

REVIEW ARTICLE

Benefit Non-Enzymatic Antioxidant Effects on Allergic Asthma

Nader Chaparzadeh¹, Bahram Yavari¹ and Seyyed Shamsadin Athari^{2&3*}

1. Department of Plant Biology and Halophytes Biotechnology Center, Azarbaijan Shahid Madani University, Tabriz, Iran

2. Department of Immunology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

3. Health policy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Email: SS.Athari@gmail.com

ABSTRACT

Asthma and COPD are inflammatory lung diseases that are characterized by chronic localized inflammation and oxidative stress. The exact cause of asthma is not known yet. Also, asthma is a complex syndrome with many clinical phenotypes that multiple factors such as autonomic system, immunology, infections, endocrine psychological agents and antioxidant/oxidant balance status play an important role in the development of the disease. Sources of oxidative stress arise from the increased burden of inhaled oxidants, as well as elevated amounts of ROS released from inflammatory cells. Dietary has main effect in pathophysiology of this problem. Food safety and suitable dietary are the most important methods to control and treatment of diseases. Antioxidant supplements have central role to alter the cellular redox milieu of immune cells and inflammatory load in the lung. The aim of this study is to highlight importance of four non-enzymatic antioxidant compounds (including glutathione, ascorbate, flavonoids, tocopherols and Polyphenols precursors) in supplement and their benefits on allergic asthma. Therefore, high protection against of asthma could be given with safe dietary.

Keywords: Asthma, Glutathione, Ascorbate, Tocopherols, Flavonoids, Polyphenols

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INTRODUCTION

For many years, the scientists had believed that free radicals (FRs) roles were the preserve of physical and inorganic chemists. However, at first did not foresee the effect of FRs in biology and on disease pathology. Recently FRs have increasingly recognized as ROS (reactive oxygen species) which playing a major role in many disease processes. ROS are a group of free radicals, reactive molecules, and ions that are derived from O₂, such as singlet oxygen (¹O₂), superoxide (O₂^{•-}), hydrogen peroxide (H₂O₂) and hydroxyl radical (OH[•]). ROS may be generated endogenously by metabolic reactions or during activation of circulating inflammatory cells or phagocytes, and/or exogenously by toxic gaseous such as O₃, NO₂, SO₂, cigarette smoke and especially air pollution. ROS may have short lived nature oxidants, such as O₂^{•-} and NO, or long lived organic radicals, such as semiquinones. Sources of oxidative stress rise from the enhanced burden of inhaled oxidants, as well as elevated amounts of ROS released from inflammatory cells (macrophages, neutrophils, eosinophils, lymphocytes, and mast cells). The eosinophil, is implicated as a major source of oxidative injury [1]. There is correlation between asthmatic severity and ROS products in asthmatic subjects [2]. ROS may be generated in several manners in lung and airways. ROS-induced degradation bioactive molecules therefore, act as pro-inflammatory and are presumed to play a significant role in several chronic inflammatory diseases [3-5]. It is proposed that ROS produced by phagocytes (cause to bronchial hyper-reactivity as well as directly mucus secretion and stimulating histamine) associated with many chronic inflammatory lung diseases including asthma [6,7]. Another product of ROS-induced tissue injury is protein nitration which can alter enzyme activity. Levels of nitrotyrosine formation are elevated in both asthma and chronic obstructive pulmonary disease (COPD) [8-10]. Dysfunctional mitochondria can be another potential source of oxidants in lung cells which, it was

