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Effect of Quercetin on Asthma and Nasal Allergies as an Immunomodulator: Review

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Abstract:

Quercetin is a flavonoid found in nature, and is rich in antioxidants. It is recognized as an important natural substance, notable for its potent effects in modulating the immune system and its anti-inflammatory characteristics. Many fruits and vegetables, such as onions, shallots, apples, and different berries, contain quercetin. Consequently, this review aims to elucidate the function of quercetin as an immune enhancer and its significance in managing asthma and nasal allergies. A variety of research studies involving both human and animal subjects have been conducted, with ongoing investigations both in vitro and in vivo continuing until 2024. The effects of quercetin as an anti-inflammatory agent and anti-asthmatic conditions, it is also linked to decreased levels of interleukin IL-4, inhibition of histamine release, and a decrease in the synthesis of pro-inflammatory cytokines and leukotrienes. Quercetin has the potential to diminish the creation of antigen-specific IgE immunoglobulin and enhance the balance between Th1 and the responses. inconclusion: the characteristics of quercetin could serve as a therapeutic approach for conditions such as asthma and nasal allergies.

Keywords: Quercetin, asthma, nasal allergies, IgE, immunomodulator

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Introduction:

In a healthy organism, the immune system plays a crucial role in preserving internal balance. Its performance and effectiveness can be affected by a range of external and internal factors, leading to either a decrease in immune response (immunosuppression) or an increase in immune activity (immunostimulation). Substances that can adjust or restore normal pathophysiological functions are called immunomodulators, typically classified into three main categories: immunoadjuvants, immunostimulants, and immunosuppressants. Immunoadjuvants are specific agents that enhance the effectiveness of vaccines (Puri *et.al*, 1994).

The identification of these compounds may lead to the creation of novel adjuvants for vaccines and therapeutic agents for conditions like allergies and infection. Many immunomodulatory agents are derived from plants such as flavonoids, including citrus-derived compounds like rutin, hesperidin, naringenin, and tangeritin; its present in a variety of fruits and vegetables, including onions, shallots, apples, and berries (Jantan *et.al*,2015).

the quercetin's effects on immunomodulation and allergic diseases, have been explored in different kinds of immune cells, such as NK cells, macrophages, mast cells, neutrophils, B cells, and T cells (Tanaka *et.al*, 2007), quercetin demonstrates the ability to inhibit a wide array of protein kinases by competing with ATP for binding at the nucleotide site (Najafi *et.al*, 2024). Additionally, quercetin has been shown to suppress LPS-induced dendritic cell activation (Tanaka *et.al*, 2007). quercetin suppresses JAK/STAT pathway in cells of the epithelium and modulates innate immunity by lowering TLR4, IL-1, IL-6, and TNF-α levels. It inhibits NF-κB activation, reducing eosinophil activation and cytokine production. Also decreases TH17 responses, enhancing Treg activity, crucial for immune tolerance against allergies. In allergic conditions like asthma, quercetin reduces Th2 cytokines and eosinophilic inflammation, promotes IL-10, and regulates the Th1/Th2 balance. Quercetin nanocrystals show strong anti-asthmatic potential at lower doses, and encapsulated forms enhance anti-inflammatory effects (Hassan & Abood, 2023; Najafi *et.al*, 2024). Quercetin inhibits neutrophilic airway inflammation and smooth muscle contraction, potentially alleviating asthma symptoms and reducing reliance on β-agonists. It also lowers mRNA

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levels of chemokines via NF-κB and PI3-kinase/Akt pathways, suppressing Th2-type cytokines and periostin production. In allergic rhinitis (AR) quercetin reduces inflammatory markers and cytokine levels, showing promise in treatments due to its anti-inflammatory properties (Najafi *et.al*, 2024 and AL-Khazraji *et.al*, 2024).

In consideration of the points discussed, this review aims to elucidate the function of quercetin as an immune enhancer and its significance in managing asthma and nasal allergies.

