APISIO Medika : Jurnal Mahasiswa Kedokteran Universitas Muhammadiyah Malang
Vol. 1, No. 2, August 2023, pp. 59-61

The Potential Of Apples In Preventing Tracheal Goblet Cell Hyperplasia

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Article Info

Article history:

Received March 01, 2023
Revised April 11, 2023
Accepted July 10, 2023

Keywords:

GCH
Smoking
DEPM
Asthma
COPD

DOI :
10.22219/apisio.Vol1.AM2.42240.

ABSTRACT

Background: Goblet cells have a role in producing mucus response to irritant gases, inflammatory mediators, ROS, and changes the biophysical environment. Goblet cell hyperplasia found in e-cigarette exposure is characterized by increased mucus secretion in respiratory tract and tobacco exposure also causes oxidative stress, increases inflammation mucosa. The compounds in apples such as phloretin was found to inhibit goblet cell hyperplasia. **Method**: Literature review 34 journals and 4 textbook. The journal from Google, NCBI and Pubmed, and research materials into new information related to the research objectives. **Result**: Factors that cause goblet cell hyperplasia include exposure to conventional cigarettes, e-cigarettes, diesel exhaust, and pathological conditions such as asthma and COPD. The liquid content (PG / VG) in e-cigarettes was found to have an effect on increasing mucin production (MUC5AC). The content of polyphenol compounds in apples such as quercetin and phloretin can prevent tracheal goblet cell hyperplasia and mucin production. **Conclusion**: Quercetin and phloretin in apples can prevent tracheal goblet cell hyperplasia and mucin production.

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1. INTRODUCTION

Goblet cells play a role in producing mucus in response to irritant gases, inflammatory mediators, ROS (Reactive Oxygen Species), and changes in the biophysical environment [1]. Goblet cell hyperplasia has been found in e-cigarette exposure, characterized by increased mucus secretion in the respiratory trac [2]. Aerosol produced by e-cigarettes has been reported to be contaminated with oxidants and copper ions. E-cigarettes have also been found to cause oxidative stress and an inflammatory response in human lung epithelial cells [3]. On the one hand, e-cigarette users are increasing every year and are popular in various countries. E-cigarette use itself is around 1.2% in Australia for those aged 14 years and over [4]. Since the invention of e-cigarettes in 2003, overall use increased from 3.3% to 8.5% between 2010 and 2013 among adults in the United States. E-cigarette use also increased from 4.6% to 8.2% in 2014 among adolescents aged 11–18 in the United Kingdom. This increase is not limited to active smokers; non-smokers are also trying it [5]. The chemical mixture in e-cigarettes consists of nicotine, propylene glycol, and vegetable glycerin [6]. Exposure to propylene glycol has been shown to increase the number of goblet cells in the respiratory tract and nosebleeds in mice [7]. Goblet cell hyperplasia is often

associated with asthma. This pathological finding is known to be found across all levels of asthma severity and is usually associated with tobacco/conventional cigarette smoking [8]. Goblet cell hyperplasia is also a common phenomenon in COPD (Chronic Obstructive Pulmonary Disease) [9]. COPD itself is a condition involving airway damage caused by oxidative stress [10]. COPD, a major and common respiratory disease, is characterized by progressive and irreversible airflow limitation in subjects exposed to harmful particles and gases, most commonly from conventional cigarette smoke [11].

Through various antioxidants, apples are known to reduce the risk of degenerative and cardiovascular diseases caused by oxidative stress, especially free radicals and ROS (Reactive Oxygen Species). There are 5 main groups of polyphenol compounds found in apples including flavanols (catechin, epicatechin and procyanidins), phenolic acids (especially chlorogenic acid), dihydrochalcones (phloretin glycosides), flavonols (quercetin glycosides) and anthocyanins (cyanidins) [12].

2. METHOD

A literature review method was used, taking references from 34 international journals indexed Q1 and Q2 on Scimagojr and 4 books. Journals were obtained from the search engines Pubmed, ELSEVIER, Wiley, and NCBI.

