



Therapeutic Potential of Medicinal Plants and Their Constituents on Lung Inflammatory Disorders

Hyun Pyo Kim*, Hyun Lim and Yong Soo Kwon

College of Pharmacy, Kangwon National University, Chuncheon 24341, Republic of Korea

Abstract

Acute bronchitis and chronic obstructive pulmonary diseases (COPD) are essentially lung inflammatory disorders. Various plant extracts and their constituents showed therapeutic effects on several animal models of lung inflammation. These include coumarins, flavonoids, phenolics, iridoids, monoterpenes, diterpenes and triterpenoids. Some of them exerted inhibitory action mainly by inhibiting the mitogen-activated protein kinase pathway and nuclear transcription factor- κ B activation. Especially, many flavonoid derivatives distinctly showed effectiveness on lung inflammation. In this review, the experimental data for plant extracts and their constituents showing therapeutic effectiveness on animal models of lung inflammation are summarized.

Key Words: Medicinal plant, Lung inflammation, COPD, Constituent, Flavonoid

INTRODUCTION

Lung inflammatory disorders comprise airway diseases including acute bronchitis and chronic obstructive pulmonary diseases (COPD) such as chronic bronchitis, chronic asthma and emphysema. Particularly, COPD is the 5th leading cause of death worldwide. They are essentially inflammatory diseases. Several classes of drugs such as antitussives, mucolytics and bronchodilators are clinically used to treat the symptom, resulting in a relatively well-controlled condition. However, chronic diseases (COPD) are hard to control with the currently available drugs, which only relieve the symptoms of bronchitis. They do not affect or reverse the pathological progress of COPD. Thus, many pharmaceutical firms are trying to develop new drugs that target the pathological courses of COPD, eventually leading to a complete cure.

Among the drug candidates, leukotriene antagonists and phosphodiesterase 4 (PDE4) inhibitors show some promising results (Reid and Pham, 2012). However, success of low molecular weight drugs remains low since COPD is a very complex disease in etiology and in disease processes as described below. Up to the present, critical target molecules that mainly affect the disease process of COPD have not been found. In this context, plant extracts having complex and diverse chemicals may be favorable. Several plant-based anti-inflammatory drugs are used frequently, especially for acute as well as

chronic bronchitis. Examples are the extracts of *Hedera helix* (Guo *et al.*, 2006), *Echinacea purpurea* (Sharma *et al.*, 2006) and *Pelargonium sidoides* (Agbabiaka *et al.*, 2008; Matthys and Funk, 2008). These contain various classes of constituents that demonstrate complex action mechanisms on the above diseases. From many plants, a variety of constituents have been isolated and tested for their potential in treating these disorders. Despite various findings concerning the inhibitory actions of lung inflammation by herbal products, few available systematic reviews are focused on the therapeutic effects on animal models of lung inflammatory disorders. Therefore, in this review, plants that have therapeutic effectiveness on the animal models of lung inflammation are summarized. Plant constituents possessing therapeutic effects on lung inflammation are also discussed. However, this review is not comprehensive. Only findings of English literature are summarized. Anti-asthmatic effects by the plant products are not included.

COPD: ETIOLOGY AND THERAPEUTICS

The pathological factors affecting COPD are diverse and intricately linked. In the deteriorating progress of COPD, various inflammatory mediators are released from epithelial cells and infiltrated inflammatory cells in the lungs, including neu-

Open Access <https://doi.org/10.4062/biomolther.2016.187>

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received Aug 18, 2016 Revised Sep 21, 2016 Accepted Oct 4, 2016

Published Online Dec 16, 2016

*Corresponding Author

E-mail: hpkim@kangwon.ac.kr

Tel: +82-33-250-6915, Fax: +82-33-255-7865

trophils, macrophages and T lymphocytes. It is important that proinflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1) and IL-6 and chemokines including IL-8 activate and attract the circulating cells in the pathological process. Transforming growth factor- β (TGF- β) has been reported to cause airway fibrosis, leading to airway destruction. Several approaches for blocking these cytokines or their receptors have been developed for clinical trial against COPD. Among them, IL-1 β and IL-18, key molecules of inflammasome, are suggested as potential targets along with other inflammasome components (Rovina *et al.*, 2009; Zhang, 2011).

Reactive oxygen species (ROS) are also critical for provoking COPD. Tobacco smoke contains high concentrations of oxidants and induces a variety of free radicals including ROS. Oxidative stress by excess generation of ROS amplifies the inflammatory responses and develops the pathological stage of COPD. Therefore, several molecules linked to oxidative stress, such as nuclear erythroid-2-related factor 2 (Nrf2), NADPH oxidase, myeloperoxidase and superoxide dismutase may be considered targets for COPD therapy. Also, an imbalance between proteases and anti-proteases leads to alveolar wall destruction. Especially, matrix metalloproteinase (MMP) and neutrophil elastase are intricately regulated in COPD pathology. Several reports indicate that the activation and/or elevated expression of matrix metalloproteinases such as MMP-2, -9 and -12 are closely related to the development of COPD (Churg *et al.*, 2012). Recently sirtuins were demonstrated to be deeply involved in COPD. The level of sirtuin 1 expression is reduced in the lungs of COPD patients. The activation of sirtuin 1 and 6 has been shown to have protective effects against COPD (Chun, 2015) and sirtuin activators may be proposed as candidates for COPD treatment.

Additionally, eicosanoids and nitric oxide (NO) have been shown to be involved. Leukotriene B₄ (LTB₄) and prostaglandin E₂ (PGE₂) levels in the exhaled breath condensate of patients with COPD are higher than in healthy subjects (Muntuschi *et al.*, 2003). LTB₄ is a potent neutrophil chemoattractant and its concentration in sputum is also increased in COPD patients (Corhay *et al.*, 2009). To reduce LTB₄ levels, antagonists of LTB₄ receptors and 5-lipoxygenase inhibitors have been developed for the treatment of COPD. Inducible nitric oxide synthase (iNOS) is widely up-regulated in the airways and peripheral lungs of COPD patients (Hesslinger *et al.*, 2009). NO synthesized by iNOS and its oxidant peroxynitrite cause oxidative stress in the lungs. In the animal model, iNOS inhibition by a selective inhibitor was shown to partially improve pulmonary vessel remodeling and functional destruction by smoke-induced emphysema (Seimetz *et al.*, 2011).

Recent investigations suggested that interrupting signal transduction pathways may alleviate COPD progress. Various kinases participate in regulating the expression of inflammatory genes and transcription factors related to COPD. The p38 mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) are proposed as promising representative targets for the development of selective inhibitors. The activation of p38 MAPK induces inflammatory mediators such as IL-1 β , IL-8 and MMP in various inflammatory cells, leading to the exacerbation of COPD symptoms. The inhibition of p38 MAPK showed efficacy in a six month clinical trial in COPD patients with $\leq 2\%$ blood eosinophils (Marks-Konczalik *et al.*, 2015). PI3K-mediated signaling in macrophages and neutro-

phils is involved in inflammation and immune responses and the activity is up-regulated in the lungs of COPD. It was found that blocking certain isoforms of PI3K reduced pulmonary neutrophilia in a murine smoke model (Doukas *et al.*, 2009). Several PI3K inhibitors have been developed as candidates for COPD therapy so far. In addition, inhibitors targeting transcription factor, nuclear transcription factor- κ B (NF- κ B), which is involved in the encoding of many inflammatory genes and relevant kinases such as I κ B kinase have been also investigated (Schuliga, 2015). However, because some approaches targeting these signaling pathways may have significant problems induced by selectivity, specificity and side effects linked to other pathways, more detailed studies will be needed to determine the best target in treating COPD.

CURRENTLY DEVELOPING DRUG CANDIDATES FOR COPD

Since COPD is characterized by chronic progression and the complexity of parameters priming the disease, previous therapies for COPD have been limited to the use of drugs such as inhaled bronchodilators and corticosteroids, which only improve the symptoms. This means that further detailed clinical trials for many other targets related to COPD are required for the development of new therapy. Recently, COPD management has been focused on anti-inflammatory therapy because COPD is basically an inflammatory disease.

Roflumilast, a PDE4 inhibitor, showed anti-inflammatory effects by inhibiting neutrophil functions and the activation of CD4⁺ and CD8⁺ T cells in COPD patients with chronic bronchitis (Pinner *et al.*, 2012). Clinical trials with new PDE4 inhibitors such as RPL554 and CHF6001, which have lower side effects and better efficacy, are ongoing for the development of more potent agents in COPD therapy (Franciosi *et al.*, 2013; Moretto *et al.*, 2015).

Among inflammatory cytokines and chemokines, TNF- α and IL-8 are primarily under development as targets for COPD treatment. TNF- α plays a role in attracting neutrophils and exists in highly variable concentrations in the blood or lungs of patients with COPD. Etanercept, infliximab and adalimumab, antibodies targeting TNF- α or TNF receptor (TNFR), have been developed to alleviate the symptoms of COPD pathogenesis. However, some studies reported adverse effects of infliximab in patients with COPD (Dentener *et al.*, 2008). Etanercept showed no beneficial effects (Aaron *et al.*, 2013). One of the reasons is assumed to be related to the TNF- α concentration of COPD patients and the stage of COPD pathogenesis. Blocking chemokines such as IL-8/C-X-C motif chemokine ligand 8 (CXCL8) with neutralizing antibody reduced neutrophil chemotactic activity in stable COPD patients (Mahler *et al.*, 2004). However, the redundancy in the chemokine network caused the therapeutic effect to be partial. Clinical application with several antagonists of C-X-C motif chemokine receptor 2 (CXCR2, CXCL8 receptor) such as navarixin (SCH 527123, MK-7123) and AZD-5069 was carried out in COPD patients but showed no effective results (Norman, 2013; Renard *et al.*, 2015). Danirixin (GSK1325756), an oral CXCR2 antagonist is in phase II development for COPD.

Besides antibodies against TNF- α and IL-8, variable antibodies targeting other cytokines have been developed so far. IL-1 β and IL-5 are potential targets for COPD therapy. Anti-

bodies against IL-1 (Canakinumab and MEDI8986) and IL-5 (Benralizumab and Mepolizumab) were developed, but their efficacy and side effects have to be determined through additional clinical trials, which are currently ongoing. Treatment with antibody blocking IL-5 receptors such as benralizumab, which have been previously developed for asthma treatment, was also attempted in certain patients with COPD and eosinophilia (Brightling *et al.*, 2014) and a clinical trial to evaluate the efficacy and safety is currently underway in patients with COPD. In particular, active IL-1 β is produced by nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain containing 3 (NLRP3) inflammasome, so the inflammasome implicated in COPD is emerging as a new COPD target (Hosseinian *et al.*, 2015). But it is unclear whether the inflammasome directly participates in COPD pathogenesis. Further detailed investigation to confirm the contribution of inflammasome to COPD pathology will be needed.

A current potential target for COPD treatment is p38 MAPK, which is shown to be related to the control of the expression of multiple inflammatory mediators. Recently, some p38 MAPK inhibitors developed for the treatment of rheumatoid arthritis were challenged in clinical trials for COPD (Watz *et al.*, 2014; Norman, 2015). The development of oral p38 MAPK inhibitors such as acumapimod is ongoing for clinical treatment of COPD. Inhaled p38 MAPK inhibitors, PF-03715455 and RV-568, are in Phase I and Phase II clinical trials, respectively (Norman, 2015). However, the development of PH-797804 and losmapimod was terminated for COPD treatment because they showed no improved effects compared to roflumilast, a PDE4 inhibitor. Another kinase, PI3K, which is upregulated in the lungs of COPD patients, can also be a potential target for COPD therapy (To *et al.*, 2010). Although TG100-115, PI3K γ and δ inhibitor, was proven to be effective in the mouse smoke-induced lung inflammation model (Doukas *et al.*, 2009), the clinical development has been discontinued at present. Recent study suggested that targeting PI3K δ was beneficial for the treatment of respiratory diseases (Srikantharajah *et al.*, 2013). GSK2269557, an inhaled PI3K δ inhibitor, is currently undergoing clinical trial for COPD.

