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Invited review article

Natural inhibitors on airway mucin: Molecular insight into the therapeutic potential targeting *MUC5AC* expression and production

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ABSTRACT

Airway mucin overproduction is the hallmark risk factor of asthma, which is associated with the reduction of lung function. An aberrant mucin expression is responsible for airway obstruction due to its high viscous characteristics. Among the mucins discovered, *MUC5AC* is the prime mucin of airway epithelia. Nowadays, mucins induced asthma and chronic obstructive pulmonary disease (COPD) are a great concern all over the world. This review focuses on the effects of natural compounds that can be beneficial to explore new drugs to halt MUC5AC secretion and production in airway epithelial, and also their underlying molecular mechanisms based on recent studies. Several researchers are seeking natural sources to identify a new potent *MUC5AC* inhibitory agent for clinical applications, because of countable limitations of existing synthetic drugs. Currently, flavonoids, glycoside and steroids like natural compounds have acquired great attention due to their anti-inflammatory and mucoregulatory effects. Most importantly, many natural compounds have shown their potential effects as the modulator of mucin expression, secretion, and production. Therefore, targeting airway *MUC5AC* expression and production represents an auspicious area of research for the development of drugs against various respiratory diseases.

1. Introduction

The primary reasons to cause different respiratory chronic diseases such as asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis are inflammation in airways and mucus hypersecretion and production [1,2]. More than 500 million people around the world are suffering from severe respiratory disease like asthma. In a day, the air passing amount through the respiratory tract is around 12,000 L, allowing direct exposure of airway epithelium to 25 million particles per hour [3]. Patients with lung disease, mucin originated are susceptible to mortality and morbidity. But till now target oriented effective treatment of mucin hyper-production in the airway of the lung is not acquired [4,5]. This non-specific pharmacotherapy in mucin overproduction triggers arising interest for researchers to develop an effective and potent agent in the treatment of mucin induced asthma.

Mucus is the first line defense barrier of airway epithelial against several types of infectious and environmental agents. The sources of mucus secretion are goblet cells present in an outer epithelial layer [6]. Respiratory mucus is a liquid solution composed of proteins, lipids, and glycoconjugates (i.e., oxidants, electrolytes, antioxidants). As mucus is lining with the outer part of airways, it executes protective mechanism by engulfing and removing inhaled insults (e.g., dust, soot and microbes) from airways by a movement process called mucociliary movement [7]. But the clearance of mucus from airways is also important to maintain homeostatic conditions such as volume between mucus production and evacuation as well as the ciliary beat frequency in the airway epithelia. More mucus production from its normal level in the airway may play a crucial role in the pathogenesis of airway diseases. Mucins are the major component of mucus, produce in the airway epithelia [8]. They are mainly classified into two categories such as transmembrane or membrane-bound (i.e., *MUC1, MUC3A, MUC3B, MUC4, MUC12, MUC16,* and *MUC17*) and secreted/gel-forming mucins (i.e., *MUC2, MUC5AC, MUC5B, MUC6,* and *MUC19*). In normal physiological condition, mucins have diverse functions such as the proliferation of cells, inflammation, immune response, and cell-cell adhesion. But somewhat, abnormal expression of mucins contributes to

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asthma through airflow obstruction and airway hyperresponsiveness [9]. From the above-mentioned information, mucins always remain as a top therapeutic target in the asthma treatment. Until the present, 20 mucin genes have been discovered in mammalian genomes [7,10]. Among them, *MUC5AC* is the first line macromolecular substance, which represents 95% of the total mucin secretion in the airway epithelium [8]. However, any disturbance between the quality and quantity of *MUC5AC* secretion and production leads to welcome an abnormal airway function rather than from its normal physiological function and causes serious airway disease, for instance, asthma and bronchitis [11,12].

Due to structural diversity of mucins, natural compounds from medicinal plants have been important to develop a potent and effective agent. For a few decades, the effects of natural sources in mucin secretion and production have not been studied immensely because of shifting focus towards antibodies success [13]. However, continues changes in an immune system and signaling pathways open the door of limitations and resistance to this kind of target-oriented agents, which push back the focus towards again on natural compounds in case of question come out of mucin dysregulation. At this time, flavonoids, glycoside and steroids like natural compounds have attained countless attention owing to their mucoregulatory and anti-inflammatory effects [14]. In fact, several natural compounds have displayed their potential effects as the modulator of *MUC5AC* expression, and production.

Since *MUC5AC* is an important contributor in the pathogenesis of asthma, inhibition of this mucin from secretion and production can have a powerful impact. In this review, we summarize the effective role of natural compounds on *MUC5AC* gene expression and production and their mode of action as well.

2. *MUC5AC*

The locus of *MUC5AC* is positioned in the middle of *MUC2* and *MUC5B* on chromosome 11p15.5 and the length of this mucin is 17.5 kb long, whereas *MUC5B* length is 10.5 kb. It is composed of N-terminal and C-terminal with large cysteine-rich von Willebrand factor (vWf)-like D-domains exon region at the center [15–17].

Foreign microbes facing respiratory submucosal surface cells, especially goblet cells, are the major sites of *MUC5AC* expression. Although this type of cells expressing mucins, *MUC5AC* gene is highly expressed as compared to others by goblet cells. Goblet cell metaplasia is highly associated with *MUC5AC* overexpression, which indicates the specificity of MUC5AC to goblet cells [18]. Enormous study evidenced that environmental particles, inflammatory cytokines, virus components, and several growth factors are a well-known inducer of *MUC5AC* expression in the airway epithelial cells (Fig. 1).

3. Alteration of *MUC5AC* in respiratory chronic diseases

Mucins are the major macromolecules of mucus and normal function of secretory mucins is to act as a defense system against influxing foreign microbes into the airways. As aforementioned, *MUC5AC* is one of the secretory mucin, which is oversecreted or overexpressed in asthma. It is believed that more dysfunctioning of *MUC5AC* is found in asthma than the other lung disease like COPD [19–22]. *MUC5AC* is consist of a long polypeptide having several cysteine-rich D-domains including D1, D2, D3 and D3 at the N-terminal site and cysteine-rich B, C and CK domains at the C-terminal site [23,24]. It also contains a large mid-section between N-terminal and C-terminal, where O-glycosylation takes place for gel/polypeptide formation [25]. These domains are very crucial for gel-forming properties and polymerization.

MUC5AC is generally fucosylated, which is one type of glycosylation. In asthma, it is highly fucosylated which leads to extending the polymerization of the chain. Because of extensive polymerization, *MUC5AC* facing more difficulties in the separation by sedimentation rate [26]. It has been reported that O-secretor mucin glycan is strongly linked to the asthma exacerbation and COPD, which is very important to gel-forming characteristics of mucins [27,28]. One study showed that asthmatic sputum is highly viscous and elastic and this plug form blocked mucociliary clearance in cystic fibrosis [29].

Several researchers have observed alterations in proteasome-mediated mucin degradation and anti-protease expression in asthma and COPD [30,31]. Moreover, mucus having a high content of *MUC5AC* is strongly associated with tethering which causes aggregation of mucus on airway and impaired mucociliary transport. One possibility of this accumulation of mucus is not fully released of *MUC5AC* from goblet cells. Another is inappropriate post-secretory packaging of mucins. But the mechanism of *MUC5AC* tethering is unknown [32]. The airway lumen pH is also co-related with post-transcriptional alteration of mucin. Many other factors are associated with post-translational modification such as secretory airway luminal environment, disulfide cross-linking (glycosylation) and hydration mediated mucin extension [33].