A. Allergic asthma:

One of the most common chronic inflammatory disorders is allergic asthma (Mukherjee et.al, 2011). Wheezing, airway blockage, and elevated airway sensitivity are typical signs of asthma (Bousquet, 2000). It is mostly dictated by CD4+ T cell immunological responses. Both severe and steroid-resistant forms of asthma are linked to T helper (Th) 1 and Th17 cells, which aid in the recruitment of neutrophils. Additionally, Th9 and Th2 cells have been connected to the control of mucus formation, the recruitment of mast cells and Eosinophils, and the generation of IgE. Other immune cells, such as CD8+ T cells, NKT cells, and γδ T cells, also play roles in modulating inflammation and airway hyperresponsiveness (AHR) related to asthma. Conversely, T regulatory (Treg) cells are known for their capacity to inhibit both innate and adaptive immune responses, thereby alleviating inflammation. Although there is an increasing recognition of the specific functions of various T cell subsets in the pathophysiology of asthma, Th2-type immune responses continue to be the most traditionally associated with the disease's pathology (Lloyd *et.al*, 2010)

Previous asthma medications can cause health issues like Cushing's syndrome, osteoporosis, increased infection risk, and mental disorders. β2-agonists may raise cardiovascular problems due to higher heart rates and lower potassium. Leukotriene inhibitors are linked to headaches and gastrointestinal issues. Thus, new compounds are needed to maintain therapeutic benefits while reducing side effects in managing respiratory diseases. Reduced generation of leukotrienes, inhibition of histamine release, suppression of interleukin (IL)-4 synthesis, and a decrease in pro-inflammatory cytokines are some of these effects. The quercetin helps to treatment late-phase and late-late-phase bronchial asthma, allergic rhinitis, and peanut-induced anaphylactic reactions because it’s able to restore the balance between Th1 and Th2 cells and diminishes the

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formation of antigen-specific IgE antibodies. Its effectiveness extends to the inhibition of various enzymes, including lipoxygenase, eosinophil peroxidase, and inflammatory mediators. These mechanisms collectively underpin quercetin's anti-inflammatory and immunomodulatory effects, making it viable treatments (Mlcek *et.al*, 2016).

Quercetin's role in modulating the immune response in asthma has been observed with notable effects. A significant positive relationship was identified between elevated Act-1 mRNA levels, increased eosinophil infiltration, and the production of lgE antibodies. The number of mast cells, subepithelial smooth muscle thickness, and epithelial thickness all decreased after quercetin treatment. Additionally, quercetin treatment significantly reduced the degranulation and release of a number of chemical mediators from activated mast cells, such as PGD2, mMCPT-1 Cys-L, and TSLP. Additionally, quercetin was found to lower the production of IL-4 and Th2 cytokines, which were previously elevated, while simultaneously enhancing the synthesis of Th1 cytokines and IFN-γ (Najafi *et.al*, 2024), fig (1).

