Unrooting the Potential of Intranasal Administration of Curcumin as a Novel Asthma Controller by Alleviating Airway Inflammation: A Narrative Review

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Abstract Asthma is a chronic disease where air passage of the lung is inflamed and swollen. It is among major non-communicable diseases (NCDs) with more than 339 million sufferers and affects patients' quality of life. Some drugs are currently used to control asthma symptoms, but it has its own economic burden. This literature review to assess the potential use of curcumin to control asthma, as curcumin is cheaper and widely available in Indonesia. A total of eight pieces of literatures were acquired after searching through PubMed, Clinical Key, Scopus, Science Direct, ProQuest, and Wiley Online databases with keywords including "intranasal", "curcumin", "asthma", "inflammation", and "airway". Since inflammation is the most common phenomenon in asthmatics that may lead to airway obstruction, it is important to lessen airway inflammation and thus control asthma. This mechanism can be seen in the administration of curcumin, which although having a wide array of interactions with pathways, is showcased to have an anti-inflammatory effect which is beneficial in asthma. The anti-inflammatory effect of curcumin also negates other pathologic events relevant to asthma and appears to be preventive if administered before exacerbation. Intranasal administration displayed to be the most efficacious in the asthma model, bested the efficacy of standard drugs. Lastly, no toxicity was observed by included studies.

Keywords *intranasal, curcumin, asthma, airway inflammation, controller*

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Introduction

As Asthma is one of the major non-communicable diseases (NCDs) in the world. It is also the most common NCD in children. Asthma is a condition when the air passage of the lung is inflamed and swollen. The burden relies globally on high, low, and middle-income countries, although death often occurs in low and lower-middle-income countries. Patients' quality of life is affected by restriction of activities, attempts to avoid asthma triggers, not to mention that patients are more susceptible to infections. Asthma is an incurable disease, but if treated properly, it can be controlled, and the quality of life will increase. Therefore, finding the right treatment is crucial for the disease.^{1,2}

The focus of this literature review is to assess an alternative treatment, curcumin. In the UK, each patient may use £100 to £500 annually to pay for asthma medication. Stepping down the treatment even may save £17,000,000 for Long-acting beta2-agonists (LABA) or £8,600,000 for Inhaled corticosteroids (ICS) nationwide. A major factor of poor adherence to treatment is the out-of-pocket cost.^{3,4,5}

Currently, curcumin is one of the widely researched phytochemicals. It is said that one of the beneficial effects of curcumin is its role to reduce inflammation, which is highly correlated with asthma pathology. In addition, curcumin may also serve as a cheaper alternative to further decrease the economic burden. Curcumin is also a commonly used spice in Asian cuisine and

has been long used as traditional medicine. Given the diversity and availability of numerous floras in Indonesia, curcumin may take the role as a great alternative. One direct route to the respiratory system is through the intranasal administration. Hence, the authors suggest intranasal administration of curcumin as a treatment to treat asthma.⁶ In this review, we will assess the effect of curcumin, especially administered intranasally, as an anti-asthmatic medication.

Methods

The literature review was assembled by searching, compiling, and analyzing various studies that investigate the administration of intranasal curcumin in airway inflammation and its effect on asthmatic. Search terms that were used include ("Intranasal" OR "inhalable") AND "curcumin" AND ("asthma" OR ("inflammation" AND "airway")). The sources cited from PubMed, Clinical Key, Scopus, Science Direct, ProQuest, and Wiley Online databases were searched for the making of this literature review. The various studies and reviews on intranasal curcumin treatment for asthma then were compiled and analyzed.

Results and Discussions

After doing searches on said databases, we acquired 8 studies that we saw fit with the topic. All of the studies are in vivo studies, using Balb/c mice as its subjects. Overall, the gathered studies show heterogeneity

of molecular targets that underlay the pathology of asthma. However, we also found that despite showcasing different targets, the effect of inhalable curcumin remains homogenous and heading toward a positive direction of having an alleviating effect in asthmatic models. All found studies relevant to this review can be seen in Table 1.^{7,8,9,10,11,12,13,14}