reported in murine models of allergic asthma [11, 12]. Cellular antioxidants effectively buffer oxidants generated by metabolism or inhaled during ventilation in the normal lung. As mentioned above and for the reason the lung is highly susceptible to injury mediated by oxidative stress because of its hyper-oxygen environment and together with its large surface area and blood supply, it must be neutralized oxidant adverse effects [13]. In order to protect itself from oxidant-induced tissue damage, the lung cells contains many antioxidant defenses which, neutralize the deleterious effects of ROS; various endogenous antioxidant strategies have evolved which employ both enzymatic and non-enzymatic mechanisms. When Oxidant stress exceeds than oxidant burden, antioxidant defense elicits a cellular response to increase antioxidant capacity and restore balance [14-15]. Enzymatic antioxidant defenses can differ in both anatomical and subcellular localization. This includes enzymes such as superoxide dismutase, catalase, thioredoxin, glutathione peroxidase, and glutathione-S-transferase therefore, acting as a sacrificial target for ROS and other products of lipid peroxidation, such as reactive carbonyls. Within the lung lining fluid, several non-enzymatic antioxidant species exist, which the major in lung lining fluid include glutathione (GSH), vitamin C, vitamin E, uric acid, polyphenols, flavonoids and albumin [16]. Glutathione is a powerful scavenger of both ROS and RNS and can protect proteins, against nitration [17]. There is Various approaches to support the role of foods, fruits and supplements which, including glutathione precursors effects to alter the cellular redox milieu of immune cells and effect pro-inflammatory cytokine production and inflammatory load in the lung [18, 19]. Evidence have been show that vitamin C and E, both the remaining two protective antioxidant molecules derived from the diet, are decreased in chronic cigarette smokers [20]. This review highlights the non-enzymatic antioxidant roles (Glutathione, polyphenols, Vitamin E and C) in the pathogenesis of asthma and COPD and their protective roles against the damaging effects of ROS. Finally we present some foods, fruits or dietary supplements which have these antioxidants in their composition. Because it has been shown that there is a correlation between increased dietary antioxidant intake and improved lung function [21].

Glutathione

Glutathione is a ubiquitous tripeptide, γ -glutamyl cysteinyl glycine, exists in two biologically active forms: the thiol-reduced (GSH) and disulfideoxidized (GSSG). As important protective antioxidants, glutathione considerably protects cells by interacting with ROS and RNS therefor, have a major role in the airspaces and intracellularly in lung epithelial cells. The concentration of glutathione in cultured human lung epithelial cells is approximately 15 mM which is considerably higher than the concentration reported for most other cells. Most cells contain a hundred times more glutathione than is present in outside cells such as blood and plasma. By contrast glutathione concentrations in lung epithelial lining fluid (*in vivo*, 450 μ M) are 100-fold higher than in plasma. These high glutathione levels in lung epithelial lining fluid appear to because of maintain the fluidity of mucus and/or glutathione combines with NO to forms nitrosoglutathione. In asthmatics nitrosoglutathione decreases about 70 to 90 percent, even during severe asthma attacks becomes undetectable in their lung fluid as healthy controls. Scientists are believed that, an enzyme destroys nitrosoglutathione. The activity of this enzyme is increased in asthma however, they suggest that glutathione itself suppresses the activity of this enzyme [22-25]. Evidence was showed that, in the epithelial lining fluid of both asthmatics and chronic cigarette smokers, glutathione levels was elevated [26-28]. Extracellular glutathione within the lung lining fluid has a powerful effect on airway epithelial cell expose to inflammation and the progressive airway hyper-reactivity [14, 15]. Many studies have firmly supports to the central biologic role of the glutathione tripeptide in cellular redox homeostasis, for example expression of glutathione genes is elevated in smoker's lungs and even more pronounced in smokers with COPD. In addition, signaling role of glutathione was reported on regulate gene expression in certain antioxidant pathways. [29-31]. Furthermore recent literature indicated that, glutathione alone can play a direct role in asthma. For example genetic loss of glutathione metabolism in lung lining fluid was shown to augment the concentration of the extracellular glutathione pool and hamper EGF (epidermal growth factors) receptor activation, airway epithelial cell mucin gene induction and airway hyper-reactivity in a cytokine-driven model of asthma [32]. Glutathione is known to enhance the bioavailability of NO, a major airway smooth muscle relaxant, moreover antagonizes histamine release by mast cells [33, 34]. Depletion of glutathione may increase airway contractility by preventing the effects of NO (35). Likely, depletion of glutathione by the local inflammatory cells may lead to increase the levels of glutathione in stable asthmatics and COPD patients [36, 37]. There are data suggesting that, the amount of oxidized glutathione had been increased in these patients and increased oxidative stress was considered [38]. The human body produces glutathione from the synthesis of three key amino acids-cysteine, glycine, and glutamic acid. Food sources with the highest amounts of naturally occurring glutathione include; asparagus, avocado, grapefruit, squash, potato, cantaloupe, peach, zucchini, spinach,

broccoli, watermelon, and strawberries. Fish, meat, egg and foods which yield sulfur containing amino acids are the preferred sources for maintaining and increasing bodily glutathione levels. In addition, supplemental glutathione is only available in one active form, GSH [39-41].