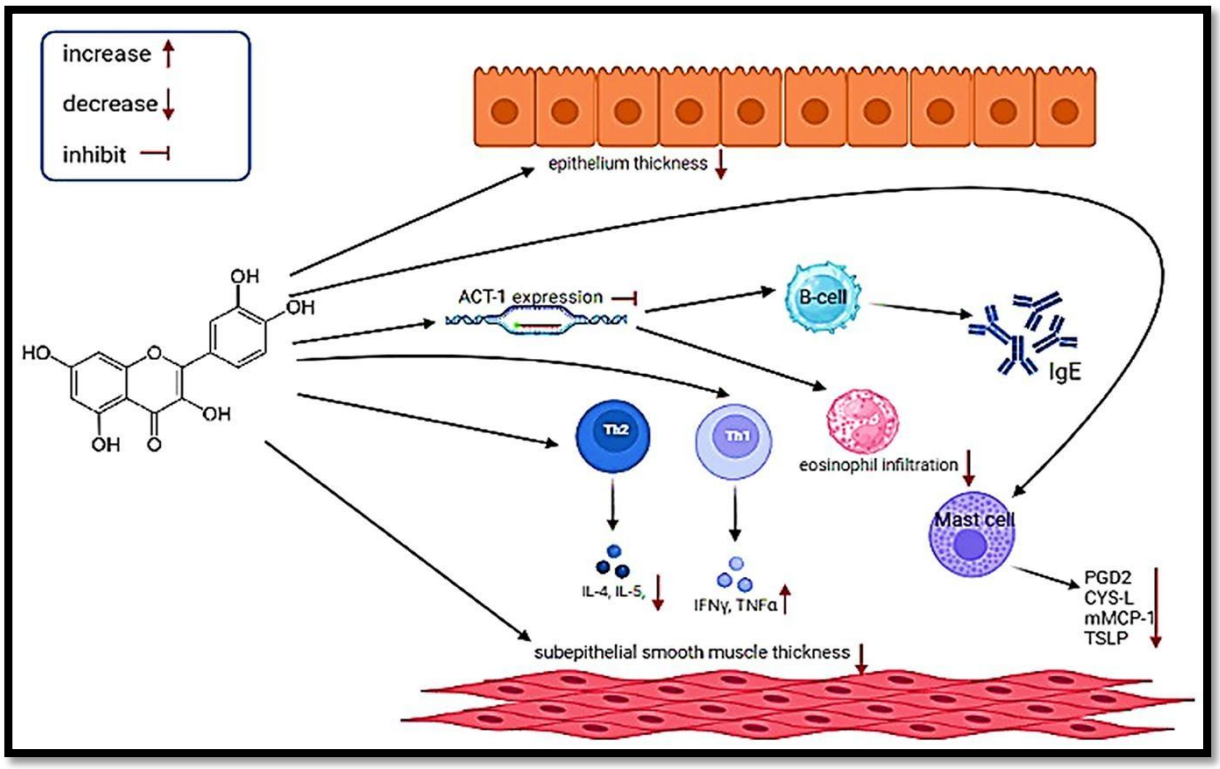

Figure (1): Mechanism action of quercetin on asthma and allergies (Najafi *et.al*, 2024)

In various animal studies, the effects of quercetin on asthma have been extensively examined:

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Ravikumar *et al.* (2020) indicated that a dosage of 30 mg/kg of quercetin led to a decrease in interleukin-4 levels produced by eosinophils while simultaneously increasing interferon-gamma in diabetic asthma models. Consequently, this resulted in diminished allergic airway inflammation and hyperglycemia, illustrating a dose-dependent adjustment of the Th1/Th2 balance and highlighting its anti-asthmatic effects. Cai *et al.* (2017) investigated that a quercetin administered at 50 mg/kg was reduce OVA-induced IgE levels, as well as interleukin-4, interleukin-17, eosinophil counts, and airway resistance. The treatment also suppressed the expression of Act-1, correlating with a reduction in allergic inflammation and airway hyperreactivity.

Sozmen *et al.* (2016): found the use of quercetin led to a decrease in the thickness of epithelial and smooth muscle layers, alongside a reduction in the number of goblet and mast cells associated with allergic airway inflammation.

Park *et al*. (2008): Findings show that Quercetin decreased IL-4 (Th2 cytokine) levels and increased IFN-gamma (Th1 cytokine) production in treated mice. Additionally, Quercetin reduced Eosinophil peroxidase (EPO) activity and significantly inhibited asthmatic reactions when administered before the final OVA challenge. Rogerio *et al*. (2009) found the quercetin suspension (QU-SP) was not as well absorbed as quercetin microemulsion (QU-ME).. QU-ME inhibited eosinophil recruitment in BALF and reduced IL-5 and IL-4 levels, while also inhibiting NF-κB activation, P-selectin expression, and mucus production in the lungs. These results indicate that QU-ME has significant anti-inflammatory effects and potential therapeutic uses for airway inflammatory diseases, highlighting Quercetin's role in reducing asthma symptoms in mice.

