Although serum IgE levels in mice fed an α-TOC diet after the final antigen challenge did not differ from those in mice fed a normal diet, other markers (such as IL-4 and IL-5 levels in BALF, eosinophil count in BALF, inflammation of lung tissue and airway responsiveness to Ach) were decreased significantly compared to those in mice fed a normal diet. This discrepancy is possibly due to OA provocation being stronger than the inhibitory effect of α-TOC and/or the fact that α-TOC affects the allergic pathways further from the IgE-mediated response. Another possibility is that α-TOC and probucol each affect a different point of the allergic pathway from Th2 cells to eosinophilic inflammation. For example, IL-5 is produced by both Th2 cells and eosinophils, but IL-4 is produced only by Th2 cells. This might explain why IL-4 levels in BALF after the final antigen challenge differ between α-TOC-fed mice and probucol-fed mice.

There is increasing evidence that inflammation from asthma results in increased oxidative stress in the airways. The H_2O_2 concentration and NO levels in exhaled air condensate are increased in stable asthmatics and they may contribute to airway edema and inflammation [39–41]. The inflammatory and immune cells in the airways (such as macrophages, neutrophils and eosinophils) release increased amounts of ROS in asthmatic patients [15, 42], and their ability to produce O_2^- correlates with the degree of bronchial responsiveness to inhaled methacholine [43]. The direct oxidative damage can result in the characteristic features of asthma [44, 45] and it may evoke AHR [46]. Leukotrienes (LT) are now thought to play an important role in AHR in asthma [1] and oxidative stress leads to AHR via LT production [47]. Centanni et al. [48] studied the effect of TOC supplementation and the results obtained showed a significant inhibition of LT production by α-TOC supplementation. These studies provide support for the hypothesis of a potential effect of α-TOC supplementation in asthma patients. As the results of our experiment, we confirmed that allergic response leads to oxidative stress in the airways of mice. However, there was no evidence of the antioxidant properties of α-TOC. We suggest that the correlation of the antioxidant dose with inflammatory intensity may contribute to this discrepancy between previous reports and our results; however, the details of these mechanisms remain unknown.

On the other hand, the effect of probucol on allergic diseases has not yet been clarified. Probucol is a cholesterol-lowering drug, and serum cholesterol increases in asthmatic patients [49]. Yeh and Huang [50] reported that dietary cholesterol enhances bronchial inflammation in a murine model of asthma. While probucol is used as an antioxidant in various diseases [51], a recent study showed that the immunomodulatory effect of probucol predicts a role in chronic inflammatory diseases [52]. This immunomodulatory effect is believed to be independent of the cholesterol-lowering effect. We believe that the pleiotropic effects of probucol outlined above are responsible for the differences in results between the α-TOC and probucol groups. From our study of AHR in animal models, we concluded that probucol may also have a potent effect on IgE-mediated atopic responses and reduces serum IgE levels.

In our study, α-TOC and probucol also suppressed AHR in asthma model mice, although they used different immunological pathways against Th2 activity and/or the IgE-mediated allergic response. Additional studies are needed to clarify the mechanism of each activity and its potential role for the treatment of asthmatic patients. The optimal dose of each drug should also be determined.

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