3. RESULTS AND DISCUSSION

In the study of Ghosh A, et al. (2018) [13] by conducting bronchoscopy on 51 subjects in September 2014 to 2016 targeting smokers, vapor users and non-smokers. It was found that the mucosa in non-smokers showed a different pale pink coloration than smokers and vapor users who showed contrast generally experienced erythematous compared to non-smokers. In this study, vapor was administered with a PG/VG composition mixed with a 55/45 ratio which is a common ratio available in the community. This experiment used 36 puffs per day on HBECs (human bronchial epithelial cultures). In addition, data was obtained that showed exposure to one of the liquid compositions used by vapor, namely PG/VG (propylene glycol, vegetable glycerin), proven by exposure for 30 minutes is enough to increase MUC5AC levels 3 to 4 times. Exposure to PG/VG containing 18 mg/ml nicotine had no effect on MUC5AC expression, suggesting that these changes were driven by PG/VG and not nicotine. Furthermore, subchronic exposure of HBECs to PG/VG was also shown to increase cellular MUC5AC levels. This observation revealed an increase in MUC5AC and MUC4 in vapor users, possibly indicating airway remodeling and causing goblet cell metaplasia/hyperplasia.

Gellatly S. et al. (2020) [14] also conducted a study to determine whether e-cigarette exposure could trigger inflammation. Small airway epithelial cells (SAEC) were exposed to 1 to 15 puffs obtained from heating e-cigarettes of the same brand and flavor as commercially available tobacco. The e-cigarettes were divided into two groups: nicotine-containing and non-nicotine-containing. Interestingly, within 24 hours of e-cigarette exposure, a significant increase in IL-6 was observed in SAECs, compared to non-nicotine-containing and non-nicotine-containing e-cigarettes. Vapors containing nicotine did not experience a significant increase in IL 6.

In line with this research, Czekala L. et al. (2019) [15] conducted a study that found increased IL-6 secretion with increasing doses of conventional cigarettes. At 24 hours, exposure doses of 27 and 45 puffs resulted in 3.4- and 4-fold higher IL-6 levels, respectively, compared to exposure to open air. It is important to note that several cytokines, such as IL-6 and IL-3, can cause increased mucin in large airway epithelial cells [14].

In the study by Gellatly S. et al. (2020) [14], to investigate whether IL-6 is dependent on mucin production, a test was conducted with SAECs exposed to nicotine-free e-cigarettes in the presence of an anti-IL-6 neutralizer/isotype control antibody (IgG). As expected, the anti-IL-6 antibody effectively neutralized IL-6 and inhibited IL-6 detection in ELISA. IL-6 neutralization significantly reduced intracellular MUC5AC protein levels in SAECs exposed to nicotine-free e-cigarettes. This indicates that increased IL-6 contributes to increased MUC5AC levels following exposure to nicotine-free e-cigarettes.

In a study by Jin, S.W. et al. (2020) [16], in their mouse model of allergic asthma, no pathological changes were found in the lungs of control mice. Lungs from mice receiving OVA (Ovalbumin) or OVA plus Diesel Exhaust Particulate Matter (DEPM) showed excessive mucus production with goblet cell hyperplasia, as measured by PAS staining. They also had higher goblet cell proliferation and mucus hypersecretion compared to control mice.

In a study by Reidel B. et al. (2018) [17], increased total mucin concentrations and a shift in the ratio between the major gel-forming airway mucins MUC5B and MUC5AC have been shown to correlate with smoking and the development of COPD. Reidel B. et al (2018) [17] observed that total mucin concentrations in sputum samples were significantly increased (P = 0.04) in smokers (1,986 mg/ml 6810 SD) compared with nonsmokers

(1,251 mg/ml 6964 SD) and that total mucin concentrations in sputum samples of e-cigarette users, although slightly increased (1,322 mg/ml 6663 SD), were not significantly different from those of nonsmokers. Analysis of individual MUC5B and MUC5AC concentrations showed that MUC5B levels were unchanged in the sputum of smokers or e-cigarette users and thus did not contribute to the observed increase in total mucin. MUC5AC concentrations, however, were significantly increased in smokers (132 pmol/ml 658 SD; P = 0.02) and in e-cigarette users (58 pmol/ml 621 SD; P = 0.05) compared with nonsmokers (15 pmol/ml 66 SD). As a result, the MUC5AC/MUC5B ratio was significantly increased in smokers (0.32; P = 0.02) and e-cigarette users (0.34; P = 0.05) compared with non-smokers (0.11).

Several studies have shown that lung diseases such as asthma and chronic obstructive pulmonary disease (COPD) are determined by chronic systemic and local inflammation associated with oxidative stress. Oxidants are known to increase inflammation through the activation of various kinase pathways and transcription factors such as NF-kappa B and AP-1 [18].

