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Recent Advances in the Development of Novel Drug Candidates for Regulating the Secretion of Pulmonary Mucus

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Abstract

Hypersecretion of pulmonary mucus is a major pathophysiological feature in allergic and inflammatory respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD). Overproduction and/or oversecretion of mucus cause the airway obstruction and the colonization of pathogenic microbes. Developing a novel pharmacological agent to regulate the production and/or secretion of pulmonary mucus can be a useful strategy for the effective management of pathologic hypersecretion of mucus observed in COPD and asthma. Thus, in the present review, we tried to give an overview of the conventional pharmacotherapy for mucus-hypersecretory diseases and recent research results on searching for the novel candidate agents for controlling of pulmonary mucus hypersecretion, aiming to shed light on the potential efficacious pharmacotherapy of mucus-hypersecretory diseases.

Key Words: Mucus, Mucin, Hypersecretion, Pharmacotherapy

INTRODUCTION

Mucus, a gel comprising macromolecules, ions, proteins, and water, in the airway plays a crucial role in defense mechanisms against a multitude of pathogens through a mechanism called the mucociliary clearance. The protective function of mucus is due to the viscoelastic property of mucous glycoproteins or mucins, the major macromolecular components of mucus, produced by epithelial goblet cells and submucosal mucous cells (Rogers and Barnes, 2006). There are the two classes of mucins in the airways: 1) mucins secreted and polymerized to form gels (gel-forming mucins, *MUC5AC*, *MUC5B*); 2) mucins associated with the apical cell membrane and having transmembrane domains (*MUC1*, *MUC4*, *MUC16*, *MUC20*). Any abnormality in the quantity or quality of mucins not only provokes the altered physiology of the airway, but also disables the host defense that often leads to serious airway pathology as exemplified in asthma, chronic bronchitis, and bronchiectasis (Voynow and Rubin, 2009). There are two ways to remove excess mucus from the airway: i) removing the mucus by the physical method, aspiration, after thining by dilution (mucolysis) of mucus, and ii) suppression of secretion and/or production of mucus by pharmacological tools. The agents affecting the physicochemical properties and transport of mucus are defined as 'mucoactive agents'. This group of agents includes mucokinetics, mucolytics, and expectorants. The mucokinetics are defined as the agents that promote the elimination of airway mucus by lowering the stickiness of adhesive airway secretions or amplifying the cough airflow expiration. Mucolytics are the agents that depolymerize and degrade airway mucus. Expectorants are defined as the agents that increase the volume of airway secretion, thereby promoting cough efficiency. However, the clinical application of the physical method for elimination of mucus using any of these three agents (mucolytics, mucokinetics or expectorants) causes the irritation of airway luminal wall and leads to hypersecretion of mucus, through a reflex mechanism (Rogers, 2007). Consequently, the development of pharmacological tools, namely the 'novel mucoactive agents' that affect the biosynthesis and/or degradation, to control secretion and/or production of mucin, have become an important strategy for regulating the pathological secretion of airway mucus observed in chronic obstructive pulmonary disease (COPD) and asthma. In the present review, we tried to give an overview

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Table 1. Conventional pharmacotherapy for the management of pulmonary diseases showing hypersecretion of mucus