Vitamin C

Vitamin C as an important water-soluble vitamin has undeniably role in most of biological systems and exists in two biologically active forms: ascorbic acid and its oxidized derivative, dehydroascorbic acid. Vitamin C can act as an antioxidant and/or hydrogen donor and therefore reacts with FRs and deactivates them before they adversely affect proteins or lipids [42]. Vitamin C is the most widely studied antioxidant for effects on asthma and has been shown in numerous case-controls and cross-sectional investigates to be related with a decreased risk of asthma [43]. Epidemiological studies have demonstrated that high dietary intake of vitamin C may be associated with a reduced risk of asthma [44]. Additionally, in mild asthmatic subjects blood concentrations of vitamin C have been reported in low level [45]. Dietary vitamin C intake in smokers with high oxidant stress was studied and reduced coughing and wheezing levels was reported [46]. Similarly in another study, elevated dietary intake of vitamin C had an improvement effect in lung function in both asthmatics and smokers [47]. Some researchers have been indicated that asthmatics are talent to have lower serum antioxidants, including vitamin C therefore, lead to asthma severity [48, 49]. It was showed that in asthmatic subjects, pretreatment with Vitamin C considerably associated with alteration in airway geometry caused by exercise [50]. Therefore, vitamin C may beneficially effect pulmonary functions of some asthmatic patients under certain forms of acute stress, such as heavy physical activity or viral respiratory tract infection(51). High content of plasma Vitamin C were associated by lower incidences of bronchial inflammation and wheezing, and epidemiologic studies have confirmed Vitamin C role as an effective factor in reducing symptoms of asthma [52, 53]. Also some studies have reported that vitamin C supplementation provides a short-term benefit in treating asthma [54]. In a study on Italian population sample of children aged 6–7 years, that were consumed frequent of fruits citrus and kiwi- fruits with high vitamin C content during winter, was a correlation with protection from respiratory symptoms over the following 12 months [55]. Additionally in another research in a group of 2,650 children in England and Wales, it was concluded that, fresh fruit intake was associated with better lung function [56]. Evidences suggest that, vitamin C might protect against common cold-induced asthma [57]. It have been reported that large doses (1-2g/day) of vitamin C may reduce asthma symptoms significantly [54]. In order to investigate the effect vitamin C on respiratory symptoms of the patients with asthma, a case-control study was carried out on 50 asthmatic patients referred to Masih Daneshvari Hospital (Tehran). As result this evidences and experiments, only 38% of subjects had plasma vitamin C deficiency and no deficiency was detected in the control group. In the patient group, the majority had normal concentration of plasma vitamin C. Therefore, between the patient and control groups there was a significant difference in plasma vitamin C levels [58]. Although positive effect of vitamin C on asthma symptoms is undeniable but, there are controversial evidences, even the role and effectiveness of dietary supplementation of vitamin C in prevention and/or treatment of asthma. Specially, in open-population samples is often not demonstrated because the evidence of a good effect of this vitamin C in bronchial asthma is derived primarily from epidemiological, observational and case-control studies. Some studies do not support any relation between vitamin C and asthma [59]. As two studies about clinical effect of supplemental intake of vitamin C or E, no observed benefit when compared to current standard therapies for mild to moderate asthma [53, 60]. Thus, some researches do not support the relationship between asthma and vitamin C [59]. At on study in primary care patients, a regular vitamin C dietary supplementation does not forgive any clinical advantages in compared to current standard therapy of asthma evaluated [61]. On the other hand the level of vitamin C is affected by some drugs like corticosteroids that used by asthmatic patients [62]. On the other hand the level of vitamin C is affected by some drugs like corticosteroids that used by asthmatic patients [62]. In conclusion, the role of vitamin C in the prevention or treatment of asthma remains controversial therefore; the effectiveness of dietary supplementation on bronchial obstruction and airway hyper responsiveness caused by exercise and the common cold especially in open-population samples has not been clearly demonstrated. Several authors have raised unresolved questions on the relationship between vitamin C diet and respiratory disease. However, we need this important vitamin as a powerful antioxidant.