MMP-9, MMP-12 and neutrophil elastase play important roles in the breakdown of collagen and elastin fibers in emphysema patients. Several protease inhibitors targeting these proteases have been developed but discontinued for various reasons such as efficacy problems and side effects in clinical trials. To date, various drug candidates that block the signaling pathway related to the induction mechanisms of COPD pathogenesis have been developed. They showed effectiveness in several animal models. But most human trials have been stopped due to their low efficacy and major side effects. Thus, continual efforts to define new target molecules and to find agents that interrupt various signaling processes are needed. As an alternative to these efforts, plants and plant products have been studied with the hope of finding new and effective agents to treat these inflammatory lung disorders.

ANIMAL MODELS OF LUNG INFLAMMATION

There are several animal models of lung inflammation used for establishing the therapeutic effects of target compounds. For acute lung inflammation, the most widely used model is the lipopolysaccharide (LPS)-induced acute lung injury (in-

flammation) model (Rojas *et al.*, 2005; Matute-Bello *et al.*, 2008). Mice used are ICR, BALB/c, C57BL/6, etc. LPS is either administered via the intratracheal or intranasal route. Sometimes, rats are used and LPS is intratracheally administered in this case. Rarely, sulfur dioxide (SO₂) gas and chlorine gas are used as inflammagens instead of LPS. From the bronchoalveolar lavage fluid (BALF), the cells are counted. Infiltrated neutrophils and macrophages are major cells. The lung tissues show typical inflammatory conditions such as alveolar wall hyperplasia and many infiltrated inflammatory cells can be observed in histological samples. In LPS-induced acute lung injury (ALI) model, proinflammatory cytokines/chemokines as well as oxidative stress contribute to provoking inflammatory responses. Thus, anti-oxidative treatments such as Nrf2 pathway activation attenuate lung inflammatory responses (Kim *et al.*, 2010). Proinflammatory cytokines/chemokines are frequently detected in the BALF. Generally, TNF- α , IL-6 and IL-8 are elevated. In our study, IL-6 and IL-8 levels are increased in the BALF 16 h after LPS treatment by the nasal route in ICR mice (Lim *et al.*, 2013). In these animal models, the NF- κ B activation pathway plays an essential role in provoking lung inflammation. The MAPK pathway is also involved.

In animal models of chronic lung inflammation, cigarette smoke-induced lung inflammation may be used. Cigarette smoke exposure to mice and rats for several days or weeks produces COPD-similar changes in the affected lung tissues (Wright *et al.*, 2008). Inflammatory cells are recruited to lung tissues. Elevated numbers of goblet cells producing mucins are also observed in some cases using Periodic acid-Schiff (PAS) staining. Similar changes are also obtained in an animal model of LPS/elastase-treated mice (Ganesan *et al.*, 2010; Lee *et al.*, 2012). Elastase administered to the lung for weeks sometimes destroys the alveolar layer to produce large emphysema-like lesions. However, this change may be confined to several strains of mice. In our experiment with ICR mice, this change was hardly observed, although elevated levels of infiltrated inflammatory cells in the BALF could be detected (data not shown). The similar finding was also demonstrated that cigarette smoke-induced lung inflammatory responses were varied on mice strains (Morris *et al.*, 2008). To date, animal models mimicking human COPD have not been adequately established. The relevance of animal models and human COPD is not satisfactory. Generally, agents showing activity in animal models of chronic lung inflammation do not show high effectiveness in clinical trials. Thus, new animal models need to be established for successful development of new drugs against COPD.

THE INHIBITION OF PLANT EXTRACTS AGAINST *IN VIVO* ANIMAL MODELS OF LUNG INFLAMMATION

In this review, findings using the septic shock model are not mentioned since intraperitoneal or intravenous injection of endotoxin (LPS) provokes systemic inflammation leading to the cytokine storm instead of local airway inflammation in the lung. LPS-induced acute lung injury (ALI) produces local lung inflammation. Some potential effects of herbal products on ALI were summarized previously (Favarin *et al.*, 2013). Recently, effects of dozens of plant-derived compounds on lung inflammatory diseases including asthma and COPD models are also described (Santana *et al.*, 2016).

Table 1. Inhibition of the animal models of lung inflammation by various plant extracts

Plants	Extracts	Doses (mg/kg) ^{a)}	Inflammagen used ^{b)}	Ref.
<i>Acanthopanax senticosus</i>	^{c)}	20 (i.v.)	LPS (i.t.)	Fei <i>et al.</i> (2014)
<i>Aconitum tanguticum</i>	Alkaloid fraction	30-60	LPS (rat)	Wu <i>et al.</i> (2014a)
<i>Alisma orientale</i> Juzepczuk	80% ethanol	300-1,200	LPS	Han <i>et al.</i> (2013)
<i>Angelica decursiva</i>	70% ethanol	400	LPS	Lim <i>et al.</i> (2014)
<i>Antrodia camphorata</i>	Methanol	25-100	LPS	Huang <i>et al.</i> (2014a)
<i>Alstonia scholaris</i>	Alkaloid fraction	7-30	LPS (i.t.) (rat)	Zhao <i>et al.</i> (2016)
<i>Azadirachta indica</i>	Water	100/day	Cigarette smoke	Koul <i>et al.</i> (2012)
<i>Callicarpa japonica</i> Thunb.	Methanol	15-30/day	Cigarette smoke	Lee <i>et al.</i> (2015d)
<i>Canarium lyi</i> C.D. Dai & Yakovlev	Methanol	30/day	LPS	Hong <i>et al.</i> (2015b)
<i>Chrysanthemum indicum</i>	Supercritical CO ₂ extract	40-120/day	LPS (i.t.)	Wu <i>et al.</i> (2014b)
<i>Cnidium monnieri</i>	Water	50-200/day	Cigarette smoke extract/ LPS (i.t.)	Kwak and Lim (2014)
<i>Eleusine indica</i>		400 (i.p.)	LPS	De Melo <i>et al.</i> (2005)
<i>Euterpe oleracea</i> Mart.	50% ethanol	300/day	Cigarette smoke	Moura <i>et al.</i> (2012)
<i>Galla chinensis</i>		100/day	Cigarette smoke	Lee <i>et al.</i> (2015a)
<i>Ginkgo biloba</i>	Egb761	0.01-1 (i.p.)	LPS (i.t.)	Huang <i>et al.</i> (2013)
<i>Gleditsia sinensis</i>	Water	3.3-10/day	LPS	Choi <i>et al.</i> (2012)
<i>Glycyrrhiza uralensis</i>	Flavonoid fraction	3-30	LPS (i.t.)	Xie <i>et al.</i> (2009)
<i>Houttuynia cordata</i>	70% ethanol	400	LPS	Lee <i>et al.</i> (2015b)
<i>Juglans regia</i> L. kernel	Methanol	50-100/day	Cigarette smoke (rat)	Qamar and Sultana (2011)
<i>Lonicera japonica flos</i>	50% ethanol	0.4-40	LPS (i.t.)	Kao <i>et al.</i> (2015)
<i>Lysimachia clethroides</i> Duby	Methanol	20-100 (i.p.)	LPS	Shim <i>et al.</i> (2013)
<i>Mikania glomerata</i> Spreng and <i>Mikania laevigata</i> Schultz Bip. Ex Baker	70% ethanol	100 (s.c.)	Mineral coal dust (i.t.) (rat)	Freitas <i>et al.</i> (2008)
<i>Morus alba</i>	70% ethanol	200-400	LPS	Lim <i>et al.</i> (2013)
<i>Nigella sativa</i>	Hydroethanolic extract	80/day	Sulfur mustard (guinea-pigs)	Hossein <i>et al.</i> (2008)
<i>Paeonia suffruticosa</i>	Granule	2,000	LPS (i.t.) (rat)	Fu <i>et al.</i> (2012)
<i>Phellodendri cortex</i>	Methanol	100-400	LPS (i.t.)	Mao <i>et al.</i> (2010)
<i>Punica granatum</i>	0.9% NaCl	200 (i.p.)	LPS (i.t.)	Bachoual <i>et al.</i> (2011)
<i>Rabdosia japonica</i> var. <i>glaucoalyx</i>	Flavonoid fraction	6.4-25.6/day	LPS (i.t.)	Chu <i>et al.</i> (2014)
<i>Schisandra chinensis</i> Baillon	Water	10-100	LPS	Bae <i>et al.</i> (2012)
<i>Schisandra chinensis</i> Baillon	Aqueous ethanol	1,000/day	Cigarette smoke-induced cough hypersensitivity (guinea pig)	Zhong <i>et al.</i> (2015)
<i>Stemona tuberosa</i>	Water	50-200/day	Cigarette smoke	Lee <i>et al.</i> (2014)
<i>Taraxacum officinale</i>	Water	2.5-10/day	LPS	Liu <i>et al.</i> (2010)
<i>Taraxacum mongolicum</i> hand.-Mazz	Water	5,000-10,000	LPS	Ma <i>et al.</i> (2015a)
<i>Uncaria tomentosa</i>	Water		Ozone	Cisneros <i>et al.</i> (2005)
<i>Viola yedoensis</i>	Petroleum ether	2-8	LPS	Li <i>et al.</i> (2012b)
Formula: <i>Dangkwisoo-san</i>	Mixture	100-1,000/day	LPS	Lyu <i>et al.</i> (2012)
Formula: <i>Gingyo-san</i>	Mixture	1-2	LPS (i.t.)	Yeh <i>et al.</i> (2007b)
Formula: <i>Hochu-ekki-to</i> (TJ-41)	Mixture	1,000/day	LPS	Tajima <i>et al.</i> (2006)
Formula: <i>Xia-Bai-San</i>	Mixture	1	LPS (i.t.)	Yeh <i>et al.</i> (2006)
Formula: <i>BP+LJ</i>	Mixture	100-400	LPS (i.t.) (rat)	Ko <i>et al.</i> (2011)

^{a)}All extracts were orally administered unless otherwise stated. ^{b)}Mice were used as experimental animals unless otherwise indicated. Administration route of inflammagens was intranasal. Intratracheal route (i.t.) was indicated. Cigarette smoke was administered by inhalation route. ^{c)}Due to the insufficient information provided, space remained blank.

Many medicinal plants have shown regulatory effects on lung inflammation at doses of approximately 100-300 mg/kg as summarized in Table 1. On the other hand, *Gleditsia sinensis*, *Glycyrrhiza uralensis*, *Lonicera japonica*, *Taraxacum officinale* extracts and the petroleum ether fraction of *Viola*

yedoensis showed potent inhibitory activity by oral administration against LPS-induced lung inflammation at low doses (Xie *et al.*, 2009; Liu *et al.*, 2010; Choi *et al.*, 2012; Li *et al.*, 2012b; Kao *et al.*, 2015). They showed significant inhibition at doses as low as 3 mg/kg. *Gleditsia sinensis* is known to possess

