BIOMOLECULES & THERAPEUTICS

Review
Biomol Ther 25(2), 91-104 (2017)

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

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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-κB 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**

Received Aug 18, 2016 **Revised** Sep 21, 2016 **Accepted** Oct 4, 2016
Published Online Dec 16, 2016

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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-1β 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 B_4 (LTB_4) and prostaglandin E_2 (PGE_2) levels in the exhaled breath condensate of patients with COPD are higher than in healthy subjects (Montuschi *et al*., 2003). LTB_4 is a potent neutrophil chemoattractant and its concentration in sputum is also increased in COPD patients (Corhay *et al*., 2009). To reduce LTB_4 levels, antagonists of LTB_4 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-1β, 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 ≤2% blood eosinophils (Marks-Konczalik *et al*., 2015). PI3K-mediated signaling in macrophages and neutrophils 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-κB (NF-κB), which is involved in the encoding of many inflammatory genes and relevant kinases such as IκB 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 CODP patients but showed no effective results (Norman, 2013; Rennard *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-1β 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-1β 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 CODP therapy (To *et al*., 2010). Although TG100-115, PI3Kγ 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 PI3Kδ was beneficial for the treatment of respiratory diseases (Sriskantharajah *et al*., 2013). GSK2269557, an inhaled PI3Kδ 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 (inflammation) 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 (SO_2) 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-κB 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.
Acanthopanax senticosus	[c]	20 (i.v.)	LPS (i.t.)	Fei *et al*. (2014)
Aconitum tanguticum	Alkaloid fraction	30-60	LPS (rat)	Wu *et al*. (2014a)
Alisma orientale Juzepzuk	80% ethanol	300-1,200	LPS	Han *et al*. (2013)
Angelica decursiva	70% ethanol	400	LPS	Lim *et al*. (2014)
Antrodia camphorata	Methanol	25-100	LPS	Huang *et al*. (2014a)
Alstonia scholaris	Alkaloid fraction	7-30	LPS (i.t.) (rat)	Zhao *et al*. (2016)
Azadirachta indica	Water	100/day	Cigarette smoke	Koul *et al*. (2012)
Callicarpa japonica Thunb.	Methanol	15-30/day	Cigarette smoke	Lee *et al*. (2015d)
Canarium lyi C.D. Dai & Yakovlev	Methanol	30/day	LPS	Hong *et al*. (2015b)
Chrysanthemum indicum	Supercritical CO_2 extract	40-120/day	LPS (i.t.)	Wu *et al*. (2014b)
Cnidium monnieri	Water	50-200/day	Cigarette smoke extract/ LPS (i.t.)	Kwak and Lim (2014)
Eleusine indica		400 (i.p.)	LPS	De Melo *et al*. (2005)
Euterpe oleracea Mart.	50% ethanol	300/day	Cigarette smoke	Moura *et al*. (2012)
Galla chinensis		100/day	Cigarette smoke	Lee *et al*. (2015a)
Ginkgo biloba	Egb761	0.01-1 (i.p.)	LPS (i.t.)	Huang *et al*. (2013)
Gleditsia sinensis	Water	3.3-10/day	LPS	Choi *et al*. (2012)
Glycyrrhiza uralensis	Flavonoid fraction	3-30	LPS (i.t.)	Xie *et al*. (2009)
Houttuynia cordata	70% ethanol	400	LPS	Lee *et al*. (2015b)
Juglans regia L. kernel	Methanol	50-100/day	Cigarette smoke (rat)	Qamar and Sultana (2011)
Lonicera japonica flos	50% ethanol	0.4-40	LPS (i.t.)	Kao *et al*. (2015)
Lysimachia clethroides Duby	Methanol	20-100 (i.p.)	LPS	Shim *et al*. (2013)
Mikania glomerata Spreng and *Mikania laevigata* Schultz Bip. Ex Baker	70% ethanol	100 (s.c.)	Mineral coal dust (i.t.) (rat)	Freitas *et al*. (2008)
Morus alba	70% ethanol	200-400	LPS	Lim *et al*. (2013)
Nigella sativa	Hydroethanolic extract	80/day	Sulfur mustard (guinea-pigs)	Hossein *et al*. (2008)
Paeonia suffruticosa	Granule	2,000	LPS (i.t) (rat)	Fu *et al*. (2012)
Phellodendri cortex	Methanol	100-400	LPS (i.t.)	Mao *et al*. (2010)
Punica granatum	0.9% NaCl	200 (i.p.)	LPS (i.t.)	Bachoual *et al*. (2011)
Rabdosia japonica var. *glaucocalyx*	Flavonoid fraction	6.4-25.6/day	LPS (i.t.)	Chu *et al*. (2014)
Schisandra chinensis Baillon	Water	10-100	LPS	Bae *et al*. (2012)
Schisandra chinensis Baillon	Aqueous ethanol	1,000/day	Cigarette smoke-induced cough hypersensitivity (guinea pig)	Zhong *et al*. (2015)
Stemona tuberosa	Water	50-200/day	Cigarette smoke	Lee *et al*. (2014)
Taraxacum officinale	Water	2.5-10/day	LPS	Liu *et al*. (2010)
Taraxacum mongolicum hand.-Mazz	Water	5,000-10,000	LPS	Ma *et al*. (2015a)
Uncaria tomentosa	Water		Ozone	Cisneros *et al*. (2005)
Viola yedoensis	Petroleum ether	2-8	LPS	Li *et al*. (2012b)
Formula: *Dangkwisoo-san*	Mixture	100-1,000/day	LPS	Lyu *et al*. (2012)
Formula: Gingyo-san	Mixture	1-2	LPS (i.t.)	Yeh *et al*. (2007b)
Formula: Hochu-ekki-to (TJ-41)	Mixture	1,000/day	LPS	Tajima *et al*. (2006)
Formula: Xia-Bai-San	Mixture	1	LPS (i.t.)	Yeh *et al*. (2006)
Formula: BP+LJ	Mixture	100-400	LPS (i.t.) (rat)	Ko *et al*. (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