This effective antioxidant cannot be stored by the body, so it's important to get some regularly not a difficult task if people eat fruits and vegetables. Important sources include citrus fruits, green peppers, broccoli, green leafy vegetables, strawberries, raw cabbage, and potatoes. The adequate and official recommendation for most people normally is less than 100mg vitamin C per day. For a 70kg adult, this is

the equivalent of about 1mg/kg/day. Fish and milk also include small amounts of vitamin C. There is a gradual decrease in the amount of vitamin C as foods age [63]. Although the minimum requirement for vitamin C in humans is known, the optimal need is still under investigation [64, 65].

Vitamin E

Vitamin E contains two closely related groups: tocopherols and tocotrienols, each are assorted in four isomeric forms, α , β , γ , and δ that inhibits oxidation of components such as unsaturated fatty acid. This vitamin stimulates poly-unsaturated fatty acid against antioxidants, additionally causes improvement of T-cells and granulocytes functions. Approximately 90% of the vitamin E activity in tissues appropriate for α -tocopherol which has central biological potency [66-68]. Vitamin E has complex interactions with allergic inflammatory processes. Vitamin E intake was associated with low serum IgE concentrations and low frequency of allergen sensitization therefore, it seems that during allergic diseases like asthma, vitamin E can suppress IgE response [69-71]. In this regard, in patients with bronchial asthma, vitamin E supplements may enhance the phagocytic activity of peripheral granulocytes and induce elevate the functional activity of T-lymphocytes [72]. There are contradictory reports about vitamin E role on asthma. It was reported that, using a combination of 50mg/day vitamin E can improve pulmonary Function Test in children with asthma so, vitamin E deficiency has been associated with decreased pulmonary Function Test and enhanced asthma manifestations. A significant decrease was reported of Vitamin E concentration in asthmatics respect to non-asthmatic patients. During pregnancy low maternal intake of vitamin E may cause to asthma in children [73, 67, 74]. There was a direct relation between low levels of Vitamin E and mediocre to severe asthma [75, 76, 68]. It was suggested that vitamin E is mobilized toward the lung tissue in response to oxidative stress thus, have Protective effect on small airways [77, 78]. Vitamin E has lower side effects because it can decrease inhaled corticosteroids dose (79). Unlike α -tocopherol has anti-inflammatory, γ -tocopherol has inflammatory properties [80]. As reported literatures in Finland and Italy α -tocopherol has positive impacts on lung function, wheezing and adult-onset asthma. However, in English adults with mild-to-moderate asthma, α -tocopherol dietary supplementation had no show effect on asthma symptoms [81]. Pretreatment of endothelial cultured cells with α -tocopherol inhibits cytokine and decreases adhesion of monocytes to these cells [82, 83]. Contrary, a meta-analysis showed that Vitamin E did not decrease prevalence of asthma [84]. Also a study demonstrated that there was no relation between prenatal diets enriched with vitamin E and allergic disorders in one-year-old infants [85]. However, supplementation with vitamin E not been consistently associated with improved asthma outcomes. A possible explanation for this contrast is that, dietary antioxidants primarily effect the development of asthma during a critical time period early in life, thus a decreased antioxidant intakes during this period increase the likelihood of asthma in later life [53, 60, 67]. Vitamin E as physiological first-line defense against oxidants play its role and therefore, an enough diet may be a potentially modifiable factor in the development of bronchial asthma. This vitamin is a fat-soluble vitamin that can be stored with fat in the liver and other tissues, which is promoted for a range of purposes from delaying aging to healing sunburn. While it's not a miracle worker, it's another powerful antioxidant. Some hypotheses for increasing of asthma are presented by scientists such as declined intake of antioxidant diets or whole grains enriched with vitamin E, high consumption of processed and synthetic foods (with oxidant's) diet and Genetic and environmental factors. For example, in 1950-2006 the intake of vitamin E was decreased from 13-15mg/day to 10.66mg/day. Important sources include wheat germ, nuts, seeds, whole grains, green leafy vegetables, vegetable oil, and fish-liver oil [86, 79, 60, 84].

