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Cordyceps Extracts and the Major Ingredient, Cordycepin: Possible Cellular Mechanisms of Their Therapeutic Effects on Respiratory Disease

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1. Introduction

Cordyceps militaris (CM), also known as the caterpillar fungus, is a well-known, traditional Chinese medicine that can be artificially cultivated on a large scale (Fig. 1). In recent decades, CM extract has been reported to have different biological activities, such as anti-tumor activity (Park et al., 2009) and immunomodulation (Shin et al., 2010). Similar to *Cordyceps sinensis* (CS), an expensive, wild-fruiting species of *Cordyceps*, CM can be used to treat certain respiratory diseases, such as asthma, bronchitis, and chronic obstructive pulmonary disease (COPD) (Paterson, 2008). In contrast to CS, CM can be artificially cultivated on a large scale and hence is much cheaper to produce. While CM has medicinal properties similar to CS, it is widely used as a substitute for CS in health supplements. A recent clinical trial demonstrated that naturally grown and cultivated mycelia of *Cordyceps* are effective for the treatment of asthma (Wang et al., 2007). In addition to the treatment of respiratory diseases, CM has beneficial therapeutic effects for patients with influenza A viral infections (Ohta et al., 2007).

Recently, we demonstrated that the water extracts of both CS and CM can stimulate anion secretion across Calu-3 airway epithelia with similar prosecretory activities (Yue et al., 2008). Calu-3 monolayers have characteristics of both serous and mucus cells and more closely resemble submucosal glands (Shan et al., 2011). Therefore, our recent paper has challenged the traditional belief that natural *Cordyceps* has better therapeutic medicinal value than cultivated *Cordyceps*. We show that the two have similar pharmacological properties in stimulating transepithelial anion secretion in airway epithelia. While both CS and CM have established efficacies for the treatment of pulmonary disorders, the cellular mechanisms that are responsible for the medicinal properties of *Cordyceps* are not entirely clear. The aim of this chapter is to discuss the potential cellular mechanisms and signal transduction pathways underlying the prosecretory action of CS and CM extracts and their major ingredient, cordycepin. We propose that the activation of ion transport processes by *Cordyceps* extracts and cordycepin in airway epithelia may have clinical relevance and partly explain their traditional use in the treatment of respiratory diseases, such as asthma and COPD. In addition, the purported therapeutic effects of CS, CM, and cordycepin may be due

to their anti-inflammatory effects on airway epithelial cells. Asthma is now defined as a chronic inflammatory disorder of the airways, in which many immune cells (e.g. mast cells, eosinophils) are involved. There are many similarities and differences between asthma and COPD, but a full description of their pathophysiology and management is beyond the scope of this chapter.

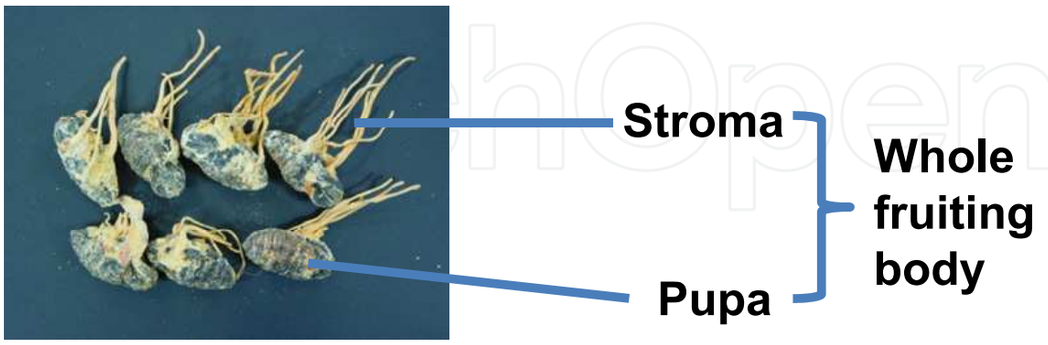

Fig. 1. Photograph of *Cordyceps militaris*, showing the different parts of the fruiting bodies.

