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-κB (NF-κB)), 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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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-1β) and generation of inflammatory mediators in response to microbial products (LPS, lipopolysaccharide), such as reactive oxygen species (ROS), prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), nitric oxide (NO) and interferon-γ (IFN-γ). These mediators are potent activators of components of the pro-inflammatory signal transduction cascade, including NF-κB-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, cimiracemate A, ligustilide and schicantherin 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-κB 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 Evodiae Fructus (吳茱萸 wú zhū yú; the fruits of Evodia rutaecarpa), was also demonstrated to be effective in inhibiting the production of COX-2-mediated PGE<sub>2</sub> and expression of iNOS through inhibition of PI3K/Akt/p70S6K signaling and inhibition of hypoxia-inducible factor-1α (HIF-1α) 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-1β 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-1β, iNOS and COX-2 expression, and by blocking NF-kB activation in murine BV-2 microglial cells (Zhu et al., 2011b; Or et al., 2011b). In vivo studies have shown that cholic acid, hydoxycholic acid and total glucosides of peony (TGP) can prevent cerebral ischemia and Alzheimer’s disease by inhibiting inflammatory cytokine (TNF-α, IL-1β 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-kB expression and may provide a novel therapeutic strategy for the treatment of autoimmune myocarditis. In addition, Salviae Miltiorrhizae Radix (丹参; 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-kB 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-1β 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 glycyrrhetinic 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 γt (RORγt) expression (Cui et al., 2009).

Recently, the active principles in Astragali Radix (黃耆 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-β1 (TGF-β1), ICAM-1, p-ERK 1/2, p-NF-kB 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 (黃耆 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 (地黃 di 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-κB 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, hyponatine 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 PGE2) (Zhang et al., 2011; Suo et al., 2009). The colitis model in rats has indicated that berberine, hyponatine, skimmianine, oxymatrine and rhubarbs can ameliorate acetic acid- and 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis and bowel pain via decreases in TNFα, LBP, IL-12, TLR-4 and NF-κB 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 Vitis Fructus (参萸子 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 (蔓寄生 hú ji shēng; the dried stem, with leaf Viscum coloratum), Ganoderma (靈芝 kǔ shēn) and Glycyrrhizae Radix (甘草 hòu pò) and baicalin were also shown to alleviate inflammation of the liver by down-regulation of TNF-α, IL-6 and NF-κB activity (Fujimoto et al., 2010; Zhang et al., 2008). 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-kB 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-1β, 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 Arisaeamatis 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-kB to inhibit NF-kB 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.

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, keishi-bukuryo-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-κB, 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-β1) 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 | Mechanism(s) of action (refs) |
|----------------------------------|---------------|---------------------|-----------------------------|
| Blood and lymph diseases         |               |                     |                             |
|                                  | *Zingiber officinale* (Mu jiang) | a. LPS-stimulated macrophage cells (RAW264.7) (20-80 μM) | a. Decreases inducible nitric oxide synthase (iNOS) and tumor necrosis factor-α (TNF-α) expression by blocking nuclear factor-xB (NF-κB) and protein kinase C-α (PKC-α) signaling (Lee et al., 2009c) |
|                                  |               | b. 6-shogaol        |                             |
|                                  | *Andrographis paniculata* (Chuanxion) | LPS-stimulated bone marrow-derived murine macrophage cells (1.5-90 μM) | 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) |
|                                  | *Phylligenin* | a. LPS-stimulated RAW264.7 cells (1-100 μM) | a. Inhibits cyclooxygenase-2 (COX-2)-mediated PGE and iNOS-mediated NO synthesis by down-regulation of NF-κB signaling pathways |
|                                  |               | b. Carrageenan-induced paw edema in mice (12.5-100 mg/kg) |                             |
|                                  | *Mori Ramulus* (Sangzhi) | LPS/Interferon-gamma (IFN-γ) stimulated macrophage cells | EtoAc and n-BuOH extractions: inhibits NO production (Ling et al., 2010) |
|                                  | *Phellodendron Amurense* (Ma huang) | LPS/IFN-γ stimulated RAW264.7 cells (50-100 μM) | Decreases NO, IL-1β and PGE, production, and iNOS and COX-2 protein expression by blocking of NF-κB activation (Pan et al., 2008) |
|                                  | *Ganoderma lucidum* (Lingzhi) | One cembrane-type diterpenoid | Decreases NO production in vitro and in vivo (Xu, 2006) |
|                                  |               | Two benzenoids       |                             |
|                                  |               | Five flavonoids      |                             |
|                                  |               | Six phenyl propanoids |                             |
|                                  | Triterpenes and polysaccharides were extracted by 95% EtOH from *G. lucidum* (GLT) | a. LPS-induced RAW264.7 cells (3-50 μg/mL) | a. Reduces TNF-α, IL-6, PGE, and NO production, and protein expressions of iNOS and COX-2 by inhibiting ERK and JNK-mediated NF-κB and AP-1 activation. Inhibits the production of TNF-α and IL-6 (Dudhgaonkar et al., 2009) |
|                                  |               | b. LPS-induced endotoxemic mice (12 mg/kg) |                             |