4. Signaling pathways involved in *MUC5AC* overproduction

Up to date, there are many molecular pathways have been reported, those are involved in abnormal *MUC5AC* secretion and production. Among the established pathways, nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) signaling pathway is considered as a classical pathway that plays a central role in *MUC5AC* secretion and production. Other signaling pathways such as mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 6 (STAT6) signaling are also considered as front line pathways of *MUC5AC* overexpression in airway epithelium. The cAMP response element binding protein (CREB) signaling also has crosstalk with MAPK signaling pathway in terms of *MUC5AC* production (Fig. 2). The molecular mechanisms involved in abnormal *MUC5AC* expression are briefly summarized in the next part.

4.1. NFκB signaling pathway

NFκB is a well-known transcription factor in inflammatory diseases such as asthma, bowel diseases and rheumatoid arthritis [34]. It is already well established that pro-inflammatory cytokine such as tumor necrosis factor-α (TNF-α) secretes by airway epithelial, thought to play a crucial role in *MUC5AC* gene expression and production through activation of the NFκB signaling pathway in airway epithelial cells [35]. Evidence suggested that the presence of high amount of TNF-α has been found in sputum with increased asthma exacerbation [7,10]. A number of signaling pathways (intracellular) can be activated by TNF-α, among them activation of the NFκB signaling pathway is prime attention in the treatment of MUC5AC hyperproduction [36].

NFκB signaling pathway plays a pivotal role in the regulation of *MUC5AC* gene expression in airway epithelial [37]. Briefly, the binding of TNF-α to its receptor (TNFR) is the pre-requisite step to activates adaptors such as TNFR1-associated death domain protein (TRADD), TNFR-associated factor 2 (TRAF2), receptor interacting protein kinase 1 (RIP1) and transforming growth factor-β-activated kinase 1 (TAK1). Further, these adaptors are formed TNFR1 signaling complex (TNF-RSC) and this complex has an essential for the activation of NFκB signaling cascade [38,39]. More clearly, the formation of the TNF-RSC complex leads to recruitment of TAK1 and IκB kinase (IKK) [8,40]. IKK is composed of catalytic subunits (i.e., IKKα and IKKβ) and a regulatory subunit (i.e., IKKγ) [41]. IKK phosphorylates IκBα, an inhibitor of NFκB, starting ubiquitination and consequent degradation of IκBα by the proteasome, which facilitates the releasing of NFκB subunits into the nucleus.

Hence, NFκB is composed of two subunits, a protein of 50 kDa and a protein of 65 kDa, both of which act as a transcription factor. After localization into the nucleus, transcription factor binds with a specific promoter region of the inflammatory gene including *MUC5AC*. Lora et al., [42] observed, both in vitro and in vivo, *MUC5AC* production

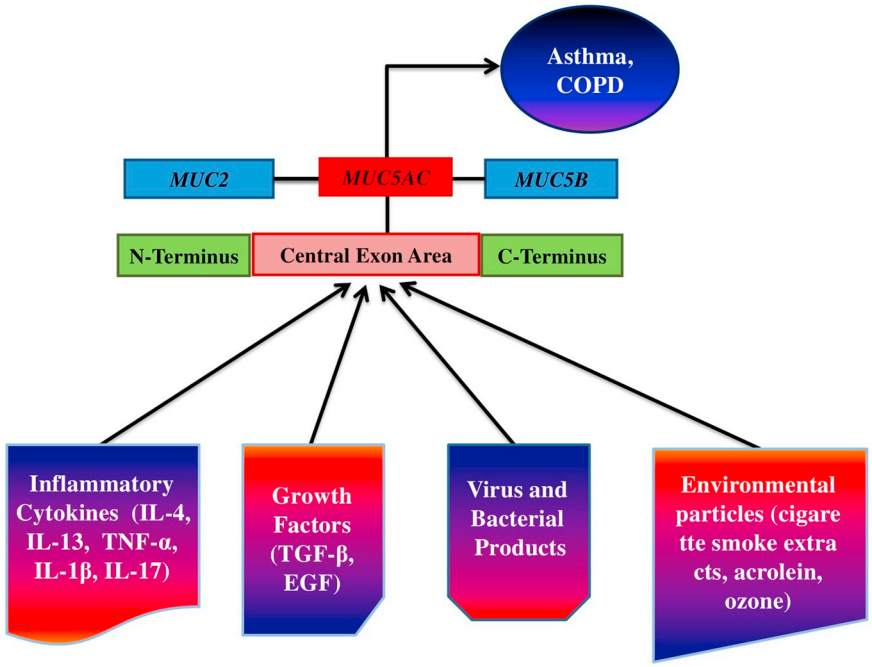


Fig. 1. Structural domains and distinct stimulus of *MUC5AC*.

could be blocked by IKKβ knockdown. One group of researcher reported that *MUC5AC* promoter region has many NFκB binding sites [43]. Some other molecular event like MAPK can also trigger NFκB activation [43]. Moreover, a study demonstrated that induction of *MUC5AC* expression is possible through the mechanism of the extracellular-signal-regulated kinase (ERK) and NFκB activation [38]. A putative NF_kB site (−3594/−3581) in the promoter region of *MUC5AC* is responsible for the induction of ERK and NFκB induced *MUC5AC* gene expression.

An upstream line of NFκB activation, for instance, IKKβ signaling also can be activated by some other pathway like NTHI induced signaling pathway [44]. There is strong evidence that reactive oxygen species (ROS) generation by several stimuli, via NADPH oxidase, activates NFκB signaling pathway to induce *MUC5AC* expression requiring protein kinase C (PKC) activation [8,39]. However, inhibition of NF_kB signaling pathway may reduce many molecular events associated with asthma, particularly in *MUC5AC* gene expression and production.