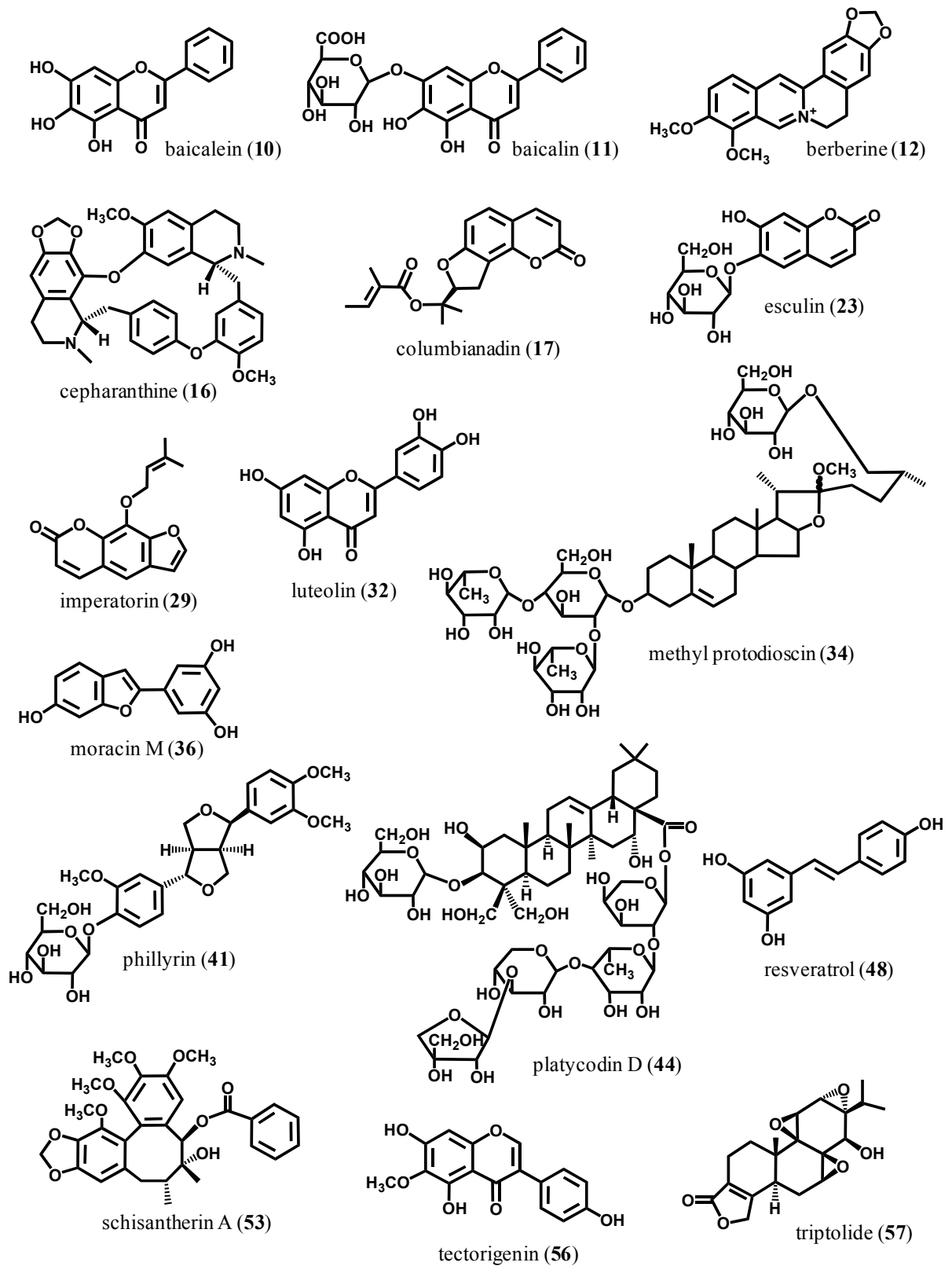


Fig. 1. The chemical structures of some selected plant constituents mentioned in this study.

anti-allergic and anti-inflammatory activity (Dai *et al.*, 2002; Ha *et al.*, 2008). It contains various triterpenoids as major components (Lim *et al.*, 2005). Many triterpenoids were previously found to possess anti-inflammatory activity (Kim *et al.*, 1999). All this information suggests that *G. sinensis* has potential for treating lung inflammatory diseases.

Lonicera japonica is a well-known anti-inflammatory agent (Lee *et al.*, 1998). The entire plant including the leaves and flowers is widely used in traditional medicine as an anti-inflammatory agent especially for treating upper airway inflammatory diseases. *L. japonica* is an ingredient of many complex prescriptions for lung inflammatory disease in ancient literatures. It contains iridoids and flavonoids as major components, which show significant anti-inflammatory activity (Lee *et al.*, 1995).

In addition, the alkaloid fractions of *Aconitum tanguticum* and *Alstonia scholaris* inhibited LPS-induced ALI in rats at low doses (Wu *et al.*, 2014a; Zhao *et al.*, 2016).

Ginkgo biloba leaves extract showed considerable inhibition of lung inflammation in LPS-induced ALI at low doses when they were administered intraperitoneally (Huang *et al.*, 2013). *G. biloba* leaves extract has been used to enhance blood circulation, prevent neurodegeneration and enhance cognitive function. The anti-inflammatory action of *G. biloba* leaves is well known (Ilieva *et al.*, 2004). *G. biloba* leaves also exert an anti-asthmatic effect (Babayigit *et al.*, 2009). Thus, this medicinal plant material has the potential to treat lung-related inflammatory/allergic diseases. The major constituents are ginkgolides and flavonoids. Many flavonoid derivatives show inhibitory action on lung inflammation as described below.

Against the COPD model induced by cigarette smoke, several plant extracts such as *Azadirachta indica*, *Callicarpa japonica*, *Cnidium monnieri*, *Euterpe oleracea*, *Galla chinensis*, *Juglans regia*, *Schisandra chinensis* and *Stemona tuberosa* were found to inhibit inflammatory responses in the lung (Qamar and Sultana, 2011; Koul *et al.*, 2012; Moura *et al.*, 2012; Kwak and Lim, 2014; Lee *et al.*, 2014, 2015a, 2015d; Zhong *et al.*, 2015), suggesting their therapeutic potential in chronic lung inflammatory diseases. Particularly, *S. chinensis* has been widely used for lung disorders in traditional medicine in the East Asia region, and the findings above provide the scientific basis for this traditional use. This extract was found to inhibit acute as well as chronic inflammatory condition of lung inflammation. But no report is available establishing the activity of its constituents. The therapeutic potential of the major constituents such as schizandrin and gomisins remains to be discovered in the near future.

Hedera helix (ivy leaf, Guo *et al.*, 2006), *Echinacea purpurea* (Sharma *et al.*, 2006; Agbabiaka *et al.*, 2008) and *Pelargonium sidoides* (Matthys and Funk, 2008) are frequently used for treating bronchitis in Asian and European countries. The extracts alleviate the symptoms of acute and chronic bronchitis such as sputum production and coughing. Ivy leaves extract has been prescribed for treating bronchitis under the name Prospan® (Ahngook Pharm., Seoul, Korea). *Pelargonium sidoides* ethanol extract under the name Umckamin syrup® (Han Wha Pharma Co., Seoul, Korea) is used for acute bronchitis. It is significant to note that ivy extract also showed some effectiveness against influenza A virus infection in mice when simultaneously administered with the antiviral drug, Tamiflu (Hong *et al.*, 2015a). The therapeutic effectiveness of some herbal remedies in COPD patients has been

summarized (Guo *et al.*, 2006). In human clinical study, some ginseng products showed promising results in COPD patients (Gross *et al.*, 2002). Recently, we have found that some ginseng products and ginsenosides clearly inhibited lung inflammatory responses in a mouse model of ALI (data not shown).

Sometimes, a combination of herbal plants gives more promising results. Several herbal mixtures were also demonstrated to possess inhibitory action on lung inflammation. Particularly, Xia-Bai-San demonstrated efficacy at the dose of 1 mg/kg against LPS-induced ALI (Yeh *et al.*, 2006). Recently, a new formula, Synatura® (Ahngook Pharm., Seoul, Korea) containing ivy leaf and *Coptis chinensis* was developed for treating chronic bronchitis.

THE INHIBITION OF PLANT CONSTITUENTS AGAINST *IN VIVO* ANIMAL MODELS OF LUNG INFLAMMATION AND ACTION MECHANISMS

Resveratrol (stilbenoid, 48) (Fig. 1) was found to show strong inhibitory action against acute lung inflammation and the COPD model (Donnelly *et al.*, 2004; Liu *et al.*, 2014a). Resveratrol showed effectiveness through the reduction of proinflammatory cytokine and prostanoid generation. In one study, resveratrol was revealed to reduce the inflammatory responses in cigarette smoke-induced COPD mice by inhibiting NF- κ B activation and the elevation of heme oxygenase-1 (HO-1) expression (Liu *et al.*, 2014a). The detailed anti-inflammatory action mechanisms of resveratrol, curcumin and glycyrrhetic acid are well summarized in the previous review paper (Sharafkhaneh *et al.*, 2007).

Some phenolics also showed effectiveness against lung inflammation by oral administration. These include apocynin (8), caffeic acid derivative (13), ellagic acid (19), paeonol (39) and zingerone (59) (Table 2). Particularly, paeonol, a major ingredient from *Paeonia suffruticosa*, inhibited a mice model of COPD, cigarette smoke-induced lung inflammation at 10 mg/kg/day (Liu *et al.*, 2014b). This finding is well correlated with the inhibitory potential of *P. suffruticosa* extract against LPS-induced ALI in rats (Fu *et al.*, 2012). Ellagic acid protected against lung damage induced by acid treatment (Cornélio Favarin *et al.*, 2013). This compound was demonstrated to reduce IL-6 production along with the increase of anti-inflammatory cytokine, IL-10, in BALF, but, no inhibition of NF- κ B and activator protein-1 (AP-1) activation was observed. Similar pharmacological mechanisms were also found in zingerone (phenol) treatment for LPS-induced ALI (Xie *et al.*, 2014).

The benzoic acid derivative, protocatechuic acid (46), significantly inhibited LPS-induced ALI by inhibiting NF- κ B activation via inhibiting I κ B α degradation and the translocation of p65 to the nucleus (Wei *et al.*, 2012). Limonene (monoterpene, 30) also inhibited LPS-induced ALI by the down-regulation of MAPK and NF- κ B activation (Chi *et al.*, 2013). Linalool (31) demonstrated inhibitory activity in the cigarette smoke-induced COPD model by the same action mechanism of blocking NF- κ B activation (Ma *et al.*, 2015b). Phillyrin (lignan, 41) reduced proinflammatory cytokine production mainly by inhibiting MAPK and NF- κ B activation in LPS-induced ALI (Zhong *et al.*, 2013b). The same action mechanisms were also demonstrated by schisantherin A (53) treatment inhibiting MAPK and NF- κ B activation (Zhou *et al.*, 2014). It is important to mention that berberine (12) intraperitoneally injected re-

Table 2. Inhibition of the animal models of lung inflammation by plant constituents