Pathophysiology of Asthma

Pathophysiology and Progression of Asthma

Asthma is a syndrome characterized by variable airflow obstruction. Asthma has a special type of inflammation in the airways that makes them more responsive to a wide range of stimuli or triggers, including allergens and irritants, leading to excessive narrowing with consequently reduced airflow. While narrowing of airways is usually reversible, patients with chronic asthma may have irreversible airflow obstruction. Inflammation causes two major asthmas characteristic pathophysiologic, including bronchoconstriction and airway hypersensitivity. Bronchoconstriction happens when bronchial smooth muscle contraction occurs quickly to narrow the airways in response to exposure to triggers. Consequently, airway hyperresponsiveness can happen when a bronchoconstrictor exaggerates its response to a wide variety of triggers.^{15,16,17}

Persistent inflammation may happen in the airway and causes structural changes that are called airway remodelling, such as smooth muscle hyperplasia, blood vessel

proliferation, infiltration of inflammatory cells, mucus hypersecretion, and subepithelial fibrosis.^{18,19} Smooth muscle hyperplasia occurs by epithelial cells transition to mesenchymal, increasing the smooth muscle content. Epithelial cells lose their cell adhesion and functional polarity with tight junctions, reformatting their cells to develop into mesenchymal cells. Additionally, eosinophils can further exacerbate airway remodelling due to its release of TGF- β and cytokines by interactions of mast cells. These mechanisms of airway remodelling may worsen inflammation and aggravate asthma over time if not treated and managed correctly. As the disease becomes more persistent and inflammation more progressive, other factors further limit airflow, such as mucus hypersecretion and the formation of inspissated mucus plugs, as well as structural changes including hypertrophy and hyperplasia of the airway smooth muscle. Mucus hypersecretion happens when inflammation causes over secretion of mucin components MUC5AC and MUC5B in the airway, and damage to the epithelium, cause the exfoliation of ciliated cells, goblet cell hyperplasia, and submucosal gland hypertrophy, all of which ultimately lead to the airway. Another characteristic finding of remodelling is subepithelial fibrosis which is the thickening of the basement membrane due to subepithelial collagen deposition.^{17,20,21}

Inflammation as The Key Factor of Asthma Progression

The chronic inflammatory response has several effects on the target cells of the airways, resulting in the characteristic pathophysiologic and remodelling changes associated with asthma. This inflammatory mechanism makes the air passages particularly sensitive to irritants and asthma triggers and thus asthma can develop.^{22,23} There are two phases of asthma development including the early phase and late phase. The early phase is initiated by IgE antibodies that are sensitized and released by plasma cells. IgE antibodies respond to certain triggers in the environment and then bind to high-affinity mast cells and basophils. When a trigger such as a pollutant gets inhaled, the mast cells release cytokines, degranulate and in turn, contract the smooth muscle and cause airway tightening. Th2 lymphocytes play an integral role where they produce a series of interleukins, including IL-4, IL-5, IL-13 which aid in communication with other cells and sustain inflammation. IL-3 and IL-5 help eosinophils and basophils survive. IL-13 attributes to remodelling, fibrosis, hyperplasia. The late phase occurs within the next several hours in which eosinophils, basophils, neutrophils, and helper and memory T-cells perform bronchoconstriction and cause inflammation. Mast cells also play an essential role in bringing the late phase reactants to the inflamed sites. It is critical to recognize both of these two mechanisms to target therapy and relieve both bronchoconstriction and inflammation, depending on the severity

of the disease. Inflammation and bronchoconstriction cause an intermittent airflow obstruction, resulting in increased work of breathing in asthma.^{16,24,25}

Formal Treatment of Asthma

Treatment of asthma consists of controller therapy and quick relief therapy. The first is taken daily and long-term to control persistent asthma while the latter is taken upon onset of symptoms to relieve the symptoms.²⁶

Inhaled Corticosteroids as Asthma Controller: An Anti-inflammatory Agent

Inhaled corticosteroids are often used to prevent asthma exacerbations in patients with persistent asthma, in which the patient experiences symptoms more than two days a week, more than three nighttime awakenings per month. The drug can be administered in low, medium, or high doses. Some of the drug examples are beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, and triamcinolone.^{26,27}