Classification of conventional pharmacologic agents	Drugs
Mucolytics	N-acetyl L-cysteine (NAC) (Sheffner *et al*., 1964; Hansen *et al*., 1994; Hauber *et al*., 2007a)
	S-carboxymethyl cysteine (Decramer *et al*., 2005)
	Letocysteine (Rogers, 2007)
	Erdosteine (Decramer *et al*., 2005)
	2-Mercaptoethane sulfonate sodium (Sheffner *et al*., 1964; Hansen *et al*., 1994; Hauber *et al*., 2007a)
	Sobrerol (Allegra *et al*., 1981; Guo *et al*., 2006)
	Myrtol (Allegra *et al*., 1981; Guo *et al*., 2006)
	Recombinant human deoxyribonuclease (Henke *et al*., 2004, 2007)
	Thymosin β-4 (Vasconcellos *et al*., 1994; Rubin *et al*., 2006; Kater *et al*., 2007)
Expectorants/Mucokinetics	Mannitol dry powder (Bennett *et al*., 2016)
	Hypertonic saline solution (Bennett *et al*., 2016)
	Iodide compounds (Jager, 1989; Rubin *et al*., 1996)
	Ambroxol (Germouty and Jirou-Najou, 1987; Guyatt *et al*., 1987; No authors listed, 1989; Albers *et al*., 1996)
	Bromhexine (Germouty and Jirou-Najou, 1987; Guyatt *et al*., 1987; No authors listed, 1989; Albers *et al*., 1996)
Anti-inflammatory and miscellaneous agents	Glucocorticoids (Chen *et al*., 2012)
	Azithromycin (macrolide antibiotics) (Tamaoki *et al*., 1995; Shimizu *et al*., 2003; Tamaoki, 2004)

of the conventional pharmacotherapy for mucus-hypersecretory diseases (Table 1) and report recent results of research in searching for the novel candidate agent for controlling the hypersecretion of pulmonary mucus (Table 2). Our intention is to shed light on the potentially efficacious pharmacotherapy of mucus-hypersecretory diseases.

CONVENTIONAL PHARMACOTHERAPY FOR THE MANAGEMENT OF PULMONARY DISEASES SHOWING HYPERSECRETION OF MUCUS

Glucocorticoids

Glucocorticoids are well-known anti-inflammatory compounds manifesting diverse physiological activities. They have been reported to mitigate the gene expression and production of MUC5AC mucin via binding to the glucocorticoid receptors (Chen *et al*., 2012). Glucocorticoids are clinically used to regulate the production of pulmonary mucus through anti-inflammatory activity (Barnes, 1998; Wojtczak *et al*., 2001). However, severe adverse effects of glucocorticoids that include amplified susceptibility to infection restrict their use as an efficacious and safe drug for regulating the production and secretion of airway mucus.

Mannitol dry powder and hypertonic saline solution

Inhaled mannitol dry powder or hypertonic saline solution is known to enhance the transport of airway mucus by increasing the amount of water in airway lumen and decreasing the solid concentration of mucus (Bennett *et al*., 2016). Furthermore, an aerosol or tracheal irrigation of 2% sodium bicarbonate aqueous solution can be used for controlling the expectoration of airway mucus by decreasing the viscoselasticity. However, these medications do not regulate mucus secretion and production and are associated with the adverse effects such as cough, chest tightness, and bronchospasm (Shim *et al*., 1987; Valderramas and Atallah, 2009; Bilton *et al*., 2014).

Iodide compounds

Glyceryl guaiacolate (guaifenesin), iodinated glycerol and super-saturated potassium iodide have been broadly used to provoke the secretion of airway fluid and mucus, although their efficacy as expectorants has not been proven in the clinic (Jager, 1989; Rubin *et al*., 1996).

Ambroxol and Bromhexine

Ambroxol and Bromhexine are classified as expectorants and are used to potentiate the secretion of pulmonary surfactant. The surfactant has been known to decrease the adhesivity of mucus and facilitate the transfer of the moving energy to the layer of mucus. The tenacity of mucus gives the biggest impact on the clearability of sputum by the cough and surfactant diminishes the tenacity of mucus (Albers *et al*., 1996). Ambroxol and Bromhexine have long been utilized for the regulation of chronic bronchitis in Europe and Asian countries, although they have not been approved for medical use in Canada and the United States of America. The clinical trials on the effectiveness of Ambroxol failed to show consistently positive results (Germouty and Jirou-Najou, 1987; Guyatt *et al*., 1987; No authors listed, 1989).