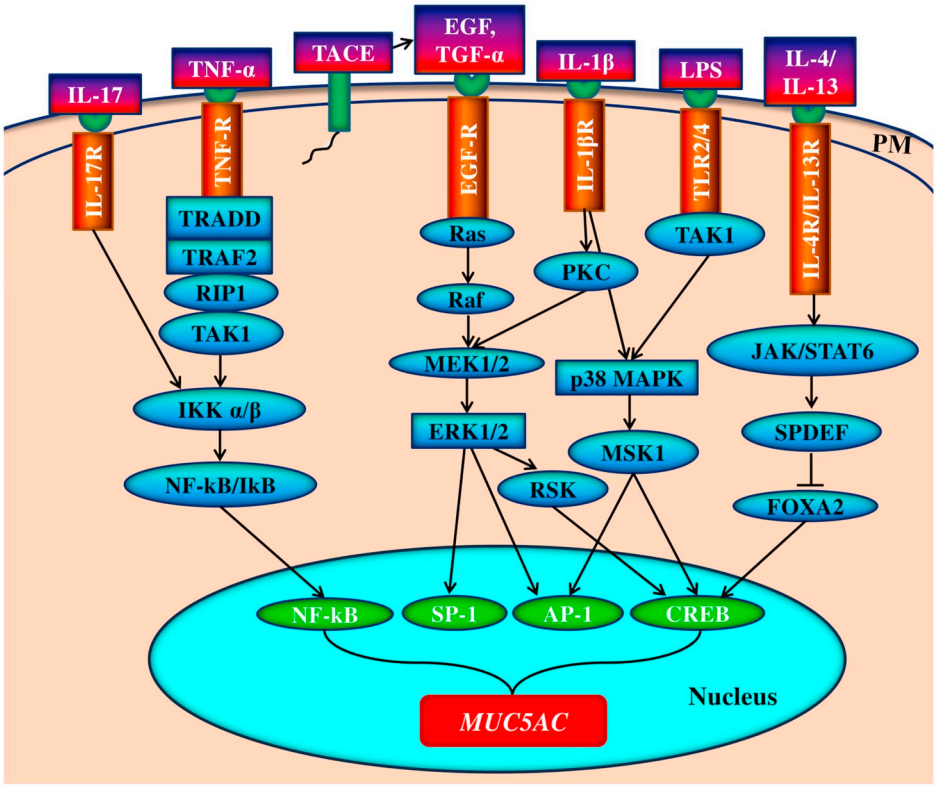


Fig. 2. Major signaling pathways involved in *MUC5AC* expression. IL-17, Interleukin-17; IL-17R, Interleukin-17 receptor; TNF-α, Tumor necrosis factor-α; TNF-R, Tumor necrosis factor-receptor; TRADD, TNFR1-associated death domain protein; TRAF-2, TNFR-associated factor 2; RIP-1, Receptor interacting protein kinase 1; TAK-1, Transforming growth factor β-activated kinase 1; IKK, IκB kinase; NFκB, Nuclear factor kappa-light-chain-enhancer of activated B cells; EGF, Epidermal growth factor; EGF-R, Epidermal growth factor-receptor; PM: Plasma membrane; MEK, Mitogen-activated protein kinase kinase; MAPK, Mitogen-activated protein kinase; TLR2, Toll-like receptor 2; TLR4, Toll-like receptor 4; TACE, Tumor necrosis factor-alpha converting enzyme; TGF-α, Transforming growth factor alpha; IL-4R, Interleukin-4 receptor; IL-13R, Interleukin-13 receptor; ERK, Extracellular regulated kinase; IL-1β, Interleukin-1 beta; IL-1βR, Interleukin-1 beta receptor; PKC, Protein kinase C; RSK, Ribosomal s6 kinase; LPS, Lipopolysaccharide; TLR, Toll-like receptor; MSK 1, Mitogen and stress-activated protein kinase; IL-4, Interleukin-4; IL-13, Interleukin-13; JAK, Janus kinase; STAT-6, Signal transducer and activator of transcription 6; SPDEF, SAM pointed domain containing ETS transcription; FOXA2, Forkhead Box A2; SP-1, Specificity protein-1; AP-1, Activator protein-1; CREB, Cyclic AMP response element binding protein.

4.2. EGFR signaling pathway

Increase in the size of goblet cells is a hallmark of chronic airway diseases like asthma [7]. Growth factors have a great connection with cell proliferation and metastasis. Of the growth factors, epidermal growth factor and its receptors are largely expressed by many cells surfaces including airway cell surface [5]. Epidermal growth factor receptor (EGFR) signaling in airway has also been believed to play a vital role in the expression of the *MUC5AC* gene [7,45]. In asthma, a good number of stimuli, including inflammatory cytokine (TNF-α), proteolytic enzymes (e.g., neutrophil elastase and matrix metalloproteases), ROS and bacterial products, can stimulate the production of *MUC5AC* through the activation of EGFR signaling pathway.

Airway epithelial cells are expressed EGFR and also its ligands like TGF-α on the membrane with their inactive form. In stimulated condition, TNF-α converting enzyme (TACE) is converted to its active form by cleaving pro-tumor growth factor (TGF)-α into its soluble form, which initiates the Ras/MEK/ERK signaling of MAPK cascade. MAPKs enzymes play an important role in the expression of the *MUC5AC* gene in asthma. MAPKs are composed of three subgroups including extracellular signal-regulated kinase (ERK), p38 and c-Jun N-terminal kinase (JNK), and all are having tyrosine residues and serine/threonine kinases [46]. These kinases are strongly associated with several pulmonary diseases such as asthma and COPD.

A previous study reported that the phosphorylation form of MAP kinases is positively co-related to *MUC5AC* gene over-expression through the activation of SP-1 transcription factor [47]. Moreover, it is assumed that the binding of SP-1 to its binding sites (−231/−211, −87/−73 and −192/63) in *MUC5AC* promoter regions are responsible for *MUC5AC* trans-activation in NCI-H292 cell line [46,48]. In addition, ERK has been found as a key regulator for mucin production [46]. Moreover, MAP kinases like ERK and p38 can activate CREB signaling through the activation of p90 ribosomal S6 kinase 1/2 (RSK1/2) which lead to the induction of *MUC5AC* gene expression by binding to their particular sites (−878/−871 and −938/−930) [49–51] in *MUC5AC* promoter region in airway epithelial cells.

Activation of ERK1/2 with JNK dramatically increases *MUC5AC* gene expression via activating another transcription factor such as AP-1, and the binding sites of AP-1 in *MUC5AC* gene promoter region are −3752 and − 3327 in NCI-H292 cells. However, Perrais et al., [48] have demonstrated that MEK/ERK is essential for SP-1 activation, but the role of other kinases, for instance, p38 and JNK, were not clear. Takeyama et al., [7] evidenced that TNF-α enhances activation of EGFR via cleaving pro-ligand TGF-α which helps to direct stimulation of MUC5AC overproduction in both in vitro and in vivo.

Moreover, neutrophil elastase (NE) activates PKC isoforms by recruiting cytosolic components ($p47^{phox}$ and $p67p^{hox}$) to the plasma membrane to generate ROS, which in turn activates TACE downstream pathway for MUC5AC synthesis [8]. Similarly, ROS from cigarette smoke has also the capability to induce *MUC5AC* expression via ERK activation, which further activates transcription factor Sp1 [52,53]. Additionally, ROS from a cigarette also can induce *MUC5AC* expression by not only activating the EGFR/ERK pathway but also through Src/JNK pathway [54].

4.3. IL-13/IL-4/IL-9 mediated STAT6 signaling pathway

Immune cells play an important role in the pathogenesis of asthma by increasing mucins production in airway epithelial cell. Interleukin (IL) 4 and IL-13 are well known T helper cells (Th2) cytokines; those are responsible for accelerating mucus production in asthma. Patients with Th2 induced asthma found that they have a high level of *MUC5AC* mRNA expression levels as compared to control individuals [55]. Of the pro-inflammatory cytokines, IL-13, IL-4, and IL-9 have been enormously observed because of their crucial role in *MUC5AC* production in both in vitro and in vivo. Among them, IL-13 plays a critical role in goblet cell hyperplasia, whereas the role of IL-4 is less clear [56,57]. In a study, only IL-13 knockdown confirms complete inhibition of mucin production, though both of them (IL-4 and IL-13) bind to the same receptor [41]. Hence, STAT6 signaling is activated by the binding of IL-13 and IL-4 to their specific receptor, which leads to phosphorylation of STAT6, an inhibitor of forkhead box A2 (FoxA2).

In a normal cell, FoxA2 blocks the goblet cell hyperplasia by inhibiting *MUC5AC* transactivation, but upon stimulation, STAT6 gets phosphorylated and this phosphorylated form impaired inhibitory activity of FoxA2 in case of *MUC5AC* production. Epithelial cell proliferation was present in FoxA2 knockout mice but opposite results found in the presence of FoxA2. There is strong evidence that IL-13 has a prominent association with the direct induction of *MUC5AC* production in airway epithelial cells [58–60]. However, phosphorylated STAT6, downstream events of IL-13 and IL-4, does not act directly on *MUC5AC* transactivation [61]. One research group demonstrated that there is no clear binding site of STAT6 in *MUC5AC* promoter region in both humans and mouse model [61].