Constituent	Class	Plant origin	Doses (mg/kg ^a)	Inflammagen used ^b	Reference
Acteoside (1)	Phenylethanoid	<i>Rehmannia glutinosa</i>	30-60 (i.p.)	LPS (i.t.)	Jing et al. (2015)
Afzelin (2), hyperoside (3), quercitrin (4)	Flavonoid	<i>Houttuynia cordata</i>	100, 100, 100	LPS	Lee et al. (2015b)
Alpinetin (5)	Flavonoid	<i>Alpinia katsumadai</i>	50 (i.p.)	LPS (i.t.)	Huo et al. (2012)
Andrographolide (6)	Diterpene	<i>Andrographis paniculata</i>	1/day (i.p.)	Cigarette smoke	Yang et al. (2013)
Apigenin-7-glucoside (7)	Flavonoid	^c	2.5-10 (i.p.)	LPS (i.t.)	Li et al. (2015)
Apocynin (8)	Phenol	<i>Picrothiza kurroa</i>	0.002-0.2/ml	LPS (hamster)	Stolk et al. (1994)
Asperuloside (9)	Iridoid		20-80 (i.p.)	LPS	Qiu et al. (2016)
Baicalin (10)	Flavonoid	<i>Scutellaria baicalensis</i>	20 (i.p.)	LPS (i.t.) (rat)	Tsai et al. (2014)
Baicalin (11)	Flavonoid	<i>Scutellaria baicalensis</i>	25-100/day	Cigarette smoke	Li et al. (2012a)
Baicalin (11)	Flavonoid	<i>Scutellaria baicalensis</i>	20	LPS (i.t.) (rat)	Huang et al. (2008)
Berberine (12)	Alkaloid		5-10/day (i.p.)	Cigarette smoke	Xu et al. (2015)
Caffeic acid phenethyl ester (13)	Phenol	Honey-bee propolis	10 µmol/kg/day	Cigarette smoke (rabbit)	Sezer et al. (2007)
Cannabidiol (14)	Cannabinoid	<i>Cannabis sativa</i>	20	LPS	Ribeiro et al. (2012)
Carvacrol (15)	Monoterpene	<i>Plectranthus amboinicus</i>	20-80 (i.p.)	LPS	Feng and Jia (2014)
Cepharanthine (16)	Alkaloid	<i>Stephania cepharantha</i> Hayata	5 (i.p.)	LPS	Huang et al. (2014b)
Columbianadin (17)	Coumarin	<i>Angelica decursiva</i>	20-60	LPS	Lim et al. (2014)
p-cymene (18)	Monoterpene		25-100 (i.p.)	LPS (i.t.)	Xie et al. (2012)
Ellagic Acid (19)	Phenol		10	Acid	Cornélio Favarin et al. (2013)
Ergosterol (20)	Sterol	<i>Scloderma polyrhizum</i> Pers.	25-50	LPS	Zhang et al. (2015)
Eriodictyol (21)	Flavonoid	<i>Draccephalum rupestre</i>	30/day	LPS	Zhu et al. (2015)
Esculentoside A (22)	Saponin	<i>Phytolacca esculenta</i>	15-60	LPS	Zhong et al. (2013a)
Esculin (23)	Coumarin		20-40	LPS (i.t.)	Tianzhu and Shumin (2015)
Flavone (24), fisetin (25), tricetin (26)	Flavonoid		22.2, 28.6, 30.2	LPS (i.t.)	Geraets et al. (2009)
Gossypol (27)	Sesquiterpene		15 (i.p.)	LPS	Huo et al. (2013b)
Hesperidin (28)	Flavonoid		200	LPS (i.t.)	Yeh et al. (2007a)
Imperatorin (29)	Coumarin		15-30	LPS	Sun et al. (2012)
Limonene (30)	Monoterpene		25-75 (i.p.)	LPS (i.t.)	Chi et al. (2013)
Linalool (31)	Monoterpene	Aromatic plant	25 (i.p.)	LPS	Huo et al. (2013a)
Linalool (31)	Monoterpene	Aromatic plant	10-40 (i.p.)	Cigarette smoke	Ma et al. (2015b)
Luteolin (32)	Flavonoid	<i>Lonicera japonica</i>	70 µmol/kg (i.p.)	LPS (i.t.)	Lee et al. (2010)
Mangiferin (33)	Xanthone	<i>Mangifera indica</i> L.	450-4,050/day	LPS	Wang et al. (2015)
Methyl protodioscin (34)	Steroidal saponin	<i>Asparagus cochinchinensis</i>	30-60	LPS	Lee et al. (2015c)
Mogroside V (35)	Triterpene saponin	<i>Momordica grosvenori</i>	2.5-10	LPS	Shi et al. (2014)
Moracin M (36)	2-arylbenzofuran	<i>Morus alba</i>	20-60	LPS	Lee et al. (2016)
Morin (37)	Flavonoid		20-40	LPS	Tianzhu et al. (2014)
Naringin (38)	Flavonoid		20-80/day	Cigarette smoke (rat)	Nie et al. (2012)
Paeonol (39)	Phenol	<i>Paeonia suffruticosa</i>	10/day	Cigarette smoke	Liu et al. (2014b)
Patchouli alcohol (40)	Sesquiterpene	<i>Pogostemon cablin</i>	10-40 (i.p.)	LPS	Yu et al. (2015)
Phillyrin (41)	Lignan	<i>Forsythia suspensa</i>	10-20	LPS	Zhong et al. (2013b)
Picroside II (42)	Iridoid	<i>Picrothiza scrophulariiflora</i>	0.5-1 (i.t.)	LPS (i.t.)	Noh et al. (2015)
Pinocembrin (43)	Flavonoid	<i>Alpinia katsumadai</i>	20-50 (i.p.)	LPS	Soromou et al. (2012)

Table 2. Continued

Constituent	Class	Plant origin	Doses (mg/kg) ^{a)}	Inflammagen used ^{b)}	Reference
Platygodin D (44)	Triterpenoid saponin	<i>Platygodon grandiflorum</i>	50-100	LPS (i.t.)	Tao <i>et al.</i> (2015)
Prime-O-glucosylcimifugin (45)	Chromone	<i>Saposhnikovia divaricata</i>	2.5-10 (i.p.)	LPS	Chen <i>et al.</i> (2013)
Protocatechuic acid (46)	Benzoic acid		30 (i.p.)	LPS	Wei <i>et al.</i> (2012)
Quercetin (47)	Flavonoid		10/day	LPS/elastase	Ganesan <i>et al.</i> (2010)
Quercetin (47)	Flavonoid		25-30/day (i.p.)	Cigarette smoke (rat)	Yang <i>et al.</i> (2012)
Resveratrol (48)	Stilbene			LPS	Donnelly <i>et al.</i> (2004)
Resveratrol (48)	Stilbene		1-3/day	Cigarette smoke (3 days)	Liu <i>et al.</i> (2014a)
Sakuranetin (49)	Flavonoid	<i>Baccharis retusa</i>	20 (i.n.)	Elastase-induced emphysema	Taguchi <i>et al.</i> (2015)
Schaftoside (50), vitexin (51)	Flavonoid	<i>Eleusine indica</i>	0.4, 0.4 (i.p.)	LPS	De Melo <i>et al.</i> (2005)
Shikonin (52)	Naphthoquinone	<i>Lithospermum erythrorhizon</i>	12.5-50	LPS (i.t.)	Bai <i>et al.</i> (2013)
Schisantherin A (53)	Lignan	<i>Schisandra sphenanthera</i>	10-40	LPS	Zhou <i>et al.</i> (2014)
Stevioside (54)	Diterpene	<i>Stevia rebaudiana</i>	12.5-50	LPS	Yingkun <i>et al.</i> (2013)
Taraxasterol (55)	Triterpene	<i>Taraxacum officinale</i>	2.5-10 (i.p.)	LPS	San <i>et al.</i> (2014)
Tectorigenin (56)	Flavonoid	<i>Belamcanda chinensis</i>	5-10 (i.v.)	LPS (i.t.)	Ma <i>et al.</i> (2014)
Triptolide (57)	Diterpene	<i>Tripterygium wilfordii</i>	0.005-0.015	LPS	Wei and Huang (2014)
Ursolic acid (58)	Dibenzofuran	Lichen species	25-100/day	LPS	Su <i>et al.</i> (2014)
Zingerone (59)	Phenol		10-40	LPS	Xie <i>et al.</i> (2014)

^{a)}All compounds were orally administered unless otherwise stated. ^{b)}Mice were used as experimental animals unless otherwise indicated. Administration route of inflammagens was intranasal. Intratracheal route (i.t.) was indicated. Cigarette smoke was administered by inhalation route. ^{c)}Constituents from commercial sources were purchased or could be isolated from various plant sources.

duced the inflammatory response of cigarette smoke-induced COPD model in mice. The compound inhibited the activation of extracellular signal-regulated kinase (ERK) and p38 MAPK activation in lung tissue (Xu *et al.*, 2015). Shikonin (52) and stevioside (54) reduced the inflammatory response of LPS-induced ALI by inhibiting NF-κB activation (Bai *et al.*, 2013; Yingkun *et al.*, 2013). Asperuloside (iridoid, 9) inhibited LPS-induced ALI mainly via the inhibiting MAPK and NF-κB activation (Qiu *et al.*, 2016). Prime-O-glucosylcimifugin (chromone, 45) also inhibited lung inflammation by a similar mechanism of MAPK and NF-κB inhibition (Chen *et al.*, 2013). Although many compounds have been found to attenuate lung inflammation by interrupting the MAPK and NF-κB pathways, it is interesting that cannabidiol (14) inhibited LPS-induced ALI at least partly by stimulating the adenosine A(2A) receptor (Ribeiro *et al.*, 2012). Part of the attenuating effect of eriodictyol (21) against LPS-induced ALI was due to the activation of the Nrf2 pathway (Zhu *et al.*, 2015).

Most of all, various flavonoids have been shown to inhibit lung inflammation. Flavonoids are well-known anti-inflammatory plant constituents. Certain flavonoids have shown inhibitory action in various animal models of inflammation. For example, some flavonoids were revealed to inhibit the animal models of acute inflammation: paw edema, ear edema and pleurisy. They also inhibited animal models of chronic inflammation: adjuvant-induced arthritis and collagen-induced arthritis. Certain derivatives inhibited lung inflammation. Flavone derivatives including flavone (24), tricetin (26), luteolin (32), apigenin-7-glucoside (7), baicalein (10) and baicalin (11), flavonol derivatives such as afzelin (2), hyperoside (3), quercitrin (4), morin (37), quercetin (47) and fisetin (25), isoflavones such as tectorigenin (56), flavanones such as eriodictyol (21), naringin (38), hesperidin (28) and sakuranetin (49) were demonstrated to possess inhibitory activity in lung inflammation models. Quercetin, baicalin and naringin orally administered were effective in the COPD model (Ganesan *et al.*, 2010; Li *et al.*, 2012a; Nie *et al.*, 2012). Particularly, quercetin inhibited lung inflammation and mucus production in the cigarette smoke-induced COPD model (Yang *et al.*, 2012). This inhibitory action might be mediated by inhibiting oxidative stress, inhibiting NF-κB activation and epidermal growth factor receptor (EGFR) phosphorylation. The structurally related flavonoid, baicalein, inhibited LPS-induced ALI in rats by augmenting Nrf2/HO-1 pathways and inhibiting NF-κB activation (Tsai *et al.*, 2014). Luteolin reduced lung inflammation possibly by inhibiting NF-κB activation via the inhibition of MAPK and AKT/Protein kinase B (Lee *et al.*, 2010). Fisetin treatment by oral administration reduced proinflammatory molecule production such as IL-1β, IL-6, TNF-α, macrophage inflammatory protein-1α (MIP-1α), MIP-2 and IκBα (Geraets *et al.*, 2009). Similar inhibitory mechanisms were revealed in tectorigenin which reduced lung inflammation via inhibiting the p65 NF-κB component (Ma *et al.*, 2014). Hesperidin reduced the production of proinflammatory cytokines including TNF-α and IL-6, whereas it increased the production of anti-inflammatory cytokines such as IL-4 and IL-10. These actions of hesperidin might be mediated by the interruption of NF-κB and AP-1 pathways (Yeh *et al.*, 2007a). Thus it is concluded that certain flavonoids act as inhibitory agents against lung inflammatory diseases. Their action mechanisms include anti-oxidative action and NF-κB inhibition. Indeed, herbal extracts that have flavonoids as major constituents have been used against lung inflam-

mation. For example, *Morus alba*, which contains prenylated flavonoids as major constituents, has been used in traditional medicine to treat lung inflammatory disorders (Nomura, 2001). *Scutellaria baicalensis* has also been used in lung inflammatory conditions. This plant material contains various types of flavone derivatives such as baicalein and baicalin. Baicalein and especially baicalin exert strong inhibitory action against acute as well as chronic lung inflammation by oral administration (Huang *et al.*, 2008; Li *et al.*, 2012a).

In the elastase-induced emphysema model, NF- κ B was also activated in the lung tissue. Under this condition, sakuranetin reduced the NF- κ B response (Taguchi *et al.*, 2015). It also regulated the expression of MMPs. In the elastase/LPS-induced COPD model, quercetin reduced inflammatory responses with concomitant inhibition of MMP-9 and -12 (Ganesan *et al.*, 2010).

Other groups of plant constituents also demonstrated inhibitory action on lung inflammation. Some diterpenoids and triterpenoids have demonstrated inhibitory activity against lung inflammation. For instance, the triterpenoid saponins are major constituents of *Hedera helix*, which is used for lung inflammation (Gepdiremen *et al.*, 2005; Hocaoglu *et al.*, 2012). Platycodin D (44), a triterpenoid saponin from *Platycodon grandiflorum*, also showed inhibitory action against ALI (Tao *et al.*, 2015). This compound was found to inhibit the expression of NF- κ B, caspase-3 and Bax. *P. grandiflorum* has been used as an expectorant (State Pharmacopoeia Commission of PR China, 2000). Methyl protodioscin (34), a steroidal saponin, showed inhibitory action against LPS-induced ALI at 30-60 mg/kg (Lee *et al.*, 2015c). Taraxasterol (55) from *Taraxacum officinale*, in this case through intraperitoneal injection, showed inhibitory action against lung inflammation (San *et al.*, 2014). This inhibitory action was mediated by the inhibition of MAPK and NF- κ B pathways. Another triterpene derivative, mogrosin V (35), reduced lung inflammation by the down-regulation of COX-2 and iNOS via inhibiting NF- κ B activation (Shi *et al.*, 2014). The famous diterpenoid, triptolide (57) from *Trypterygium wilfordii*, was also shown to inhibit LPS-induced lung inflammation at concentrations as low as 1 mg/kg via intraperitoneal injection (Wei and Huang, 2014). Especially, triptolide inhibited the activation of MAPK and NF- κ B pathways, and toll-like receptor 4 (TLR4) expression in LPS-induced ALI in mice. Esculentoside A (saponin, 22) also reduced TNF- α and IL-6 production possibly via inhibition of MAPK and NF- κ B pathways (Zhong *et al.*, 2013a).