Table 2. The novel candidate agents under investigation for regulating the secretion of pulmonary mucus

Classification of novel candidate agents	Compounds
Novel compounds and/or repositioned drugs targeting for regulating the secretion of pulmonary mucus under investigation	11,12- epoxyeicosatrienoic acids (EET) (Lasker *et al*., 2000) FK224 and CP99994 (Bertrand and Geppetti, 1996; Advenier *et al*., 1997) Sildenafil (Wang *et al*., 2009) Niflumic acid (Nakanishi *et al*., 2001; Zhou *et al*., 2002; Hauber *et al*., 2005b, 2007b) Blockers of P2Y2 purinoceptor (Davis, 2002) Peptides related to myristoylated alanine-rich C kinase substrate (MARCKS) (Singer *et al*., 2004; Green *et al*., 2011) Blockers of retinoic acid receptor (RAR)-α (Koo *et al*., 1999; Aggarwal *et al*., 2006)
Natural products targeting for regulating the secretion of pulmonary mucus under investigation	4′,7-dihydroxyflavone (Zhou *et al*., 2015) Apigenin (Seo *et al*., 2014; Sikder *et al*., 2014b) Baicalein (Lee *et al*., 2003, 2004a, 2004b; Heo *et al*., 2007a) Baicalin (Heo *et al*., 2007a) Berberine (Sikder *et al*., 2011) Carbenoxolone (Heo *et al*., 2007b; Lee *et al*., 2011a) Chrysin (Shin *et al*., 2012) Coixol (Lee *et al*., 2015b) Curcumin (Heo *et al*., 2009) Daidzein (Lee *et al*., 2011c) Dioscin (Lee *et al*., 2015a) Ebeiedine (Kim *et al*., 2016) Genistein (Heo *et al*., 2009) Gingerol (Kim *et al*., 2009; Chang *et al*., 2010) Glyceryl trilinoleate (Lee *et al*., 2015b) Glycyrrhizin (Heo *et al*., 2007b; Nishimoto *et al*., 2010; Lee *et al*., 2011a) Hesperidin (Lee *et al*., 2003, 2004a, 2004b) Kaempferol (Kwon *et al*., 2009) Lobetyol (Yoon *et al*., 2014) Lobetyolin (Yoon *et al*., 2014) Lupenone (Yoon *et al*., 2015) Lupeol (Yoon *et al*., 2015) Luteolin (Lee *et al*., 2015c) Methyl linoleate (Yoon *et al*., 2014) Methylprotodioscin (Lee *et al*., 2015a) Morusin (Lee *et al*., 2014) Naringin (Nie *et al*., 2012) Obtusifolin (Choi *et al*., 2019) Oleanolic acid (Cho *et al*., 2011) Ophiopogonin D (Park *et al*., 2014) Platycodins (Shin *et al*., 2002; Choi *et al*., 2011; Ryu *et al*., 2014) Prunetin (Lee *et al*., 2011b; Ryu *et al*., 2013) Quercetin (Kwon *et al*., 2009; Yang *et al*., 2012) Resveratrol (Lee *et al*., 2012) Scutellarin (Jiang *et al*., 2011) Silibinin (Kim *et al*., 2012b) Spicatoside A (Park *et al*., 2014) Suchengbeisine (Kim *et al*., 2016) Taraxerol (Yoon *et al*., 2015) Tilianin (Song *et al*., 2017) Tussilagone (Choi *et al*., 2018) Ursolic acid (Cho *et al*., 2011) Verproside (Lee *et al*., 2015d) Verticine (Kim *et al*., 2016) Wogonin (Sikder *et al*., 2014a, 2014b)

N-acetyl L-cysteine (NAC), S-carboxymethyl cysteine, Letocysteine, Erdosteine, 2-Mercaptoethane sulfonate sodium (MESNA)

