Review

The Relations Between Antioxidant Intake and Biomarkers of Bronchial Asthma by Smoking Status

Naser A. Alsharairi *

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The Relations between Antioxidant Intake and Biomarkers of Bronchial Asthma by Smoking Status

Naser A. Alsharairi

Heart, Mind & Body Research Group; Griffith University, Gold Coast, P.O. Box 4222, QLD, Australia; naser.alsharairi@gmail.com

Abstract: Bronchial asthma (BA) is considered a chronic inflammatory disorder associated with airway hyperresponsiveness (AHR). Increased oxidative stress (OS) is a clinical feature of BA, which promotes the inflammatory responses in bronchial/airway epithelial cells. Smokers and nonsmokers with asthma have been shown to have increases in several OS and inflammatory biomarkers. A few studies suggest a relationship between antioxidant intake from diet/supplements and BA in smoking and nonsmoking asthmatics. Dietary carotenoids and vitamin C (VC) intake might reduce BA risk in smokers and/or non-smokers. Evidence is lacking on the protective role of antioxidant vitamin and/or mineral consumption against BA in smokers and nonsmokers with respect to inflammation and OS biomarkers. Therefore, the aim of this review is to highlight current knowledge regarding the relations between antioxidant intake, BA and its associated biomarkers in smokers and nonsmokers.

Keywords: bronchial asthma; antioxidant; vitamins; minerals; supplements; biomarkers; oxidative stress; inflammation; smokers; nonsmokers

1. Introduction

Smoking is regarded as a significant risk factor for asthma progression [1]. The number of asthma deaths due to smoking in 2019 was higher in men than in women [1,2]. Bronchial asthma (BA) is characterized by airway hyperresponsiveness (AHR) and reversible airflow obstruction, which is attributed to increased airway smooth muscle (ASM) contraction [3–5]. BA is associated predominantly with mast/$CD4^+$ cells, T lymphocytes and eosinophils. Mucous hypersecretion, luminal obstruction, goblet cell hyperplasia and thickening of bronchial walls are commonly observed features in BA [3].

Tobacco smoke is associated with reduced lung function measured as forced expiratory volume in 1s (FEV_1), and increased bronchial hyperresponsiveness in smokers with BA [6]. Smoking ≥10 pack/year at age 46 years was associated with a rapid decline in FEV_1 and forced vital capacity (FVC) in asthmatic patients after 12-year follow-up [7]. Secondhand smoke (SHS) exposure has been linked to asthma risk in active and/or former smokers [8]. Exposure to SHS in public places was associated with a marked decrease in peak expiratory flow rate (PEFR) and FVC in asthmatic smokers [9]. The risk of BA among nonsmokers who were exposed to SHS has increased in a large adult-onset asthma population with 16 years of follow-up [10].

Tobacco smoke consists a range of toxic chemicals (e.g., benzopyrene, acrolein, crotonaldehyde, phenols, ammonia, nitrosamines, hydrocarbons, aromatic amines), which are potentially harmful to human bronchial epithelial cells (HBECs), causing airway inflammation by increasing mitochondrial reactive oxygen species (ROS) and pro-inflammatory interleukin (IL)-8 cytokine production [11,12]. Cigarette smoke extract (CSE) exposure in HBECs results in increased oxidative stress (OS) and pro-inflammatory cytokines IL-6, IL-8, and tumor necrosis factor α (TNF-α) by the activation of several inflammatory signaling pathways, including the transcription factor-kappaB (NF-κB), extracellular signal-regulated kinases (ERK 1/2), c-Jun N-terminal kinase (JNK) and mitogen-activated protein kinases (MAPKs) [13]. Tobacco smoke alters immune responses in the lung triggering BA by

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activating Toll-like receptors (e.g., TLR-2 and TLR-4)-stimulated pro-inflammatory cytokine production and increasing total serum immunoglobulin E (IgE) levels in airway epithelial cells [14]. In asthmatic patients, exposure to environmental tobacco smoke (ETS) results in oxidant/antioxidant imbalance, which leads to increased pro-inflammatory biomarkers, as assessed by increased TNFα, IL-6 and IL-8 [14]. Evidence suggests that nicotine is not carcinogenic, but it may affect the airway epithelial cells of asthmatic smokers by activating nitrosamine 4(methylnitrosamino)-1-(3–pyridyl)-1-butanone (NNK), which binds to the α7 nicotinic acetylcholine receptor (α7nAChR), leading to AHR and inflammation by upregulating the α7nAChR-mediated signaling pathways [15].

The genetic variants-tobacco smoke exposure interaction has been shown to increase BA risk in smokers and nonsmokers. Evidence of the interaction between variants of rs9969775 on chromosome 9, rs5011804 on chromosome 12, and active tobacco smoking was reported in asthmatic adults [16]. Genetic variants of NLR Family CARD Domain Containing 4 (NLRP4) inflammasome are implicated in BA exacerbation in current and former adult smokers as evidenced by high genotype-specific expression of rs16986718G [17]. The presence of mutant AG/GG genotype for *CD14* rs2569190 and rs13150331 (TLR) polymorphism in asthmatic adult smokers increases the risk of the disease [18]. Asthmatic non-smokers carrying allele homozygotes of rs1384006 C > T of the OS responsive kinase 1 (*OXSR1*) gene are at higher asthma exacerbation risk than asthmatics smokers [19].

Few studies have evaluated evidence-based treatment for BA in smokers. Pycnogenol®, a herbal dietary supplement-based extract derived from French *Pinus pinaster* bark, is regarded as an option for the treatment of asthma when used in combination with the inhalation corticosteroid (ICS) therapy, resulting in improvement of BA symptoms [20]. Asthmatic smokers have ICS insensitivity as compared to asthmatic nonsmokers, and are less responsive to the benefits of ICS treatment alone. Alterations of inflammatory phenotypes, glucocorticoid receptors, and reduction of histone deacetylase (HDAC) activity are considered potential mechanisms of corticosteroid insensitivity in asthmatic smokers [21,22]. The combination of ICS therapy and a long-acting β2 adrenergic (LABA), displays a better clinical improvement for smoking and nonsmoking asthmatics than using ICS alone [23,24]. The use of nicotine replacement therapy, varenicline or bupropion, may significantly improve lung function and AHR in asthmatic smokers [23].

