

## Editorial

# Quercetin as Drug to Treat Asthma - What is Missing?

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## Editorial

Asthma is an inflammatory disease of the airways characterized by migration and accumulation of leukocytes (particularly eosinophils), mucus hyper secretion, increased production of Immunoglobulin E (IgE) and bronchial hyperactivity [1]. Although knowledge regarding the roles of different T cell subsets in the asthma has increased in recent years, Th2- type immune responses are most classically associated with the pathophysiology of allergic asthma [2]. Most patients with asthma have intermittent or persistent symptoms that are readily controllable by standard asthma therapies including 2-adrenergic agonists, low doses of inhaled corticosteroids or leukotriene modifiers [3]. However, some asthmatic individuals have poorly controlled asthma that is refractory to these standard therapies, leading to exacerbations that require intensive treatment in physician offices, emergency departments and hospitals [4]. Although the drugs described above have potent effects when used individually or in combination, they also have adverse side effects that limit their long-term use [5]. Agents of natural origin that induce very few side effects should be considered for therapeutic substitution or as complementary treatments. Furthermore, natural compounds may serve as the basis for new drugs in the treatment of many diseases [6]. Several plant-derived compounds can decrease the expression and production of inflammatory mediators and their receptors, down-regulate the production and activity of second messengers and inhibit the expression of transcription factors that promote the production of inflammatory molecules [7,8]. Such effects provide symptom relief similar to that afforded by allopathic medicines. Quercetin is a flavonoid (family of plant compounds with a similar flavone backbone composed of two aromatic rings and an oxygen heterocyclic with hydroxyl groups attached) that occurs naturally in fruits and vegetables, including onions, apples, grapes and nuts. Therefore, quercetin has been present in the human diet throughout the history of humanity, and it is currently used as a food additive [9,10]. Quercetin may have already been used in treating human disease (phototherapy), as it is present in the seeds, stems, barks, roots and/or flowers of several medicinal plants. Several epidemiological studies and clinical trials as well as animal and *in vitro* studies have been performed to evaluate the safety of quercetin [9,11]. However, quercetin, similar to other substances, may interfere with the pharmacokinetics of other medicines, such as dioxin and cyclosporine, which could lead to significant adverse events [12,13]. Quercetin has a wide range of therapeutic properties such as antioxidant, anti-

cancer, anti-inflammatory and anti-allergic activities [14,15]. For instance, the incidence of asthma is lower in individuals who ingested higher quantities of total flavonoids, including quercetin [16,17]. However, studies with quercetin in the airways, especially in the asthma, were carried out only in experimental models. In a murine model of ovalbumin-induced allergic airways inflammation, quercetin (10 mg/kg; oral dose) reduced eosinophils numbers and IL-5 concentration in the Bronchoalveolar Lavage Fluid (BALF) [18]. Similar results were found by other studies employing the same experimental models in mice and guinea pigs but using different routes of quercetin administration (intraperitoneal or aerosol route) [19-22]. In another experimental model induced by *Bulimia tropicalis* (dust mite allergen), quercetin also reduced inflammatory parameters (eosinophils recruitment to airways and production of Th2 cytokines) [23]. The pronounced effect of quercetin in the allergic models could be associated to modulation of Th1/Th2 phenotypes. Quercetin suppressed the expression of transcription factors GATA-3, which is associated to Th2 cell differentiation [24], and increased the expression of T bet, which is determinant for Th1 cell differentiation [25], in the lungs of ovalbumin-sensitized and challenged mice [21]. In addition to modulate the airway inflammation, quercetin also demonstrates potential to reduce airway hyper responsiveness [26,27] and mucus production [28]. Quercetin also acts as a potent bronchodilator *in vitro* (tracheal smooth muscle) and *in vivo* (guinea pigs sensitized with ovalbumin) [23,29,30]. These effects could be associated with inhibitory effect of quercetin on releasing of histamine and pro-inflammatory mediators (TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and IL-8) from mast cells [31-33] as well as eosinophil activation [34]. These results demonstrate potential role of quercetin in both early and late phase asthmatic response. The airway epithelium plays significant role in chronic inflammatory processes such as asthma [35]. Quercetin reduced the expression of IL-8 and chemokines (C-C motif) ligand 2 (CCL2/MCP-1) in bronchial epithelial cells stimulated by TNF- $\alpha$  [36], a cytokine involved in asthma pathogenesis [37]. In an *in vivo* study, quercetin reduced the epithelial thickness, sub epithelial smooth muscle thickness and goblet cell numbers in ovalbumin-sensitized and challenged mice [22]. So, the anti-inflammatory effects of quercetin in these cells might modulate the activation of immune responses as well as their exacerbations in the airways. Quercetin is known to be poorly soluble in water and generally, Diethyl Sulfoxide (DMSO) and polyethylene glycol were used as adjuvant to improve quercetin solubilisation and absorption. However, these substances are not approved for human use. Interesting, studies demonstrate that quercetin glycosides (linked to sugars such as glucose (isoquercitrin) or rutenes (rutin)) are more absorbed than quercetin and that their absorptions seem to depend on the type and position of the sugar moieties [38-40]. However, after ingestion, enzymes in the mouth and the intestines hydrolyze quercetin glycosides to quercetin increasing its bioavailability [41,42]. In a murine model of ovalbumin-induced allergic airways inflammation, both quercetin and isoquercetin (quercetin attached to glucose) was able to reduce the eosinophilic inflammation, however only

isoquercitrin was effective to reduce IL-5 concentration in the BALF [18] suggesting the improve of bioavailability of quercetin. Colloidal drug delivery systems, such as micro emulsions, have been proposed to improve the absorption and therapeutic index of several drugs [43]. Using the murine model of ovalbumin-induced allergic airway inflammation Rogério, et al. [44] demonstrated Quercetinloaded Micro Emulsion (QU-ME) was more effective in reducing eosinophil recruitment, production of pro-inflammatory mediators (IL-4, IL-5, CCL11 and LTB4), mucus production and NF- $\kappa$ B activation than quercetin suspension. Thus, the higher efficacy of QU-ME was due to the increased oral absorption of quercetin [44] demonstrating this delivery system improved the oral bioavailability of quercetin. In another study using the same experimental model, Gupta, et al. [45] demonstrated quercetin nanocrystals (nQ), which is water soluble, was more effective in reducing the eosinophilic airways inflammation as well as IgE and Th2 cytokines production when compared to quercetin. Quercetin demonstrates significant effects to reduce the most significant phenotypes of asthma (migration and accumulation of eosinophils, mucus hyper secretion, production of IgE and bronchial hyper reactivity) with no known significant adverse effects. These results in association with the low incidence of asthma in individuals with moderate dietary intake of flavonoids, including quercetin, suggest that quercetin could be used medicinally, either alone or as a complement to other drugs currently used for the treatment of asthma. In this way, clinical investigations with quercetin, quercetin in drug delivery systems and/or its glycosides such as isoquercitrin should be conducted to evaluate its potential to prevent or treat episodes of asthma.

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