2. Ion transport in airway epithelia

2.1 Role of airway epithelia in transepithelial electrolyte and fluid transport

Epithelial cells characteristically grow as distinct sheets that form the anatomical boundaries between the relatively stable internal environment of the body and the constantly changing environment of the outside world. Many epithelia have become specialized to permit the controlled secretion and/or absorption of salt and water. These transport processes can be controlled by hormones and neurotransmitters that bind to specific cell surface receptors. Receptor occupation causes the production of characteristic 'second messenger' signals within the cytoplasm, which then modifies cellular metabolism and evokes ion transport. This regulated transport of salt and water is essential to the integrated function of many organ systems, including the respiratory tract.

The hydration of the normal airway surface is dependent on the active ion transport processes of the airway epithelia, which are highly water-permeable (Chambers et al., 2007). Airway fluid secretion is a passive process that is driven by osmotic forces generated by ion transport. The main determinant of a luminally directed osmotic gradient is the mucosal transport of chloride ions (Cl^-) into the lumen. Airway Cl^- secretion is an energy-dependent process that generates an electrical potential across the mucosal epithelium (i.e., electrogenic). Cations are drawn into the lumen by the established electrochemical gradient, and water loss is an obligatory consequence of the efflux of salt. The coordinated regulation and balance of Cl^- secretion and Na^+ reabsorption, therefore, controls the mass of salt (NaCl) on airway surfaces. This is important in maintaining the thickness and composition of airway surface liquid (ASL), which in turn affects airway mucus clearance (Tarran et al., 2006). Mucus clearance is an important component of the innate defense of the lungs against disease. Abnormal ASL volume, salt content, or mucus clearance can compromise airway immunity and predispose the airway to various respiratory diseases and infection (Danahay and Jackson, 2005).

2.2 Stimulation of Cl^- secretion by cAMP and Ca^{2+}

The mechanism of airway Cl^- secretion is well understood. Increases in cAMP levels activate Cl^- secretion via luminal cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channels (Boucher, 2002). In addition, cAMP also increases basolateral K^+ conductance, probably via K_vLQT_1-type K^+ channels, which hyperpolarize the membrane and increase the driving force for apical Cl^- exit (Bardou et al., 2009). Calcium-activated Cl^- channels (CaCCs) are also involved in Cl^- secretion, and their molecular identity has recently been determined (Caputo et al., 2008). Increases in intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$) lead to the opening of CaCCs and basolateral SK4-type K^+ channels (Bardou et al., 2009), which provide an additional driving force for Cl^- exit through apical Cl^- channels (i.e., CFTR and CaCCs). Therefore, $[Ca^{2+}]_i$ and cAMP are the two major signal transduction cascades involved in the regulation of airway ion transport.