Phenolic compounds

Phenolic compounds are great and widespread member of plant substance which more than 8,000 are known in different plant species. These compounds have useful properties such as anti-allergic, anti-inflammatory, anti-microbial, anti-viral, anti-oxidant, estrogenic, enzyme inhibition, vascular and cytotoxic anti-tumor activity. Polyphenol antioxidants are characterized by the presence of several phenol functional groups. Phenolic compounds effects on asthma are abundant but we summarize available data [87-88]. Plant phenolic compounds such as flavonoids and terpenoids have anti-asthmatic effects by inhibition of chemical mediator release in bronchoalveolar lavage fluids [89]. Flavonoids for their antioxidant, anti-allergic and anti-inflammatory properties could plausibly reduce asthma inflammation. Flavonoids as avid scavengers of NO, can prevent arachidonic acid metabolism, histamine release and cytokine production [90-92]. Furthermore, one historical used flavonoid, khellin, known for its bronchodilator properties [93]. By contrast it was reported that, intake of total flavonols and total catechins (a flavones) of apple, onions and tea were not associated with asthma [94-95]. Evidence

suggested that, flavones and flavonols were not associated to COPD, but catechins might be protective [96]. It was reported that, phenolic compounds from *Gastrodia elata* plants had anti-inflammatory and analgesic properties *in vivo* via inhibition ROS generation in a dose-dependent manner. Also hydroxy-3-methoxybenzyl alcohol, a phenolic compound, was the most active in modulating asthmatic responses. (97). Intakes of luteolin (a flavonoid) decreases inflammation in the bronchial epithelium and reduces bronchial hyper-reactivity (98). Asthma pathophysiology are highly associated with increasing IL-4, IL-5, IL-9, and IL-13 levels (which produced by T-cells, mast cells and eosinophils) mediate T-helper-2 (Th2) cytokine responses (99). Apigenin ,Another flavonoid, inhibits the production of cytokines such as IL-6, IL-8, and certain prostaglandins (100). Also apigenin reduces the quantity of Th2 cells and the production of IL-4 [101]. literatures have demonstrated that apigenin modulates the initial development stages of inflammation via inhibition dendritic cells maturation (102). Also apigenin may impact the remodeling of the bronchial tree in asthma, Indeed inhibits the activity of metalloproteinases2 and 9 (103). Quercetin as the most widespread flavone is able to inhibit the activity of basophils, 5-lipoxygenase, phospholipase A2, Th2 cells and the release of leukotrienes [104-106]. This compound could reduce the secretion of mucus in the bronchial tree, like dexamethasone [105]. Kaempferol (another very popular phenolic compound is present in the greatest quantities in green tea leaves and broccoli) reduces infiltration in the epithelium of bronchial inflammation, Th2 lymphocytes, inhibits bronchial hyper-reactivity and expression of CD40 on basophils and mast cells. In addition, it could block the generation of IL-5 and IL-13, key cytokines in allergic inflammation in the bronchi of patients with bronchial asthma [107-108]. This compound with a slightly lower activity respect to dexamethasone, has a significant impact on allergic inflammation in the bronchial tree [109]. Consumption of kaempferol and quercetin in large quantities could significantly reduce the risk of developing asthma (110). Genistein (a group of isoflavones which is abundant in soya bean seeds) by influencing protein kinases, blocking calcium channels in bronchial smooth muscle, inhibits the release of mediators of anaphylaxis and bronchial smooth muscle contraction [111]. As recommendation, there are more than 4,000 unique flavonoids and they are most effective when several types are consumed together [112]. Another effective phenolic compound is caffeic acid which known a selective inhibitor of leukotriene biosynthesis. And its, caffeic acid phenethyl ester, is a caffeic acid derivative, attenuates allergic airway inflammation [113, 114, 115]. In addition, caffeoyl glycoside has immunopotential, and acteoside inhibits leukocyte accumulation, and histamine release [116, 115, 117]. Recently, resveratrol (a phenolic compound which is rich in grapes) has been suggested that could reduce inflammatory mediators in COPD patients [92]. Evidence indicate that, oral administration of resveratrol is benefit for treatment of allergic diseases such as asthma [118]. Sciences and literatures about ROS and RNS metabolism and relation between these oxidative markers and chronic diseases; identification of flavonoids and other dietary polyphenol antioxidants exist in plant foods as bioactive molecules; supporting the idea that health benefits associated with fruits, vegetables in the diet are probably linked to the polyphenol antioxidants they contain [87, 88]. In human health these compounds, are thought to be instrumental in expose to oxidative stress. The main source of polyphenol antioxidants are naturally found largely in the fruits, vegetables, cereals, olive and beverages. Typically per 100 grams fresh weight of fruits such as grapes, apple, pear, berries, and cherries contain about 200–300 mg polyphenols. Other polyphenols-rich fruits are blackberries, strawberries cantaloupe, cranberries, pears, plums. Vegetables such as broccoli, cabbage, celery, onion, and parsley are rich in polyphenol antioxidants. Typically a cup of tea or coffee and a glass of red wine have about 100 mg polyphenols. Also cereals, dry legumes and chocolate have adequate amount of polyphenols [119, 120].