Gupta *et al*. (2016) examined the effects of quercetin nanocrystals (nQ) on allergic asthma using an ovalbumin (OVA) sensitized BALB/c mice model. nQ, produced via high-energy sonication, exhibited superior water solubility and stability compared to bulk quercetin. The study revealed that nQ had significant anti-asthmatic effects at a reduced dosage (1 mg/kg) than bulk quercetin, reducing OVA-specific immunoglobulin E (sIgE) levels and alleviating anaphylaxis symptoms. Furthermore, nQ influenced Th2 cytokines (IL-4, IL-5) and decreased mast cell mediators (PGD2, mMCPT-1, Cys-L, TSLP). Treated mice showed lower levels of key proteins (FcεR1, Syk, c-Yes,

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PI-3, p-PI-3, PLC-γ2, p-PLC-γ2). In conclusion, nQ represents a promising treatment for allergic asthma by effectively reducing pulmonary inflammation and airway hypersensitivity.

Townsend *et al*. (2013) reported that quercetin diminished the activity of phospholipase C as well as the intracellular calcium responses elicited by agonists. In an in vivo study, the administration of nebulized quercetin at a concentration of 100 μM significantly lowered airway resistance triggered by methacholine. These results imply that quercetin may provide therapeutic advantages for asthma, potentially decreasing the reliance on β-agonists. The research conducted by Joskova *et al.* (2011) revealed that quercetin at a dosage of 20 mg/kg demonstrated significant bronchodilation effects, as evidenced by both in vivo and in vitro investigations.

A study by Moon *et al*. (2008) examined quercetin inhalation's effects on asthmatic responses in guinea pigs sensitized to aerosolized ovalbumin. Quercetin reduced histamine, protein levels, PLA2 activity, and leukocyte recruitment in bronchoalveolar lavage fluid, with slight improvements in eosinophil and neutrophil infiltration. It had anti-asthmatic properties comparable to those of dexamethasone and cromolyn sodium., Quercetin effectively decreased airway hyperreactivity, a key feature of allergic asthma. Chen *et al*. (2021) examined how quercetin and isoquercitrin reduced inflammation in atypical asthma. finding both compounds reduced inflammatory cells and cytokines in bronchoalveolar lavage fluid (BALF). Quercitrin increased IFN-γ levels, while both compounds raised IgG2a and lowered total and OVA-specific IgE in serum and BALF. Rutin and quercitrin had minimal adverse effects, indicating their potential for atypical asthma treatment, unlike isoquercitrin.

Oliveira *et al.* (2015) investigated the effects of Allium cepa L. extract (AcE) and quercetin (Qt) on smooth muscle contraction and cytokine production in vitro and in a mouse model of asthma. Their findings indicated that treatment with AcE or Qt led to a reduction in inflammatory cytokine levels, tracheal rings relaxing, and a decrease in the total cell count observed in bronchoalveolar lavage (BAL) and eosinophil peroxidase (EPO) in the lungs. Wang *et al*. (2023) found that quercetin effectively diminished neutrophilic airway inflammation linked to ferroptosis and also hindered the polarization of M1 macrophages. This suggests that targeting ferroptosis with quercetin could be a promising therapeutic

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approach for managing neutrophilic airway inflammation.

B. Nasal allergies:

Nasal allergy (NA) is a chronic inflammatory disorder of the respiratory system that is mediated by Immunoglobulin E (IgE). It has a significant prevalence, affecting as many as 40% of individuals, which leads to loss of productivity, decreased quality of life, and associated health issues (Irie *et.al*, 2016). In patients with NA, various inflammatory cells infiltrate the nasal mucosa after exposure to specific allergens, which most commonly include airborne particles such as dust mite feces, cockroach remnants, pet dander, mold spores, and pollen. The T cells that invade the nasal lining in allergic individuals are primarily of the Th2 subtype, producing cytokines that encourage plasma cells to produce IgE, such as IL-3, IL-4, IL-5, and IL-13. The release of mediators such as histamine and leukotrienes is triggered when allergens cross-link with IgE on mast cells, which cause symptoms such as vasodilation, increased permeability of blood vessels, itching, runny nose, mucus production, and bronchial smooth muscle contraction. Within 4 to 8 hours of the first immunological reaction to an allergen, mediators and cytokines are released, which trigger a subsequent cellular inflammatory response (referred to as the late-phase inflammatory response). This might result in persistent symptoms, mainly nasal congestion. (Ebihara *et.al*, 2018). Various treatment options for allergic rhinitis (AR) exist, including antihistamines, corticosteroids, montelukast (Singulair), and immunotherapy. Nonetheless, these treatments may not always be effective (Kulka, 2009). In order to create models of NA and assess the effects of various medications, like quercetin, research has been done both in vitro and in vivo.

