Quercetin: a flavonoid with the potential to treat asthma

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Allergic asthma is a complex inflammatory disorder characterized by airway hyperresponsiveness, eosinophilic inflammation and hypersecretion of mucus. Current therapies include β2-agonists, cysteinyl leukotriene receptor 1 antagonists and corticosteroids. Although these drugs demonstrate beneficial effects, their adverse side effects limit their long-term use. Thus, the development of new compounds with similar therapeutic activities and reduced side effects is both desirable and necessary. Natural compounds are used in some current therapies, as plant-derived metabolites can relieve disease symptoms in the same manner as allopathic medicines. Quercetin is a flavonoid that is naturally found in many fruits and vegetables and has been shown to exert multiple biological effects in experimental models, including the reduction of major symptoms of asthma: bronchial hyperactivity, mucus production and airway inflammation. In this review, we discuss results from the literature that illustrate the potential of quercetin to treat asthma and its exacerbations.


INTRODUCTION

Asthma is a chronic inflammatory disease common worldwide (Mukherjee, Zhang, 2011). According to the guidelines issued by the U.S. National Heart, Lung and Blood Institute and the Global Initiative for Asthma (GINA), asthma severity can be classified based on clinical features into intermittent, mild persistent, moderate persistent, and severe persistent asthma (Wenzel, 2006). The most common signs of asthma include airway obstruction, wheezing and airway hyperresponsiveness (Bousquet et al., 2000). In addition, patients also exhibit airway inflammation characterized by the recruitment of eosinophils and other leukocytes, airway smooth muscle hypertrophy/hyperplasia, systemic IgE production and mucus hypersecretion.

The pathophysiology of allergic asthma is mediated by CD4+ T cell immune responses. T helper (Th) 1 and Th17 cells promote neutrophil recruitment and have been associated with both severe and steroid-resistant asthma. Th9 cells have been shown to affect mucus production, mast cell recruitment and IgE production. CD8+ T cells,
NKT cells and γδ T cells are also able to modulate asthma-associated inflammation and/or airway hyperresponsiveness (AHR). In contrast, Treg cells are known to suppress innate and adaptive immune responses and decrease inflammation. 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 pathology of asthma (Lloyd, Hessel, 2010).

Asthma exacerbations are common, and their prevention and treatment are perhaps the most important clinical issues for optimal asthma control (Messer et al., 2010). Episodes of asthma exacerbation can be triggered by allergen inhalation, viruses, pollutant exposure, exercise, non-steroidal anti-inflammatory medications and occupational agents (Chua, Lai, 2007; Tillie-Leblond et al., 2005). In episodes of asthma exacerbation, in addition to eosinophils, neutrophils are recruited to the airway. In fact, neutrophils are the most prevalent inflammatory cell population in the airways of individuals who have died from asthma attacks (Sur et al., 1993).

Typical asthma treatments include β2-agonists and systemic corticosteroids (Mukherjee, Zhang, 2011; NIH, 1997). Administration of nebulized β2-agonists (continuous or repetitive), such as salbutamol, causes bronchodilation and is considered a first-line treatment for the management of asthma (NIH, 1997; Wort, 2003). Corticosteroids are the most commonly prescribed therapeutics for controlling nearly all types of inflammatory reactions and exert strong effects on leukocyte recruitment when administered orally or systemically (Harris, 1972; Flower, 1988; Perretti, Flower, 1993). The most striking effect of corticosteroids is their ability to inhibit the expression of multiple inflammatory mediators whose genes are regulated by transcription factors, such as nuclear factor-κB (NF-κB) (Barnes, 1998). Thus, inhibition of the NF-κB pathway is associated with decreased expression of genes encoding cytokines (e.g., IL-5), chemokines (e.g., eotaxins) and adhesion molecules (e.g., E-selectin), all of which play critical roles in regulating eosinophil recruitment (Rabier et al., 1991; Faccioli et al., 1996). Inhibitors of LT synthesis (such as zileuton, which directly inhibits 5-LO) or CysLT1 antagonists (such as montelukast, zafirlukast, and pranlukast) may also be used as complementary therapies to treat asthma, reducing the requirement for corticosteroids (Salvi et al., 2001; Peters-Golden, Henderson, 2007; Montuschi et al., 2007).