The function of corticosteroids is to reduce inflammation. This is done by recruiting histone deacetylase 2 (HDAC2), which reverses histone acetylation, then switches off inflammation genes, and therefore reduces inflammation. At the cellular level, corticosteroids also inhibit the production of chemotactic mediators and adhesion molecules, thereby inhibiting the recruitment of inflammatory cells. Not only that, but corticosteroids also reduce the survival of inflammatory cells like

eosinophils, T-lymphocytes, and mast cells.²⁸

Inhaled corticosteroids have some adverse effects, including local adverse effects, such as dysphonia, oral candidiasis, reflex cough, and bronchospasm. The risks of adverse effects correspond with the dose of the inhaled corticosteroids. Higher the dose, the adverse effects are also more common.²⁸

Reduction in growth velocity is one of the systemic adverse effects associated with inhaled corticosteroids. In some cases, although rare, the systemic adverse effects of inhaled corticosteroids are cataracts, glaucoma, hypothalamic-pituitary-adrenal axis dysfunction, and impaired glucose metabolism. It is also shown that a high dose of inhaled corticosteroids may lead to an increased risk of bone fracture.²⁸

Inhaled corticosteroids are also prohibited to be used in some conditions, such as for people with hypersensitivity to the medication itself or milk proteins/ lactose. The latter is often used as a stabilizer for dry powdered inhalers. Patients with untreated fungal, bacterial, and tubercular infections of the respiratory tract are also better off without this medication.²⁸

Beta2-agonists as Quick Reliever: A Bronchodilator Agent

Beta2-agonists have a bronchodilation effect on asthma. It interacts with G-protein-coupled beta-receptors in smooth muscle cells, mimicking catecholamines. They are used to relieve symptoms due to bronchoconstriction.^{29,30}

Beta2-agonists may be short-acting or long-acting. Short-acting beta2-agonists (SABA) are used for their quick relieving effects of asthma symptoms. Long-acting beta2-agonists (LABA) are only used when the patient has already been using inhaled steroids, but asthma remains symptomatic. Examples of SABA include salbutamol/albuterol and levalbuterol. Generic names of LABA include formoterol fumarate, salmeterol xinafoate, arformoterol tartrate, formoterol fumarate, olodaterol, or combinations.^{31,32}

Excessive use of SABA is implicated in asthma deaths/near-deaths, worse clinical outcomes, and increased degrees of airway reactivity. A review comparing LABA and SABA treatment in adults and children shows that LABA is significantly better. LABA outcomes include lower scores for asthma symptoms during day and night time. Rescue medication used in LABA treatment is also significantly lower.³⁰

Generally, beta2-agonists' most common adverse effects include desensitization of the receptor to the agonist. It may stimulate un-targeted receptors and cause unwanted effects on the cardiac, musculoskeletal, or metabolic system. The examples include arrhythmias, hypokalemia, hypoxemia, and others.³⁰

Besides said adverse effects, there are some concerns relating to the use of Beta2-agonists. The asthma mortality rate is higher compared to the placebo group. Second, if ICS is underused in severe

asthmatic, it can be dangerous. In addition, LABA should not be used as a substitute for ICS and especially should be avoided if the patient experiences significantly worsening asthma.³⁰

Intranasal Curcumin as an Anti-asthmatic Agent

Overview of Curcumin as an Anti-inflammatory Agent

Curcumin, a yellow substance found in turmeric root, is a polyphenol that has been investigated and researched extensively in recent years. These investigations and researches have shown curcumin possesses pleiotropic effects by interacting with various molecular signaling pathways, many of which are responsible for the progressivity and pathophysiology of asthma (Fig. 1).^{33,34} The pleiotropic effects of curcumin, displayed in the summary table, were shown to be beneficial in both chronic and acute models, administered intranasally.

A Summary of Molecular Targets and Interaction of Curcumin.³⁴

Multiple studies included in the summary table portray curcumin to be an excellent anti-inflammatory agent, which is a very substantial aspect of the pathophysiology of asthma. The effective inhibitory effect, better than those of standard drugs (namely dexamethasone and disodium glycate), has been observed as curcumin displayed superior inhibition of proinflammatory cells infiltration in all summarized studies. This superior effect might be contributed to its multiple interactions with the proinflammatory pathway (MAPK, TLR-4, chemotaxis, pro-inflammatory cytokines, NF-κB), as seen in Table 1, which constitute a wide array of inflammatory genes expressions, collectively modulating inflammation.^{7-14,35}