|                                  | *Eurybia koreana* (Nakai) | LPS-stimulated primary mouse splenocytes | Represses hypoxia-induced COX-2-mediated PGE production and iNOS expression by down-regulation of p-Akt and p-p70S6K-mediated HIF-1α translational process (Liu et al., 2009b) |
|                                  |               | (Berberine: 0.8-3.3 μM) | Inhibits IL-6/IL-10 or TNF-α/IL-10 ratios (Lin and Lin, 2011) |
|                                  | *Evodia rutaecarpa* (Wu zhu yu) | Hypoxia (1% O₂)-induced RAW264.7 cells (0.3-3 μM) |                             |
|                                  | *Berberis aristata* (Yin du xian si) Citrus pseudocitrus (Pu lao yu) | LPS-stimulated primary mouse splenocytes (Berberine: 0.8-3.3 μM) (Naringenin: 18-70 μM) |                             |
| Group of diseases (target organ) | Chinese herbs | Experimental models Studied type (Dose) | Mechanism(s) of action (refs) |
|----------------------------------|--------------|---------------------------------------|-------------------------------|
| Cerebrovascular diseases (brain and neuron) | Houttuynia cordata 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) |
| | Cimicifugacinate (Sheng ma) | LPS-induced human primary blood macrophages (140 μM) | Inhibits TNF-$
\alpha$ production by down-regulation of ERK and NF-kB activities (Yang et al., 2009) |
| | Acanthopanax senticosus extract (ASE) | LPS/IFN-$
\gamma$-stimulated RAW264.7 cells (100-1000 μg/mL) | Suppresses iNOS and NO production through the inhibition of intracellular peroxides levels and NF-kB activity (Lin et al., 2008) |
| | S. hemiphyllum sulfated polysaccharide extract (SHSP) | LPS-stimulated RAW264.7 cells (1-5 mg/mL) | Reduces TNF, IL-6, IL-1β and NO production, and RNA expressions of IL-1β, iNOS and COX-2 by down-regulation of NF-kB translocation (Hwang et al., 2011) |
| | Citrus fruit peels were extracted by heat treatment (naringin, hesperidin, nobiletin and tangeretin) | LPS-stimulated RAW264.7 cells (0.5-4 mg/mL) | Inhibits NO production, and iNOS gene expression (Ho and Lin, 2008) |
| | Ligustilide | LPS-stimulated RAW264.7 cells (5-250 μM) | Suppresses NO, PGE$_2$, and TNF-$
\alpha$ 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-kB (Zhu et al., 2011b) |
| | Schisandra chinensis | LPS-stimulated RAW264.7 cells (0.5-25 mg/mL) | Reduces TNF-$
\alpha$, IL-6, PGE$_2$, and NO production, and protein expressions of iNOS, and COX-2 by blocking NF-kB and MAPKs (JNK, p-38 and ERK) signaling (Ci et al., 2010) |
| | Total alkaloids from Radix Linderae (TARL) | LPS-stimulated RAW264.7 cells (10-100 mg/mL) | Prevents NO, IL-1β and TNF-$
\alpha$ production, and mRNA expressions of iNOS, IL-1β and TNF-$\alpha$ by blocking MAPKs (p-38 and ERK) and NF-kB p65 protein phosphorylation (Luo et al., 2009) |
| Neuroinflammation | | LPS-stimulated murine BV2 microglia (10-50 μM) | Suppresses NO and PGE$_2$ production, and TNF-TNF$\alpha$, COX-2 and IL-1β expression by blocking the activation of NF-kB signaling (Zhu et al., 2011a) |
| Alzheimer's disease | Valeriana amurensis was extracted by 50% EtOH | | Reduces iNOS, COX-2 and IkB-$\alpha$B 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            | Total glucosides of paony (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             | 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              | 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        | Cerebral ischemia model in rat brain (21 mg/kg) | Decreases TNF-α and IL-1β levels (Hua et al., 2009) |
| Cardiovascular diseases (heart) | 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) |
| Autoimmune myocarditis         | 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) |
| Cardiac inflammation           | Rhesus 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                | Total glucosides of paony (TGP) capsules: paonoinflorin (40 %),hydroxy-paonoinflorin (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  | 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                | TNF-1-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    | 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 (Ssou)** | Zymosan (10 mg/kg) high-cholesterol diet induced chronic inflammation in rabbits (120 mg/kg/day by oral gavage) | Reduces monocyte chemotactic protein-1 (MCP-1) and NF-κB mRNA expressions and serum level of IL-6 (Liu et al., 2010b) |
| **Atherosclerosis**              | **Monascus purpureus (Hong qu )** | 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               | **Berberis vulgaris (Ku nu lei)** | 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) |
| 2. Inflammatory responses and insulin resistance | **** | | |
| **Diabetic nephropathy**         | **Asaragenus radix (Huangqi)** | Advanced glycation end products (AGEs)-induced macrophages infiltration in HUVECs (10^6 M) | Reduces macrophage migration and adhesion to endothelial cells by down-regulation of transforming growth factor-b1 (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 hypertriglycerideremia** | **Radix astragali (Huangqi)** | a. Human THP-1 macrophages (5-10 μg/mL) b. LPS-induced mouse RAW-264.7 macrophage (10-20 μg/mL) c. C57BL/6J 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) |
| **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 (HS27) proliferation and promotion of HUVEC cell migration and tube formation (Tam et al., 2011) |
| **Intestinal disease**            | **Rubia cordifolia (Qian cao)** | 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) |
| **Colorectal inflammation**      | **Sophora flavescens (Kushen)** | 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 | Chinese herbs | Experimental models Studied (Type, Dose) | Mechanism(s) of action (refs) |
|-------------------|---------------|-----------------------------------------|-------------------------------|
| Ulcerative colitis | 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-TTTLBP and PGE<sub>2</sub> levels (Zhang et al., 2011) |
| Immunoregulatory effects and colitis | Rhuarbbs 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 | 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 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 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 | Partially purified extract (PPE-SVC) and viscolin were extracted from Viscum coloratum 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 | Ganoderma lucidum, Radix Sophorae flavescenti, Radix Glycyrrhiza | 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 | Gq-coupled tachykinin 1 receptor with substance P or TNF- stimulated A549 cells | a. Reduces IP<sub>1</sub> and IL-6 expression in A549 cells b. Suppresses NF-κB and TLR3 protein expressions in the lung tissue (Busse et al., 2010) | |