Some coumarin derivatives also possess inhibitory action against lung inflammation. Examples are columbianadin (17), esculin (23) and imperatorin (29) (Sun *et al.*, 2012; Lim *et al.*, 2014; Tianzhu and Shumin, 2015). Esculin inhibited LPS-induced ALI by inhibiting the activation of myeloid differentiation primary response gene 88 (MyD88) (an upstream molecule of NF- κ B) and NF- κ B p65 activation (Tianzhu and Shumin, 2015).

Recently, moracin M (arylbenzofuran, 36) was found to inhibit LPS-induced ALI at 20-60 mg/kg (Lee *et al.*, 2016). Moracin M was found to suppress NF- κ B activation in the inflamed lung. This compound is a minor constituent in *Morus alba*, which showed significant inhibition against the same animal model (Lim *et al.*, 2013). These results may support the scientific basis of *M. alba* for treating lung diseases.

As described above, reports on many plant constituents demonstrating inhibitory action on lung inflammation are in-

creasing continuously, and some have demonstrated promising results. In the near future, the clinical effectiveness of some molecules may be proven in human trials.

CONCLUSION AND FUTURE PROSPECTS

Various plant extracts possess potential therapeutic effectiveness against lung inflammatory disorders including COPD. Additionally, many different classes of plant constituents were found to inhibit inflammatory responses in the lung. Especially, flavonoids are promising therapeutics since they affect signaling pathways essential to lung inflammation.

Up to the present, the regulatory effects of many natural products on NF- κ B activation have been widely demonstrated. Despite the importance of NF- κ B in lung inflammatory disorders, there are some contradicting results showing that NF- κ B does not exert a role in cigarette smoke-induced COPD models of mice and in human lungs (Rastrick *et al.*, 2013). Other cellular pathways need to be evaluated to examine the effectiveness of natural products. For instance, sirtuins were recently described as target molecules in COPD disorders. MMPs are also important for controlling lung elasticity. With continuous study, some plant extracts and constituents will hopefully be developed as new disease modifying drugs acting on lung inflammatory disorders.

ACKNOWLEDGMENTS

The authors declare no conflict of interest. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (NRF-2016R1A2B4007756), 2016 Research Grant from Kangwon National University (No. 520160100) and BK21 PLUS program from the Ministry of Education, Republic of Korea.

REFERENCES

- Aaron, S. D., Vandemheen, K. L., Maltais, F., Field, S. K., Sin, D. D., Bourbeau, J., Marciniuk, D. D., FitzGerald, J. M., Nair, P. and Mallik, R. (2013) TNF α antagonists for acute exacerbations of COPD: a randomised double-blind controlled trial. *Thorax* **68**, 142-148.
- Agbabiaka, T. B., Guo, R. and Ernst, E. (2008) *Pelargonium sidoides* for acute bronchitis: a systematic review and meta-analysis. *Phyto-medicine* **15**, 378-385.
- Babayigit, A., Olmez, D., Karaman, O., Ozogul, C., Yilmaz, O., Kivcak, B., Erbil, G. and Uzuner, N. (2009) Effects of Ginkgo biloba on airway histology in a mouse model of chronic asthma. *Allergy Asthma Proc.* **30**, 186-191.
- Bachoual, R., Talmoudi, W., Boussetta, T., Braut, F. and El-Benna, J. (2011) An aqueous pomegranate peel extract inhibits neutrophil myeloperoxidase *in vitro* and attenuates lung inflammation in mice. *Food Chem. Toxicol.* **49**, 1224-1228.
- Bae, H., Kim, R., Kim, Y., Lee, E., Kim H. J., Jang Y. P., Jung S.-K. and Kim, J. (2012) Effects of *Schisandra chinensis* Baillon (Schizandraceae) on lipopolysaccharide induced lung inflammation in mice. *J. Ethnopharmacol.* **142**, 41-47.
- Bai, G. Z., Yu, H. T., Ni, Y. F., Li, X. F., Zhang, Z. P., Su, K., Lei, J., Liu, B. Y., Ke, C. K., Zhong, D. X., Wang, Y. J. and Zhao, J. B. (2013) Shikonin attenuates lipopolysaccharide-induced acute lung injury in mice. *J. Surg. Res.* **182**, 303-311.
- Brightling, C. E., Bleecker, E. R., Panettieri, R. A. Jr., Bafadhel, M., She, D., Ward, C. K., Xu, X., Birrell, C. and van der Merwe, R.

- (2014) Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. *Lancet Respir. Med.* **2**, 891-901.
- Chen, N., Wu, Q., Chi, G., Soromou, L. W., Hou, J., Deng, Y. and Feng, H. (2013) Prime-O-glycosylcimifugin attenuates lipopolysaccharide-induced acute lung injury in mice. *Int. Immunopharmacol.* **16**, 139-147.
- Chi, G., Wei, M., Xie, X., Soromou, L. W., Liu, F. and Zhao, S. (2013) Suppression of MAPK and NF- κ B pathways by limonene contributes to attenuation of lipopolysaccharide-induced inflammatory responses in acute lung injury. *Inflammation* **36**, 501-511.
- Choi, J. Y., Kwun, M. J., Kim, K. H., Lyu, J. H., Han, C. W., Jeong, H. S., Ha, K. T., Jung, H. J., Lee, B. J., Sadikot, R. T., Christman, J. W., Jung, S. K. and Joo, M. (2012) Protective effect of the fruit hull of *Gleditsia sinensis* on LPS-induced acute lung injury is associated with Nrf2 activation. *Evid. Based Complement. Alternat. Med.* **2012**, 974713.
- Chu, C. J., Xu, N. Y., Li, X. L., Xia, L., Zhang, J., Liang, Z. T., Zhao, Z. Z. and Chen, D. F. (2014) *Rabdosia japonica* var. glaucocalyx flavonoids fraction attenuates lipopolysaccharide-induced acute lung injury in mice. *Evid. Based Complement. Alternat. Med.* **2014**, 894515.
- Chun, P. (2015) Role of sirtuins in chronic obstructive pulmonary disease. *Arch. Pharm. Res.* **38**, 1-10.
- Churg, A., Zhou, S. and Wright, J. L. (2012) Series "matrix metalloproteinases in lung health and disease": Matrix metalloproteinases in COPD. *Eur. Respir. J.* **39**, 197-209.
- Cisneros, F. J., Jayo, M. and Niedziela, L. (2005) An *Uncaria tomentosa* (cat's claw) extract protects mice against ozone-induced lung inflammation. *J. Ethnopharmacol.* **96**, 355-364.
- Corhay, J. L., Henket, M., Nguyen, D., Duysinx, B., Sele, J. and Louis, R. (2009) Leukotriene B₄ contributes to exhaled breath condensate and sputum neutrophil chemotaxis in COPD. *Chest* **136**, 1047-1054.
- Cornélio Favarin, D., Martins Teixeira, M., Lemos de Andrade, E., de Freitas Alves, C., Lazo Chica, J. E., Arterio Sorgi, C., Faccioli, L. H. and Paula Rogerio, A. (2013) Anti-inflammatory effects of ellagic acid on acute lung injury induced by acid in mice. *Mediators Inflamm.* **2013**, 164202.
- Dai, Y., Chan, Y. P., Chu, L. M. and Bu, P. P. (2002) Antiallergic and anti-inflammatory properties of the ethanolic extract from *Gleditsia sinensis*. *Biol. Pharm. Bull.* **25**, 1179-1182.
- De Melo, G. O., Muzitano, M. F., Legora-Machado, A., Almeida, T. A., De Oliveira, D. B., Kaiser, C. R., Koatz, V. L. and Costa, S. S. (2005) C-glycosylflavones from the aerial parts of *Eleusine indica* inhibit LPS-induced mouse lung inflammation. *Planta Med.* **71**, 362-363.
- Dentener, M. A., Creutzberg, E. C., Pennings, H. J., Rijkers, G. T., Mercken, E. and Wouters, E. F. (2008) Effect of infliximab on local and systemic inflammation in chronic obstructive pulmonary disease: a pilot study. *Respiration* **76**, 275-282.
- Donnelly, L. E., Newton, R., Kennedy, G. E., Fenwick, P. S., Leung, R. H., Ito, K., Russell, R. E. and Barnes, P. J. (2004) Anti-inflammatory effects of resveratrol in lung epithelial cells: molecular mechanisms. *Am. J. Physiol. Lung Cell Mol. Physiol.* **287**, L774-L783.
- Doukas, J., Eide, L., Stebbins, K., Racanelli-Layton, A., Dellamary, L., Martin, M., Dneprovskaja, E., Noronha, G., Soll, R., Wrasidlo, W., Acevedo, L. M. and Cheresch, D. A. (2009) Aerosolized phosphoinositide 3-kinase gamma/delta inhibitor TG100-115 [3-[2,4-diamino-6-(3-hydroxyphenyl)pteridin-7-yl]phenol] as a therapeutic candidate for asthma and chronic obstructive pulmonary disease. *J. Pharmacol. Exp. Ther.* **328**, 758-765.
- Favarin, D. C., de Oliveira, J. R., de Oliveira, C. J. and de Paula Rogerio, A. (2013) Potential effects of medicinal plants and secondary metabolites on acute lung injury. *Biomed. Res. Int.* **2013**, 576479.
- Fei, X. J., Zhu, L. L., Xia, L. M., Peng, W. B. and Wang, Q. (2014) *Acanthopanax senticosus* attenuates inflammation in lipopolysaccharide-induced acute lung injury by inhibiting the NF- κ B pathway. *Genet. Mol. Res.* **13**, 10537-10544.
- Feng, X. and Jia, A. (2014) Protective effect of carvacrol on acute lung injury induced by lipopolysaccharide in mice. *Inflammation* **37**, 1091-1101.
- Franciosi, L. G., Diamant, Z., Banner, K. H., Zuiker, R., Morelli, N., Kamberling, I. M., de Kam, M. L., Burggraaf, J., Cohen, A. F., Cazzola, M., Calzetta, L., Singh, D., Spina, D., Walker, M. J. and Page, C. P. (2013) Efficacy and safety of RPL554, a dual PDE3 and PDE4 inhibitor, in healthy volunteers and in patients with asthma or chronic obstructive pulmonary disease: findings from four clinical trials. *Lancet Respir. Med.* **1**, 714-727.
- Freitas, T. P., Silveira, P. C., Rocha, L. G., Rezin, G. T., Rocha, J., Citadini-Zanette, V., Romao, P. T., Dal-Pizzol, F., Pinho, R. A., Andrade, V. M. and Streck, E. L. (2008) Effects of *Mikania glomerata* Spreng. and *Mikania laevigata* Schultz Bip. ex Baker (Asteraceae) extracts on pulmonary inflammation and oxidative stress caused by acute coal dust exposure. *J. Med. Food* **11**, 761-766.
- Fu, P. K., Yang, C. Y., Tsai, T. H. and Hsieh, C. L. (2012) *Moutan cortex* radices improves lipopolysaccharide-induced acute lung injury in rats through anti-inflammation. *Phytomedicine* **19**, 1206-1215.
- Ganesan, S., Faris, A. N., Comstock, A. T., Chatteraj, S., Chatteraj, A., Burgess, J. R., Curtis, J. L., Martinez, F. J., Zick, S., Hershenson, M. B. and Sajjan, U. (2010) Quercetin prevents progression of disease in elastase/LPS-exposed mice by negatively regulating MMP expression. *Respir. Res.* **11**, 131.
- Gepdiremen, A., Mshvildadze, V., Süleyman, H. and Elias, R. (2005) Acute anti-inflammatory activity of four saponins isolated from ivy: alpha-hederin, hederasaponin-C, hederacolchiside-E and hederacolchiside-F in carrageenan-induced rat paw edema. *Phytomedicine* **12**, 440-444.
- Geraets, L., Haegens, A., Brauers, K., Haydock, J. A., Vernoooy, J. H. J., Wouters, E. F. M., Bast, A. and Hageman, G. J. (2009) Inhibition of LPS-induced pulmonary inflammation by specific flavonoids. *Biochem. Phys. Res. Commun.* **382**, 598-603.
- Gross, D., Shenkman, Z., Bleiberg, B., Dayan, M., Gillelson, M. and Efrat, R. (2002) Ginseng improves pulmonary functions and exercise capacity in patients with COPD. *Monaldi Arch. Chest Dis.* **57**, 242-246.
- Guo, R., Pittier, M. H. and Ernst, E. (2006) Herbal medicines for the treatment of COPD: a systematic review. *Eur. Respir. J.* **28**, 330-338.
- Ha, H. H., Park, S. Y., Ko, W. S. and Kim, Y. H. (2008) *Gleditsia sinensis* thorns inhibit the production of NO through NF- κ B suppression in LPS-stimulated macrophages. *J. Ethnopharmacol.* **118**, 429-434.
- Han, C. W., Kwun, M. J., Kim, K. H., Choi, J. Y., Oh, S. R., Ahn, K. S., Lee, J. H. and Joo, M. (2013) Ethanolic extract of *Alismatis rhizoma* reduces acute lung inflammation by suppressing NF- κ B and activating Nrf2. *J. Ethnopharmacol.* **146**, 402-410.
- Hesslinger, C., Strub, A., Boer, R., Ulrich, W. R., Lehner, M. D. and Braun, C. (2009) Inhibition of inducible nitric oxide synthase in respiratory diseases. *Biochem. Soc. Trans.* **37**, 886-891.
- Hocaoglu, A. B., Karaman, O., Erge, D. O., Erbil, G., Yilmaz, O., Kivcak, B., Bagriyanik, H. A. and Uzuner, N. (2012) Effect of *Hedera helix* on lung histopathology in chronic asthma. *Iran. J. Allergy Asthma Immunol.* **11**, 316-323.
- Hong, E.-H., Song, J.-H., Shim, A., Lee, B.-R., Kwon, B.-E., Song, H.-H., Kim, Y.-J., Chang, S.-Y., Jeong, H. G., Kim, J. G., Seo, S.-U., Kim, H. P., Kwon, Y. S. and Ko, H.-J. (2015a) Coadministration of *Hedera helix* L. extract enabled mice to overcome insufficient protection against influenza A/PR/8 virus infection under suboptimal treatment with oseltamivir. *PLoS ONE* **10**, e0131089.
- Hong, J. M., Kwon, O. K., Shin, I. S., Jeon, C. M., Shin, N. R., Lee, J., Park, S. H., Bach, T. T., Hai do, V., Oh, S. R., Han, S. B. and Ahn, K. S. (2015b) Anti-inflammatory effects of methanol extract of *Cannarium luyi* C.D. Dai & Yakovlev in RAW 264.7 macrophages and a murine model of lipopolysaccharide-induced lung injury. *Int. J. Mol. Med.* **35**, 1403-1410.
- Hossein, B. M., Nasim, V. and Sediga, A. (2008) The protective effect of *Nigella sativa* on lung injury of sulfur mustard-exposed guinea pigs. *Exp. Lung Res.* **34**, 183-194.
- Hosseinian, N., Cho, Y., Lockey, R. F. and Kolliputi, N. (2015) The role of the NLRP3 inflammasome in pulmonary diseases. *Ther. Adv. Respir. Dis.* **9**, 188-197.
- Huang, C. H., Yang, M. L., Tsai, C. H., Li, Y. C., Lin, Y. J. and Kuan, Y. H. (2013) *Ginkgo biloba* leaves extract (EGb761) attenuates lipopolysaccharide-induced acute lung injury via inhibition of oxidative

