS 2A and IL-5RA) by mitogen-activated protein kinase pathway (Sohn et al., 2009)
Airway inflammation	 Viscum coloratum (Hujisheng)	Partially purified extract (PPE-SVC) and viscolin were extracted from <i>Viscum coloratum</i> Nakai	Ovalbumin (OVA)-sensitized mice (5 mg/kg)	Suppresses airway hyperresponsiveness (AHR) and eosinophil infiltration of the lungs via reducing levels of chemokine (C-C motif) ligand (CCL) (CCL11 and CCL24), IgE and Th2-associated cytokines (IL-5) in bronchoalveolar lavage fluid (BALF) (Shen et al., 2011)
Lung inflammation	 Eriobotrya japonica (Pi pa)	 Ursolic acid	LPS-stimulated A549 cells (50 µg/mL)	Inhibits IL-8 production, NF-κB activation, and iNOS mRNA Expression (Lee et al., 2008)
Acute lung injury Lung inflammation	 Tripterygium wilfordii (Lei gong teng)	 Triptolide	a. Gq-coupled tachykinin 1 receptor with substance P or TNF- stimulated A549 cells b. Chlorine-exposed mice (1.4-2.3x10 ⁻⁸ M or 12.5 mg/mL)	a. Inhibits IL-8 production and NF-κB activation b. Inhibits neutrophilic inflammation and the production of CXC chemokine KC (Cxcl1) (Hoyle et al., 2010)
Lung inflammation	 ASHMI	<i>Ganoderma lucidum</i> , <i>Radix Sophorae flavescenti</i> , <i>Radix Glycyrrhiza</i>	OVA or concanavalin A (ConA)-sensitized and challenged mice (10 mg/day)	Reduces levels of IgE and the Th2 cytokines (IL-4, IL-5, and IL-13) in lung and splenocyte cultures and increases IFN-γ secretion (Busse et al., 2010)
Pneumonia	 Magnolia officinalis (Houpu)	Polyphenol rich extract from <i>M. officinalis</i> bark (MPE)	Influenza virus A (IVA)-infected mice (10-20 mg/kg)	Reduces levels of serum NO, IL-6 and TNF-α, inhibits pneumonia and decreases lung viral titers through downregulation of NF-κB and TLR3 protein expressions in the lung tissue (Wu et al., 2011)

Group of diseases (target organ)	Chinese herbs	Experimental models Studied type (Dose)	Mechanism(s) of action (refs)	
Lung inflammation	 Baicalin (Huangqin)	Pneumocystis carinii infected rats (100-400 mg/kg/day)	Decreases the contents of TNF- α and soluble ICAM-1, and alleviate inflammation in lung tissues (Zhou and Zhou, 2009)	
Joint diseases				
Arthritis	 Arisaema rhizomatum (Xue li jian)	Petroleum ether (PE), ethyl acetate (EE) n-butyl alcohol (n-BE) and water (WE) were extracted from ARCF rhizome	Type II bovine collagen (CII)-induced BALB/c mice (ME 130, 261, 522 mg/kg; EE 10.2, 20.4, 40.8 mg/kg; n-BE 52, 104, 208 mg/kg)	Suppresses paws and joints swelling and reduced the spleen indexes and reduces serum levels of inflammatory cytokines TNF- α , IL-1 β , IL-6, IL-33 and rheumatoid factor (RF) (Chunxia et al., 2011)
Septic arthritis	 Epimedii pubescens (Yinyanghuo)	Icariin	LPS-simulate chondrocytes (0.056-7.7 %)	Increases chondrocytes viability and extracellular matrix synthesis through inhibition of NO production, iNO, COX-2 and matrix metalloproteinase (MMP)-1, MMP-3, and MMP-13 expressions (Liu et al., 2010a)
Arthritis	 Erycibe obtusifolia Benth (Ding gong teng)	Scopolin	Adjuvant-induced rats (50-100 mg/kg)	Inhibits paw swelling and articular index scores, and reduces IL-6, VEGF and fibroblast growth factor (FGF-2) expressions in rat synovial tissues (Pan et al., 2009b)
Arthritis Synovial inflammation	 Siegesbeckia (Xi xian cao)	Kirenol	Type II collagen-induced wistar rats (1-4 mg/kg)	Up-regulates nuclear Annexin-1 expression and inhibits NF- κ B activity in synovium, reduces IL-1 β level and thereby depresses paw swelling (Wang et al., 2011)
Pain	 Pogostemon cablin (Guanghuoxiang)	<i>Pogostemon cablin</i> (PC) was extracted with methanol	a. Acetic acid-induced writhing response b. Formalin-induced paw licking c. γ -carrageenan (Carr)-induced mice paw edema (0.5-1.0 g/kg)	Decreases malondialdehyde (MDA) level, COX-2 and TNF- α activities by increasing the activities of anti-oxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GRx) (Lu et al., 2009b)
Pain	 Pterocephalus hookeri (Yi shou cao)	<i>Pterocephalus hookeri</i> (C.B. Clarke) was extracted with ethanol and aqueous	a. λ -carrageenan (Carr)-induced mice paw edema b. Cotton pellet-induced granuloma formation in rats c. Acetic acid-induced mice d. Xylene-induced ear edema (1-4 g/kg)	Increases the hot-plate pain threshold and reduced writhing response, rat paw edema perimeter, vascular permeability and granuloma weight (Zhang et al., 2009)
Pain Rheumatoid arthritis	 Ranulus mori (Sang zhi)	cis-mulberroside A	a. Acetic acid-induced pain and Evans blue leakage in mice b. Carrageenan-induced mouse paw edema (25 and 50 mg/kg) c. LPS-stimulated RAW264.7 cells (25-50 (g/mL)	Inhibits pain, Evans blue leakage, paw edema, NO production and iNOS expression (Zhang and Shi, 2010)
Pain	 Zanthoxylum armatum (Zhu ye jiao)	Eudesmin, horsfieldin, fargesin, kobusin, sesamin, asarinin, planispine A, and pinoselinol-di-3,3-dimethylallyl	a. Acetic acid-induced mice b. Formalin induced mice c. Xylene-induced mice (100 and 800 mg/kg)	Decreases writhing numbers, licking times and ear swelling (Guo et al., 2011)
Pain Edema	 Saussurea involucreta (Xuelianhua)		a. Carrageenan-induced rats b. Xylene-induced mice c. Acetic acid-induced and d. Hot-plate test model (400 mg/kg)	Inhibits paw edema, ear edema, writhing and pain (Yi et al., 2010)