N-acetyl L-cysteine (NAC), S-carboxymethyl cysteine, Letocysteine, Erdosteine, and MESNA are the mucolytics containing sulfhydryl moieties in their molecular structures. They might degrade the disulfide bonds present in cysteine residues of mucins and thus break down the polymeric structure of mucins (Sheffner *et al*., 1964). They have been generally used to expectorate mucus more easily by lowering the viscoelasticity of mucus, thereby helping to regulate the chronic inflammatory pulmonary diseases. However, oral or inhaled NAC aerosol and oral administration of S-carboxymethyl cysteine, Letocysteine, and Erdosteine did not show the consistent efficacy in clinical trials (Decramer *et al*., 2005; Rogers, 2007). It has been suggested that some of the demonstrated efficacy of NAC might be due to its antioxidative activity rather than its donor activity of sulfhydryl moieties (British Thoracic Society Research Committee, 1985; Hansen *et al*., 1994; Hauber *et al*., 2007a).

Sobrerol and Myrtol

Sobrerol and Myrtol are known to be mucolytics. They are derived from one of the natural products, terpenes. Sobrerol is a single compound and Myrtol is a essential oil mixture. They were reported to show the potentiating effect on mucociliary transport (Allegra *et al*., 1981). However, their pharmacological efficacy has not be proven in spite of their medical use in European and Asian countries (Matthys *et al*., 2000; Guo *et al*., 2006).

Recombinant human deoxyribonuclease/dornase alfa (rhDNase) and Thymosin β-4

In mucus, there are the polymers of mucins and polymeric network of deoxyribonucleic acid (DNA) and filamentous actin derived from the cells involved in inflammation. Especially, the patients suffering from cystic fibrosis (CF) have nearly no mucin in their airway secretion. Their airway secretion consists mainly of DNA and filamentous actin (Henke *et al*., 2004, 2007). The two mucolytics, rhDNase and Thymosin β-4, degrade the polymers of DNA and the network of filamentous actin, respectively (Vasconcellos *et al*., 1994; Rubin *et al*., 2006; Kater *et al*., 2007). Although rhDNase, approved for medical use in the United States of America, is efficacious in CF patients, it did not show the sufficient clinical efficacy in patients suffering from non-CF, chronic bronchitis (Rubin, 1999; Henke and Ratjen, 2007).

Azithromycin and related macrolide antibiotics

In addition to their antibiotic effect, Azithromycin and related macrolide antibiotics suppress the production and/or secretion of pulmonary mucin and are clinically used for regulation of diffuse panbronchiolitis and CF (Tamaoki *et al*., 1995; Shimizu *et al*., 2003; Tamaoki, 2004). Its efficacy has been reported to be due to an anti-inflammatory action mediated via affecting the NF-κB signaling pathway (Desaki *et al*., 2000; Ou *et al*., 2008).

THE NOVEL CANDIDATE AGENTS UNDER INVESTIGATION FOR REGULATING THE SECRETION OF PULMONARY MUCUS

11,12- epoxyeicosatrienoic acids (EET)

11,12-EET, an eicosanoid produced by cytochrome P450 (CYP) epoxygenase from arachidonic acid, was reported to exert anti-inflammatory activity through regulation of NF-κB signaling pathway and this compound, as well as an induction of CYP epoxygenase by fibrate analogs, are able to mitigate the overproduction of mucus and pulmonary inflammation (Lasker *et al*., 2000).

FK224 and CP99994

It was reported that neurokinin 1 (NK1) and NK2, tachykinins, receptors mediate the secretion of airway mucus and substance P activates the NK1 receptor, thereby provoking the secretion (Bertrand and Geppetti, 1996; Advenier *et al*., 1997). Theoretically, antagonists of NK receptors, including FK224 and CP99994, might control the hypersecretion of mucus. However, the clinical trials failed to prove their pharmacological effects (Joos *et al*., 1995).

Sildenafil

Sildenafil, an inhibitor of phosphodiesterase (PDE) type 5 (PDE 5), has been reported to inhibit the acrolein-induced respiratory inflammation as well as goblet cell metaplasia (GCM) and the production of muc5ac by the nitric oxide (NO)/cGMP signaling pathway (Wang *et al*., 2009).