Moreover, curcumin also possesses anti-allergy, anti-airway remodeling, anti-airway hyperresponsiveness, and anti-mucus hypersecretion effects which are relevant in the pathology of asthma as shown in the table. These effects might have originated from the modulation of inflammatory mediators which are underlies and intertwined with other aspects of asthma. For example, a pleiotropic cytokine, TGF-β, which plays an important part in airway remodelling, also acts as a proinflammatory cytokine (along with IL-6).³⁶ Curcumin suppresses the expression of TGF-β along with other proinflammatory cytokines, therefore, not only it serves as both an anti-airway remodelling agent and an anti-inflammatory agent.¹¹

Mechanism of Curcumin as a Potential Asthma Controller (Exacerbation Prophylaxis)

Curcumin serves not only as a direct anti-asthmatic agent but potentially also prophylaxis. A study conducted by Kumari et al showed curcumin possesses a preventive effect against inflammation and airway remodelling by downregulating the expression of TGF- β and iNOS.³⁶ Furthermore, a study conducted by Subhashini et al (2015), displayed curcumin superior effectiveness than that of a conventional preventer drug, disodium cromoglycate, to prevent various inflammatory mediators activities, namely those that belong in MAPK pathways and proinflammatory cytokines, while administered only a tenth of the latter doses intranasally an hour before inducing asthma.⁷ These findings signify the preventive effect of curcumin against exacerbation of symptoms and overall airway health in asthma.

Not only as a disease-modifying agent, but curcumin also promotes healing through its antioxidant activity, as seen in the studies conducted by Kumari et al (2015) and Subhashini et al (2016). These studies have shown the suppression of ROS synthesis which is either absent or minute in a standard drug (dexamethasone).^{13,14} ROS synthesis itself plays a critical role, according to a review conducted by Cho & Moon, as it might contribute to the exacerbation of asthma (by activating Th2 response) if left unattended.³⁷ Moreover, curcumin alleviates pain and mucus hypersecretion which causes major discomfort by inhibiting COX-2 and LOX-2 which are responsible for inflammation

pain.^{9,11,14} These facts further solidify the idea of exploiting the beneficial effect of curcumin as a potential preventer and also reliever in asthmatic patients.

Comparison of Intranasal Curcumin over Other Administration Routes

In asthmatic patients, where the problems originated from the airways, it is axiomatic that the ideal treatment is via inhalation. As the therapeutic agent travels to the lung, it passes through the airways first, thus creating a more localized interaction. Also, this type of administration allows smaller doses, higher efficacy to safety ratio compared to its counterparts, and faster onset of the said agent in diseases originating from respiratory organs.³⁸ This same principle, showcased by Chauhan et al, appears to be the case in the administration of curcumin for alleviating asthma in mice model of chronic asthma. This study showed intranasal administration of curcumin possesses equivalent, if not better effect, measured in IgG, eosinophil peroxidase activity, ROS, and nitrite concentration, than the groups that are administered intraperitoneally with higher concentration (up to 4 times higher) and bioavailability enhancer (piperin).³⁹ Results from Subhashini et al (2013) showed similar results with said study, further validating the fact that a more pronounced result can be achieved by intranasal administration.⁸

However, a study, conducted by Kumari et al, disagrees with the previously mentioned result. Intraperitoneal administration was shown to be more effective to prevent the inflammation

caused by LPS. Despite this, we found the study design of said paper to be different from that claimed by Chauhan et al and Subhashini et al, as asthma was induced by administering LPS intraperitoneally, therefore inducing endotoxemia.⁴⁰ This contradiction might serve as a proof that the activity of curcumin is greatly influenced by its administration route.

Advantages and Possible Disadvantages of Intranasal Curcumin over Current Treatments

Curcumin offers some advantages over the standard drugs that are used regularly in asthma. Possessing pleiotropic effects, it offers a wide array of beneficial effects, which alleviate many aspects of asthma pathophysiology. These effects have been showcased and observed multiple times by included studies. It has also been shown to be more effective than standard drugs (e.g. dexamethasone and disodium glycate) in repressing several important mediators in the pathology of asthma as shown and explained previously. This repression proved to be beneficial as better histological findings and other measurements, such as airway hyperresponsiveness were also found across studies. Lastly, curcumin showcases null toxicity toward the liver and kidney, which is important in treating patients with comorbidity or predisposed to said organs as treatment might be prolonged indefinitely.⁷⁻¹⁴