There is still significant amount of uncertainty in the safety and efficacy of dietary supplements for the treatment of lung diseases among smokers and/or nonsmokers due to limited number of randomised controlled trials (RCTs) [25,26]. Thus, there is a need to focus on the role of antioxidant in smoking-related BA risk. A recent review investigating the effects of dietary antioxidant intake on lung cancer (LC) risk among smokers and nonsmokers suggests that dietary vitamins (C, D, E and carotenoids) and minerals (zinc and copper) may exert protective effects against cigarette smoke (CS)-induced OS and/or inflammation. However, dietary retinol and iron intake did not provide any protection, and research suggests caution in recommending these for LC treatment [27]. There is a direct association between LC and BA in smokers [28,29]. Given that smoking is considered a risk factor for BA through increased levels of OS and inflammatory cytokine production [15], targeting dietary/supplement-derived antioxidants might help our understanding of their role in protecting bronchial/airway epithelial cells against CS-induced-OS/inflammatory biomarkers in smokers and nonsmokers. This paper explores this connection to gain insight into the health consequences of antioxidant consumption, and makes recommendations for future studies. To date, there have been no reviews to evaluate antioxidant intake and the biomarkers of OS and inflammation in BA, according to smoking status.

2. Methods

A literature review in the PubMed/MEDLINE database and Google scholar was conducted for English language studies published between 1 January 2000, and 31 April 2023. The following search terms were used: asthma, diet, supplements, antioxidant, vitamins, minerals, OS, lipid peroxidation (LP), inflammation, biomarkers, antioxidant/oxidant enzymes, bronchial/airway epithelial cells, smokers and nonsmokers. Studies focusing on the chronic obstructive pulmonary disease (COPD) were excluded, as the diagnostic biomarkers in BA are different from both COPD and the BA-COPD

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overlap. All studies relevant to the search terms were included, and the search was not limit to a particular study design.

3. Antioxidant Intake and Its Relationship with BA in Smokers and Nonsmokers

Studies investigating the associations between antioxidant intake and BA in smokers and nonsmokers are limited. Smokers with low dietary vitamin C (VC) intake had chronic bronchitis symptoms associated with BA compared with those who had higher intake [30]. According to quartiles of carotenoid dietary/supplement intake (carotene, lycopene and lutein with zeaxanthin), the risk of BA was reported to be lower in the fourth quartile (≥165.59 μg/kg per day) than the first quartile (<41.43 (μg/kg per day) among current smokers, former smokers and nonsmokers with BA [31]. One trial revealed no effects of 6 weeks of supplemental vitamin E (VE) on AHR in nonsmokers with BA [32]. Supplementation with selenium (Se) had no significant improvement in BA-related quality of life (QoL) and lung function regardless of smoking status [33]. These findings suggest that dietary VC and carotenoids intake may reduce BA in smokers and/or nonsmokers. Supplementation with VE and Se had no effect on BA in smokers and nonsmokers. The associations between antioxidant intake and BA risk are summarized in Table 1.

Table 1. Antioxidants and BA risk in smokers and nonsmokers.

Design	Study population	Antioxidants	Main findings	Ref.
Cross-sectional	Total subjects = 2112 12th grade US students Smokers = 515	VC, VE (diet)	Low dietary VC intake (<110 mg/day) was associated with FEV_1 decline and respiratory symptoms in smokers with BA VE intake was not associated with BA	[30]
Cross-sectional	Total subjects = 13,039 US adults (20-80 yrs) Current asthma=1784; non-current asthma= 11,255 Nonsmokers= 7106; current smokers= 3304; former smokers= 2624	Total carotenoids (diet and supplement)	High intake of carotenoids (≥165.59 μg/kg/day) was associated with reduced BA risk in nonsmokers (OR= 0.63, 95% CI = 0.42 to 0.93), current smokers (OR= 0.54, 95% CI = 0.36 to 0.83) and former smokers (OR= 0.64, 95% CI = 0.42 to 0.97)	[31]
RDBPC	Total subjects = 72 UK nonsmoking asthmatic (18-60 yrs)	VE (supplement) 500 mg VE capsules (D-α-tocopherol) in soya bean oil or matched placebo (capsules, gelatine base) for 6 weeks	VE had no beneficial effects on BA	[32]
RDBPC	Total subjects = 197 UK smoking and nonsmoking asthmatic (18-54 yrs)	Se (supplement) 100 μg/day high-Se yeast	Plasma Se was increased by 48% in the Se group. However, no significant	[33]

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	preparation or matched placebo (yeast only) for 24 weeks	improvement in QoL score was observed in the Se group compared with placebo

Abbreviation: RDBPC, randomized double blind placebo control; VC, vitamin C; VE, vitamin E; Se, selenium; BA, bronchial asthma; QoL, quality of life; OR, odds ratio.

4. Biomarkers of OS and Inflammation in Smoking and Nonsmoking Asthmatics

OS is regarded as the major contributor to CS-induced airway inflammation [34]. Evidence from many studies, mostly derived from cross-sectional and/or longitudinal case-control design, has shown that CS activates OS by augmenting airway inflammation in smoking and nonsmoking asthmatics.