Group of diseases (target organ)	Chinese herbs	Experimental models Studied type (Dose)	Mechanism(s) of action (refs)	
Pain Edema	 <i>Celandine</i> (Bai qu cai)	 Chelerythrine	a. Xylene-induced ear edema b. Formaldehyde-induced rats c. Acetic acid-induced mice d. LPS-stimulated peritoneal macrophages (1-5 mg/kg or 0.0001-0.1 µg/mL)	Inhibits writhing response, ear swelling and paw edema and decreases PGE ₂ production and COX-2 expression (Niu et al., 2011)
Pain Edema	 <i>Alstonia scholaris</i> (Dengtaishushu)	16-formyl-5α-methoxystrictamine, picralinal and tubotaiwine were extracted with ethanol from <i>Alstonia scholaris</i>	a. Acetic acid-induced mice b. Hot-plate and formalin tests in mice. c. Xylene-induced and mice d. Carrageenan-induced air pouch formation in mice (50-100 mg/kg)	Reduces writhing response, ear edema, NO, PGE2 and MDA, COX-1, COX-2 and 5-lipoxygenase (5-LOX) levels, and increases SOD activity (Shang et al., 2010)
Pain Edema	 <i>Myrica rubra</i> (Yangmei)	 Myricetin	a. Xylene, acetic acid and carrageenan-induced models b. Leukocyte migration assay c. Cotton pellet granuloma models (35 mg/kg)	Decreases ear edema, vascular permeability, paw edema, MDA level, leukocyte count and granuloma tissue formation by increases the serum level of SOD (Wang et al., 2010)
Pain Edema Osteoarthritis	 <i>Murraya exotica</i> (Jiuxiang)	Dried leaves of <i>M. exotica</i> . was extracted with ethanol	a. Acetic acid, hot-plate, carrageena and xylene-induced models b. Rat knee osteoarthritis model (Ethanol 70% extracts)	Decreases writhing response, paw edema, ear swelling, iNOS activity, IL-1β and TNF-α contents, and increases SOD activity and hot-plate pain latency (Wu et al., 2010)
Pain	 <i>Oxytropis falcate</i> (Lian xing ji dou)	 2', 4'-dihydroxy-chalcone	a. Acetic acid-induced writhing response b. Complete Freund's adjuvant (CFA)-induced rats c. Thermally induced mice d. Xylene-induced ear edema (90.6 mg/kg)	Reduces ear edema and writhing (Chen et al., 2011)
Cutaneous diseases				
Skin inflammation	 <i>Chrysanthemum indicum</i> Linne (Yeju)	<i>Chrysanthemum indicum</i> Linne (CIE) was extracted with 70% ethanol	12-O-tetradecanoyl-phorbol-13-acetate (TPA)-induced mouse ear edema (200 mg/kg)	Reduces skin thickness and tissue weight, inflammatory cytokine production (IL-1β and TNF-α), neutrophil-mediated myeloperoxidase (MPO) activity, and various histopathological indicators (Lee et al., 2009a)
Skin inflammation	 <i>Asparagus cochinchinensis</i> (Tiandong)	<i>Asparagus cochinchinensis</i> Merrill (ACE) was extracted with 70% ethanol	a. TPA-induced mouse ear edema (200 mg/kg) b. Acetic acid-induced mice (200 mg/kg)	Reduces skin thickness and tissue weight, inflammatory cytokine production (IL-1β and TNF-α), neutrophil-mediated MPO activity, vascular permeability and various histopathological indicators (Lee et al., 2009b)
Liver disease				
Alcoholic fatty liver disease (NAFLD)	 <i>Keishibukuryogan</i> (gui-zhi-fu-ling-wan)	<i>Cinnamomum cassia</i> blume, <i>Paeonia lactiflora</i> Pallas, <i>Prunus persica</i> Batsch, <i>Poria cocos</i> Wolf and <i>Paeonia suffruticosa</i> Andrews	NASH animal model and patients (Cinnamomi cortex 3 g Paeoniae radix Pallas 3 g Persicae semen Batsch 3 g Hoelen 3 g Moutan cortex 3 g)	Decreases liver injury and blood cholesterol (Fujimoto et al., 2010)
Non-alcoholic steatohepatitis (NASH)	Qu Yu Hua Tan Tong Luo decoction (QYHTTLD)		NASH patients (Radix Bupleuri 10 g Radix Scutellariae 12 g Rhizoma Pinelliae 10 g Radix Codonopsis Pilosulae 30 g, Radix Glycyrrhizae Praeparata 6g Fructus Ziziphi Jujubae 9 g, Rhizoma Polygoni Cuspidati 30 g, Radix Morindae Officinalis 8 g, Herba Hedyotis Diffusae 30 g)	Decreases IL-8, TNF-α and MDA levels and increases SOD activity (Zhang et al., 2008)