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 (Papiris et al., 2009). Prolonged use of corticosteroids can lead to iatrogenic Cushing’s syndrome, osteoporosis, susceptibility to infections, and psychiatric disorders, along with various other disorders (Macfarlane, Forbes, Walker, 2008; Dias et al., 2010). Increased cardiovascular complications in patients who use β2-agonists might be the consequence of increased heart rates and reduced potassium levels (Salpeter, Ormiston, Salpeter, 2004; Cazzola, Matera, Donner, 2005). Usage of inhibitors of LT synthesis has been associated with headaches and gastrointestinal disturbances (Cung, 1995). Thus, it is necessary to develop new compounds with similar therapeutic potential and less adverse effects for the continuous treatment of airway diseases.

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 (Verpoorte, 1999). In an ongoing search for bioactive plant-derived natural products, several groups, including ours, have successfully employed experimental methods to screen plant extracts and plant secondary metabolites for pharmacological activity. In addition, several groups have also demonstrated the effectiveness of extracts from plants, such as Ginkgo biloba and Hypericum perforatum, in clinical trials (Wadsworth et al., 2001, Canning et al., 2010).

The earliest written records on the use of medicinal plants were found in Assyrian clay tablets (2000 BC), the Egyptian Ebers Papyrus (1550 BC) and in Ayurveda works from 900 BC. Moreover, Hippocrates, Dioscorides, Galen, Paracelsus and Arab scholars in Europe preserved knowledge regarding the use of medicinal plants (Sneader, 1997). In addition, several groups have also demonstrated the effectiveness of extracts from plants, such as Hypericum, Salvia, and Hypericum perforatum, in clinical trials (Wadsworth et al., 2001, Canning et al., 2010).

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Flavonoids are a family of plant compounds with a similar flavone backbone composed of two aromatic rings and an oxygen heterocycle with hydroxyl groups attached. There are many classes of flavonoids, such as flavones, flavanones, isoflavones, flavonols, flavanonols, flavan-3-ols, and anthocyanidins. Flavonoid molecules may or may not be attached to sugars. Compounds containing no sugars are known as aglycones (Pietta, 2000). The quercetin aglycone is a flavonol that occurs naturally in fruits and vegetables, including onions, apples, grapes and nuts. Therefore, it is commonly included in human diets (Middleton et al., 2000). Quercetin may have already been used in treating human disease (phytotherapy), as it is present in the seeds, stems, barks, roots and/or flowers of several medicinal plants.

Typically, quercetin is linked to sugars, such as glucose (quercetin-3-glucoside, isoquercitrin) or rutinose (rutin). However, after ingestion, enzymes in the mouth and the intestines hydrolyze quercetin glycosides to quercetin aglycones (Egert et al., 2010; Perez-Vizcaino et al., 2009). Interestingly, quercetin and its metabolites have been observed in the lungs of rats (De Boer et al., 2005). In human, quercetin metabolites have also been found to be present in the carbon dioxide (CO₂) exhaled from the lung (Walle et al., 2001).

**POTENTIAL EFFECTS OF QUERCETIN ON ASTHMA**

Quercetin has a wide range of therapeutic properties, including, but not limited to, its antioxidant, anti-cancer, anti-inflammatory and anti-allergic activities. Recently, key findings have been made regarding the effects of quercetin on the airway (Figure 1).

Mast cells play an important role in the early and late phases of asthma, as they release several mediators, including histamine, leukotrienes and cytokines, which modulate airway hyperreactivity and inflammation. IgE binds to mast cells and basophils through their high-affinity IgE Fc receptor (FceRI) (Gould, Sutton, 2008; Furuichi, Rivera, Isersky, 1985), and subsequent exposure to antigen induces IgE-sensitized mast cell degranulation. During degranulation, both pre-formed and newly generated mediators are released. These mediators, either alone or in conjunction with Th2 cytokines, increase smooth muscle cell contractility, epithelial cell permeability and mucus production. Furthermore, mast cell degranulation triggers the recruitment of macrophages, eosinophils and basophils to the inflammatory site (Holgate, Polosa, 2008). Previous findings have shown that treatment with quercetin inhibits the release of histamine and pro-inflammatory mediators (TNF-α, IL-1β, IL-6 and IL-8) from mast cells stimulated with IgE (Cruz et al., 2012; Park et al., 2008; Kempuraj et al., 2005), likely due to inhibition of NF-κB and p38 mitogen-activated protein kinase (p38 MAPK) (Min et al., 2007). Thus, quercetin demonstrates the potential to modulate the early and late phases of asthma.

