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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 marine 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 tropical* is (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-α, IL-1β, 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-α [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 retinues (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 odel of ovalbumin-induced allergic airways inflammation, both quercetin and isoquercetin (quercetin attached to glucose) was able to reduce the eosinophilic inflammation, however only

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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 Rogerio, 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-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 isoquercetrin should be conducted to evaluate its potential to prevent or treat episodes of asthma.

References

1. Kubo M. Innate and adaptive type 2 immunity in lung allergic inflammation. Immunol Rev. 2017; 278: 162-172.
2. Lloyd CM, Hessel EM. Functions of T cells in asthma: more than just T(H)2 cells. Nat Rev Immunol. 2010; 10: 838-848.
3. Busse WW, Lemanske RF Jr. Asthma. N Engl J Med. 2001; 344: 350-362.
4. Global Initiative for Asthma. Global strategy for asthma management and prevention. Bethesda: National Heart, Lung and Blood Institute, National Institutes of Health, 2002. NIH Publication: 02-3659.
5. Papiris SA, Manali ED, Kolilekas L, Triantafillidou C, Tsangaris I. Acute severe asthma: new approaches to assessment and treatment. Drugs. 2009; 69: 2363-2391.
6. Verpoorte, R. Exploration of nature's chemodiversity: the role of secondary metabolites as leads in drug development. Drug Discov Today. 1998; 3: 232-238.
7. Asadi-Samani M, Bagheri N, Rafieian-Kopaei M, Shirzad H. Inhibition of Th1 and Th17 cells by medicinal plants and their derivatives: a systematic review. Phytother Res. 2017.
8. Calixto JB, Campos MM, Otuki MF, Santos ar. Anti-inflammatory compounds of plant origin. Part II. Modulation of pro-inflammatory cytokines, chemokines and adhesion molecules. Planta Med. 2004; 69: 973-983.
9. Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, Lines TC. A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. Food ChemToxicol. 2007; 45: 2179-2205.
10. Middleton E Jr, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacol Rev. 2000; 52: 673-751.
11. Okamoto T. Safety of quercetin for clinical application (Review). Int J Mol Med. 2005; 16: 275-278.
12. Li Y, Revalde J, Paxton JW. The effects of dietary and herbal phytochemicals on drug transporters. Adv Drug Deliv Rev. 2016; 16: 169-409
13. Srinivas NR. Recent trends in preclinical drug-drug interaction studies of flavonoids--Review of case studies, issues and perspectives. Phytother Res. 2015; 29: 1679-1691.
14. Chirumbolo S. Quercetin as a potential anti-allergic drug: which perspectives?. Iran J Allergy Asthma Immunol. 2011; 10: 139-140.
15. Marunaka Y. Actions of quercetin, a flavonoid, on ion transporters: its physiological roles. Ann N Y Acad Sci. 2017; 1: 142-151.
16. La Vecchia C, Decarli A, Pagano R. Vegetable consumption and risk of chronic disease. Epidemiology. 1998; 9: 208-210.
17. Knekt P, Kumpulainen J, Järvinen R, Rissanen H, Heliövaara M, Reunanen A, et al. Flavonoid intake and risk of chronic diseases. Am J Clin Nutr. 2002; 76: 560-568.
18. Rogerio AP, Kanashiro A, Fontanari C, da Silva EV, Lucisano-Valim YM, et al. Anti-inflammatory activity of quercetin and isoquercitrin in experimental murine allergic asthma. Inflamm Res. 2007; 56: 402-408.
19. Moon H, Choi HH, Lee JY, Moon HJ, Sim SS, Kim CJ. Quercetin inhalation inhibits the asthmatic responses by exposure to aerosolized-ovalbumin in conscious guinea-pigs. Arch Pharm Res. 2008; 31: 771-778.
20. Jung CH, Lee JY, Cho CH, Kim CJ. Anti-asthmatic action of quercetin and rutin in conscious guinea-pigs challenged with aerosolized ovalbumin. Arch Pharm Res. 2007; 30: 1599-1607.
21. Park HJ, Lee CM, Jung ID, Lee JS, Jeong YI, Chang JH, et al. Quercetin regulates Th1/Th2 balance in a murine model of asthma. Int Immunopharmacol. 2009; 9: 261-267.
22. Caglayan Sozmen S, Karaman M, Cilaker Micili S, Isik S, Bagriyanik A, ArikanAyyildiz Z, et al. Effects of quercetin Treatment on epithelium-derived cytokines and epithelial cell apoptosis in allergic airway inflammation mice model. Iran J AllergyAsthmaImmunol. 2016; 15: 487-497.
23. Oliveira TT, Campos KM, Cerqueira-Lima AT, Cana Brasil Carneiro T, da Silva Velozo E, Ribeiro Melo IC, et al. Potential therapeutic effect of Allium cepa L. and quercetin in a murine model of Blomia tropicalis induced asthma. Daru. 2015; 23: 18.
24. Barnes PJ. Pathophisiology of allergic inflammation. Immunol Rev. 2011; 242: 31-50.
25. Lazarevic V, Glimcher LH. T-bet in disease. Nat Immunol. 2011; 12: 597-606.
26. Ko WC, Shih CM, Chen MC, Lai YH, Chen JH, Chen CM, et al. Suppressive effects of 3-O-methylquercetin on ovalbumin-induced airway hyperresponsiveness. Planta Med. 2004; 70: 1123-1127.
27. Jiang JS, Chien HC, Chen CM, Lin CN, KO WC. Potent suppressive effects of 3-O-methylquercetin 5, 7, 3', 4'-O-tetraacetate on ovalbumin-induced airway hyperresponsiveness. Planta Med. 2007; 73: 1156-1162.
28. Chang JH, Song KJ, Kim HJ, Kim JH, Kim NH, Kim KS. Dietary polyphenols affect MUC5AC expression and ciliary movement in respiratory cells and nasal mucosa. Am J Rhinol Allergy. 2010; 24: 59-62.
29. Joskova M, Franova S, Sadlonova V. Acute bronchodilator effect of quercetin in experimental allergic asthma. BratislLekListy. 2011; 112: 9-12.
30. Townsend EA, Emala CW Sr. Quercetin acutely relaxes airway smooth muscle and potentiates β-agonist-induced relaxation via dual phosphodiesterase inhibition of PLCβ and PDE4. Am J Physiol Lung Cell Mol Physiol. 2013; 305: 396-403.
31. Cruz EA, Reuter S, Martin H, Dehzad N, Muzitano MF, Costa SS, et al. Kalanchoe pinnata inhibits mast cell activation and prevents allergic airway disease. Phytomedicine. 2012; 19: 115-121.
32. Park HH, Lee S, Son HY, Park SB, Kim MS, Choi EJ, et al. Flavonoids inhibit histamine release and expression of proinflammatory cytokines in mast cells. Arch Pharm Res. 2008; 31: 1303-1311.