4.1. Smokers

4.1.1. Biomarkers of OS

Asthmatic current smokers showed increased serum levels of malondialdehyde (MDA), and decreased levels of ferric reducing ability of plasma (FRAP) [35]. Higher MDA levels in expired breath condensate (EBC) have been reported in active smoking asthmatics than former smoking and nonsmoking counterparts [36]. The levels of protein carbonyls and peroxynitrite in plasma were reported to be higher in smoking asthmatics than nonsmoking counterparts [37]. Smoking asthmatics with a lower FEV_1 have higher erythrocyte antioxidant enzyme activity, including glutathione peroxidase (GPx), superoxide dismutase (SOD), and reduced OS biomarker glutathione disulfide/oxidized glutathione (GSH) activity than nonsmoking counterparts. Increased antioxidant enzyme activity in smoking asthmatics may protect airway epithelial cells against the harmful effects of free radicals [38]. Active smoking asthmatics exhibit higher pro-oxidant biomarker NADPH oxidase 2 (NOx2) mRNA levels in bronchial epithelial cells, together with increased urinary LP biomarker isoprostane-8-iso prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) as compared to former smoking and non-smoking asthmatics. Smoking asthmatics showed higher levels of hydrogen peroxide (H_2O_2) and NOx in EBC [39].

4.1.2. Biomarkers of Inflammation

Fractional exhaled nitric oxide (FeNO) was reported in lower levels in smoking asthmatics than nonsmoking counterparts. This reduction could be attributed to higher levels of exhaled carbon monoxide in smokers or suppression of nitric oxide synthase (NOS) levels of exogenous nitrite (NO_2) in *tobacco smoke* [40]. Smoking asthmatics had lower FeNO levels than nonsmoking counterparts, but this decrease does not appear to reflect improvement of BA control [41]. When compared with asthmatic smoking groups, FeNO was associated with NOS_2 mRNA levels in active smokers [42]. Current smoking asthmatics exhibit a lower FEV_1/FVC ratio, FeNO value, together with higher blood/sputum neutrophil proportions than nonsmoking counterparts [43,44]. Current smokers with severe asthma have lower FeNO value than former smokers and nonsmokers [45]. Increased FeNO levels have been observed in smokers with uncontrolled asthma, which are associated with percentages of sputum eosinophils [46]. Increased levels of FeNO and blood eosinophil count in current/former smokers with asthma gave a poor to fair prediction of type-2 high status in airway epithelial cells [47].

High-sensitivity C-reactive protein (hs-CRP) was reported to be higher in asthmatic smokers than nonsmokers [48]. Matrix metallopeptidase (MMP-1) and (MMP-9) levels, which mediate CS-induced inflammation, have been observed in higher proportions in the nasal tissues of smoking asthmatics compared to nonsmoking counterparts [49]. Sputum MMP12 mRNA levels were found to be higher in smoking asthmatics than in healthy control [50]. Higher levels of MMP-12, C-X-C motif chemokine ligand-8 (CXCL8), neutrophil elastase, azurocidin 1 (AZU-1) and pro-platelet basic

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protein (PPBP) were observed in the sputum of former smoking asthmatics, which are linked to neutrophilic inflammation [44]. The pro-inflammatory IL-17A mRNA has been detected in higher levels in the nasal tissues of smoking asthmatics than nonsmoking counterparts [51]. Higher sputum eosinophils, eosinophilic cationic protein (ECP), neutrophils and IL-8 levels were observed in asthmatic smokers compared to asthmatic nonsmokers, which were associated with FEV_1 and neutrophil count [52]. Comparatively greater levels of sputum IL-1β, IL-5 and Interleukin 18 receptor 1 (IL-18R1) have been reported in current/former smoking severe asthmatics compared to healthy controls [53]. Current and former smokers with BA have higher frequencies of sputum type 3 innate lymphoid cells (ILC3) which has been identified as a biomarker of airway eosinophilic inflammation, and peripheral blood CD45RO-expressing memory-like ILC3s compared with nonsmokers counterparts. ILC3 was associated with M1 alveolar macrophage and circulating neutrophil counts [54]. Eotaxin as an inflammatory biomarker for the prediction of BA, was found at higher levels in the sputum from smokers than nonsmokers. High levels of sputum eotaxin 2 were associated with sputum neutrophil and eosinophil counts and percentages [55].

Overall findings suggest that the oxidant/antioxidant imbalance derived by CS is likely to exist in smoking asthmatics. OS and inflammation biomarkers are increased in current and/or former smokers, but the increase in the enzymatic antioxidants and the reduction in FeNO levels may be insufficient to protect bronchial/airway epithelial cells against oxidative damage. Figure 1 shows the OS and inflammatory biomarkers in smoking asthmatics.

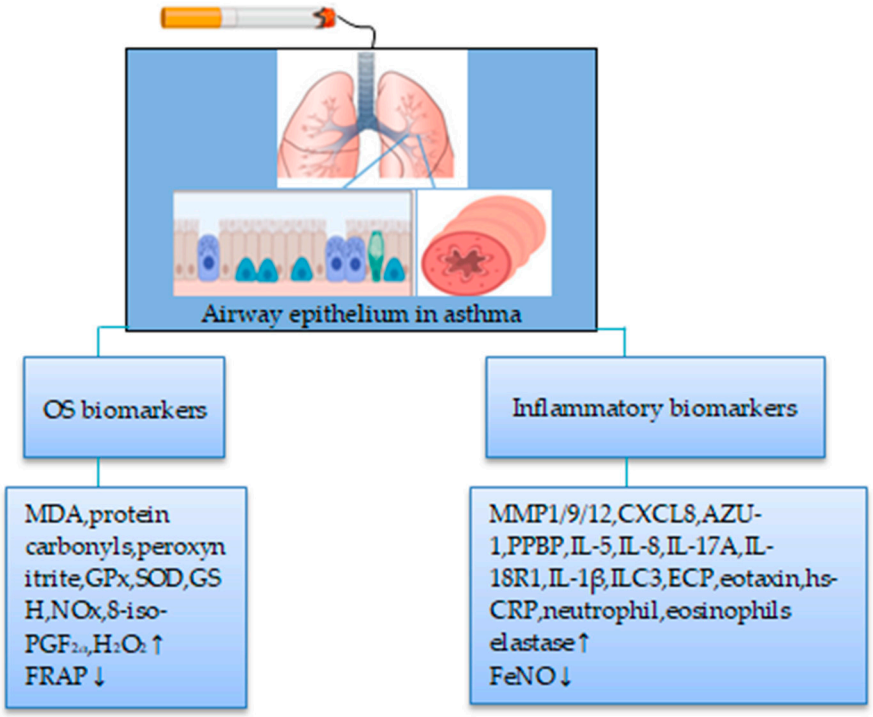

Figure 1. Schematic diagram of the OS and inflammatory biomarkers in smoking asthmatics. Smokers have higher levels of OS and inflammatory biomarkers. High levels of enzymatic antioxidants (GPx,SOD, and GSH) and low levels of FeNO were inadequate to protect smokers from oxidative damage in the airway. (↓) decrease, (↑) increase.