3. Stimulation of ion transport by CM extract and its active ingredient, cordycepin, in Calu-3 and 16HBE14o- cells

3.1 Calu-3 cells

To study the effects of extracts of CS and CM, and its active ingredient, cordycepin, on ion transport activities in Calu-3 epithelia, the cells were grown on permeable supports (Transwell-COL membranes) until confluent (Wong et al., 2009a). Calu-3 cells have many properties of serous cells of the submucosal glands and express the highest levels of natural CFTR of any known immortalized cell line (Haws et al., 1994; Shen et al., 1994). The monolayers were mounted in Ussing chambers and bathed in normal Krebs-Henseleit solution with a basolateral-to-apical Cl^- gradient. An increase in short-circuit currents (I_{SC}), which is an index of electrogenic ion transport, was measured by an electrophysiological technique. Our data demonstrate that extracts of CS and CM, as well as its isolated compound, cordycepin, all stimulate ion transport in a dose-dependent manner in Calu-3 monolayers. Apical application of 300 μg/ml CM extract or 300 μM cordycepin stimulates the highest peak increase in I_{SC}. The transport mechanisms involve both basolateral Na^+-K^+-$2Cl^-$ cotransporters and apical CFTR Cl^- channels for the uptake and exit of Cl^-, respectively (Yue et al., 2008). These data indicate for the first time that extracts of CS and CM, and cordycepin could stimulate transepithelial Cl^- secretion and may therefore promote fluid secretion by human airway epithelial cells. Insufficient fluid secretion leads to airway dehydration, which hampers clearance of secreted mucus and promotes airway inflammatory conditions, such as asthma and bronchitis. In addition, the fluid lining the airway serves as an anatomical barrier between inspired pathogens/particulates and the epithelial surface. Decreased ion transport activity of the surface epithelium may therefore compromise its innate lung defense function and exacerbate airway inflammation (Clunes et al., 2008). Since *Cordyceps* has proven clinically efficacy for treating patients with chronic bronchitis and COPD, the effects observed in promoting Cl^- secretion may partially explain the mechanism that underlies this efficacy.

3.2 16HBE14o- cells

Apart from the recent data on Calu-3 cells, our laboratory has further investigated the cellular signal transduction mechanisms underlying the prosecretory effects of CM extract

and cordycepin in 16HBE14o- cells, an immortalized cell line that was derived from human bronchial surface epithelium (Cozens et al., 1994). It is a good model to study transepithelial Cl^- secretion (Bernard et al., 2003; Bernard et al., 2005), airway inflammation, and airway remodeling (Holgate et al., 1999; Kidney and Proud, 2000; Puddicombe et al., 2000). An electrophysiological technique, similar to that described above, was employed to examine the prosecretory effects of CM extract and cordycepin on 16HBE14o- cells. The involvement of various ion channels located at the apical and basolateral membranes was investigated by pharmacological approaches. Different ion channels inhibitors, such as $CFTR_{inh\text{-}172}$ (CFTR inhibitor), DIDS (Ca^{2+} activated Cl^- channel inhibitor), 293B (cAMP-dependent K^+ channel blocker), etc., were used to delineate the transport mechanism. The involvement of different second messengers, such as Ca^{2+} or cAMP, was examined by fluorescence imaging techniques using specific pathway inhibitors. Our data suggest that CM extract stimulated transepithelial Cl^- secretion in 16HBE14o- cells through apical CFTR Cl^- channels and/or CaCCs. Basolateral cAMP- or Ca^{2+}-activated K^+ channels were activated by CM extract to provide a driving force for apical Cl^- secretion. The underlying signal transduction mechanisms involve both cAMP- and Ca^{2+}-dependent pathways (Fung et al., 2011).

The pharmacological properties of CM have been studied for more than 50 years since cordycepin (3′-deoxyadenosine) was isolated from CM (Cunningham et al., 1950). Cordycepin is a major bioactive component of CM and has been detected in different parts of the CM fruiting body, ranging from 0.16 to 0.25% (w/w) (Yue et al., 2008). In 16HBE14o- cells, apical or basolateral application of cordycepin resulted in a stimulation of I_{SC}, which has been shown to be due to Cl^- secretion (Fung et al., 2011). Both apical and basolateral addition of cordycepin stimulates a concentration-dependent increase in I_{SC} (Fig. 2).