In addition to its excellent pharmacological properties, curcumin also serves as a cheaper, cost-effective alternative as it is extracted from turmeric, which is produced by a hundred

thousands of metric tons in Indonesia.⁴⁰ This cost-effectiveness might help those who cannot afford standard drugs, as nearly a tenth of the Indonesian population still lives below the poverty line, while still serve as an excellent alternative for currently available adjuvants and preventers.⁴¹ Moreover, the increase of local turmeric production might help the economics of local farmers, which in turn, help the economy and self-sustenance of Indonesia by creating jobs, not only as a raw material producer but also in the refinement industry.

However, curcumin does not come without disadvantages. One of the most prominent is its lack of human trial, thus limiting the strength of evidence leading to curcumin's actual efficacy in the human case of asthma, especially the intranasal administration. Even so, two clinical trials administered curcumin as an oral supplement, both resulted in amelioration and better control of symptoms and attacks.^{42,43} Therefore, further research regarding the efficacy and safety of curcumin, most importantly, in inhalable or intranasal administration, should be conducted for reasons that have been shown and explained previously.

Conclusion and Recommendation

Asthma is one of the major NCDs which inflicts a huge burden on its sufferers, economically and physically. Therefore, a cost-effective solution is needed to ease the economic burden while also effectively controlling asthma. Inflammation, which is an essential pathological event in asthma,

triggers further events, such as airway remodelling and hyperresponsiveness. This event is constituted by cytokines, transcription factors, and receptors that trigger pathways, leading to increased pro-inflammatory gene transcription. Conventional therapy, such as corticosteroids and beta2 agonists, target this pathway. However, these therapies come with several drawbacks and contraindications. Curcumin, which in recent years has been researched extensively, promises high effectiveness in inhibiting inflammation. It possesses unique pleiotropic effects, but positively influences the inflammation and other pathologic events in asthma models across reviewed studies. Not only during inflammation, but it also prevents the progression of inflammation and promotes healing via its antioxidant property, administered before the attack. These promises are further magnified by intranasal administration, as it enables a more localized interaction with the problemated part of the airway. Also, intranasal curcumin was shown to be more effective than standard preventer drugs and other administration routes in all reviewed studies while remaining relatively non-toxic. Moreover, the abundance of curcumin in Indonesia, which is readily extractable from turmeric, further solidifies the reason to consider intranasal curcumin as a cost-effective, highly efficacious controller.

Albeit have been researched and proven to be efficacious for asthmatic patients as a supplement, authors suggest further

research toward intranasal curcumin to confirm its safety and efficacy, such as its long-term effect, as well as its therapeutic dosing in the human body.