The association between periostin expression (a member of fasciclin-containing family) and IL-13 induced asthma is newly observed [62]. Periostin production is induced by IL-13 through the JAK/STAT6 and MEK/ERK pathways [63]. Despite it has weak effects on mucus secretion [63], Periostin knockout mice could be able to reduce MUC5AC production in human airway epithelial cells [64]. In addition to IL-13, IL-9 and IL-17 have also been associated with *MUC5A*C mRNA expression in airway epithelial cell [65]. IL-9 has been reported as a *MUC5AC* expression inducer in both in vitro and in vivo [66–70], but the role of IL-9 in direct induction of *MUC5AC* gene expression remained controversial [58]. Later, Teman et al., [70] found that the ability of IL-9 in *MUC5AC* overexpression was totally abolished in the absence of IL-13. However, they concluded that *MUC5AC* expression by IL-9 was dependent on IL-13 mediated pathway.

Additionally, among six isoforms of IL-17 such as IL-17 A, B, C, D, E and F [71], IL-17A has also been strongly associated with inflammatory conditions such as asthma and COPD [72,73]. IL-17 is a member of pro-inflammatory cytokines, which accelerates *MUC5AC* gene expression in normal bronchial epithelial (NHBE) cells [58]. By the *MUC5AC* gene expression in airway cells, IL-17 plays a critical role in asthma. Thus, a recent study reported that IL-17A induces *MUC5AC* gene expression through activation of NFκB in airway epithelial cells, and the binding sites of NF_kB in *MUC5AC* gene promoter region are −3594 and −3582 [44].

4.4. IL-1β mediated CREB signaling

IL-1β is a well-known pro-inflammatory cytokine [74], involved in the *MUC5AC* gene overexpression in respiratory epithelial cell line NCI-H292 [49,75,76]. It is secreted by asthmatic epithelial cells and/or immune cells upon exposure to bacterial and viral challenges. Interleukin 1 beta (IL-1β) has two mechanisms to induce *MUC5AC* expression in normal human bronchial epithelial cells (NHBE) such as direct mechanism and indirect mechanism. In the direct mechanism, CREB signaling is activated by PKC/ERK/RSK/CREB pathway [77]. This mechanism induces the expression of cyclooxygenase (COX)-2 which facilitate to produce prostaglandin (PG) E_2, which binds to its G-protein-coupled receptors (i.e., EP-2). This binding leads to the activation of cyclic AMP-dependent protein kinase (cAMP-PKA) mediated downstream signaling of *MUC5AC* gene expression [75].

Unlikely, another report suggested that IL-1β also increases *MUC5AC* expression by acting on immune cells ($CD4^+$) [78]. Prostaglandin F_2 ($PGF2_\alpha$), another major product of COX_2, plays a major role in *MUC5AC* mRNA expression was noticed by Wen et al., [77]. It activates CREB phosphorylation again via $PGF2_\alpha$/FP/PKC/ERK/RSK/CREB pathway. $PGF2_\alpha$ activates CREB signaling in case of longtime treatment compared to short term treatment of EP-2 which acts as an important factor to convert normal non secreting epithelial cells to mucin gene expressing

cells [75]. A previous study showed that IL-1β induced *MUC5AC* gene expression in epithelial cells through ERK and p38 mediated CREB signaling pathway but not through JNK signaling [49].

In addition, ribosomal s6 kinase (RSK) and mitogen and stress-activated kinase (MSK) are two activators of CREB signaling have also been reported in several studies [49,79]. Using different cell lines, culture conditions and treatment time may be the causes of this discrepancy.

5. Natural inhibitors on *MUC5AC* expression and production in airway epithelial

5.1. MUC5AC regulatory effects of naturally derived flavonoids

Flavonoids are derivatives of polyphenolic secondary metabolites which are available in vegetables, fruits, nuts, seeds, roots, barks, and they are common ingredients in daily food intake [80–82]. Flavonoids showed diverse biological effects, among them antioxidant, anti-inflammatory, anti-obesity, anti-diabetic, anti-allergic and anti-carcinogenic effects are well characterized [80–88]. Of the mucoregulatory agents derived from the natural source, quercetin [89], silibinin [90], luteolin [91], apigenin, wogonin [92], kaempferol [93], curcumin, genistein [94], *Panax ginseng* [94], gingerol [95,96] and 7,4′-dihydroxyflavone (7,4′-DHF) [97] were reported for their most potent suppressive activity on *MUC5AC* gene expression, production and secretion in airway epithelial cells.

Yang et al., [89] reported that quercetin, available in apples, berries and onions, attenuated *MUC5AC* mRNA expression at 20 μM by down-regulating NFκB signaling pathway in NCI-H292 cell line. In addition, they confirmed the potent inhibitory activity of quercetin (i.e., 50 mg/kg) on cigarette smoke-induced inflammatory rat model such as mucin synthesis and oxidative stress production in rat airways as well as the release of TNF-α in rat bronchoalveolar lavage fluid (BALF) [89]. In this study, they suggested that rat extinguishing through the abdominal aorta is not a proper way, but perfusing the right ventricle to remove the pulmonary vasculature would be more preferable to get ambitious results. Park et al., [90] found that silibinin, isolated from *Silybum marianum*, reduced *MUC5AC* gene overexpression through diminishing SP-1 expression (reducing ERK phosphorylation) at 40 μg/ml in NCI-H292 cell line as well as at 40 mg/kg in mice exposed to cigarette smoke or lipopolysaccharide (LPS). Similarly, it also reduced IL-6 and TNF-α in rat BALF.

Another group, Lee et al., [91] concluded that luteolin, from *Lonicera japonica* Thumb. and *Chrysanthemum indicum* L. significantly attenuated MUC5AC production and secretion by suppressing nuclear translocation of NFκB 65 by effecting IκBα degradation in the cytoplasm at 20 μM. An early study described the suppressive effects of apigenin and wogonin (i.e., 20 μM), isolated from *Scutellaria baicalensis* Georgi, on *MUC5AC* expression and production in NCI-H292 cell line. But they did not clear about the molecular mechanism of inhibition. However, a recent study showed both of them attenuated *MUC5AC* gene expression and production by interrupting phosphorylation of p38 and p44/42 MAPKs in the same cell line [98].

Kwon et al., [93] screened out the effects of five compounds isolated from *Ginkgo biloba* extract on *MUC5AC* mRNA expression in NCI-H292 cell line. Of the isolated compounds, 40 μM of kaempferol and quercetin effectively reduced *MUC5AC* mRNA expression as compared to others. Moreover, another group has examined the effects of genistein and curcumin, derived from Puerariae *Radix* and Curcumae Longae Rhizoma, respectively, on *MUC5AC* gene expression and production in airway epithelial cell [94]. They found the required concentration to inhibit *MUC5AC* expression and production at 50 μM in NCI-H292 cell line but the underlying mechanism was not elucidated [94].