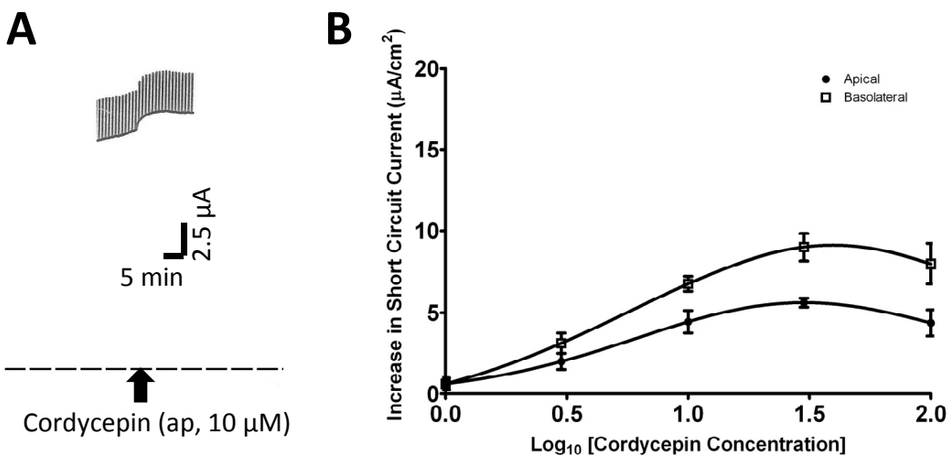

Fig. 2. Stimulation of Cl^- secretion by cordycepin in 16HBE14o- cells. (A) A representative I_{SC} trace in response to cordycepin applied apically to 16HBE14o- epithelia (ap, 10 µM). The horizontal dotted line represents zero I_{SC}. The transient current pulses are the result of intermittently clamping of the potential at 1 mV for the calculation of transepithelial resistance using Ohm's law. The record is representative of six experiments.
(B) Concentration-response curves for changes in I_{SC} in response to cordycepin added either apically or basolaterally. Each point represents the mean ± S.E. for at least six experiments.

In order to ascertain which types of Cl^- and/or K^+ channels mediated the stimulation of Cl^- secretion caused by cordycepin, the CFTR Cl^- channel ($CFTR_{inh172}$) and CaCC (DIDS) blockers as well as the intermediate conductance Ca^{2+}-dependent (TRAM-34) and cAMP-dependent K^+ channel (293B) blockers were used. As shown in Figure 3, the current evoked by cordycepin could be significantly inhibited in the presence of Ca^{2+}- and cAMP-dependent Cl^- and K^+ channel blockers.

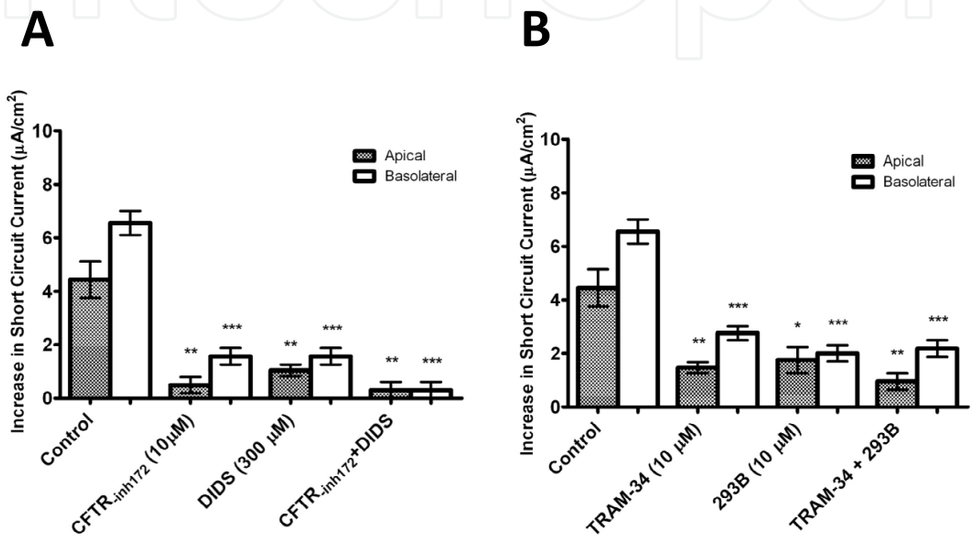

Fig. 3. Effects of Cl^- (A) and K^+ (B) channel blockers on I_{SC} responses to cordycepin. The control was the apical or basolateral application of cordycepin (10 μM) alone. Each column represents the mean ± S.E. (**$p < 0.01$, ***$p < 0.001$, Student's t test compared with control, $n = 4–5$).