- stress and NF- κ B-dependent matrix metalloproteinase-9 pathway. *Phytomedicine* **20**, 303-309.
- Huang, G. J., Deng, J. S., Chen, C. C., Huang, C. J., Sung, P. J., Huang, S. S. and Kuo, Y. H. (2014a) Methanol extract of *Andropogon camphorata* protects against lipopolysaccharide-induced acute lung injury by suppressing NF- κ B and MAPK pathways in mice. *J. Agric. Food Chem.* **62**, 5321-5329.
- Huang, H., Hu, G., Wang, C., Xu, H., Chen, X. and Qian, A. (2014b) Cepharanthine, an alkaloid from *Stephania cepharantha* Hayata, inhibits the inflammatory response in the RAW264.7 cell and mouse models. *Inflammation* **37**, 235-246.
- Huang, K. L., Chen, C. S., Hsu, C. W., Li, M. H., Chang, H., Tsai, S. H. and Chu, S. J. (2008) Therapeutic effects of baicalin on lipopolysaccharide-induced acute lung injury in rats. *Am. J. Chin. Med.* **36**, 301-311.
- Huo, M., Chen, N., Chi, G., Yuan, X., Guan, S., Li, H., Zhong, W., Guo, W., Soromou, L. W., Gao, R., Ouyang, H., Deng, X. and Feng, H. (2012) Traditional medicine alpinetin inhibits the inflammatory response in Raw 264.7 cells and mouse models. *Int. Immunopharmacol.* **12**, 241-248.
- Huo, M., Cui, X., Xue, J., Chi, G., Gao, R., Deng, X., Guan, S., Wei, J., Soromou, L. W., Feng, H. and Wang, D. (2013a) Anti-inflammatory effects of linalool in RAW 264.7 macrophages and lipopolysaccharide-induced lung injury model. *J. Surg. Res.* **180**, e47-e54.
- Huo, M., Gao, R., Jiang, L., Cui, X., Duan, L., Deng, X., Guan, S., Wei, J., Soromou, L. W., Feng, H. and Chi, G. (2013b) Suppression of LPS-induced inflammatory responses by gossypol in RAW 264.7 cells and mouse models. *Int. Immunopharmacol.* **15**, 442-449.
- Ilieva, I., Ohgami, K., Shiratori, K., Koyama, Y., Yoshida, K., Kase, S., Kitamei, H., Takemoto, Y., Yazawa, K. and Ohno, S. (2004) The effects of *Ginkgo biloba* extract on lipopolysaccharide-induced inflammation *in vitro* and *in vivo*. *Exp. Eye Res.* **79**, 181-187.
- Jing, W., Chunhua, M. and Shumin, W. (2015) Effects of acteoside on lipopolysaccharide-induced inflammation in acute lung injury via regulation of NF- κ B pathway *in vivo* and *in vitro*. *Toxicol. Appl. Pharmacol.* **285**, 128-135.
- Kao, S. T., Liu, C. J. and Yeh, C. C. (2015) Protective and immunomodulatory effect of flos *Lonicerae japonicae* by augmenting IL-10 expression in a murine model of acute lung inflammation. *J. Ethnopharmacol.* **168**, 108-115.
- Kim, J., Cha, Y. N. and Surh, Y. J. (2010) A protective role of nuclear factor-erythroid 2-related factor-2 (Nrf2) in inflammatory disorders. *Mutat. Res.* **690**, 12-23.
- Kim, S. Y., Son, K. H., Chang, H. W., Kang, S. S. and Kim, H. P. (1999) Inhibition of mouse ear edema by steroidal and triterpenoid saponins. *Arch. Pharm. Res.* **22**, 313-316.
- Ko, H. J., Jin, J. H., Kwon, O. S., Kim, J. T., Son, K. H. and Kim, H. P. (2011) Inhibition of experimental lung inflammation and bronchitis by phytoformula containing *Broussonetia papyrifera* and *Lonicera japonica*. *Biomol. Ther. (Seoul)* **19**, 324-330.
- Koul, A., Kapoor, N. and Bharati, S. (2012) Histopathological, enzymatic, and molecular alterations induced by cigarette smoke inhalation in the pulmonary tissue of mice and its amelioration by aqueous *Azadirachta indica* leaf extract. *J. Environ. Pathol. Toxicol. Oncol.* **31**, 7-15.
- Kwak, H. G. and Lim, H. B. (2014) Inhibitory effects of *Cnidium monnieri* fruit extract on pulmonary inflammation in mice induced by cigarette smoke condensate and lipopolysaccharide. *Chin. J. Nat. Med.* **12**, 641-647.
- Lee, H., Jung, K. H., Park, S., Kil, Y. S., Chung, E. Y., Jang, Y. P., Seo, E. K. and Bae, H. (2014) Inhibitory effects of *Stemona tuberosa* on lung inflammation in a subacute cigarette smoke-induced mouse model. *BMC Complement. Altern. Med.* **14**, 513.
- Lee, H., Kim, Y., Kim, H. J., Park, S., Jang, Y. P., Jung, S., Jung, H. and Bae, H. (2012) Herbal Formula, PM014, attenuates lung inflammation in a murine model of chronic obstructive pulmonary disease. *Evid. Based Complement. Alternat. Med.* **2012**, 769830.
- Lee, H., Yu, S. R., Lim, D., Lee, H., Jin, E. Y., Jang, Y. P. and Kim, J. (2015a) *Galla chinensis* attenuates cigarette smoke-associated lung injury by inhibiting recruitment of inflammatory cells into the lung. *Basic Clin. Pharmacol. Toxicol.* **116**, 222-228.
- Lee, J. H., Ahn, J., Kim, J. W., Lee, S. G. and Kim, H. P. (2015b) Flavonoids from the aerial parts of *Houttuynia cordata* attenuate lung inflammation in mice. *Arch. Pharm. Res.* **38**, 1304-1311.
- Lee, J. H., Ko, H. J., Woo, E. R., Lee, S. K., Moon, B. S., Lee, C. W., Mandava, S., Samala, M., Lee, J. and Kim, H. P. (2016) Moracin M inhibits airway inflammation by interrupting the JNK/c-Jun and NF- κ B pathways *in vitro* and *in vivo*. *Eur. J. Pharmacol.* **783**, 64-72.
- Lee, J. H., Lim, H. J., Lee, C. W., Son, K. H., Son, J. K., Lee, S. K. and Kim, H. P. (2015c) Methyl protodioscin from the roots of *Asparagus cochinchinensis* attenuates airway inflammation by inhibiting cytokine production. *Evid. Based Complement. Alternat. Med.* **2015**, 640846.
- Lee, J. P., Li, Y. C., Chen, H. Y., Lin, R. H., Huang, S. S., Chen, H. L., Kuan, P. C., Liao, M. F., Chen, C. J. and Kuan, Y. H. (2010) Protective effects of luteolin against lipopolysaccharide-induced acute lung injury involves inhibition of MEK/ERK and PI3K/Akt pathways in neutrophils. *Acta Pharmacol. Sin.* **31**, 831-838.
- Lee, J. W., Shin, N. R., Park, J. W., Park, S. Y., Kwon, O. K., Lee, H. S., Kim, J. H., Lee, H. J., Lee, J., Zhang, Z. Y., Oh, S. R. and Ahn, K. S. (2015d) *Callicarpa japonica* Thunb. attenuates cigarette smoke-induced neutrophil inflammation and mucus secretion. *J. Ethnopharmacol.* **175**, 1-8.
- Lee, S. J., Shin, E. J., Son, K. H., Chang, H. W., Kang, S. S. and Kim, H. P. (1995) Anti-inflammatory activity of the major constituents of *Lonicera japonica*. *Arch. Pharm. Res.* **18**, 133-135.
- Lee, S. J., Son, K. H., Chang, H. W., Kang, S. S. and Kim, H. P. (1998) Anti-inflammatory activity of *Lonicera japonica*. *Phytother. Res.* **12**, 445-447.
- Li, K. C., Ho, Y. L., Hsieh, W. T., Huang, S. S., Chang, Y. S. and Huang, G. J. (2015) Apigenin-7-glycoside prevents LPS-induced acute lung injury via downregulation of oxidative enzyme expression and protein activation through inhibition of MAPK phosphorylation. *Int. J. Mol. Sci.* **16**, 1736-1754.
- Li, L., Bao, H., Wu, J., Duan, X., Liu, B., Sun, J., Gong, W., Lv, Y., Zhang, H., Luo, Q., Wu, X. and Dong, J. (2012a) Baicalin is anti-inflammatory in cigarette smoke-induced inflammatory models *in vivo* and *in vitro*: A possible role for HDAC2 activity. *Int. Immunopharmacol.* **13**, 15-22.
- Li, W., Xie, J. Y., Li, H., Zhang, Y. Y., Cao, J., Cheng, Z. H., Chen, D. F. (2012b) *Viola yedoensis* liposoluble fraction ameliorates lipopolysaccharide-induced acute lung injury in mice. *Am. J. Chin. Med.* **40**, 1007-1018.
- Lim, H. J., Jin, H. G., Woo, E. R., Lee, S. K. and Kim, H. P. (2013) The root barks of *Morus alba* and the flavonoid constituents inhibit airway inflammation. *J. Ethnopharmacol.* **149**, 169-175.
- Lim, H. J., Lee, J. H., Choi, J. S., Lee, S. K., Kim, Y. S. and Kim, H. P. (2014) Inhibition of airway inflammation by the roots of *Angelica decursiva* and its constituent, columbianadin. *J. Ethnopharmacol.* **155**, 1353-1361.
- Lim, J.-C., Park, J. H., Budensinsky, M., Kasal, A., Han, Y.-H., Koo, B.-S., Lee, S.-I. and Lee, D.-U. (2005) Antimutagenic constituents from the thorns of *Gleditsia sinensis*. *Chem. Pharm. Bull.* **53**, 561-564.
- Liu, H., Ren, J., Chen, H., Huang, Y., Li, H., Zhang, Z. and Wang, J. (2014a) Resveratrol protects against cigarette smoke-induced oxidative damage and pulmonary inflammation. *J. Biochem. Mol. Toxicol.* **28**, 465-471.
- Liu, L., Xiong, H., Ping, J., Ju, Y. and Zhang, X. (2010) *Taraxacum officinale* protects against lipopolysaccharide-induced acute lung injury in mice. *J. Ethnopharmacol.* **130**, 392-397.
- Liu, M. H., Lin, A. H., Lee, H. F., Ko, H. K., Lee, T. S., Kou, Y. R. (2014b) Paeonol attenuates cigarette smoke-induced lung inflammation by inhibiting ROS-sensitive inflammatory signaling. *Mediators Inflamm.* **2014**, 651890.
- Lyu, J. H., Kim, K. H., Kim, H. W., Cho, S. I., Ha, K. T., Choi, J. Y., Han, C. W., Jeong, H. S., Lee, H. K., Ahn, K. S., Oh, S. R., Sadikot, R. T., Christman, J. W. and Joo, M. (2012) Dangkwisoo-san, an herbal medicinal formula, ameliorates acute lung inflammation via activation of Nrf2 and suppression of NF- κ B. *J. Ethnopharmacol.* **140**, 107-116.
- Ma, C., Zhu, L., Wang, J., He, H., Chang, X., Gao, J., Shumin, W. and Yan T. (2015a) Anti-inflammatory effects of water extract of *Taraxacum mongolicum* hand.-Mazz on lipopolysaccharide-induced