| Lung inflammation | | | |
| Pneumonia | Polyphenol rich extract from M. officinalis 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 | Mechanism(s) of action (refs) |
|----------------------------------|--------------|---------------------|------------------------------|
| **Lung inflammation**            |              |                     |                              |
|                                  | Baicalin     | 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                        |              |                     |                              |
| Petroleum ether (PE), 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-1β, IL-6, IL-33 and rheumatoid factor (RF) (Chunxia et al., 2011) |
| Arthritis                        |              |                     |                              |
| Arthritis                        |              |                     |                              |
| Septic arthritis                 |              |                     |                              |
| Epimedium phelmae (Shan yang huo) | LPS-simulate chondrocytes (0.056-7.7 %) | Increases chondrocytes viability and extracellular matrix synthesis through inhibition of NO production, iNOS, COX-2 and matrix metalloproteinase (MMP)-1, MMP-3, and MMP-13 expressions (Lu et al., 2009b) |
| Arthritis                        |              |                     |                              |
| Arthritis                        |              |                     |                              |
|                                     |              |                     |                              |
| Arthritis                        |              |                     |                              |
| Scopolin (Sheng ghuang jiang)     | 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                        |              |                     |                              |
| Arthritis                        |              |                     |                              |
| Synovial inflammation            |              |                     |                              |
| Epimedium phelmae (Shan yang huo) | Type II collagen-induced wistar rats (1-4 mg/kg) | Up-regulates nuclear Annexin-1 expression and inhibits NF-κB activity in synovium, reduces IL-1β level and thereby depprese paw swelling (Wang et al., 2011) |
| Arthritis                        |              |                     |                              |
| Pain                             |              |                     |                              |
| Pogostemon cablin (PC) was extracted with methanol | a. Acetic acid-induced writhing response | 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                             |              |                     |                              |
| Pain                             |              |                     |                              |
| Pterocephalus hookeri (C.B. Clarke) was extracted with ethanol and aqueous | a. Acetic acid- and (Carr)-induced mice paw edema (0.5-1.0 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                             |              |                     |                              |
| Pain                             |              |                     |                              |
| Pain                             |              |                     |                              |
| Pain                             |              |                     |                              |
| Pain                             |              |                     |                              |
| Pain                             |              |                     |                              |
| Pain                             |              |                     |                              |
| Pain                             |              |                     |                              |
| Pain                             |              |                     |                              |
| Group of diseases (target organ) | Chinese herbs | Experimental models Studied type (Dose) | Mechanism(s) of action (refs) |
|---------------------------------|---------------|---------------------------------------|-------------------------------|
| Pain                            | Chelerythrine (Boi qua cao) | a. Xylene-induced ear edema b. Formaldehyde-induced mice 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 production and COX-2 expression (Niu et al., 2011) |
| Pain                            | 16-formyl-5α-methoxyxstrictamine, picroalinal and tabotaiwine were extracted with ethanol from Alstonia scholaris | 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                            | 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                            | Dried leaves of M. exotica. 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                            | 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) |
| Skin inflammation               | Chrysanthemum indicum 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               | Asparagus cochinchinensis 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                   | Cinnamomum cassia blume, Paonia lactiflora Pallas, Prunus persica Batsch, Porta cocos Wolf and Paonia suffruticosa Andrews | NASH animal model and patients (Cinnamomi cortex 3 g Paoniae 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) |
| Liver disease                   | 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 6 g 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**

| Abbreviation       | Description                          |
|---------------------|--------------------------------------|
| 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                 | prostaglandin E                       |
| 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                |
| TGF                 | transforming growth factor-α          |
| 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                | 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       |
| TGFβ-1              | transforming growth factor-β          |
| 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                 | Chrysanthemum indicum                 |
| ACE                 | Asparagus cohnichinensis 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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