4.2. Nonsmokers

4.2.1. Biomarkers of OS

High sputum GSH and NO_2 levels were reported in nonsmokers with stable and acute BA [56]. Nonsmoking asthmatics demonstrated increased levels of NO_2, protein carbonyls, lipid peroxide,

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SOD activity, and decreased protein sulfhydrils and GPx activity in leukocytes and red blood cells [57].

4.2.2. Biomarkers of Inflammation

Increased levels of FeNO have been observed in the airways of current nonsmoking asthmatics [58,59]. This increase is associated with a decrease in the FEV_1 and FEV_1/FVC ratio [59]. Compared to active and former smokers with asthma, nonsmokers with asthma had higher FeNO levels [60,61]. FeNO and EBC pH values were higher in nonsmokers with uncontrolled BA than those with partly/well-controlled BA [62]. High FeNO levels and blood eosinophil count provide a moderate prediction of type 2 high status in severe asthmatic nonsmokers [47].

Serum periostin, a biomarker of airway eosinophilia inflammation, has been observed in higher levels in nonsmokers than smokers with BA [63]. In asthmatic patients with persistent obstruction where nonsmokers represented the vast majority, high sputum periostin levels were associated with FEV_1 decline and high sputum eosinophil counts, resulting in increased FeNO value, blood eosinophil counts and transforming growth factor beta 1 (TGF-β1) [64]. High serum periostin, TNFα, IL-4, IL-5 and the chitinase-like protein YKL-40 levels, and low serum IL-37 levels were associated with exacerbated BA in nonsmokers [65]. Nonsmokers with BA have significantly elevated sputum and blood eosinophil counts [44]. Compared to healthy nonsmokers, nonsmoking asthmatics demonstrated higher sputum ECP and eosinophil levels [52]. High IL-18 levels in the sputum of nonsmoking asthmatics were associated with FEV_1 decline [66]. Bronchoscopy and Bronchoalveolar Lavavge Fluid (BALF) levels of eotaxin-1 and serum/sputum levels of IL-5 were observed to be higher in nonsmoking asthmatics and smoking counterparts. Higher sputum levels of IL-4, IL-5, IL-1β, Interleukin 1 receptor-like 1 (IL-1RL1), Interleukin 1 receptor, type I (IL-1R1), IL-1R2, IL-18R1 and NLRP3 were detected in nonsmoking severe asthmatics compared to mild-moderate asthmatics and healthy controls [53]. High BALF eotaxin-1 was associated with increased BALF eosinophil and neutrophil counts and percentages [55]. Eotaxin-1 in EBC was associated with blood eosinophil count, FeNO value and serum ECP in nonsmoking asthmatics [67].

Levels of serum IgE used as a biomarker of T-helper 2 (Th2)-driven inflammation were associated with reduced risk of small airway obstruction in nonsmoking asthmatics compared to current and former smoking counterparts [68]. A number of inflammation biomarkers (e.g., IL-6, TNF receptor superfamily member 11a; TNFRSF11A, TGF-β1) have been identified in higher proportions in nonsmokers with severe asthma compared to nonsmokers with mild-to-moderate BA [69]. High levels of peripheral blood ILC2, FeNO, and blood eosinophil counts were associated with sputum eosinophil counts in nonsmokers with mild to moderate BA [70]. Higher serum hs-CRP levels were reported in nonsmokers with mild-to-moderate BA than healthy controls, and were associated with sputum eosinophils and impaired FEV_1 [71,72]. It can be suggested that nonsmoking asthmatics exhibit higher levels of OS and inflammation biomarkers, which have the potential to increase the risk. Figure 2 shows the OS and inflammatory biomarkers in nonsmoking asthmatics.

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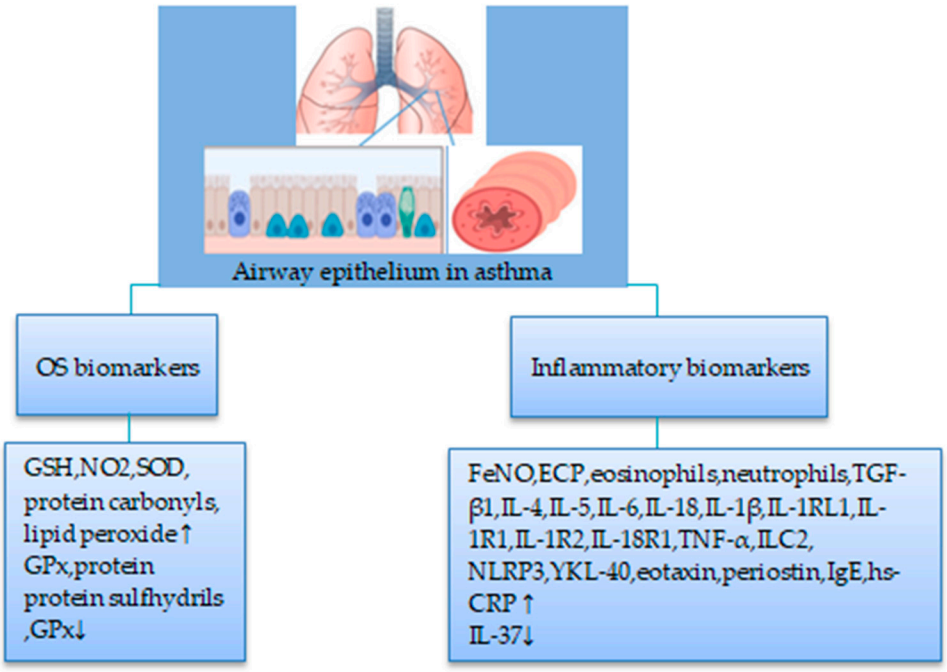

Figure 2. Schematic diagram of the OS and inflammatory biomarkers in nonsmoking asthmatics. Nonsmokers have higher levels of inflammatory than OS biomarkers. (↓) decrease, (↑) increase.