Conversely, curcumin, like hesperidin of citrus fruits, suppresses *MUC5AC* gene expression at low concentration (i.e., 10 μM) but surprisingly it increases mucin gene expression at high concentration (i.e., 40 μM) [95]. Ginseng, the root of *Panax ginseng*, significantly suppressed *MUC5AC* gene expression at 10 μM via the ERK and p38 MAPKs as well as NFκB dependent signaling pathway have been proclaimed, and they also found that the involvement of COX2, MMP9 and prostaglandin E_2 in mucin gene expression [96]. Lee et al., [91] identified the stimulatory effects of an aqueous extract of *Morus alba* L. (AMA) on mucin secretion from airway in an in vivo model, though isolated compounds, including kuwanon E, kuwanon G, muberrofuran G, and morusin, have inhibitory activity in mucin production.

Kim et al., [96] narrated as gingerol, from *Zingiber officinale* Rosco, is the most effective inhibitor of *MUC5AC* gene expression in respiratory epithelia. They disclosed that the required minimum inhibitory concentration (MIC) of gingerol in *MUC5AC* gene expression was 0.1 μM. Gingerol suppressed the *MUC5AC* expression via modulating the activity of phosphorylated form of ERK and p38 MAPKs induced by IL-1β [95,96]. Despite gingerol reported as an effective inhibitor of *MUC5AC* gene expression, 20 μM of 7,4′-DHF, from *Glycyrrhiza uralensis,* is considered as a most potent inhibitor of *MUC5AC* gene expression, production and secretion by suppressing NF-kB, STAT6 signaling pathways and accelerating histone deacetylase 2 (HDAC2) expression. It was 28 fold more effective compared to that of glycyrrhizin, isolated from *Glycyrrhiza uralensis,* with the IC_{50} value of 1.4 and 38 μM, respectively. 7,4′-DHF abolished *MUC5AC* secretion around 38% in BALF of ovalbumin (OVA)-sensitized mice with very low concentration at 1.5 μM [97]. Along with the above-mentioned agents, resveratrol, prunetin, naringin and trilianin also have suppressing effects on *MUC5AC* gene expression, secretion, and production in airway epithelial cell line NCI-H292 [92,93].

Scutellarin, from the Chinese herb, is the only compound which is clinically safe without having any toxicity in liver and kidney has been reported [94]. Moreover, it has suppressive effects on neutrophil elastase-induced *MUC5AC* production through phosphorylation of protein kinase C (PKC) inhibition but not through IL-13 induced *MUC5AC* production in the bronchial epithelial cell. Role of flavonoids on *MUC5AC* is summarized in Table 1 and Fig. 3.

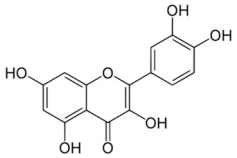
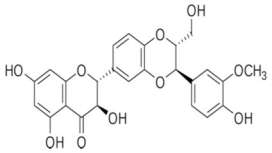
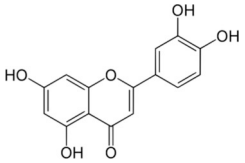
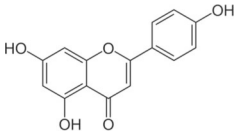
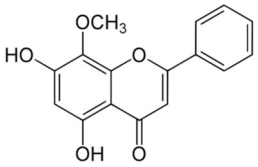
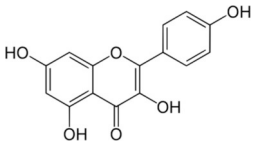
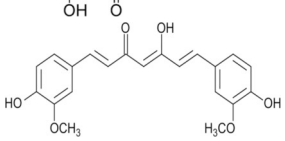
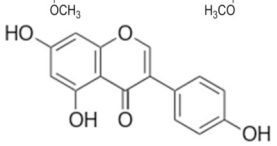
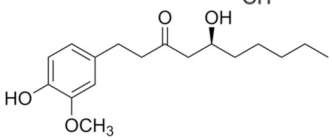
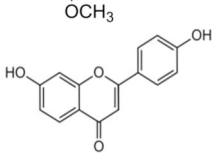
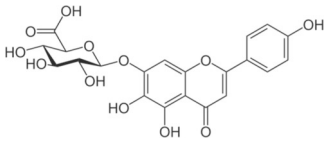
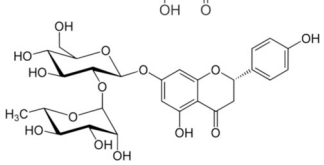
5.2. MUC5AC regulatory effects of naturally derived glycosides

The roots of traditionally used oriental medicinal plants are a rich source of glycosides. Nishimoto et al., [102] described that glycyrrhizin (GL), from *Glycyrrhiza glabra*, potentially attenuated *MUC5AC* mRNA expression and goblet cell hyperplasia induced by IL-4 or LPS in 7 weeks aged mice. They also confirmed the inhibitory effects of GL on *MUC5AC* mRNA and protein expression induced by TGF-α via in vitro study [102]. One research group demonstrated that oleanolic acid and ursolic acid isolated from *Cornus officinalis* Sieb. Et Zucc. suppressed mucin production in NCI-H292 cell line [103], although the underlying molecular mechanism was not figured out. Previously, they also reported these compounds effects on airway mucin release in a cultured hamster tracheal surface epithelial cell [104].

More likely, Yoon et al., [105] also showed that some natural compounds such as lupenone, lupeol, and taraxerol, derived from *Adenophora triphylla*, have effects on *MUC5AC* gene expression and production in airway epithelial cells. In mice, *Callicarpa japonica* Thunb extract significantly reduced TNF-α, IL-6 and ROS generation in BALF. In addition, it also reduced *MUC5AC* expression through inhibiting only ERK phosphorylation but not JNK or p38 phosphorylation and cytokines production in lung cell. Moreover, they suggested that ERK phosphorylation has an inevitable connection with *MUC5AC* production in airway epithelial cells [106]. As of the screening process, Yoon et al., [107] have isolated three compounds, including lobetyolin, lobetyol, and methyl linoleate, from *Codonopsis pilosula.* Among the isolated components, only methyl linoleate showed inhibitory effects on *MUC5AC* production and secretion in NCI-H292 cell line, but they did not clarify the underlying molecular mechanism [107].

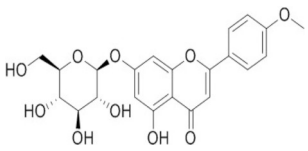
Traditional oriental medicine platycodin D3 and deapi-platycodin, isolated from *Platycodon grandiflorum* A. De Candolle (APG), act as an

Table 1
Outline of the effects of natural flavonoids on *MUC5AC*.