In human research, Tanaka *et al.* (2020) explored the impact of quercetin on the inhibition of Th2-type cytokine production and its potential to mitigate allergic reactions (AR). They cultured human peripheral blood CD4+ T cells at a density of 1×10^6 cells/mL with 10.0 ng/mL of IL-4, both with and without quercetin. The findings indicated that quercetin concentrations exceeding 5.0 µM could inhibit the synthesis of IL-5 and IL-13 by CD4+ T cells in response to IL-4 encouragement. This inhibition was attributed to the prevention of activation of the transcription factors NF-kB and STAT6, along with reduced cytokine mRNA expression. Furthermore, quercetin was shown to counteract the suppressive effects of IL-4 on the ability of CD4+ T

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cells to produce INF-γ. In a separate investigation, Ebihara *et al*. (2018) examined quercetin's influence on nitric oxide (NO) production. They used 10.0 ng/mL of IL-4 to activate human nasal epithelial cells (HNEpCs) at a density of 1 x 105 cells/mL, both with and without quercetin. Quercetin reduced STAT6 activation and iNOS mRNA expression when added to the cells at a minimal dose of 1.0 nM. This prevented HNEpCs from producing NO after IL-4 stimulation.

In animal research, Xing *et.al*. (2021) examined Quercetin's effects on mice's airway inflammation. Their findings indicated that administering a dosage of 50 mg/kg of quercetin led to a significant reduction in allergic symptoms, Including mice models of sneeze, nasal rubbing, and nasal redness. Additionally, they observed a dose-dependent decrease in levels of nitric oxide (NO), histamine, immunoglobulin E (IgE), and various cytokines such as TNF-α, IL-1β, IL-4, and IL-5. Conversely, there was an increase in interferon (IFN-) levels in mice with allergic asthma induced by ovalbumin (OVA).

In a separate investigation, Sagit *et.al*. (2017) studied the therapeutic effects of quercetin on rat models of allergic rhinitis (AR). The rats were treated with quercetin at a dosage of 80 mg/kg/day administered intranasally, histopathological assessments revealed a notable reduction in vascular dilation, mucosal inflammation, and the enlargement of ducts in serous glands among the quercetin-treated rats. Furthermore, immunohistochemical evaluations showed diminished expressions of COX-2 and vasoactive intestinal peptide (VIP) in this group.

Lastly, Kashiwabara *et al*. (2016) explored the influence of quercetin on AR in rat models. They induced sneezing and nasal rubbing by exposing the rats to toluene 2,4-diisocyanate (TDI) through nasal challenges. Their results demonstrated that an oral dose of quercetin, starting at 25 mg/kg over periods of 5 and 7 days, effectively inhibited these symptoms. Additionally, the amounts of substance P, calcitonin gene-related peptide (CGRP), and nerve growth factor (NGF) in nasal lavage fluids were much lower.

Conclusions:

In this study, we examined the impact of quercetin on allergic asthma and nasal. Allergic conditions pose significant challenges and incur substantial healthcare expenses. Quercetin, a compound with a long history of human use and animal studies, has shown considerable effectiveness with minimal adverse effects. It may be able to alleviate major asthma-related issues, including eosinophil and

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neutrophil recruitment, the bronchial epithelial cells' activation, as well as mucus production, and airway hyperresponsiveness. Additionally, quercetin can inhibit the production of periostin and the eosinophil chemo attractants it induces, leading to improvements in the clinical management of asthma and nasal allergies. Consequently, it represents a promising candidate for supplementation in the treatment of allergic diseases. Given that medicinal plants are generally inexpensive, derived from natural sources, and associated with reduced adverse effects, quercetin appears to be a strong therapeutic candidate for allergic conditions in clinical studies.

Conflict of interest

Regarding the publishing and/or funding of this work, the authors affirm that they have no conflicts of interest.

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