The oxidative stress response in vitro to cigarette and vapor exposure was assessed by measuring the release of 8-isoprostane as a biomarker of oxidative stress and antioxidant deficiency [19]. In the study by Czekala L. et al. (2019), tissues exposed to conventional cigarettes produced higher levels of 8-isoprostane depending on the exposure dose. Exposure to 27 and 45 puffs of conventional cigarettes correlated with increased 8-isoprostane levels compared to open-air controls. Furthermore, 8-isoprostane levels were higher at higher doses in conventional cigarettes (27 and 45 puffs) than in vapor. The 8-isoprostane levels of exposure to 27 conventional cigarette puffs were found to be no different from those of 80 unflavored vaporizers. Therefore, it can be concluded that exposure to only 27 conventional cigarette puffs already increases 8-isoprostane levels compared to high-dose vaporizers.

Fruits and vegetables have high antioxidant properties and can protect the lungs from oxidative damage caused by tobacco smoke and potentially prevent Chronic Obstructive Pulmonary Disease (COPD). Among certain foods, consumption of apples, pears, and bananas is strongly associated with an increased risk of COPD. Smokers with low fruit consumption (<1 serving/day) have a 38-fold higher risk of COPD compared to smokers with high consumption (3 servings/day). Former smokers with low fruit consumption (<1 serving/day) have a 13-fold higher risk of COPD compared to smokers with high consumption (3 servings/day) [20].

According to Kschonsek J. et al. (2018) [12], there are five main groups of polyphenolic compounds found in apples: flavanols (catechin epicatechin and procyanidins), phenolic acids (chlorogenic acid), dihydrochalcones (phloretin glycosides), flavonols (quercetin glycosides), and anthocyanins (cyanidin). Samsuzzaman et al. (2019) [21] in their review, citing Yang et al., reported that quercetin, found in apples, berries, and onions, can reduce MUC5AC mRNA expression at 20 μM by decreasing the NFκB signaling pathway in the NCI-H292 cell line. They also confirmed the inhibitory activity of quercetin (e.g., 50 mg/kg) in a mouse model of conventional cigarette-induced inflammation, such as mucin synthesis and oxidative stress production in the mouse airways, as well as TNF-α release in bronchoalveolar lavage fluid (BALF). Quercetin's ability to provide numerous beneficial health effects is claimed, including protection against various diseases such as osteoporosis, lung cancer, and cardiovascular disease. Research shows a reduced risk of cardiovascular disease in subjects with a high flavonoid intake. Chronic obstructive pulmonary disease (COPD), a progressive disorder of the lung parenchyma and airways, is the third leading cause of death in the US. Unfortunately, current therapies for COPD are said to be partially effective with possible side effects. Previous preclinical studies have shown that a fourfold increase in plasma quercetin levels significantly reduces lung inflammation and prevents disease progression. The effects of quercetin and its derivatives on inflammation in an in vivo model suggest that quercetin is a potent anti-inflammatory agent. In vivo studies in mice have reported reduced inflammatory gene expression using a quercetin-enriched diet. In a 12-week clinical trial, quercetin (1000 mg/day) reduced the rate of upper respiratory tract infections in middle-aged and older subjects [22].

In line with Samsuzzaman et al (2019) found in the study of Huang W. et al (2017) [23] Phloretin (PT) is able to reduce eosinophil infiltration in the lungs of asthmatic mice. They also evaluated tracheal goblet cell hyperplasia with PAS (periodic acid-Schiff) staining and found that PT can inhibit goblet cell hyperplasia. In addition, PT also significantly reduced the levels of CCL11, CCL24, TNF-α, IL-6, IL-5, and IL-13 and PT also inhibited IL-4, IL-5, IL-13, MUC5AC, Gob5, iNOS, and COX-2 gene expression. They also found that PT reduced ROS production in BEAS-2B cells activated by TNF-α. Furthermore, they examined intracellular ROS in intact cells with fluorescence microscopy and found that PT attenuated intracellular ROS expression in BEAS-2B cells activated by TNF-α. Research using PT doses (5, 10, or 20 mg/kg) in mice aged 5-8 weeks found that the higher the dose, the less goblet cell hyperplasia was found.

4. CONCLUSION

Goblet cell hyperplasia is caused by conventional cigarettes, e-cigarettes, diesel exhaust, asthma, and COPD, which have been shown to increase mucin (MUC5AC) production. Apples contain polyphenol compounds such as quercetin and phloretin, which can prevent goblet cell hyperplasia and mucin production.

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