Compound name	Chemical structure	Mode of action	Experimental condition	References
Quercetin		Inhibition of *MUC5AC* through NFκB signaling	NCI-H292 human lung cells	[89]
Silibinin		Inhibition of *MUC5AC* by down-regulation of SP-1 expression through MAPK signaling	NCI-H292 human lung cells and cigarette smoke/LPS induced asthma mice model	[90]
Luteolin		Inhibition of *MUC5AC* through NFκB signaling	NCI-H292 human lung cells	[91]
Apigenin		Inhibition of *MUC5AC*	NCI-H292 human lung cells	[98]
Wogonin		Inhibition of *MUC5AC*	NCI-H292 human lung cells	[98]
Kaempferol		Attenuation of IL-1β induced *MUC5AC* expression	NCI-H292 human lung cells	[93]
Curcumin		Reducing *MUC5AC* expression and production	NCI-H292 human lung cells	[94]
Genistein		Reducing *MUC5AC* expression and production	NCI-H292 human lung cells	[94]
Gingerol		Attenuation of *MUC5AC* expression through MAPK signaling	NCI-H292 human lung cells	[95,96]
7,4′-Dihydroxyflavone		Inhibition of *MUC5AC* expression, production, and secretion via regulation of NF-κB, STAT6, and HDAC2	NCI-H292 human lung cells and allergen-induced mice model	[97]
Scutellarin		Inhibition of *MUC5AC* production	Neutrophil elastase-induced HBE-16 bronchial epithelial cell	[99]
Naringin		Suppression of *MUC5AC* expression and secretion via EGF induced MAPK signaling pathway	A549 human lung cells	[100]

(*continued on next page*)

Table 1 (*continued*)

Compound name	Chemical structure	Mode of action	Experimental condition	References
Tilianin		Inhibition of *MUC5AC* expression through EGF induced MEK-ERK-SP1 signaling pathway	NCI-H292 human lung cells	[101]

expectorant by stimulating mucin secretion from the airway and inhibiting mucin production in the airway cell line. Therefore, they found APG has the same effects on airway in an in vivo model [108]. Previously, Chan et al., [109] documented that the ability of mucin release from airway was more efficient with platycodin D and D3 than others recommended mucolytic medicines, for instance, adenosine triphosphate (ATP) and ambrox, but they did not figure out the exact mechanism of mucolytic action of platycodin D and D3 in rat or hamster. Following enrich natural library for inhibition of *MUC5AC* aberrant expression, chankil saponin (CKS) was isolated, which inhibited *MUC5AC* expression via down-regulating NF-kB through ROS-PKCδ-MAPK signaling pathways in A549 cell line [110]. However, verproside, an iridoid glycoside from *Pseudolysimachion*, is considered as the most potent anti-asthmatic agents among the glycosides. 20 μM of verproside significantly suppressed the *MUC5AC* expression via down-regulating NF_kB signaling pathway in human respiratory epithelial cells [111]. All naturally derived glycosides are compiled in Table 2 and Fig. 3.

5.3. MUC5AC regulatory effects of naturally derived steroids

Terrestrial plant like *Asparagus cochinchinensis* has been used as expectorants and mucoregulators in distinguished respiratory diseases. Dioscin and methylprotodioscin isolated from this plant abolished *MUC5AC* gene expression and production in NCI-H292 cell line [112]. But the molecular mechanism of *MUC5AC* inhibition is not well-established. Researchers suggested examining the bioavailability of these compounds after administration in the systemic circulation [112].

Similarly, coixol, glyceryl trilinoleate, linoleic acid, oleic acid, and β-stigmasterol obtained from *Coixlachryma-Jobi* var. *ma-yuen* suppressed *MUC5AC* gene expression and production [113]. Moreover, carbenoxolone, a steroid-like compound, also strongly inhibited MUC5AC production and gene expression in airway epithelial cells [114]. But Kanoh et al., [115] found that sometimes steroid like agents (e.g., glucocorticosteroids) are not able to inhibit IL-13 induced mucin gene expression and goblet differentiation in airway epithelia. Steroids effects on *MUC5AC* are shown in Table 3 and Fig. 3.

5.4. MUC5AC regulatory effects of naturally derived alkaloids

There are not so many reports on the effects of the alkaloid group on airway *MUC5AC* expression and production. Berberine, a bioactive component, belongs to the group of alkaloid has been reported for its suppressive effects on *MUC5AC* expression and inhibitory effects on MUC5AC production in airway epithelial cells, without showing any effects on the basal secretion of mucin [116]. On the other hand, another study found that berberine moderately induces mucin release from primary hamster tracheal epithelial cell [117]. They suggested

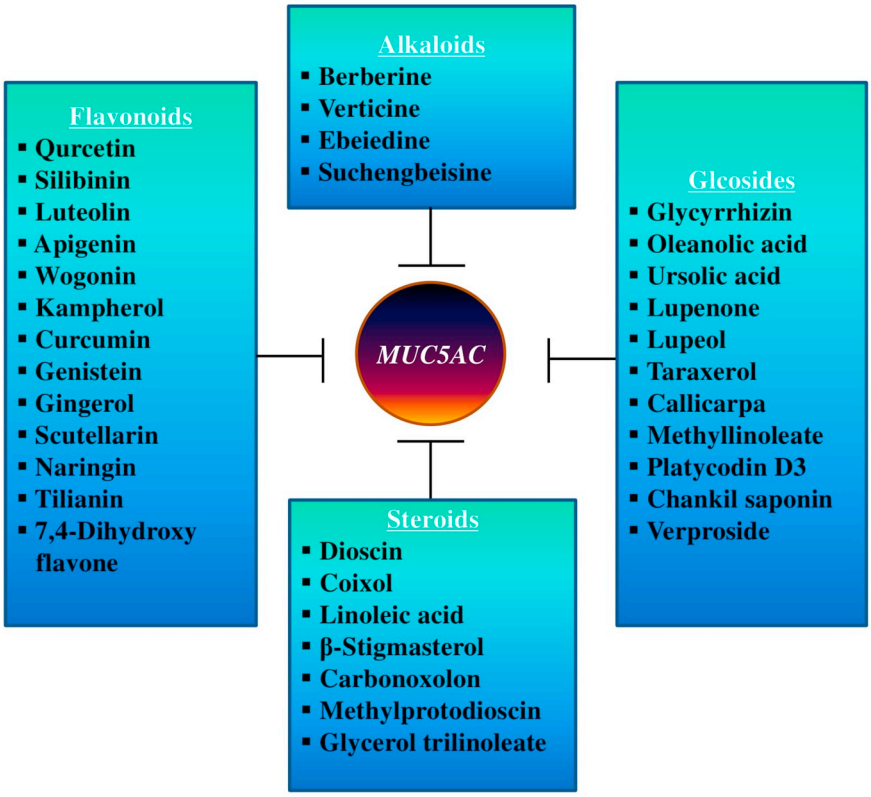
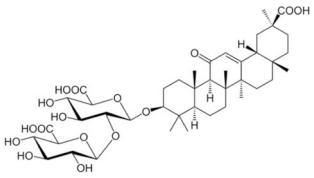
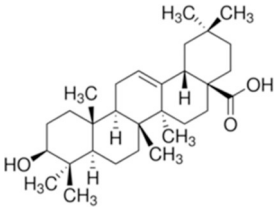
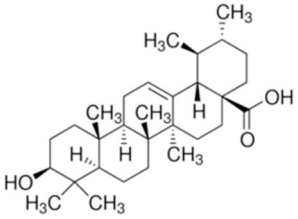
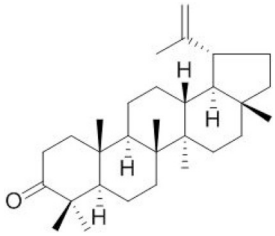
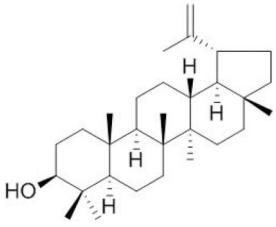
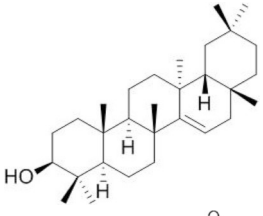
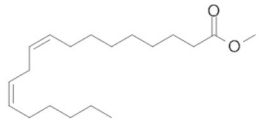
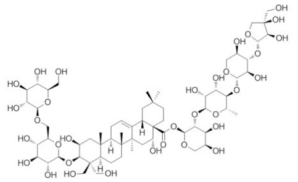


Fig. 3. Natural agents targeting *MUC5AC*.