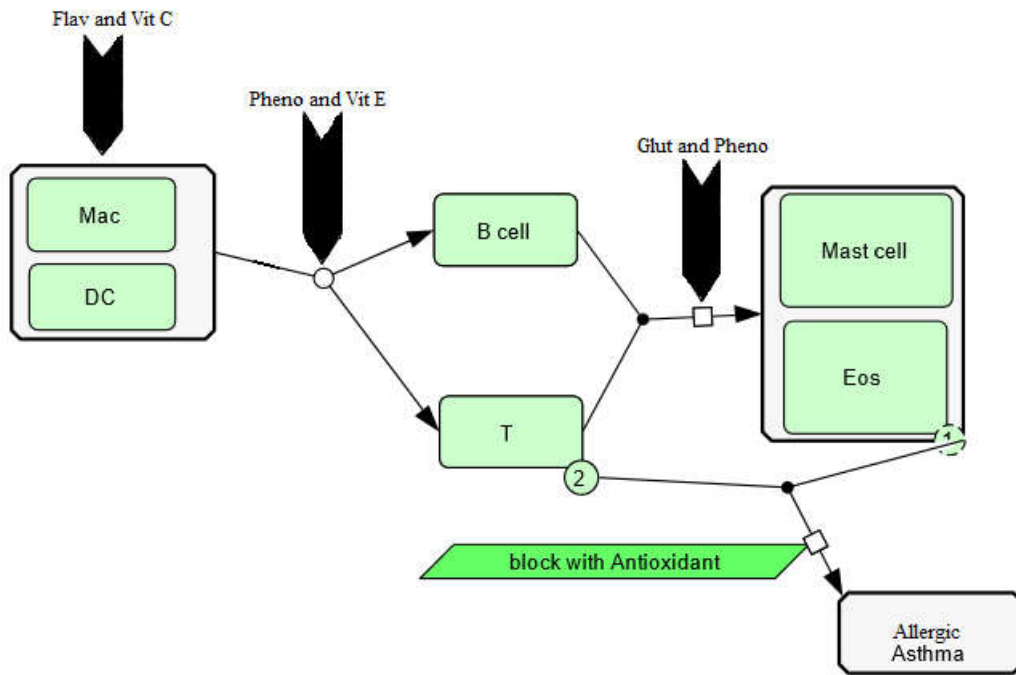


Figure 1. Allergic asthma inhibition pathways by anti-oxidant components.