5. Potential Effects of Antioxidant on BA-Associated CS-Induced OS and Inflammation Biomarkers

5.1. Antioxidant Vitamins

5.1.1. Vitamin A

Vitamin A (VA) derived from dietary animal-source foods has an active metabolite retinoic acid (RA), which binds retinoic acid receptors (RARs) and retinoid X receptors (RXRs) with high affinity, resulting in a regulation of ASM cell proliferation in BA [73]. Low RA levels in human ASM cells increases the severity of asthma [74]. ASM cells treated with RARγ-specific agonist and all-*trans* RA (ATRA) lead to inhibition of activator protein-1 (AP-1) and platelet-derived growth factor (PDGF)-stimulated cell proliferation [74]. TGF-β increases the expression of ATRA and 9-*cis* RA in the ASM cells of patients with severe BA compared with those with mild-to-moderate BA, which results in upregulation of the mRNA of β1-integrin, MMP-9 and hepatocyte growth factor receptor (HGF-R). Treatment with anti-TGF-β reduces the levels of MMP-9 mRNA in ASM cells. This concludes that TGF-β increases ASM cell inflammation in response to exaggerated RA receptor expression, which may lead to airway epithelial repair defects in severe BA [75]. Administration of ATRA suppresses PDGF-induced ASM cell migration via RAR-RXR heterodimer activation and Serine-threonine kinase/Phosphatidylinositol-3 kinase (Akt/PI3K) signaling pathway inhibition [76]. Treatment with RA improves barrier strength of HBECs by reducing TNF-α-induced airway barrier leaks, decreased occludin/claudin-4 and increased ERK1/2 activation [77]. ATRA treatment inhibits airway inflammation in vivo but not in in vitro experimental allergic asthma by suppressing Th2 and Th17-related cytokines IL-4, IL-5, IL-17 [78]. Administration of ATRA and 9-*cis* RA suppresses IL-4-induced eotaxin mRNA expression in HBECs [79]. 9-*cis*-RA treatment results in reversing RAR-beta (RAR-β) expression loss in the HBECs of former smokers, suggesting that RA may be considered as a potential agent against BA risk in smokers [80]. Nonsmoker patients with lung emphysema treated with ATRA resulted in improvement in lung function and reduction of airway inflammation through inhibition of TNF-α and IL-3 plasma levels [81]. Overall findings suggest that VA exerts anti-inflammatory effects on ASM/HBECs cells.

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5.1.2. Carotenoids

β-carotene, also termed provitamin A/non-polar carotenoid, and other non-provitamin A/polar carotenoids (e.g., lycopene, lutein, zeaxanthin) are natural pigments present primarily in fruits and vegetables, which have been shown to exert anti-inflammatory/OS agents for several diseases [82], including BA [83]. It has been shown that supplementation of HBECs "BEAS-2B" with β-carotene does not promote membrane LP/lactate dehydrogenase (LDH) leakage and α-tocopherol/GSH depletion caused by gas phase smoke [84]. β-carotene exerts a protective effect in HBECs treated with CS-induced lung carcinogen benzo[a]pyrene (BaP) through increasing RAR-β expression [85].

Lycopene exerts a therapeutic effect against BA in vivo by reducing eosinophilic infiltrates and Th2-mediated cytokines IL-4 and IL-5 production in the airways [86]. An in vitro experiment showed that apo-10'-lycopenoic acid treatment, an active metabolite of lycopene, increases accumulation of nuclear factor-E2 related factor 2 (Nrf2)-mediated heme-oxygenase-1 (HO-1) activation, intracellular GSH levels, and decreases intracellular ROS levels and H_2O_2-induced LDH production in BEAS-2B [87]. Treatment of BEAS-2B with β-cryptoxanthin (BCX) reduces inflammation in vitro, as indicated by increased sirtuin1 (SIRT1) protein levels and inhibited lipopolysaccharide (LPS)-induced TNF-α, MMP2/9, IL-6 and monocyte chemoattractant protein-1 (MCP-1) mRNA levels [88]. BCX supplementation of ferrets led to inhibited CS-induced NF-kB, AP-1 and TNFα expression in HBECs [89]. These findings suggest that β-carotene, lycopene and BCX may protect HBECs against CS-induced inflammation and OS biomarkers.

5.1.3. Vitamin C and E

Epidemiological studies regarding the role of antioxidant VC and VE in the treatment of BA have demonstrated inconsistent findings [90]. The ascorbic acid supplemented diet has been shown to reduce the bronchoconstrictive responses in asthmatic patients, as demonstrated by decreasing post-exercise FeNO, FEV_1, and urinary 9α, 11β-PGF2 levels [91]. Administration of VC to ovalbumin (OVA)-sensitized and challenged asthmatic mice attenuates airway inflammation by reducing eosinophilic infiltration into BALF [92].