Niflumic acid

Calcium-activated chloride channel (CLCA) proteins in human are overexpressed in the pulmonary epithelium of patients suffering from chronic obstructive pulmonary disease (COPD), asthma, and cystic fibrosis (Hoshino *et al*., 2002; Toda *et al*., 2002; Hauber *et al*., 2004, 2005a). Blocking human CLCA-1 suppresses the expression of mucin. Niflumic acid inhibits human CLCA-1 and has been shown to mitigate the expression of mucin in NCI-H292 cells, in Calu-3, a mucoepidermoid cells, and in human airway mucosa (Nakanishi *et al*., 2001; Zhou *et al*., 2002; Hauber *et al*., 2005b, 2007b).

Blockers of P2Y2 purinoceptor

Stimulation of P2Y2 purinoceptor by adenosine triphosphate or uridine triphosphate initiates the secretion of airway mucus (Davis, 2002). Thus, the development of antagonists of P2Y2 purinoceptor might provide the potential tool for decreasing the secretion of airway mucus. As of yet, no well-designed clinical trials have been performed.

Peptides related to myristoylated alanine-rich C kinase substrate (MARCKS)

It was reported that MARCKS plays an important role in the secretion of airway mucin (Li *et al*., 2001) and that the peptides related to MARCKS might inhibit the hypersecretion of airway mucus *in vivo* (Singer *et al*., 2004; Green *et al*., 2011).

Blockers of the retinoic acid receptor (RAR)-α

It is well-known that retinoic acid initiates the gene expression of pulmonary mucin through the retinoic acid receptor (RAR)-α. Therefore, the development of specific antagonists of the receptor might decrease the expression of mucin; how-

ever, no well-designed clinical trials have been performed up to now (Koo *et al*., 1999; Aggarwal *et al*., 2006).

Natural products affecting the release of mucin from airway epithelial goblet cells

Lee and his research group reported that several natural products including Baicalein, Berberine, Curcumin, Hesperidin, Ursolic acid suppressed the release of airway mucin from primary cultured airway epithelial cells (Lee *et al*., 2003, 2004a, 2004b).

Obtusifolin

Obtusifolin and natural products derived from *Cassia obtusifolia* were reported to affect the production and gene expression of MUC5AC mucin in airway epithelial NCI-H292 cells. In particular, among the active natural products, obtusifolin suppresses the production and gene expression of airway mucin by affecting the phosphorylation of inhibitory kappa B kinase (IKK), phosphorylation and degradation of inhibitory kappa B alpha (IκBα), and nuclear translocation of nuclear factor kappa B (NF-κB) p65 (Choi *et al*., 2019).

Tussilagone

A natural product isolated from *Tussilago farfara*, tussilagone, inhibits the gene expression and production of MUC5AC mucin in airway epithelial NCI-H292 cells, by controlling IKK phosphorylation, IκBα phosphorylation and degradation, and nuclear translocation of NF-κB p65 (Choi *et al*., 2018).

Verticine, ebeiedine, and suchengbeisine

The three natural compounds, verticine, ebeiedine, and suchengbeisine isolated from *Fritillaria thunbergii*, suppress the production and gene expression of MUC5AC mucin from human airway epithelial NCI-H292 cells (Kim *et al*., 2016).

Lupenone, Lupeol, and Taraxerol

Lupenone, Lupeol, and Taraxerol isolated from *Adenophora triphylla*, a medicinal plant empirically used for regulating inflammation in folk medicine, suppressed the production and gene expression of MUC5AC mucin from human airway epithelial NCI-H292 cells (Yoon *et al*., 2015).

Dioscin and Methylprotodioscin

Dioscin and Methylprotodioscin isolated from *Asparagus cochinchinensis*, a medicinal plant used for pulmonary inflammatory diseases in traditional Chinese medicine, inhibited the gene expression and production of airway MUC5AC mucin (Lee *et al*., 2015a).