33. Kempuraj D, Madhappan B, Christodoulou S, Boucher W, Cao J, Papadopoulou N, et al. Flavonols inhibit proinflammatory mediator release, intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells. Br J Pharmacol. 2005; 145: 934-944.

34. Sakai-Kashiwabara M, Asano K. Inhibitory action of quercetin on eosinophil activation in vitro. Evid Based Complement Alternat Med. 2013; 2013:127105.

35. Loxham M, Davies DE. Phenotypic and genetic aspects of epithelial barrier function in asthmatic patients. J Allergy ClinImmunol. 2017; 139: 1736-1751.

36. Nanua S, Zick SM, Andrade JE, Sajjan US, Burgess JR, Lukacs NW, et al. Quercetin blocks airway epithelial cell chemokine expression. Am J Respir Cell Mol Biol. 2006; 35: 602-610.

37. Romagnani S. Cytokines and chemoattractants in allergic inflammation. MolImmunol. 2002; 38: 881-885.

38. Hollman PC, de Vries JH, van Leeuwen SD, Mengelers MJ, Katan MB. Absorption of dietary quercetin glycosides and quercetin in healthy ileostomy volunteers. Am J ClinNutr. 1995; 62: 1276-1282.

39. Hollman PC, van Trijp JM, Buysman MN, van der Gaag MS, Mengelers MJ, de Vries JH, et al. Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man. FEBS Lett. 1997; 418: 152-156.

40. Rogerio AP, Sá-Nunes A, Faccioli LH. The activity of medicinal plants and secondary metabolites on eosinophilic inflammation. Pharmacol Res. 2010; 62: 298-307.

41. Egert S, Boesch-Saadatmandi C, Wolffram S, Rimbach G, Müller MJ. Serum lipid and blood pressure responses to quercetin vary in overweight patients by apolipoprotein e genotype. J Nutr. 2010; 140: 278-284.

42. Perez-Vizcaino F, Duarte J, Jimenez R, Santos-Buelga C, Osuna A. Antihypertensiveeffectsoftheflavonoidquercetin. Pharmacol Rep. 2009; 61: 67-75.

43. Gupta S, Moulik SP, Lala S, Basu MK, Sanyal SK, Datta S. Designing and testing of an effective oil-in-water microemulsion drug delivery system for in vivo application. DrugDeliv. 2005; 12: 267-273.

44. Rogerio AP, Dora CL, Andrade EL, Chaves JS, Silva LF, et al. Anti-inflammatory effect of quercetin-loaded microemulsion in the airways allergic inflammatory model in mice. Pharmacol Res. 2010; 61: 288-297.

45. Gupta K, Kumar S, Gupta RK, Sharma A, Verma AK, Stalin K, et al. Reversion of Asthmatic Complications and Mast Cell Signalling Pathways in BALB/c Mice Model Using Quercetin Nanocrystals. J Biomed Nanotechnol. 2016; 12: 717-731.

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