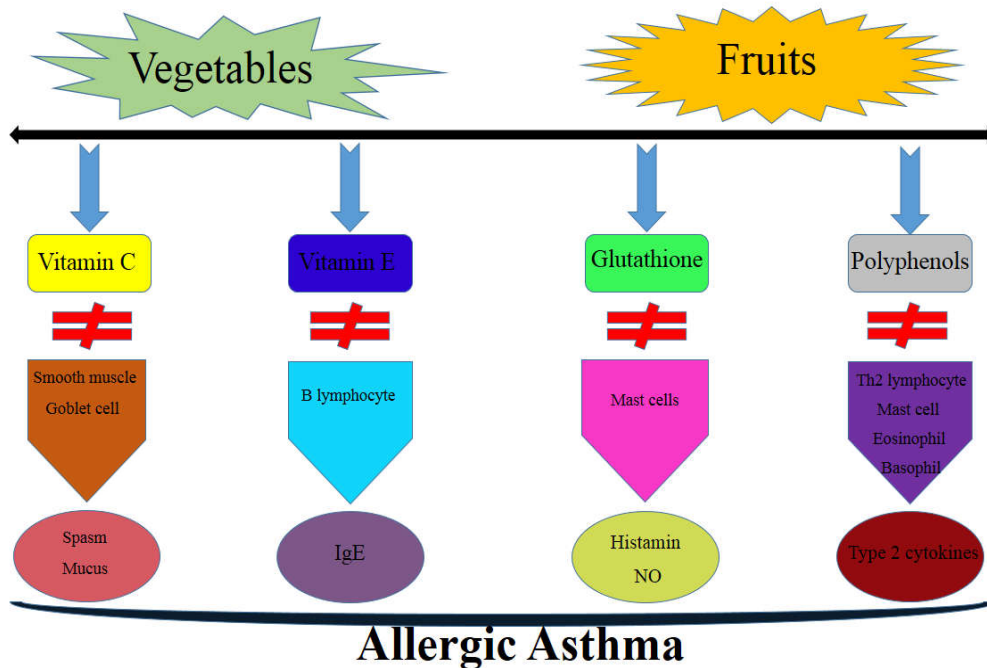


Figure 2. Allergic pathways inhibition effects of food anti-oxidants in the allergic asthma disease pathophysiology.

CONCLUSION

Despite at this time, asthma is a disease without a cure that alters morbidity and mortality rates. It is undeniable that scientists seriously explore potential genetic and environmental factors including diet and antioxidants, in the onset and cure of asthma [121]. Available data suggest that the nature, source and location of oxidative stress, are likely affect the success of an antioxidant intervention. It was proved that, imbalance in antioxidant/oxidant status is associated with chronic airflow restriction (figure 1). Dietary manners and oxidative stress and high antioxidant status accompanied with lower risk of COPD and

asthma [61,122]. Antioxidant deficiency obviously accompanied with asthmatic subjects thereby cause to increased oxidative stress level that requires higher levels of ROS/RNS scavenging antioxidants [123]. As discussed above, safe dietary may help to high protection against of asthma and guarantee healthy communities and healthy individuals. It was believed that, increasing prevalence of asthma in Britain is for the reason low tendency dietary intake of antioxidants has caused to a susceptibility of the pulmonary airways to ROS (figure 2). Also food supplementation is benefits on asthmatic adults exposed to air pollutants [62,124]. Unfortunately in developed countries pulmonary diseases induced by harmful inhaled materials are progressing and associated with reduced consumption of proper amounts of fresh vegetables and fruits in dietary regimen [62]. Supplementation studies demonstrated that, application Supplements with individual antioxidants alone may not be beneficial in improving lung function or asthma [123,125]. Researchers firmly have been shown that, combinational antioxidant therapy to be effective in improving of clinical symptoms in asthmatic patients [73]. However, future research needs to discover the mechanisms behind the protective effects of antioxidants, the synergistic effect of other nutrients and specially the genetic-environmental relation. Recently consumption artificial supplement with high antioxidant are increasing. But at this time there is insufficient evidence to support the addition of antioxidant supplementation as an adjunctive therapy or clinical practice guidelines for asthma improvement thus, there is considerably achievements to support the promotion of increased dietary fruit and vegetable intake in adults with asthma [121]. Multivitamins as an agent may help many people to acquire their nutritional needs, but is not recommended taking large doses of individual vitamins [65]. Further study would indicate whether benefit antioxidants can be obtained through food or supplementation. The authors foresee that in the future, applications antioxidant adjuncts may confirm to be beneficial in the treatment of asthma [126]. So deeper attention to improve healthy eating, dietary control of hazardous substances, the content and quality of foods, and food hygiene can play a major role in prevention, control and treatment of asthma. In conclusion further research should be design what combination of antioxidants will be most effective in correcting airway dysfunction, and/or whether dietary manipulation, high in natural antioxidants, is effective against asthma. Several unresolved questions are raised, which should be addressed in future studies on the relationship between diet and asthma.

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