Conflict of Interest

None to be declared

Acknowledgment

None to be declared

Abbreviations

NCDs: *Non-communicable diseases*

LABA: *Long-acting beta2-agonists*

ICS: *Inhaled corticosteroids*

TGF- β : *Transforming growth factor beta*

HDAC2: *Histone deacetylase 2*

SABA: *Short-acting beta2-agonists*

MAPK: *Mitogen-Activated Protein Kinase*

TLR-4: *Toll Like Receptor-4*

iNOS: *inducible Nitric Oxide Synthase*

NF- κ B: *nuclear factor-kappaB*

ROS: *Reactive oxygen species*

LPS: *Lipopolysaccharide*

EPO: *Eosinophil Peroxidase*

Table 2. Summary of the Included Studies

No	Author	Subject Characteristics		Intervention Characteristics		Study Outcomes		
		Type of Asthma	Asthma Inducing Protocols	Dosage Forms	Doses	Targeted Mediators/Pathway	Pathophysiologic Changes	Studies Results
1.	Subhashi ni et al, 20157	Acute Asthma	i.p OVA + alum followed by i.n OVA	Curcumin in DMSO (nasal drop)	2.5 mg/kg (i.n) 5 mg/kg (i.n)	(-) MAPK (p-p38, p-ERK, p-JNK) (-) sLPA2 (-) Cytokines (IL-4, IL-5, IFN- γ and TNF- α) (-) COX-2	(-) airway hyperresponsiveness (-) Allergy (-) Inflammation	More effective than disodium cromoglycate in downregulate pro-asthmatic mediators, such as IgE, cytokines (IL-4, IL-5, IFN- γ , TNF- α), and JNK pathway, but not in ERK, p38, and PGD2
2.	Subhashi ni et al, 20138	Acute Asthma	i.p OVA + alum followed by i.n OVA	Curcumin in DMSO	2.5 mg/kg (i.n) 5 mg/kg (i.n) 10 mg/kg (i.p) 20 mg/kg (i.p)	(-) Histamine (-) EPO (=) ALT/AST (=) Creatinine	(-) Allergy (-) Bronchoconstriction (-) Inflammation	Better suppression of allergy mediator, biomarker, and histological findings compared to other groups (including i.p curcumin and dexamethasone) Intranasal curcumin did not show hepato- and nephrotoxicity
3.	Chauhan et al, 20149	Chronic Asthma	i.p OVA + alum followed by i.n OVA	Curcumin in DMSO (nasal drop)	5 mg/kg (i.n)	(-) EPO (-) Histamine (-) Cytokines (IL-4, IL-5 and IFN- γ) (-) IgE (-) Eosinophil	(-) inflammation (-) goblet cell metaplasia (-) mucus hypersecretion (-) allergy (-) airway remodelling	Prevented pro-inflammatory cells infiltration, structural alteration, and airway remodelling Better than dexamethasone in suppressing cytokines (IL-4 & 5, TNF- α) and overall histological findings, pro-inflammatory cells infiltration, but not in EPO and IgE
4.	Chauhan et al, 201610	Chronic Asthma	i.p OVA + alum followed by i.n OVA	Curcumin in DMSO (nasal drop)	5 mg/kg (i.n)	(-) MMP-9 (=) TIMP-1 (-) Eotaxin (=) ALT/AST (=) Creatinine	(-) inflammation (-) allergy (-) airway remodelling	Inhibited inflammatory cells infiltration, structural change, and ECM deposition No hepato- and nephrotoxicity observed
5.	Kumari et al, 201911	Acute Asthma	i.p OVA + alum followed by i.n OVA and LPS	Curcumin in DMSO (nasal drop)	10 mg/kg (i.p)	(-) TLR-4 (-) MMP-9 (-) MAPK (p-Erk, p-JNK, p-p38) (-) COX-2 & LOX-2 (=) ALT/AST (=) Creatinine	(-) inflammation (-) ROS production (-) airway remodelling (-) airway hyperresponsiveness	Better than dexamethasone in suppressing proinflammatory cells infiltration, ROS, MMP-9, COX-2, LOX-2 (peripheral inflammation), (MAPK pathway) and TGF- β , but not in TLR-4, p-JnK No hepato- and nephrotoxicity observed
6.	Chauhan et al, 201812	Chronic Asthma	i.p OVA + alum followed by i.n OVA	Curcumin in DMSO	5 mg/kg (i.n)	(-) NF- κ B (-) COX-2 & LOX-2	(-) inflammation (-) ROS production	Better than dexamethasone in suppressing inflammatory cells infiltration, ROS, and TNF α , but not in inhibition of MAPK pathway, and NF- κ B expression

7.	Kumari et al, 201513	Acute and Chronic Asthma	i.p OVA + alum followed by i.n OVA + i.p LPS	Curcumin in DMSO (nasal drop)	5 mg/kg (i.n) 10 mg/kg (i.n)	(-) EPO (=) MPO (-) Histamine (10 mg/kg) (-) IgE (-) Cytokines (IL-4 & 5, IFN- γ , TNF- α) (-) ROS	(-) inflammation (-) ROS production	Better than dexamethasone in inhibiting inflammatory cells infiltration, ROS, cytokines production, and overall histologic findings but not in suppressing allergy
8.	Subhashi ni et al, 201614	Acute and Chronic Asthma	i.p OVA + alum followed by i.n OVA	Curcumin in DMSO (nasal drop)	5 mg/kg (i.n) before i.n OVA	-	(-) inflammation (-) airway remodelling (-) mucus hypersecretion (-) bronchoconstriction	Prevent peribronchial inflammation, mucus hypersecretion, proinflammatory cells infiltration, and airway remodelling.
Legend of the table: (-) decrease (=) no change (+) increase								

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