Table 2
Outline of the effects of natural glycosides on *MUC5AC*.

Compound name	Chemical structure	Mode of action	Experimental design	References
Glycyrrhizin		Attenuation of *MUC5AC* mRNA expression	IL-4 induced mice model and TNF-α induced NCI-H292 human lung cells	[102]
Oleanolic acid		Inhibition of *MUC5AC* expression and production	EGF and phorbol ester-induced NCI-H292 human lung cells	[103]
Ursolic acid		Inhibition of *MUC5AC* expression and production	EGF and phorbol ester-induced NCI-H292 human lung cells	[103]
Lupenone		Inhibition of *MUC5AC* expression and production	TNF-α induced NCI- NCI-H292 human lung cells	[105]
Lupeol		Inhibition of *MUC5AC* expression and production	TNF-α induced NCI- NCI-H292 human lung cells	[105]
Taraxerol		Inhibition of *MUC5AC* expression and production	TNF-α induced NCI- NCI-H292 human lung cells	[105]
Methyl linoleate		Reduced *MUC5AC* expression and production	NCI-H292 human lung cells	[107]
Platycodin D3		Inhibition of *MUC5AC* expression and production	Mice model and NCI-H292 human lung cells	[108]

(*continued on next page*)

Table 2 (*continued*)

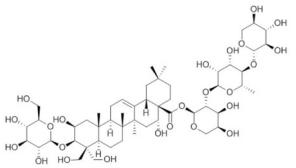
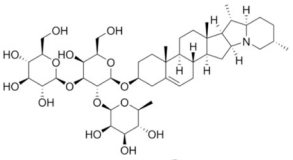
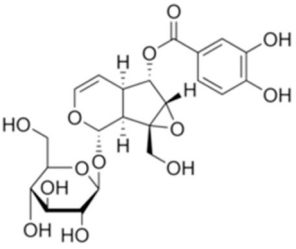
Compound name	Chemical structure	Mode of action	Experimental design	References
Deapi-platycodin D		Inhibition of *MUC5AC* expression and production	Mice model and NCI-H292 human lung cells	[108]
Saponin		Inhibition of *MUC5AC* expression via down-regulating NF-kB through ROS-PKCδ-MAPK signaling pathway	A549 human lung cells	[110]
Verproside		Suppressed the *MUC5AC* expression via down-regulating NFκB signaling pathway	NCI-H292 human lung cells	[111]

Table 3
Outline of the effects of natural steroids on *MUC5AC*.

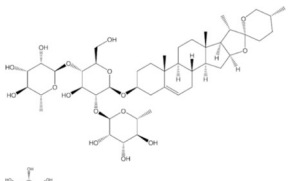
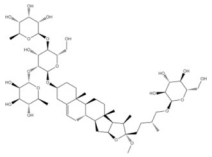
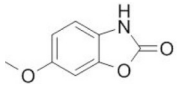
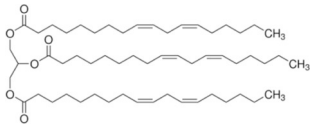
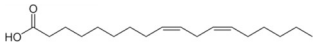
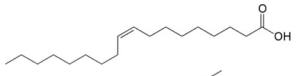
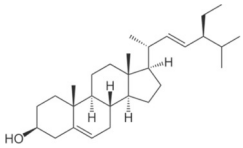
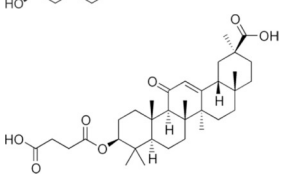
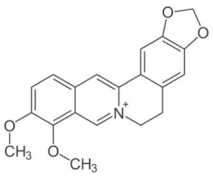
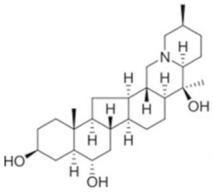
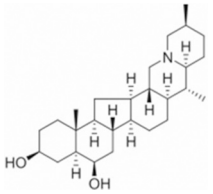
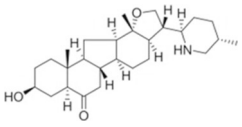
Compound name	Chemical structure	Mode of action	Experimental design	References
Dioscin		Reduction of *MUC5AC* expression and production	NCI-H292 human lung cells	[112]
Methyl protodioscin		Reduction of *MUC5AC* expression and production	NCI-H292 human lung cells	[112]
Coixol		Reduction of *MUC5AC* expression and production	NCI-H292 human lung cells	[113]
Glyceryl trilinoleate		Reduction of *MUC5AC* expression and production	NCI-H292 human lung cells	[113]
Linoleic acid		Reduction of *MUC5AC* expression and production	NCI-H292 human lung cells	[113]
Oleic acid		Reduction of *MUC5AC* expression and production	NCI-H292 human lung cells	[113]
β-Stigmasterol		Reduction of *MUC5AC* expression and production	NCI-H292 human lung cells	[113]
Carbenoxolone		Suppression of *MUC5AC* expression	NCI-H292 human lung cells	[114]

Table 4
Outline of the effects of natural alkaloids on *MUC5AC*.

Compound name	Chemical structure	Mode of action	Experimental design	References
Berberine		Suppression of *MUC5AC* expression and production	EGF, PMA, TNF-α induced MUC5AC production in NCI-H292 cells	[117]
Verticine		Suppression of *MUC5AC* expression and production	EGF, PMA, TNF-α induced MUC5AC production in NCI-H292 cells	[118]
Ebeiedine		Suppression of *MUC5AC* expression and production	EGF, PMA, TNF-α induced MUC5AC production in NCI-H292 cells	[118]
Suchengbeisine		Suppression of *MUC5AC* expression and production	EGF, PMA, TNF-α induced MUC5AC production in NCI-H292 cells	[118]

that berberine can suppress the *MUC5AC* gene through the binding with phospholipase A_2 (PLA_2), which has a crucial role in NF_kB mediated *MUC5AC* induction. The underlying molecular mechanism of this biphasic role of berberine on *MUC5AC* regulation is not clear. More study needs to be carried out on berberine to uncovered its actual mechanism on mucin, as berberine has diverse biological effects such as anti-inflammatory and anti-cancer. Some other compounds, including verticine, ebeiedine, and suchengbeisine, have been isolated from *Fritillaria thunbergii*, as a part of screening [118]. Study found that all of these isolated compounds (Table 4 **and** Fig. 3) suppressed *MUC5AC* expression and production in airway epithelial cells, but they did not elucidate the underlying molecular mechanism. However, the information on alkaloid effects on *MUC5AC* is very limited. Therefore, enormous studies will be needed to screen out potent mucoregulatory agents with fewer side effects and to identify their exact molecular mechanism in cellular and animal model.