VE treatment reduces BaP-induced ROS levels by downregulating poly[ADP-ribose] polymerase 1 (PARP-1) and protein 53 (p53) activity in BEAS-2B [93]. Treatment with natural-source d-α-tocopheryl acetate increases plasma levels of α-tocopherol isoform of VE in atopic asthmatics, resulting in reduced BAL levels of IL-3 and IL-4 [94]. In allergic asthmatic adults, γ-tocopherol treatment led to suppression of LPS-induced JNK phosphorylation and Inhibitory kappa B kinase (IkBα) degradation [95]. In human and mice models, supplementation with γ-tocopherol reduced LPS-induced sputum percentages of neutrophils and eosinophils [96]. γ-tocopherol supplementation reduces sputum mucins and eosinophils in mild asthmatics compared to healthy controls [97]. VE-supplemented diet results in decreased IL-4 and IL-5 levels in the bronchial epithelial cells of mice [98]. Treatment with VE attenuates AHR in asthmatic mice through reducing OS and inflammatory biomarkers, as indicated by decreasing LPS-induced IL-5, IL-13 levels, H_2O_2-mediated ROS production, and increasing Nrf2 levels [99]. Administration of VE reduces exacerbated OVA-induced asthma in mice by decreasing IL-4 levels, ROS producing, serum IgE levels, and increasing GSH levels [100]. VE treatment of OVA-sensitized allergic asthma murine model reduced levels of 8-iso-PGF2α, NO_2, IgE, eotaxin, TGF-β1, IL-4, IL-5 and IL-13 [101]. In mice models of asthma, administration of supplemental α-and γ-tocopherol resulted in reduced BAL IL-5, IL-12 and IL-13 levels [102]. This suggests that VC may reduce airway inflammation, while VE may have protective effects against both OS and inflammatory biomarkers.

5.1.4. Vitamin D

Evidence from in vitro and in vivo studies has supported the protective role of VD against BA, by which VD supplementation reduces airway inflammation and improves lung function in asthmatic patients [103]. VD treatment has been shown to decrease IL-6 levels in cultured HBECs from asthmatic donors [104]. In asthmatic patients, supplementation with VD increases serum anti-

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inflammatory IL-10, and decreases serum levels of IgE, eosinophil, IL-5, IL-9, and IL-13 [105]. Supplementation with VD reduces OS in a murine model of OVA-stimulated asthmatic airway inflammation, as evidenced by decreased levels of IL-4 in BALF and NO_2 in serum and BALF [106]. In an asthmatic mouse model, VD treatment decreases the index of airway collagen deposition, mucus reserve, and increases autophagy-related protein expression levels of hypoxia-inducible factor 1 alpha (HIF-1α) and neurogenic locus notch homolog protein 1 (Notch1), resulting in reduced airway inflammation associated with IL-6 and IL-17 cytokines [107]. Supplementation of VD reduces AHR and IgE levels in BALF and serum in asthmatic mice [108]. Administration of VD to VD-deficient mice with asthma reduces BALF levels of neutrophil, eosinophil, IL-5 and IL-13 [109]. In a mouse model of allergic asthma, it has been demonstrated that 1,25(OH)(2)D(3) supplementation reduces serum OVA-specific IgE levels, accompanied with increased serum levels of IL-10 and TGF-β1 via inhibition of NF-ĸB signaling pathway [110]. It has been shown that VD-supplemented OVA-sensitized and challenged mice with asthma reduce BALF eosinophil numbers, BALF IL-6, IL-17, TNF-α levels, and increase BALF IL-10 levels [111]. In asthmatic mice, VD was found to reduce serum levels of IL-6, IL-1β, TNF-α, and increase serum levels of IL-10 through downregulating high mobility group box 1 proteins (HMGB1)/TLR4/NF-κB signaling pathway [112]. Overall findings suggest that VD may have anti-inflammatory/oxidants effects on HBECs, due to its ability to reduce inflammatory/OS biomarkers, which may therefore be involved in CS-induced BA treatment.

The potential effect of antioxidant vitamins on BA-associated CS-induced biomarkers was shown in Figure 3.

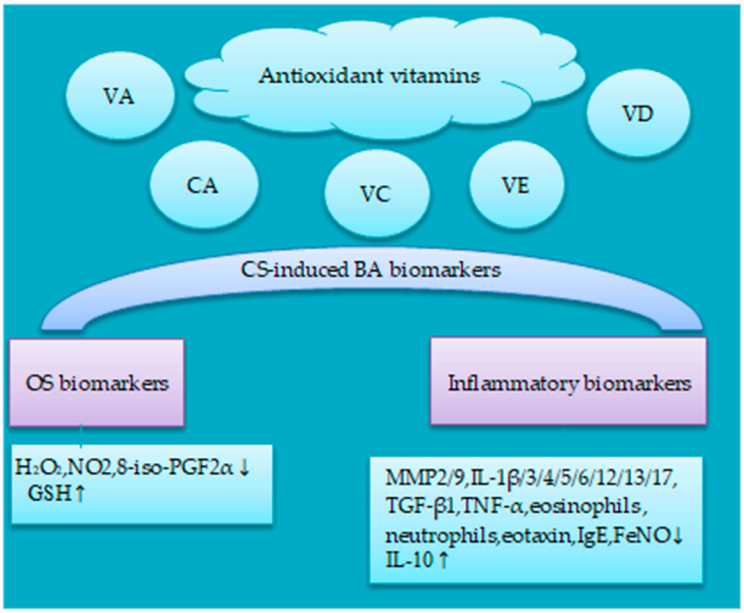

Figure 3. Potential influence of antioxidant vitamins on CS-induced biomarkers. Antioxidant vitamins may reduce CS-induced OS and inflammatory biomarkers. It may also exert antioxidants and anti-inflammatory effects by increasing GSH and IL-10 levels. Abbreviation: VA, vitamin A; CA, carotenoids, VC, vitamin C; VE, vitamin E; VD, vitamin D; BA, bronchial asthma; CS, cigarette smoke; OS, oxidative stress. (↓) decrease, (↑) increase.