The cordycepin-evoked I_{SC} was sensitive to both cAMP- and Ca^{2+}-dependent channel blockers, suggesting that Cl^- secretion was mediated by these two signaling molecules. Indeed, the cordycepin-evoked I_{SC} could be inhibited by the adenylate cyclase inhibitor, MDL-12330A, and the protein kinase A inhibitor, H-89. Adenylate cyclase is responsible for the generation of intracellular cAMP, while protein kinase A is the downstream signaling target of cAMP. Therefore, both CFTR Cl^- channels and cAMP-dependent K^+ channels expressed in 16HBE14o- cells could by stimulated by cordycepin through the activation of the cAMP/protein kinase A signaling pathway (Bleich and Warth, 2000; Li and Naren, 2010). In addition to the activation of the cAMP-dependent pathway, cordycepin evoked a concentration-dependent increase in intracellular [Ca^{2+}] as measured by Fura-2 imaging (Lau et al., 2011) (Fig. 4). Our experimental data, therefore, indicate that cordycepin exerts a similar prosecretory action and activates the same signal transduction pathways, namely Ca^{2+} and cAMP, in human airway epithelia compared with CM extract, suggesting that cordycepin is responsible, at least in part, for the medicinal effects of CM.

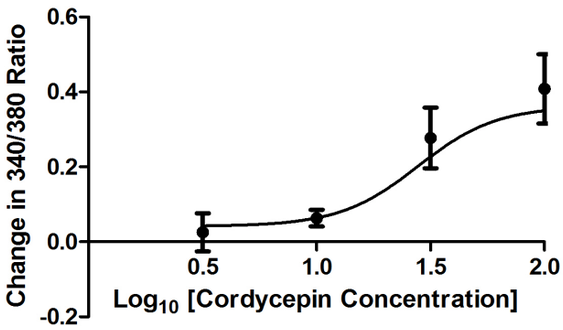

Fig. 4. Concentration-response curve for changes in $[Ca^{2+}]_i$ (represented by 340/380 nm Fura-2 ratio) elicited by cordycepin (in μM). Changes in $[Ca^{2+}]_i$ were plotted against the logarithm of cordycepin concentration (n = 4–9). Each data point represents the mean ± S.E.

4. Anti-inflammatory effects of CM extract

4.1 Role of airway epithelium in inflammation

In addition to the regulation of electrolyte and fluid transport, airway epithelia also play a key role as regulators of inflammation and immunity (Bals and Hiemstra, 2004). The airway epithelium participates in inflammation in many ways. The cells can act as targets that respond to exposure to a variety of inflammatory mediators and cytokines by altering one or several of their functions, such as mucin secretion or ion transport (Adler et al., 1994). Moreover, the surface epithelium itself is responsible for the synthesis and release of cytokines that cause the selective recruitment, retention, and accumulation of various inflammatory cells (Jeffery, 2000). Certain inflammatory cytokines alter the fluid and electrolyte transport of the airway epithelium. Therefore, airway diseases, such as asthma, can be considered diseases of the bronchial epithelium, which could contribute to the pathophysiology of airway inflammation (Holgate et al., 1999).