6. Anti-asthmatic effects of natural agents on patients with respiratory chronic diseases

There is limited data of the clinical study of the natural agents on the respiratory mucin regulation. As stated earlier, mucins have a crucial role in respiratory tract infection such as COPD. In a clinical study, quercetin reduced respiratory tract infection in middle and older age patients [119,120]. Moreover, quercetin effects on asthma are also summarized by another group [121]. They also mentioned that the long term use of quercetin has no side effects to be appeared [121]. Abidi et al. [122] reported curcumin improves airway obstruction in bronchial asthmatic patients. Picroside II, a constituent of YPL-001, has been developed as botanical agents for COPD. Currently, YPL-001 is under phase-2a clinical trial in COPD. Verproside is metabolized to picroside II in vivo [123]. All of the compounds are derived from a plant named *Pseudolysimachion*. However, verproside could be a potent therapeutic agent in asthmatic patients. Till now, clinical study has not been done of verproside to check its effects in mucin induced asthmatic patients. Some derivatives of oleanolic acid are considered for phase clinical study to evaluate their safety, dose of administration, side effects and other kinetic profiles. Among them, the most effective one is bardoxolone methyl, which is in a clinical trial [124]. Despite some mucomodulatory natural agents have been identified, their clinical effects are remaining compromised due to high toxicity at little high doses as well as poor pharmacokinetic and bioavailability profile. Scientists are trying to overcome these limitations by inviting modification in natural compounds through glycosylating, acylating and formulating the natural product. For instance, curcumin has been encapsulated in nano gels or polymer micelles [125]. However, there is no report of a clinical trial with any natural compounds directly targeting *MUC5AC* in asthma. Copious clinical studies are needed to find out potent mucoregulatory agent from the natural library in terms of controlling mucin-induced asthma.

7. Current gaps and future prospects

Nowadays, controlling mucin expression, production and secretion by natural compounds have become a common interest in asthma treatment. It is now more privilege to understanding the actual mechanism involved in a disease like mucin-induced asthma because of using different cell culture, animal models and updated molecular biology techniques. *MUC5AC* contains so many binding areas in its promoter region those are targeted by several upstream signaling pathways, implicated in mucin aberrant expression. Promoter regions of the mucins could be the mainstream target in terms of targeting their over-expression.

At present, therapeutic agents are very limited in controlling *MUC5AC* expression and secretion, though it is the most prominent mucin in airway epithelia. Corticosteroid is considered as the first line therapy in airway diseases such as asthma, chronic bronchitis, and cystic fibrosis as an anti-inflammatory agent [126,127]. It inhibits mucins production in airway via modulating prostaglandin E2 (PGE_2), synthesized from cyclooxygenase-2 (COX-2) expression. But their

effects in *MUC5AC* gene induced asthma to remain controversial; especially in cytokines (Th2) induced mucin production in airway epithelia. During new drug development, cytokines specific target therapy should be a considerable point to control the abnormal expression of mucins. For instance, the anti-IL-13 antibody showed beneficial effects in case of improving lung function [128].

The molecular mechanism of most of the compounds isolated from a natural source has not been fully elucidated. In some research, despite the good inhibitory activity of natural compounds on *MUC5AC* overproduction has been found, they did not go further clinical trial due to their lower level of bioavailability and pharmacokinetics [129]. From this point, researchers trying to overcome these limitations of natural compounds such as curcumin have already been encapsulated, while some compounds showing toxicity at a little higher dose [130]. Growing chemical and mechanical industries around the globe are an important risk factor for respiratory disease development. For this reason, the availability of airborne particular matter such as transition metal, reactive gases, ions (i.e., sulfate, nitrate) and free radicals are increasing which causes fatal outcome including *MUC5AC* overproduction in asthma. The underlying mechanisms of particular matter-induced *MUC5AC* through cytokines in airway epithelial have not yet been studied. There are a very few studies of steroid inhibitory mechanism on *MUC5AC* gene expression and production. However, flavonoids could be the better choice as a therapeutic approach in *MUC5AC* overproduction.

Till to date, most of the natural *MUC5AC* regulatory agents have been found those are all from the terrestrial plant and microorganism. For several decades, marine resources have been used in the pharmaceutical and cosmeceutical industry. Marine plants are common food habit in East Asia, but surprisingly, very little research work has been carried out to see the effects of any agent isolated from the marine source on *MUC5AC* regulation. Marine sources might be a new approach to discover the new effective agent in *MUC5AC* gene regulation. However, targeting single receptor tyrosine kinase or ligand binding site could be a promising way to inhibit *MUC5AC* overproduction, but not through its secretion. Because inhibition of secretion of *MUC5AC* could lead to mucin accumulation in the airway. This inhibition can be overcome promptly by more powerful stimuli through over flooding mucin into the airways. However, principle mucin inhibition is very important in the treatment of diseases like asthma and COPD, though it always remains a challenge to design this level of selectivity.

8. Conclusion

MUC5AC is the major secretory components of mucus in the airway protective system. Aberrant *MUC5AC* gene expression is a predominating factor for the airway to go under obstruction through tethering or high viscous gel formation. It contains diverse binding elements responsive sites for stimulator (i.e., inflammatory cytokines, growth factors, and other viral agents) in its promoter region. Despite, there are a good number of mucus modulatory natural drugs have been discovered, most of them showed greater drawbacks in terms of pharmacokinetics and pharmacodynamics parameters. Most importantly, uncovering the clear underlying mechanism of *MUC5AC* tethering/plugging and the elements binding sites specific inhibition in the promoter region of *MUC5AC* should be a great concern in the context of developing future drug candidates as mucin modulatory agents.

Abbreviations

COPD	Chronic obstructive pulmonary disease
NTHI	Nontypeable Haemophilus influenza
NADPH	Nicotinamide adenine dinucleotide phosphate
ROS	Reactive oxygen species
IL-17	Interleukin-17
IL-17R	Interleukin-17 receptor
TNF-α	Tumor necrosis factor-α
TNF-R	Tumor necrosis factor-receptor
TRADD	TNFR1-associated death domain protein
TRAF-2	TNFR-associated factor 2
RIP-1	Receptor interacting protein kinase 1
TAK-1	Transforming growth factor–β-activated kinase 1
IKK	IκB kinase
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
EGF	Epidermal growth factor
EGF-R	Epidermal growth factor-receptor
MEPK	Mitogen-activated protein kianse
ERK	Extracellular regulated kinase
IL-1β	Interleukin-1 beta
IL-1βR	Interleukin-1 beta receptor
PKC	Protein kinase C
RSK	Ribosomal s6 kinase
LPS	Lipopolysaccharide
TLR	Toll-like receptor
MSK 1	Mitogen and stress activated protein kinase
IL-4	Interleukin-4
IL-13	Interleukin-13
JAK	Janus kinase
STAT-6	Signal transducer and activator of transcription 6
SPDEF	SAM pointed domain containing ETS transcription
FOXA2	Forkhead box A2
SP-1	Specificity protein-1
AP-1	Activator protein-1
CREB	Cyclic AMP response element binding protein
TACE	TNF-α converting enzyme
JNK	c-Jun N-terminal kinase
NE	Neutrophil elastase
Th2	T helper cells
NHBE	Normal bronchial epithelial
COX-2	Cyclooxygenase-2
PGE2	Prostaglandin (PG) E_2
CD4 +	Cluster of differentiation 4
PGF2	Prostaglandin F_2
EP-2	G-protein-couple receptors
MMP9	Metrix metallopeptidase 9
HDAC2	Histone deacetylase 2
BALF	Bronhcoalveolar lavage fluid
7,4′-DHF	7,4′-Dihydroxyflavone
OVA	Ovalbumin

Authors' contributions

This work was carried out in collaboration between all authors. MS prepared the draft of the manuscript. MSU supervised and reviewed the scientific contents of the manuscript. MAS and BM helped to revise the manuscript. All authors read and approved the final submitted version of the manuscript.

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Declaration of Competing Interest

The authors proclaim no conflict of interest.

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