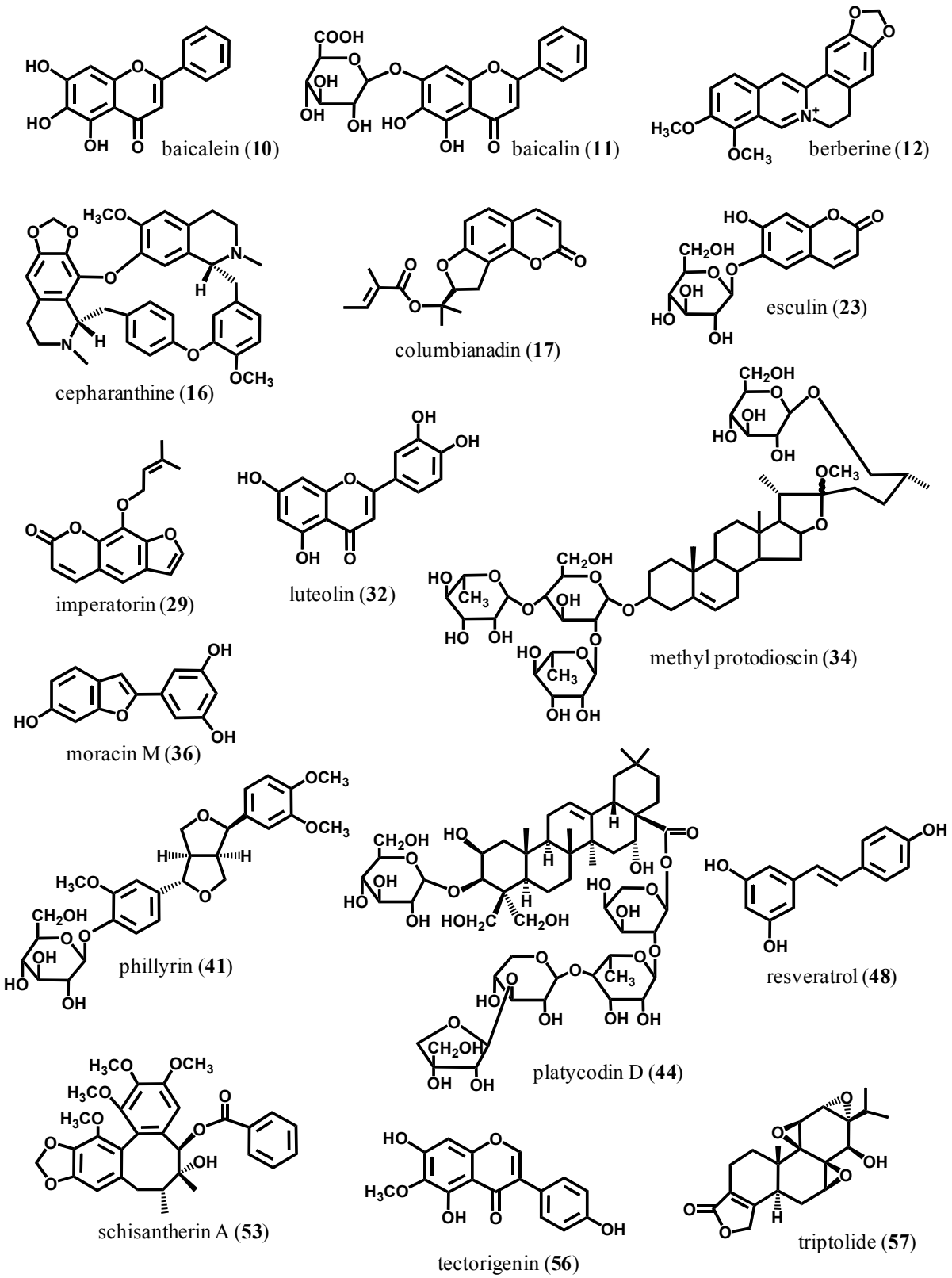

Fig. 1. The chemical structures of some selected plant constituents mentioned in this study.

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). *Pelagonium 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-κB 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-κB 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-κB activation via inhibiting IκBα 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-κB 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-κB activation (Ma *et al*., 2015b). Phillyrin (lignan, 41) reduced proinflammatory cytokine production mainly by inhibiting MAPK and NF-κB 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-κB 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	*Rehmannia glutinosa*	30-60 (i.p.)	LPS (i.t.)	Jing *et al*. (2015)
Afzelin (2), hyperoside (3), quercitrin (4)	Flavonoid	*Houttuynia cordata*	100, 100, 100	LPS	Lee *et al*. (2015b)
Alpinetin (5)	Flavonoid	*Alpinia katsumadai*	50 (i.p.)	LPS (i.t.)	Huo *et al*. (2012)
Andrographolide (6)	Diterpene	*Andrographis paniculata*	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	*Picrorhiza kurroa*	0.002-0.2/ml	LPS (hamster)	Stolk *et al*. (1994)
Asperuloside (9)	Iridoid		20-80 (i.p.)	LPS	Qiu *et al*. (2016)
Baicalein (10)	Flavonoid	*Scutellaria baicalensis*	20 (i.p.)	LPS (i.t.) (rat)	Tsai *et al*. (2014)
Baicalin (11)	Flavonoid	*Scutellaria baicalensis*	25-100/day	Cigarette smoke	Li *et al*. (2012a)