A systematic review conducted by our group showed the anti-eosinophilic effects of medicinal plants and plant-derived substances in eosinophilic models, including models of acute peritonitis induced by either the polysaccharide-rich F1 fraction from Histoplasma capsulatum yeast or by Toxocara canis helminth infection, also known as visceral larva migrans syndrome (VLMS) or toxocariasis, and the classical ovalbumin-induced allergic asthma model (Rogerio, Sá-Nunes, Faccioli, 2010). Eosinophils produce cytokines (e.g., IL-4, IL-5 and IL-13), chemokines (e.g., CCL11) (Perretti, Flower, 1993; Barnes, 1998; Barnes, 2006), lipid mediators (LTB₄) and principal cationic proteins (major basic protein, eosinophil-derived neurotoxin, eosinophil cationic protein and eosinophil peroxidase) that can exacerbate airway inflammation and cause tissue damage (Rothenberg, Hogan, 2006; Gleich, Loegering, 1984). Our group was the first to demonstrate that quercetin (10 mg/kg; oral dose) reduces eosinophils in the blood, bronchoalveolar lavage fluid (BALF) and the pulmonary parenchyma in a murine model of ovalbumin-induced allergic airways inflammation (Rogerio et al., 2007). Interestingly, in this study, isoquercitrin (quercetin attached to glucose) was more efficient than quercetin aglycone in decreasing IL-5 concentrations in the BALF. IL-5 is the main cytokine involved in blood eosinophilia during both allergic inflammation and parasitic infection. This cytokine is essential for eosinophil migration from the bone marrow to the blood (Faccioli et al., 1996; Sanderson et al., 1985), and it specifically supports the terminal differentiation and proliferation of eosinophil precursors. Additionally, IL-5 activates mature eosinophils (Yamaguchi et al., 1988; Clutterbuck, Sanderson, 1988). Similar results were found by other groups employing the same experimental models in mice and guinea pigs but using different routes of quercetin administration (intraperitoneal or aerosol route) (Moon et al., 2008; Jung et al., 2007; Park et al., 2009). Quercetin has also demonstrated the potential to reduce airway hyperresponsiveness, bronchial hyperactivity (Ko et al., 2004; Jiang et al., 2007) and mucus production (Chang et al., 2010).

Despite its potential systemic anti-inflammatory property, quercetin aglycone is known to be poorly soluble
in water. Previous findings have shown that it is less absorbed than quercetin glycosides and that its absorption seems to depend on the type and position of the sugar moieties (Hollman et al., 1995; Hollman et al., 1997). In the above studies, dimethyl sulfoxide (DMSO) and polyethylene glycol were used as adjuvants to improve quercetin solubilization and absorption. However, these substances are not approved for human use.

Colloidal drug delivery systems, such as microemulsions, have been proposed to improve the absorption and therapeutic index of several drugs (Gupta et al., 2005). Microemulsions are isotropic liquid mixtures of oil, water and surfactant frequently found in combination with a co-surfactant and are translucent and thermodynamically stable. The dispersed phase, generally lipophilic, acts as a potential reservoir of lipophilic drugs that, when it contacts semi-permeable membranes, such as skin or a mucus membrane, can facilitate the transport of drugs through these barriers (Formariz et al., 2007; Vicentini et al., 2008).