Wogonin, Chrysin, Apigenin, baicalin, and Scutellarin

Wogonin, Chrysin, Apigenin, baicalin, and Scutellarin are derived from *Scutellaria baicalensis*, an anti-inflammatory medicinal plant utilized in traditional Chinese medicine for the management of allergic respiratory diseases. The compounds were reported to suppress the production and gene expression of airway MUC5AC mucin. Among the five natural products, Apigenin and Wogonin were found to inhibit the gene expression and production of MUC5AC mucin in NCI-H292 cells, by affecting IKK phosphorylation, IκBα phosphorylation and degradation, and nuclear translocation of NF-κB p65 (Heo *et al*., 2007a; Jiang *et al*., 2011; Kim *et al*., 2012a; Shin *et al*., 2012; Seo *et al*., 2014; Sikder *et al*., 2014a, 2014b).

Prunetin, Carbenoxolone, Glycyrrhizin, and 4′,7-dihydroxyflavone

It was reported that Prunetin, Carbenoxolone, Glycyrrhizin, and 4′,7-dihydroxyflavone derived from a well-known anti-inflammatory medicinal plant used for controlling the diverse inflammatory diseases, *Glycyrrhiza uralensis*, suppressed the gene expression, production and/or secretion of airway MUC5AC mucin. Prunetin inhibited the gene expression and production by regulating the degradation of IκBα and NF-κB p65 translocation, in the airway epithelial NCI-H292 cells. 4′,7-dihydroxyflavone mitigated the gene expression, production, and secretion of airway mucin by affecting NF-κB signaling pathway, signal transducer and activator of transcription 6 (STAT6), and histone deacetylase 2 (HDAC2) (Heo *et al*., 2007b; Nishimoto *et al*., 2010; Lee *et al*., 2011a, 2011b; Ryu *et al*., 2013; Zhou *et al*., 2015).

Lobetyolin, Lobetyol, and Methyl linoleate

The three natural products, Lobetyolin, Lobetyol, and Methyl linoleate, were reported to inhibit the secretion, production and gene expression of pulmonary mucin in airway epithelial NCI-H292 cells (Yoon *et al*., 2014).

Kaempferol, Naringin, Tilianin, Silibinin, Luteolin, and Quercetin

Kaempferol, Naringin, Tilianin, Silibinin, Luteolin, and Quercetin are the flavonoids isolated from various medicinal plants and showed the regulatory effects on the gene expression, production, and secretion of MUC5AC mucin from airway epithelial cells. Silibinin affects NF-κB and extracellular regulated kinase (ERK)-Specificity protein-1 (Sp1) signaling pathways. Quercetin suppresses the activation of NF-κB and the phosphorylation of the epidermal growth factor receptor (EGFR). Naringin inhibits NF-κB and mitogen-activated protein kinase (MAPK)-Activator protein-1 (AP-1) signaling pathways. Tilianin also suppresses the EGFR-Sp1 signaling pathway. Luteolin inhibits the degradation of IκBα and translocation of NF-κB p65 (Kwon *et al*., 2009; Kim *et al*., 2012b; Nie *et al*., 2012; Yang *et al*., 2012; Lee *et al*., 2015c; Park *et al*., 2016; Song *et al*., 2017).

Morusin and natural products derived from *Morus alba*

Morusin and natural products derived from *Morus alba*, a medicinal plant, were reported to mitigate the gene expression and production of mucin from airway epithelial cells (Lee *et al*., 2014).

Coixol

Coixol, glyceryl trilinoleate, and natural products isolated from *Coix Lachryma-Jobi*, an anti-inflammatory medicinal plant, suppress gene expression, production, and secretion of airway mucin from NCI-H292 cells (Lee *et al*., 2015b).

Platycodins

It was reported that Platycodin derivatives isolated from *Platycodon grandiflorum*, a medicinal plant utilized in folk medicine as expectorants and anti-inflammatory agent for controlling the inflammatory pulmonary diseases, regulate the production, gene expression, and secretion of airway mucin (Shin *et al*., 2002; Choi *et al*., 2011; Ryu *et al*., 2014).