Baicalin (11)	Flavonoid	*Scutellaria baicalensis*	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	*Cannabis sativa*	20	LPS	Ribeiro *et al*. (2012)
Carvacrol (15)	Monoterpene	*Plectranthus amboinicus*	20-80 (i.p.)	LPS	Feng and Jia (2014)
Cepharanthine (16)	Alkaloid	*Stephania cepharantha* Hayata	5 (i.p.)	LPS	Huang *et al*. (2014b)
Columbianadin (17)	Coumarin	*Angelica decursiva*	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	*Scleroderma polyrhizum* Pers.	25-50	LPS	Zhang *et al*. (2015)
Eriodictyol (21)	Flavonoid	*Dracocephalum rupestre*	30/day	LPS	Zhu *et al*. (2015)
Esculentoside A (22)	Saponin	*Phytolacca esculenta*	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	*Lonicera japonica*	70 μmol/kg (i.p.)	LPS (i.t.)	Lee *et al*. (2010)
Mangiferin (33)	Xanthone	*Mangifera indica* L.	450-4,050/day	LPS	Wang *et al*. (2015)
Methyl protodioscin (34)	Steroidal saponin	*Asparagus cochinchinensis*	30-60	LPS	Lee *et al*. (2015c)
Mogroside V (35)	Triterpene saponin	*Momordica grosvenori*	2.5-10	LPS	Shi *et al*. (2014)
Moracin M (36)	2-arylbenzofuran	*Morus alba*	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	*Paeonia suffruticosa*	10/day	Cigarette smoke	Liu *et al*. (2014b)
Patchouli alcohol (40)	Sesquiterpene	*Pogostemon cablin*	10-40 (i.p.)	LPS	Yu *et al*. (2015)
Phillyrin (41)	Lignan	*Forsythia suspensa*	10-20	LPS	Zhong *et al*. (2013b)
Picroside Ii (42)	Iridoid	*Picrorhiza scrophulariiflora*	0.5-1 (i.t.)	LPS (i.t.)	Noh *et al*. (2015)
Pinocembrin (43)	Flavonoid	*Alpinia katsumadai*	20-50 (i.p.)	LPS	Soromou *et al*. (2012)