4.2 Cytokines as bronchial epithelial ion transport regulators

Recent studies suggest that certain inflammatory cytokines affect transepithelial ion transport. The T-helper 1 cytokine, interferon-γ (IFN-γ), inhibits both Na^+ reabsorption and cAMP-mediated Cl^- secretion in human bronchial epithelial cells (Galietta et al., 2000). This is due to the downregulation of epithelial Na^+ channel and CFTR activities. In contrast, IFN-γ upregulates the Ca^{2+}-dependent Cl^- secretion that is stimulated by UTP (Galietta et al., 2000), which binds to $P2Y_2$ receptors (Mason et al., 1991). The net effect is a reduction in fluid absorption, which favors the hydration of mucus secretion. In 16HBE14o- cells, both IL-9 and IL-13 augment UTP-induced Cl^- secretion via the increased expression of hCLCA1, a Ca^{2+}-activated Cl^- channel (Endo et al., 2007). Inhibition of CaCCs by niflumic acid has been shown to control IL-13-induced asthma phenotypes by suppressing JAK/STAT6 activation (Nakano et al., 2006). Therefore, certain cytokines change the balance between fluid absorption and secretion to favor hydration of the airway surface and, consequently, mucus clearance (Galietta et al., 2004).

4.3 Anti-inflammatory effects of CM extract

Both CM and cordycepin have been shown to possess anti-inflammatory activities against *in vitro* and *in vivo* models of inflammation (Cheng et al., 2011; Han et al., 2011; Jeong et al., 2010). CPS-1, a polysaccharide purified from CM extract, was shown to have anti-inflammatory effects in mice, possibly via the suppression of humoral immunity (Yu et al., 2004). Similar anti-inflammatory effects of CM extract and cordycepin were also observed in a study by Won and Park (Won and Park, 2005). CM extract also suppressed intestinal inflammation in an acute colitic mouse model by inhibiting the level of pro-inflammatory cytokine mediators, such as TNFα (Han et al., 2011). In microglia, cordycepin is capable of inhibiting the expression of pro-inflammatory cytokines, such as TNFα and IL-1β (Jeong et al., 2010). However, there have been very few studies addressing the anti-inflammatory effects of *Cordyceps* extracts or cordycepin in the respiratory system. Hsu et al. reported that CM extract can modulate airway inflammation in a mouse model of asthma, but the therapeutic effects are less than those of two commonly used western medicines, namely prednisolone and montelukast (Hsu et al., 2008). On the contrary, a recent randomized, double-blind, placebo-controlled trial in asthmatic children (Wong et al., 2009b) challenged the use of CS extract as an asthma therapy. In this study, children with asthma were treated with a herbal formula of dried aqueous extracts of five herbs containing CS. However, no significant differences were found between the treated group and the placebo group (Wong et al., 2009b). Therefore, there is still controversy over the treatment of asthma using *Cordyceps* extracts.

5. Conclusion

In summary, CM extract stimulates anion secretion from both surface epithelia of the airways (16HBE14o- cells) and submucosal glands (Calu-3 cells). Figure 5 shows the cellular signaling mechanisms underlying the effects of CM extract and cordycepin. Enhancing fluid and electrolyte transport may improve both airway surface hydration and mucus clearance, which becomes hypersecreted in various respiratory diseases, such as asthma and COPD. Therefore, this stimulatory effect of CM extract and cordycepin on major secretory cell types of the upper airways may account for its traditional use in treating different respiratory diseases. Our previous study suggests that 16HBE14o- cells can secrete interleukin- (IL-) 6 and IL-8, two important pro-inflammatory cytokines, towards the mucosal side in a polarized fashion (Chow et al., 2010). This phenomenon may contribute to the pathophysiology of asthmatic inflammation and the development of other inflammatory lung diseases (Chow et al., 2010). Therefore, the therapeutic effects of CM and cordycepin on airway diseases may be attributed to their influences on immune response regulation (Das et al., 2010), although the detailed molecular mechanisms await to be elucidated.

Further study is required to delineate the immunomodulatory effects of CM extract and cordycepin in both normal and diseased airway epithelia. In particular, it would be interesting to determine whether the stimulatory effects on ion transport could be attributed to cytokine secretion. Further experiments are needed to purify and characterize the other active component(s) present in the CM extract and determine the mechanisms of action for their therapeutic effects since the prosecretory action of CM extract is not solely explained by the presence of cordycepin. Calu-3 and 16HBE14o- cells are models for submucosal glands and airway surface epithelium, respectively. The airway consists of different cell

types, such as goblet (mucous) cells, which secrete mucins. Goblet cell hyperplasia or metaplasia is commonly seen in airway diseases, such as asthma, COPD, and chronic bronchitis (Rogers, 2007). It is important to examine whether CM extract or cordycepin has any effect on mucus secretion by goblet cells. Finally, more carefully conducted clinical trials should be performed to evaluate the therapeutic potential of CM extract and its major ingredients in the treatment of respiratory diseases.