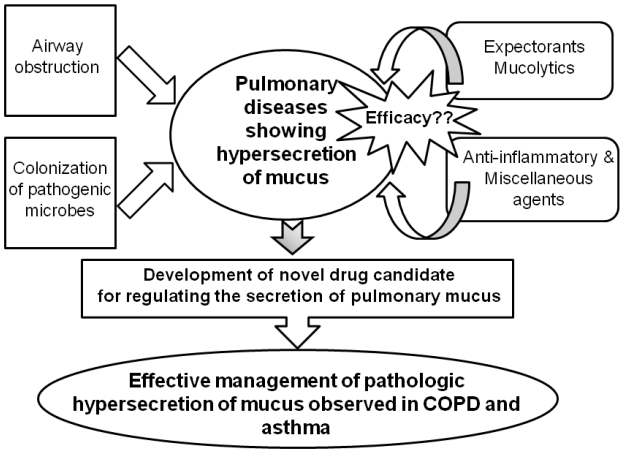

Fig. 1. The strategy for the effective management of pathologic hypersecretion of mucus observed in COPD and asthma. Hypersecretion of pulmonary mucus is a major pathophysiological feature in allergic and inflammatory respiratory diseases including asthma and COPD. Overproduction and/or oversecretion of mucus provoke the airway obstruction and the colonization of pathogenic microbes. Developing a novel pharmacological agent to regulate the production and/or secretion of pulmonary mucus can be a useful strategy for the effective management of pathologic hypersecretion of mucus observed in COPD and asthma.

Ophiopogonin D and Spicatoside A

Park and his colleagues reported that Ophiopogonin D and Spicatoside A isolated from *Liriope Tuber*, a medicinal plant utilized in traditional Chinese medicine as expectorants for controlling the inflammatory pulmonary diseases, stimulate the production and secretion of airway mucin, suggesting that the two compounds can be developed as efficacious expectorants through future study (Park *et al*., 2014).

Resveratrol, Oleanolic acid, Ursolic acid, Berberine, Daidzein, Genistein, and Curcumin

Resveratrol, Oleanolic acid, Ursolic acid, Berberine, Daidzein, Genistein, and Curcumin are the natural products manifesting a range of physiological and pharmacological effects including anti-inflammatory and antioxidative activity. These compounds showed a suppressive effect on the gene expression, production, and secretion from airway epithelial cells (Heo *et al*., 2009; Cho *et al*., 2011; Lee *et al*., 2011c; Sikder *et al*., 2011; Lee *et al*., 2012).

Gingerol

[6]-Gingerol, a natural compound, was reported to decrease the gene expression and production of MUC5AC, through affecting the ERK- and p38 MAPK signaling pathways (Kim *et al*., 2009; Chang *et al*., 2010).

Verproside

Lee *et al*. (2015d) reported that verproside, a natural product, inhibited the production and gene expression of airway mucin via regulating TGF-β-activated kinase 1 (TAK1)-IKK-IκBα-NF-κB signaling pathway.

Conclusion and future direction for research on the novel mucoactive drugs

As described above in the main text, the drugs used in the conventional pharmacological management of inflammatory pulmonary diseases accompanied by hypersecretion of mucus do not exhibit sufficient clinical efficacy in treating this condition and provokes the multiple adverse effects (Fig. 1). Several novel candidate compounds and a number of natural products derived from anti-inflammatory medicinal plants showed a regulatory effect on the gene expression, production, and secretion of airway MUC5AC mucin, the major macromolecular component in mucus, through affecting NF-κB and/or EGFR-MEK-ERK signaling pathways. However, the effective concentration of these candidate natural molecules is high in general and the pharmacokinetic profiles and druggability of each molecule are generally not adequate. Therefore, it is ideal to optimize the chemical structure of candidate natural products, using the research tools of medicinal chemistry, so as to manifest the strongest regulatory effect on the production and secretion of mucus to suggest the clinical efficacy, through future research.

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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