- inflammation in acute lung injury by suppressing PI3K/Akt/mTOR signaling pathway. *J. Ethnopharmacol.* **168**, 349-355.
- Ma, C. H., Liu, J. P., Qu, R. and Ma, S. P. (2014) Tectorigenin inhibits the inflammation of LPS-induced acute lung injury in mice. *Chin. J. Nat. Med.* **12**, 841-846.
- Ma, J., Xu, H., Wu, J., Qu, C., Sun, F. and Xu, S. (2015b) Linalool inhibits cigarette smoke-induced lung inflammation by inhibiting NF- κ B activation. *Int. Immunopharmacol.* **29**, 708-713.
- Mahler, D. A., Huang, S., Tabrizi, M. and Bell, G. M. (2004) Efficacy and safety of a monoclonal antibody recognizing interleukin-8 in COPD: a pilot study. *Chest* **126**, 926-934.
- Mao, Y. F., Li, Y. Q., Zong, L., You, X. M., Lin, F. Q. and Jiang, L. (2010) Methanol extract of *Phellodendri* cortex alleviates lipopolysaccharide-induced acute airway inflammation in mice. *Immunopharmacol. Immunotoxicol.* **32**, 110-115.
- Marks-Konczalik, J., Costa, M., Robertson, J., McKie, E., Yang, S. and Pascoe, S. (2015) A post-hoc subgroup analysis of data from a six month clinical trial comparing the efficacy and safety of losmapimod in moderate-severe COPD patients with $\leq 2\%$ and $> 2\%$ blood eosinophils. *Respir. Med.* **109**, 860-869.
- Matthys, H. and Funk, P. (2008) EPs 7630 improves acute bronchitic symptoms and shortens time to remission. Results of a randomised, double-blind, placebo-controlled, multicentre trial. *Planta Med.* **74**, 686-692.
- Matute-Bello, G., Frevert, C. W. and Martin, T. R. (2008) Animal models of acute lung injury. *Am. J. Physiol. Lung Cell Mol. Physiol.* **295**, L379-L399.
- Moretto, N., Caruso, P., Bosco, R., Marchini, G., Pastore, F., Armani, E., Amari, G., Rizzi, A., Ghidini, E., De Fanti, R., Capaldi, C., Carzaniga, L., Hirsch, E., Buccellati, C., Sala, A., Carnini, C., Patacchini, R., Delcanale, M., Civelli, M., Villetti, G. and Facchinetti, F. (2015) CHF6001 I: a novel highly potent and selective phosphodiesterase 4 inhibitor with robust anti-inflammatory activity and suitable for topical pulmonary administration. *J. Pharmacol. Exp. Ther.* **352**, 559-567.
- Morris, A., Kinnear, G., Wan, W. Y., Wyss, D., Bahra, P. and Stevenson, C. S. (2008) Comparison of cigarette smoke-induced acute inflammation in multiple strains of mice and the effect of a matrix metalloproteinase inhibitor on these responses. *J. Pharmacol. Exp. Ther.* **327**, 851-862.
- Moura, R. S., Ferreira, T. S., Lopes, A. A., Pires, K. M., Nesi, R. T., Resende, A. C., Souza, P. J., Silva, A. J., Borges, R. M., Porto, L. C. and Valenca, S. S. (2012) Effects of *Euterpe oleracea* Mart. (Açá) extract in acute lung inflammation induced by cigarette smoke in the mouse. *Phytomedicine* **19**, 262-269.
- Muntuschi, P., Kharitonov, S. A., Ciabattini, G. and Barnes, P. J. (2003) Exhaled leukotrienes and prostaglandins in COPD. *Thorax* **58**, 585-588.
- Nie, Y. C., Wu, H., Li, P. B., Luo, Y. L., Long, K., Xie, L. M., Shen, J. G. and Su, W. W. (2012) Anti-inflammatory effects of naringin in chronic pulmonary neutrophilic inflammation in cigarette smoke-exposed rats. *J. Med. Food* **15**, 894-900.
- Noh, S., Ahn, K. S., Oh, S. R., Kim, K. H. and Joo, M. (2015) Neutrophilic lung inflammation suppressed by picoside II is associated with TGF- β signaling. *Evid. Based Complement. Alternat. Med.* **2015**, 897272.
- Nomura, T. (2001) Chemistry and biosynthesis of prenylflavonoids. *Yakugaku Zasshi* **121**, 535-556.
- Norman, P. (2013) Evidence on the identity of the CXCR2 antagonist AZD-5069. *Expert Opin. Ther. Pat.* **23**, 113-117.
- Norman, P. (2015) Investigational p38 inhibitors for the treatment of chronic obstructive pulmonary disease. *Expert Opin. Investig. Drugs* **24**, 383-392.
- Pinner, N. A., Hamilton, L. A. and Hughes, A. (2012) Roflumilast: a phosphodiesterase-4 inhibitor for the treatment of severe chronic obstructive pulmonary disease. *Clin. Ther.* **34**, 56-66.
- Qamar, W. and Sultana, S. (2011) Polyphenols from *Juglans regia* L. (walnut) kernel modulate cigarette smoke extract induced acute inflammation, oxidative stress and lung injury in Wistar rats. *Hum. Exp. Toxicol.* **30**, 499-506.
- Qiu, J., Chi, G., Wu, Q., Ren, Y., Chen, C. and Feng, H. (2016) Pre-treatment with the compound asperuloside decreases acute lung injury via inhibiting MAPK and NF- κ B signaling in a murine model. *Int. Immunopharmacol.* **31**, 109-115.
- Rastrick, J. M., Stevenson, C. S., Eltom, S., Grace, M., Davies, M., Kilty, I., Evans, S. M., Pasparakis, M., Catley, M. C., Lawrence, T., Adcock, I. M., Belvisi, M. G. and Birrell, M. A. (2013) Cigarette smoke induced airway inflammation is independent of NF- κ B signalling. *PLoS ONE* **8**, e54128.
- Reid, D. J. and Pham, N. T. (2012) Roflumilast: a novel treatment for chronic pulmonary disease. *Ann. Pharmacother.* **46**, 521-529.
- Rennard, S. I., Dale, D. C., Donohue, J. F., Kanniss, F., Magnussen, H., Sutherland, E. R., Watz, H., Lu, S., Stryszak, P., Rosenberg, E. and Staudinger, H. (2015) CXCR2 Antagonist MK-7123. A phase 2 proof-of-concept trial for chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **191**, 1001-1011.
- Ribeiro, A., Ferraz-Paula, V., Pinheiro, M. L., Vitorretti, L. B., Mariano-Souza, D. P., Quinteiro-Filho, W. M., Akamine, A. T., Almeida, V. I., Quevedo, J., Dal-Pizzol, F., Hallak, J. E., Zuardi, A. W., Crippa, J. A. and Palermo-Neto, J. (2012) Cannabidiol, a non-psychotropic plant-derived cannabinoid, decreases inflammation in a murine model of acute lung injury: role for the adenosine A(2A) receptor. *Eur. J. Pharmacol.* **678**, 78-85.
- Rojas, M., Woods, C. R., Mora, A. L., Xu, J. and Brigham, K. L. (2005) Endotoxin-induced lung injury in mice: structural, functional, and biochemical responses. *Am. J. Physiol. Lung Cell Mol. Physiol.* **288**, L333-L341.
- Rovina, N., Dima, E., Gerassimou, C., Kollintza, A., Gratziou, C. and Roussos, C. (2009) Interleukin-18 in induced sputum: association with lung function in chronic obstructive pulmonary disease. *Respir. Med.* **103**, 1056-1062.
- San, Z., Fu, Y., Li, W., Zhou, E., Li, Y., Song, X., Wang, T., Tian, Y., Wei, Z., Yao, M., Cao, Y. and Zhang, N. (2014) Protective effect of taraxasterol on acute lung injury induced by lipopolysaccharide in mice. *Int. Immunopharmacol.* **19**, 342-350.
- Santana, F. P., Pinheiro N. M., Mernak, M. I., Righetti, R. F., Martins, M. A., Lago, J. H., Lopes, F. D., Tiberio, I. F. and Prado, C. M. (2016) Evidence of herbal medicine-derived natural products effects in inflammatory lung diseases. *Mediators Inflamm.* **2016**, 2348968.
- Schuliga, M. (2015) NF-kappaB signaling in chronic inflammatory airway disease. *Biomolecules* **5**, 1266-1283.
- Seimetz, M., Parajuli, N., Pichl, A., Veit, F., Kwapiszewska, G., Weisel, F. C., Milger, K., Egemnazarov, B., Turowska, A., Fuchs, B., Nikam, S., Roth, M., Sydykov, A., Medebach, T., Klepetko, W., Jaksch, P., Dumitrascu, R., Garn, H., Voswinckel, R., Kostin, S., Seeger, W., Schermuly, R. T., Grimminger, F., Ghofrani, H. A. and Weissmann, N. (2011) Inducible NOS inhibition reverses tobacco-smoke-induced emphysema and pulmonary hypertension in mice. *Cell* **147**, 293-305.
- Sezer, M., Sahin, O., Solak, O., Fidan, F., Kara, Z. and Unlu, M. (2007) Effects of caffeic acid phenethyl ester on the histopathological changes in the lungs of cigarette smoke-exposed rabbits. *Basic Clin. Pharmacol. Toxicol.* **101**, 187-191.
- Sharafkhaneh, A., Velamuri, S., Badmaev, V., Lan, C. and Hanania, N. (2007) The potential role of natural agents in treatment of airway inflammation. *Ther. Adv. Respir. Dis.* **1**, 105-120.
- Sharma, M., Arnason, J. T., Burt, A. and Hudson, J. B. (2006) Echinacea extracts modulate the pattern of chemokine and cytokine secretion in rhinovirus-infected and uninfected epithelial cells. *Phytother. Res.* **20**, 147-152.
- Shi, D., Zheng, M., Wang, Y., Liu, C. and Chen, S. (2014) Protective effects and mechanisms of mogroside V on LPS-induced acute lung injury in mice. *Pharm. Biol.* **52**, 729-734.
- Shim, D. W., Han, J. W., Sun, X., Jang, C. H., Koppula, S., Kim, T. J., Kang, T. B. and Lee, K. H. (2013) *Lysimachia clethroides* Duby extract attenuates inflammatory response in Raw 264.7 macrophages stimulated with lipopolysaccharide and in acute lung injury mouse model. *J. Ethnopharmacol.* **150**, 1007-1015.
- Soromou, L. W., Chu, X., Jiang, L., Wei, M., Huo, M., Chen, N., Guan, N., Yang, X., Chen, C., Feng, H. and Deng, X. (2012) *In vitro* and *in vivo* protection provided by pinocembrin against lipopolysaccharide-induced inflammatory responses. *Int. Immunopharmacol.* **14**, 66-74.
- Sriskantharajah, S., Hamblin, N., Worsley, S., Calver, A. R., Hessel,