In a murine model of ovalbumin-induced allergic airway inflammation, treatment with a quercetin-loaded microemulsion (QU-ME) was more effective than quercetin suspension (QU-SP) and reduced eosinophil recruitment; decreased the production of IL-4, IL-5, CCL11 and LTB_4; inhibited mucus production; and down-modulated P-selectin expression by blocking NF-κB signaling. Under inflammatory conditions, IL-5 and the eotaxins CCL11, CCL24 and CCL26 have been shown to cooperate in selectively recruiting eosinophils (Jose et al., 1994; Rothenberg et al., 1995). IL-4 and IL-13 are potent inducers of eotaxins. Additionally, when administered exogenously, eosinophils collaborate with IL-5 to induce IL-13 production in the lungs (Zimmermann et al., 2003). LTB_4,
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In the inflammation associated with asthma, the expression of multiple inflammatory mediators is regulated by transcription factors. The T-box and GATA family of transcription factors play several roles in hematopoiesis and is active in many cell lineages, including T cells. While the upregulation of GATA-3 promotes Th2 cell differentiation (Barnes, 2011), the expression of T-bet is a determinant for Th1 cell differentiation (Lazarevic, Glimcher, 2011). Quercetin suppressed GATA-3 and increased T-bet expression in a murine model of ovalbumin-induced allergic airway inflammation. Consequently, quercetin reduced IL-4 and increased IFN-γ concentration in the BALF of these animals (Park et al., 2009). IL-4 is primarily responsible for the development of Th2-type immune responses. In contrast, IFN-γ, a Th1 cytokine, inhibits Th2 immune responses and may provide some rationale for the outcome of allergic airway inflammation (Saggini et al., 2011). These results demonstrate that quercetin is able to modulate Th1/Th2 cytokine production and consequently asthma pathology.

Currently, many questions still remain concerning the nature of the inflammatory process in severe episodes of asthma exacerbation. In addition to eosinophils, neutrophils are also important cells that release oxidative products, eicosanoids and metalloproteinases (specifically MMP-9), which contribute to lung epithelial and endothelial cell injury and increase vascular permeability. Interestingly, tissue inhibitor of metalloproteinase (TIMP)-1, an inhibitor of MMP-9, is reduced in the plasma and the bronchi of patients with asthma (Belleguic et al., 2002). In an experimental model of airway inflammation induced by the intranasal administration of elastase and LPS, quercetin inhibited neutrophil recruitment and MMP-9 and MMP-12 expression and activity both in vivo and in vitro (Ganesan et al., 2010). Taken together with other published results, these findings suggest potential beneficial effects of quercetin treatment on asthmatic airway inflammation.

The airway epithelium’s function is to transport air into the alveoli and to protect the lungs against pathogens, allergens and inhaled environmental particulates through the secretion of antimicrobial molecules and pro-inflammatory cytokines and chemokines. In addition, the airway epithelium also has the ability to modulate the function of lung dendritic cells, which are essential in initiating inflammation and determining the type of effector immune response (Th1, Th2 or Th17) (Belleguic et al., 2002; Ganesan et al., 2010). Treatment with quercetin prior to TNF-α stimulation reduced the expression of IL-8 and chemokines (C-C motif) ligand 2 (CCL2/MCP-1) in bronchial epithelial cells (Nanua et al., 2006), which are involved in asthma pathogenesis (Romagnani, 2002). This effect was associated with attenuation of the PI3-kinase, Akt and NF-κB signaling pathways. Several other studies have also demonstrated this effect of quercetin on NF-κB reduction (Nam, 2006; Rahman, Adcock, 2006).

Adhesion molecules are involved in the control of leukocyte influx. Expression of intercellular adhesion molecule-1 (ICAM-1), an adhesion molecule that participates in cell-cell and cell-matrix adhesive interactions, has been associated with several inflammatory diseases, including asthma (Stanciu, Djukanovic, 1998). Quercetin has been shown to reduce ICAM-1 expression on a pulmonary epithelial cell line (A549) in a dose-dependent manner, and decreased ICAM-1 expression has been shown to be mediated through inhibition of the NF-κB, ERK-1/2 and JNK signaling pathways (Ying et al., 2009). Thus, quercetin’s effect in reducing leukocyte recruitment may be associated with a reduction in chemokines and adhesion molecules. In addition to epithelial cells, fibroblasts are also involved in asthma pathogenesis.