5.2. Antioxidant Minerals

5.2.1. Iron

Iron (Fe) is a critical mineral implicated in free radical production, which has a detrimental effect on BA, as evident by increasing plasma Fe levels in HBECs, which result in a significant increase in OS and LP biomarkers, including NOx, MDA and myeloperoxidase (MPO) [113,114]. IL-6 was shown to enhance ferroptosis in HBECs, identified as regulated cell death, by disrupting iron homeostasis

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and increasing ROS and MDA-dependent LP [115]. In mice sensitized to OVA, high expression of HO-1, an enzyme responsible for degrading heme into free iron, was found to be associated with asthmatic airway inflammation via increased levels of IL-5, IL-13 and eosinophilia in the lung tissue [116].

High serum levels of saturation of transferrin and ferritin, as indices of Fe homeostasis, were associated with airway obstruction in smokers and nonsmokers with the lowest FEV_1/FVC ratio [117]. Exposure to tobacco smoke condensate alters iron homeostasis in human respiratory epithelial cells by increasing serum Fe and ferritin accumulation in the lungs of smokers [118]. This suggests that Fe is associated with increased BA risk, and should not be recommended for smoking asthmatics.

5.2.2. Zinc, Selenium and Copper

Evidence from in vivo and in vitro studies suggests that zinc (Zn), Se and copper (Cu) play a significant role in reducing BA and protecting airway epithelial cells against OS and inflammatory biomarkers [119]. Treatment of airway epithelial (HEp-2) cells with toxic copper oxide nanoparticles (CuONPs) results in induced OS by increasing ROS and 8-isoprostane production [120]. CuONPs increase AHR and the production of ROS and pro-inflammatory cytokines via activating of MAPK signaling in OVA-induced asthmatic mice [121]. Cu and Zn are key components of SOD, which results in a reduction of OS. The plasma levels of Se, Cu, Zn and a cytosolic antioxidant enzyme copper-zinc-superoxide dismutase (CuZnSOD) were reported to be lower in asthmatics than in healthy controls [122–124]. Se was found to be associated with decreased levels of OS biomarker plasma thiobarbituric acid reactive substances (TBARS), hs-CRP levels and CD4/CD8 lymphocyte ratios [123]. An in vitro experiment has demonstrated that Zn chelator N,N,N′,N′-tetrakis(2-pyridylmethyl)ethylenediamine inhibits TNFα-induced eotaxin mRNA expression in BEAS-2B cells [125]. In a mouse model of allergic inflammation, Zn supplementation reduced BALF eosinophils and attenuated airway inflammation-induced solute carrier family 39 members 1 and 14 (ZIP1, ZIP14) [126]. Administration of Zn to mice with OVA-induced allergic asthma led to reduced monocytes, neutrophils, eosinophils in BALF, MCP-1 and eotaxin protein production [127]. This suggests that Zn and Cu may have potential antioxidant effects against inflammation biomarkers.

The potential effect of antioxidant minerals on BA-associated CS-induced biomarkers was shown in Figure 4.

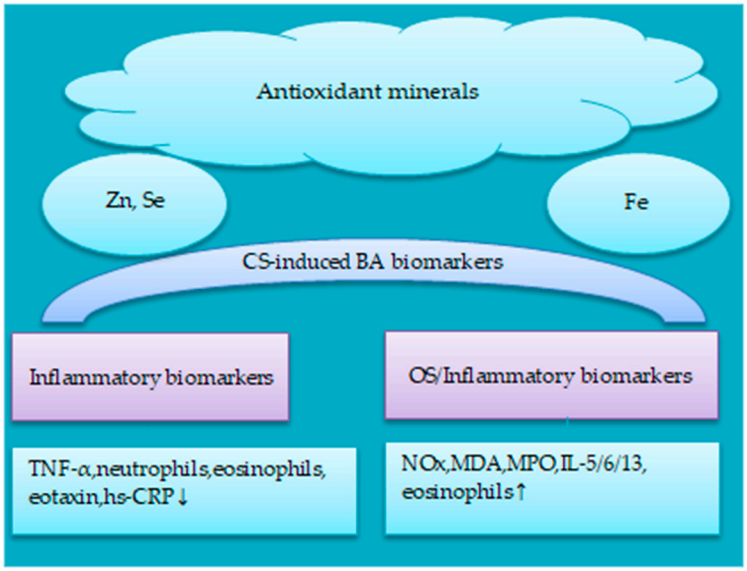

Figure 4. Potential influence of antioxidant minerals on CS-induced biomarkers. Zn and Se may reduce CS-induced inflammatory biomarkers. Fe has both oxidant and inflammatory effects on BA. Abbreviation: Zn, Zinc; Se, Selenium; Fe, Iron; BA, bronchial asthma; CS, cigarette smoke; OS, oxidative stress. (↓) decrease, (↑) increase.

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6. Concluding Remarks

CS is associated with biomarkers of OS and systemic inflammation in HBECs. Literature from cross-sectional and/or longitudinal case-control design has shown that OS and inflammation have a significant role in the pathogenesis of BA in both smokers and nonsmokers. Smoking and nonsmoking asthmatics showed some similarities in OS and inflammatory biomarkers. However, there were differences in biomarkers of CS-induced OS and/or inflammation between smokers and nonsmokers. OS biomarkers MDA, NOx, 8-iso-PGF2α, H_2O_2, and inflammation biomarkers MMPs, CXCL8, AZU-1, PPBP and elastase were found to associate with BA in smokers, but not in nonsmokers. Inflammatory biomarkers periostin, IgE, TGF-β1, TNF-α, ILC2 and NLRP3 showed positive association with BA in nonsmokers, but not in smokers. Current and/or former smokers with BA have higher levels of OS biomarkers than nonsmokers, and thus are at a heightened state of OS. The activity of the enzymatic antioxidant defense in smoking asthmatics may not adequately protect the HBECs from CS-induced OS.

Evidence from a few studies suggests that dietary VC and carotenoid intake are associated with reduced BA risk in smokers and/or nonsmokers. Supplementing VE and Se had no effects on improving lung function in smoking asthmatics.