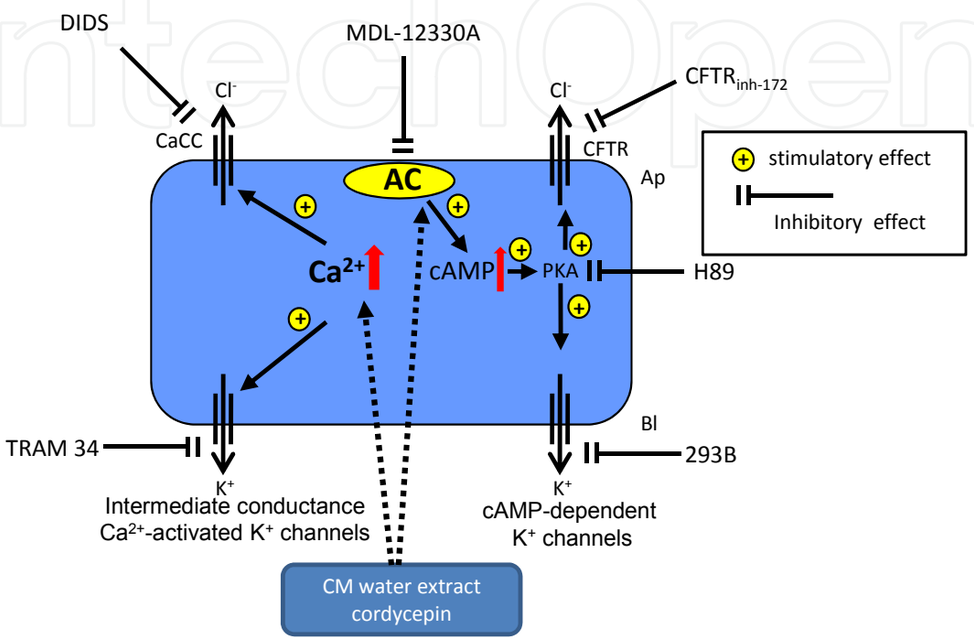

Fig. 5. Cellular mechanisms underlying the prosecretory effects of CM extract and cordycepin.

6. Acknowledgement

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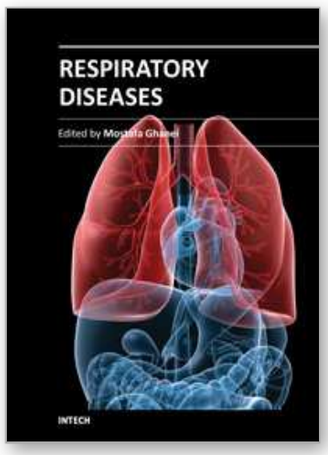

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Medicine is an ever-changing science. In this regard, Respiratory medicine is not an exception and has been evolving during recent years. As new research broadens our knowledge, advanced methods for diagnoses are better understood, providing genetic and underlying pathophysiology of diseases and new clinical experiences. Consequently, publications of new resources along with revisions of previous ones are required. The book Respiratory Diseases brings practical aspects of pulmonary diseases. It contains the result of years of experience through expert clinicians in this field from different scientific centers. The respiratory diseases are discussed according to epidemiology, pathology, diagnosis, treatment, and prognosis. It includes updated resources of the pathogenesis and some molecular aspects of the aforementioned diseases and is recommended reading for all clinicians and medical students, especially pulmonologists, to access highlighted respiratory diseases in this book.

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