Table 2. Continued

Constituent	Class	Plant origin	Doses (mg/kg)[a)]	Inflammagen used[b)]	Reference
Platycodin D (44)	Triterpenoid saponin	*Platycodon grandiflorum*	50-100	LPS (i.t.)	Tao *et al*. (2015)
Prime-*O*-glucosylcimifugin (45)	Chromone	*Saposhnikovia divaricata*	2.5-10 (i.p.)	LPS	Chen *et al*. (2013)
Protocatechuic acid (46)	Benzoic acid		30 (i.p.)	LPS	Wei *et al*. (2012)
Quercetin (47)	Flavonoid		10/day	LPS/elastase	Ganesan *et al*. (2010)
Quercetin (47)	Flavonoid		25-30/day (i.p.)	Cigarette smoke (rat)	Yang *et al*. (2012)
Resveratrol (48)	Stilbene			LPS	Donnelly *et al*. (2004)
Resveratrol (48)	Stilbene		1-3/day	Cigarette smoke (3 days)	Liu *et al*. (2014a)
Sakuranetin (49)	Flavonoid	*Baccharis retusa*	20 (i.n.)	Elastase-induced emphysema	Taguchi *et al*. (2015)
Schaftoside (50), vitexin (51)	Flavonoid	*Eleusine indica*	0.4, 0.4 (i.p.)	LPS	De Melo *et al*. (2005)
Shikonin (52)	Naphthoquinone	*Lithospermum erythrorhizon*	12.5-50	LPS (i.t.)	Bai *et al*. (2013)
Schisantherin A (53)	Lignan	*Schisandra sphenanthera*	10-40	LPS	Zhou *et al*. (2014)
Stevioside (54)	Diterpene	*Stevia rebaudiana*	12.5-50	LPS	Yingkun *et al*. (2013)
Taraxasterol (55)	Triterpene	*Taraxacum officinale*	2.5-10 (i.p.)	LPS	San *et al*. (2014)
Tectorigenin (56)	Flavonoid	*Belamcanda chinensis*	5-10 (i.v.)	LPS (i.t.)	Ma *et al*. (2014)
Triptolide (57)	Diterpene	*Tripterygium wilfordii*	0.005-0.015	LPS	Wei and Huang (2014)
Usnic acid (58)	Dibenzofuran	Lichen species	25-100/day	LPS	Su *et al*. (2014)
Zingerone (59)	Phenol		10-40	LPS	Xie *et al*. (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-κB was also activated in the lung tissue. Under this condition, sakuranetin reduced the NF-κB 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-κB, 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 agaisnt 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-κB pathways. Another triterpene derivative, mogroside V (35), reduced lung inflammation by the down-regulation of COX-2 and iNOS via inhibiting NF-κB 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-κB 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-κB 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-κB) and NF-κB 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-κB 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 increasing 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-κB activation have been widely demonstrated. Despite the importance of NF-κB in lung inflammatory disorders, there are some contradicting results showing that NF-κB 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.

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