Several in vivo and in vitro studies have demonstrated the protective effects of antioxidant vitamin and mineral against BA-associated biomarkers. Supplementing VA and VC might protect HBECs against inflammatory biomarkers, while supplementing VE, VD, β-carotene, lycopene and BCX might provide protection against both OS and inflammatory biomarkers. Antioxidants Se, Zn and Cu may potentially protect HBECs against BA-associated OS/inflammatory biomarkers. Zn supplementation might be effective in reducing BA-mediated airway inflammation. Fe has adverse effects on HBECs, and should be avoided for smoking and nonsmoking asthmatics.

The potential effects of antioxidant on BA-associated CS-induced biomarkers in both smokers and nonsmokers are difficult to determine, given a limited number of human studies. VA and carotenoids (particularly β-carotene and β-cryptoxanthin) trigger a protective effect against BA in smokers and/or nonsmokers. However, other antioxidants such VC, VE, VD, Zn and Se may have protective potential against BA-associated biomarkers. Such effects lead to the conclusion that these antioxidants might have beneficial effects in reducing BA in smokers and nonsmokers, given that smoking and nonsmoking asthmatics are susceptible to CS-induced OS and inflammatory biomarkers.

The mechanisms by which antioxidant vitamin and mineral might be effective in protecting HBECs against BA-associated biomarkers in smokers and nonsmokers have not been fully elucidated. Human studies on the exact mechanisms (signaling pathways) linking the antioxidant intake to BA in smokers and nonsmokers have not yet confirmed. Few signaling pathways might be involved, as demonstrated by mice models (e.g., TLR4/NF-κB signaling pathway in VD). Further human studies are needed to explore the mechanisms by which antioxidants might be effective in protecting HBECs against BA-associated biomarkers in smokers and nonsmokers.

More studies on smokers and nonsmokers are needed to determine the associations between antioxidant intake from both diet and supplements and BA-associated inflammation and OS biomarkers. Studies included in this review did not determine whether nonsmokers with BA are affected by SHS exposure. Thus, further studies are required to examine whether antioxidant intake in nonsmoking asthmatics exposed to SHS/ETS could protect HBECs against CS-induced BA biomarkers.

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Abbreviations

AHR	Airway hyperresponsiveness
Akt	Serine-threonine kinase
AP-1	Activator protein-1
ASM	Airway smooth muscle
ATRA	All-*trans* RA
AZU-1	Azurocidin 1
BA	Bronchial asthma
BALF	Bronchoalveolar Lavavge Fluid
BaP	Benzo[a]pyrene
BCX	β-cryptoxanthin
COPD	Chronic obstructive pulmonary disease
CS	Cigarette smoke
CSE	Cigarette smoke extract
Cu	Copper
CuONPs	Copper oxide nanoparticles
CuZnSOD	Zinc-superoxide dismutase
CXCL	C-X-C motif chemokine ligand
EBC	Expired breathe condensate
ECP	Eosinophilic cationic protein
ERK	Extracellular signal-regulated kinases
ETS	Environmental tobacco smoke
Fe	Iron
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1s
FRAP	Ferric reducing ability of plasma
FVC	Forced vital capacity
GPx	Glutathione peroxidase
GSH	Reduced glutathione
H_2O_2	Hydrogen peroxide
HBECs	Human bronchial epithelial cells
HDAC	Histone deacetylase
HGFR	Hepatocyte growth factor receptor
HIF-1α	Hypoxia-inducible factor 1 alpha
HMGB1	Mobility group box 1 protein
HO-1	Heme-oxygenase-1
hs-CRP	High-sensitivity C-reactive protein
ICS	Inhalation corticosteroid
IgE	Immunoglobulin E
IkBα	Inhibitory kappa B kinase
IL	Interleukin
ILC	Innate lymphoid cell
IL-18R1	Interleukin 18 receptor 1

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IL-1RL1	Interleukin 1 receptor-like 1
8-iso-PGF$_{2\alpha}$	ısoprostane-8-iso prostaglandin F$_{2\alpha}$
JNK	c-Jun N-terminal kinase
LABA	Long-acting β2 adrenergic
LC	Lung cancer
LDH	Lactate dehydrogenase
LP	Lipid peroxidation
LPS	Lipopolysaccharide
MAPKs	Mitogen-activated protein kinases
MCP-1	Monocyte chemoattractant protein-1
MDA	Malondialdehyde
MMP	Matrix metallopeptidases
MPO	Myeloperoxidase
α7nAChR	α7 nicotinic acetylcholine receptor
NF-κB	Nuclear transcription factor-kappaB
NLRP	NLR Family CARD Domain Containing
NNK	Nitrosamine 4(methylnitrosamino)-1-(3–pyridyl)-1-butanone
NO_2	Nitrite
NOS	Nitric oxide synthase
Notch1	Neurogenic locus notch homolog protein 1
NOX	Nitric oxidase
Nrf2	Nuclear factor-E2 related factor 2
OS	Oxidative stress
OVA	Ovalbumin
OXSR1	Oxidative stress responsive kinase 1
P53	Protein 53
PARP-1	Poly[ADP-ribose] polymerase 1
PDGF	Platelet-derived growth factor
PEFR	Peak expiratory flow rate
PGF2	Prostaglandin F2
PI3K	Phosphatidylinositol-3 kinase
PPBP	Pro-platelet basic protein
QoL	Quality of life
RA	Retinoic acid
RARs	Retinoic acid receptors
RXRs	Retinoid X receptors
RCTs	Randomised controlled trials
ROS	Reactive oxygen species
Se	Selenium
SHS	Secondhand smoke
SIRT1	Sirtuin1
SLC-39	Solute carrier family 39

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SOD	Superoxide dismutase
TBARS	Thiobarbituric acid reactive substances
TGF-β1	Transforming growth factor beta 1
Th	T-helper
TLR	Toll-like receptors
TNF-α	Tumor necrosis factor α
TNFRSF11A	TNF receptor superfamily member 11a
VA	Vitamin A
VC	Vitamin C
VD	Vitamin D
VE	Vitamin E
Zn	Zinc

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