Abbreviations

TCM	traditional Chinese medicine
NF-κB	nuclear factor-κB
TNF-α	tumor necrosis factor-α
CCL	chemokine (C-C motif) ligand
iNOS	inducible nitric oxide synthase
COX2	cyclooxygenase 2
RO/NS	reactive oxygen/nitrogen species
IL	interleukins
LPS	lipopolysaccharide
PGE ₂	prostaglandin E ₂
NO	nitric oxide
IFN-γ	interferon-γ
MAPK	mitogen-activated protein kinase
PKC	protein kinase C
AP-1	activator protein 1
HIF-1α	hypoxia-inducible factor-1α
CNS	central nervous system
TGP	total glucosides of peony
JNK	c-Jun N-terminal kinases
MEK3/6	MAPK extracellular signal-regulated kinases (ERK) kinase3/6
CVD	cardiovascular disease
MPO	myeloperoxidase
ox-LDL	oxidized low density lipoprotein
VCAM-1	vascular cell adhesion molecule-1
ICAM-1	intracellular adhesion molecule-1
MCP-1	monocyte chemoattractant protein-1
MMPs	matrix metalloproteinases
HUVEC	human umbilical vein endothelial cells
MIF	migration inhibitory factor
NOD	nonobese diabetic
RORγt	retinoic acid-related orphan receptor γt
AGEs	advanced glycation end products
TGF-β1	transforming growth factor-β1
RAGE	receptor for advanced glycation end products
VEGF	vascular endothelial growth factor
IBD	inflammatory bowel disease
UC	ulcerative colitis
ECs	endothelial cells
TNBS	2,4,6-trinitrobenzene sulfonic acid
AHR	airway hyperresponsiveness
OVA	ovalbumin
TLR	Toll like receptor
IVA	influenza virus A
RA	Rheumatoid arthritis
RF	rheumatoid factor
FGF-2	fibroblast growth factor
CFA	complete Freund's adjuvant
CIE	<i>Chrysanthemum indicum</i>
ACE	<i>Asparagus cochinchinensis</i> Merrill extract
TPA	12-O-tetradecanoyl-phorbol-13-acetate
NASH	non-alcoholic steatohepatitis
TGs	triglycerides
SOD	superoxide dismutase
GPx	glutathione peroxidase
GRx	glutathione reductase

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