Fibroblasts are responsible for the synthesis of collagen, with human fibroblasts synthesizing both type I and type III collagen. Repetitive injury of the alveolar-capillary membrane results in a loss of basement membrane integrity, and the subsequent activation of fibroblasts and myofibroblasts can lead to fibrosis. In the lungs, fibroblast accumulation and abnormal remodeling can result in respiratory failure (Bousquet, Yssel, Vignola, 2000). Studies have shown that quercetin exhibits potent antifibrotic effects in the lungs (Nakamura et al., 2011; Qi et al., 2001). Treatment with liposomal quercetin in a rat bleomycin-induced pulmonary fibrosis model suppressed lung hydroxyproline content and collagen deposition (Baowen et al., 2010). Quercetin also decreased type I and type III collagen synthesis in both keloid and normal fibroblasts in a dose-dependent manner (Long et al., 2006). Heme oxygenase (HO)-1, an inducible stress protein, has been suggested to confer protection in diseases associated with lung injury. Nakamura et al. (2011) demonstrated that quercetin reduced fibroblast collagen deposition by inducing HO-1 upregulation. In another study using a murine model of experimental infection with Schistosoma japonicum, quercetin inhibited liver fibrosis (Xu et al., 2010).
2006). These results suggest that quercetin might modulate airway remodeling in asthmatic patients. Interestingly, quercetin acts as a potent bronchodilator in vitro (tracheal smooth muscle) and in vivo (guinea pigs sensitized with ovalbumin) (Joskova et al., 2011).

In humans, there is some correlation between an increased risk for several chronic diseases and a lower dietary flavonoid intake. For instance, the incidence of asthma is lower in individuals who ingested higher quantities of total flavonoids, including quercetin (Knekt et al., 2002). Quercetin has been present in the human diet throughout the history of humanity, and it is currently used as a food additive (Harwood et al., 2007). Daily oral intake of quercetin can range from 5 to 500 mg, depending on the individual’s consumption of quercetin-rich fruits and vegetables, such as tomatoes and onions. Several epidemiological studies and clinical trials as well as animal and in vitro studies have been performed to evaluate the safety of quercetin. Nearly all reports found little association between dietary quercetin consumption and an increased risk of cancer or other adverse health effects (Harwood et al., 2007; Okamoto, 2005). However, quercetin, similar to other substances, may interfere with the pharmacokinetics of other medicines, such as digoxin, which could lead to significant adverse events (Wang et al., 2004). Evidence also suggests that quercetin may reduce the bioavailability of cyclosporine, simvastatin and other drugs. Therefore, although quercetin itself causes no direct significant side effects, it may give rise to indirect side effects when used in combination with other drugs. Thus, quercetin should be administered carefully if given concomitantly with other medications. However, no interactions have been described regarding the concomitant use of quercetin with drugs, such as β2-agonists and corticosteroids, that are currently used to treat asthma.

CONCLUSION

Asthma and its primary exacerbations demonstrate high morbidity, mortality and health care costs. In addition, some patients are refractory to the current therapies of β2-agonists and corticosteroids, whose adverse side effects limit their long-term use. Quercetin, which has been widely consumed in the diet since the beginnings of human history, has significant biological effects with no known significant adverse side effects. Quercetin demonstrates the potential to reduce the most significant pathologies of asthma, including eosinophil and neutrophil recruitment, bronchial epithelial cell activation, mucus and collagen production and airway hyperactivity. These results, in association with the low incidence of asthma in individuals with moderate dietary intake levels of quercetin, suggest that quercetin could be used medicinally, either alone or as a complement to other drugs currently used for the treatment of asthma. Additionally, it could also be used as a nutraceutical. Thus, clinical studies must be performed to evaluate the potential of quercetin to prevent or treat episodes of asthma in human patients.

LIST OF ABBREVIATIONS

AHR: airway hyperresponsiveness
ASA: acetylsalicylic acid
BALF: bronchoalveolar lavage fluids
BC: before Christ
CCL: chemokine (C-C motif) ligand
ERK: extracellular-signal-regulated kinase
FcεRI: high-affinity IgE Fc receptor
ICAM-1: intercellular adhesion molecule-1
IFN-γ: interferon gamma
Ig: immunoglobulin
IL: interleukin
JNK: c-Jun N-terminal kinase
LPS: lipopolysaccharides
LTB4: leukotriene B4
MAPK: mitogen-activated protein (MAP) kinases
MCP-1: monocyte chemoattractant protein 1
MMP: matrix metalloproteinase
NF-κB: nuclear factor-κB
NKT: natural killer T
p38 MAPK: P38 mitogen-activated protein kinase
PaCO2: pressure of carbon dioxide
PI3K: phosphatidylinositol (PI) 3-kinase
QU-ME: quercetin-loaded microemulsion
QU-SP: quercetin suspension
Th: T helper
TIMP: tissue inhibitor of metalloproteinase
TNF-α: tumour necrosis factor alpha
Treg: T regulatory cell

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