- E. M. and Amour, A. (2013) Targeting phosphoinositide 3-kinase δ for the treatment of respiratory diseases. *Ann. N. Y. Acad. Sci.* **1280**, 35-39.
- State Pharmacopoeia Commission of PR China (2000) Pharmacopoeia of the People's Republic of China. 1, pp. 225-226. Chemical Industry Press, Beijing.
- Stolk, J., Rossie, W. and Dijkman, J. H. (1994) Apocynin improves the efficacy of secretory leukocyte protease inhibitor in experimental emphysema. *Am. J. Respir. Crit. Care Med.* **150**, 1628-1631.
- Su, Z. Q., Mo, Z. Z., Liao, J. B., Feng, X. X., Liang, Y. Z., Zhang, X., Liu, Y. H., Chen, X. Y., Chen, Z. W., Su, Z. R. and Lai, X. P. (2014) Usnic acid protects LPS-induced acute lung injury in mice through attenuating inflammatory responses and oxidative stress. *Int. Immunopharmacol.* **22**, 371-378.
- Sun, J., Chi, G., Soromou, L. W., Chen, N., Guan, M., Wu, Q., Wang, D. and Li, H. (2012) Preventive effect of imperatorin on acute lung injury induced by lipopolysaccharide in mice. *Int. Immunopharmacol.* **14**, 369-374.
- Taguchi, L., Pinheiro, N. M., Olivo, C. R., Choqueta-Toledo, A., Grecco, S. S., Lopes, F. D., Caperuto, L. C., Martins, M. A., Tiberio, I. F., Camara, N. O., Lago, J. H. and Prado, C. M. (2015) A flavanone from *Baccharis retusa* (Asteraceae) prevents elastase-induced emphysema in mice by regulating NF- κ B, oxidative stress and metalloproteinases. *Respir. Res.* **16**, 79.
- Tajima, S., Bando, M., Yamasawa, H., Ohno, S., Moriyama, H., Takada, T., Suzuki, E., Geiyo, F. and Sigiyama, Y. (2006) Preventive effect of Hochu-ekki-to on lipopolysaccharide-induced acute lung injury in BALB/c mice. *Lung* **184**, 318-323.
- Tao, W., Su, Q., Wang, H., Guo, S., Chen, Y., Duan, J. and Wang, S. (2015) Platycodin D attenuates acute lung injury by suppressing apoptosis and inflammation *in vivo* and *in vitro*. *Int. Immunopharmacol.* **27**, 138-147.
- Tianzhu, Z., Shihai, Y. and Juan, D. (2014) The effects of morin on lipopolysaccharide-induced acute lung injury by suppressing the lung NLRP3 inflammasome. *Inflammation* **37**, 1976-1983.
- Tianzhu, Z. and Shumin, W. (2015) Esculin inhibits the inflammation of LPS-induced acute lung injury in mice via regulation of TLR/NF- κ B pathways. *Inflammation* **38**, 1529-1536.
- To, Y., Ito, K., Kizawa, Y., Faila, M., Ito, M., Kusama, T., Elliott, W. M., Hogg, J. C., Adcock, I. M. and Barnes, P. J. (2010) Targeting phosphoinositide-3-kinase- δ with theophylline reverses corticosteroid insensitivity in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **182**, 897-904.
- Tsai, C. L., Lin, Y. C., Wang, H. M. and Chou, T. C. (2014) Baicalein, an active component of *Scutellaria baicalensis*, protects against lipopolysaccharide-induced acute lung injury in rats. *J. Ethnopharmacol.* **153**, 197-206.
- Wang, J., Nie, Y., Li, Y., Hou, Y., Zhao, W., Deng, J., Wang, P. G. and Bai, G. (2015) Identification of target proteins of mangiferin in mice with acute lung injury using functionalized magnetic microspheres based on click chemistry. *J. Agric. Food Chem.* **63**, 10013-10021.
- Watz, H., Barnacle, H., Hartley, B. F. and Chan, R. (2014) Efficacy and safety of the p38 MAPK inhibitor losmapimod for patients with chronic obstructive pulmonary disease: a randomised, double-blind, placebo-controlled trial. *Lancet Respir. Med.* **2**, 63-72.
- Wei, D. and Huang, Z. (2014) Anti-inflammatory effects of triptolide in LPS-induced acute lung injury in mice. *Inflammation* **37**, 1307-1316.
- Wei, M., Chu, X., Jiang, L., Yang, X., Cai, Q., Zheng, C., Ci, X., Guan, M., Liu, J. and Deng, X. (2012) Protocatechuic acid attenuates lipopolysaccharide-induced acute lung injury. *Inflammation* **35**, 1169-1178.
- Wright, J. L., Cosio, M. and Churg, A. (2008) Animal models of chronic obstructive pulmonary disease. *Am. J. Physiol. Lung Cell Mol. Physiol.* **295**, L1-L15.
- Wu, G., Du, L., Zhao, L., Shang, R., Liu, D., Jing, Q., Liang, J. and Ren, Y. (2014a) The total alkaloids of *Aconitum tanguticum* protect against lipopolysaccharide-induced acute lung injury in rats. *J. Ethnopharmacol.* **155**, 1483-1491.
- Wu, X. L., Feng, X. X., Li, C. W., Zhang, X. J., Chen, Z. W., Chen, J. N., Lai, X. P., Zhang, S. X., Li, Y. C. and Su, Z. R. (2014b) The protective effects of the supercritical-carbon dioxide fluid extract of *Chrysanthemum indicum* against lipopolysaccharide-induced acute lung injury in mice via modulating Toll-like receptor 4 signaling pathway. *Mediators Inflamm.* **2014**, 246407.
- Xie, G., Chen, N., Soromou, L. W., Liu, F., Xiong, Y., Wu, Q., Li, H., Feng, H. and Liu, G. (2012) p-Cymene protects mice against lipopolysaccharide-induced acute lung injury by inhibiting inflammatory cell activation. *Molecules* **17**, 8159-8173.
- Xie, X., Sun, S., Zhong, W., Soromou, L. W., Zhou, X., Wei, M., Ren, Y. and Ding, Y. (2014) Zingerone attenuates lipopolysaccharide-induced acute lung injury in mice. *Int. Immunopharmacol.* **19**, 103-109.
- Xie, Y. C., Dong, X. W., Wu, X. M., Yan, X. F. and Xie, Q. M. (2009) Inhibitory effects of flavonoids extracted from licorice on lipopolysaccharide-induced acute pulmonary inflammation in mice. *Int. Immunopharmacol.* **9**, 194-200.
- Xu, D., Wan, C., Wang, T., Tian, P., Li, D., Wu, Y., Fan, S., Chen, L., Shen, Y. and Wen, F. (2015) Berberine attenuates cigarette smoke-induced airway inflammation and mucus hypersecretion in mice. *Int. J. Clin. Exp. Med.* **8**, 8641-8647.
- Yang, D., Zhang, W., Song, L. and Guo, F. (2013) Andrographolide protects against cigarette smoke-induced lung inflammation through activation of heme oxygenase-1. *J. Biochem. Mol. Toxicol.* **27**, 259-265.
- Yang, T., Luo, F., Shen, Y., An, J., Li, X., Liu, X., Ying, B., Liao, Z., Dong, J., Guo, L., Wang, T., Xu, D., Chen, L. and Wen, F. (2012) Quercetin attenuates airway inflammation and mucus production induced by cigarette smoke in rats. *Int. Immunopharmacol.* **13**, 73-81.
- Yeh, C. C., Kao, S. J., Lin, C. C., Wang, S. D., Liu, C. J. and Kao, S. T. (2007a) The immunomodulation of endotoxin-induced acute lung injury by hesperidin *in vivo* and *in vitro*. *Life Sci.* **80**, 1821-1831.
- Yeh, C. C., Lin, C. C., Wang, S. D., Chen, Y. S., Su, B. H. and Kao, S. T. (2006) Protective and anti-inflammatory effect of a traditional Chinese medicine, Xia-Bai-San, by modulating lung local cytokine in a murine model of acute lung injury. *Int. Immunopharmacol.* **6**, 1506-1514.
- Yeh, C. C., Lin, C. C., Wang, S. D., Hung, C. M., Yeh, M. H., Liu, C. J. and Kao, S. T. (2007b) Protective and immunomodulatory effect of Gingyo-san in a murine model of acute lung inflammation. *J. Ethnopharmacol.* **111**, 418-426.
- Yingkun, N., Zhenyu, W., Jing, L., Xinyun, L. and Huimin, Y. (2013) Stevioside protects LPS-induced acute lung injury in mice. *Inflammation* **36**, 242-250.
- Yu, J. L., Zhang, X. S., Xue, X. and Wang, R. M. (2015) Patchouli alcohol protects against lipopolysaccharide-induced acute lung injury in mice. *J. Surg. Res.* **194**, 537-543.
- Zhang, H. (2011) Anti-IL-1 β therapies. *Recent Pat. DNA Gene Seq.* **5**, 126-135.
- Zhang, S. Y., Xu, L. T., Li, A. X. and Wang, S. M. (2015) Effects of ergosterol, isolated from *Scleroderma polyrhizum* Pers., on lipopolysaccharide-induced inflammatory responses in acute lung injury. *Inflammation* **38**, 1979-1985.
- Zhao, Y. L., Shang, J. H., Pu, S. B., Wang, H. S., Wang, B., Liu, L., Liu, Y. P., Shen, H. M. and Luo, X. D. (2016) Effect of total alkaloids from *Alstonia scholaris* on airway inflammation in rats. *J. Ethnopharmacol.* **178**, 258-265.
- Zhong, S., Nie, Y. C., Gan, Z. Y., Liu, X. D., Fang, Z. F., Zhong, B. N., Tian, J., Huang, C. Q., Lai, K. F. and Zhong, N. S. (2015) Effects of *Schisandra chinensis* extracts on cough and pulmonary inflammation in a cough hypersensitivity guinea pig model induced by cigarette smoke exposure. *J. Ethnopharmacol.* **165**, 73-82.
- Zhong, W. T., Jiang, L. X., Wei, J. Y., Qiao, A. N., Soromou, L. W., Xie, X. X., Zhou, X., Ci, X. X. and Wang, D. C. (2013a) Protective effect of esculentoside A on lipopolysaccharide-induced acute lung injury in mice. *J. Surg. Res.* **185**, 364-372.
- Zhong, W. T., Wu, Y. C., Xie, X., Zhou, X., Wei, M. M., Soromou, L. W., Ci, X. X. and Wang, D. C. (2013b) Phyllirin attenuates LPS-induced pulmonary inflammation via suppression of MAPK and NF- κ B activation in acute lung injury mice. *Fitoterapia* **90**, 132-139.
- Zhou, E., Li, Y., Wei, Z., Fu, Y., Lei, H., Zhang, N., Yang, Z. and Xie, G. S. (2014) Schisantherin A protects lipopolysaccharide-induced acute respiratory distress syndrome in mice through inhibiting NF-

κ B and MAPKs signaling pathways. *Int. Immunopharmacol.* **22**, 133-140.
Zhu, G. F., Guo, H. J., Huang, Y., Wu, C. T. and Zhang, X. F. (2015)

Eriodictyol, a plant flavonoid, attenuates LPS-induced acute lung injury through its antioxidant and anti-inflammatory activity. *Exp. Ther. Med.* **10**, 2259-2266.