

## Quercetin: A Promising Treatment for the Common Cold

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### Abstract

Rhinovirus infections have afflicted humanity since the dawn of civilization, and are difficult to treat even with modern medicine. Throughout the ages many remedies have been used for the common cold, often caused by the rhinovirus. Recent research points to a flavanol anti-oxidant, quercetin, as having therapeutic properties. Quercetin has been shown to reduce viral internalization and replication in vitro, and viral load, lung inflammation and airways hyper-responsiveness in vivo.

**Keywords:** Rhinovirus; Flavonoids; Infection; Inflammation

### Common Cold and Respiratory Viruses

The common cold has afflicted humanity since antiquity. Hippocrates described the common cold as “a running at the nose and . . . a discharge from the nostrils . . . it makes the nose swell and renders it hot and inflamed.” [1]. The ancient Egyptians were also familiar with the common cold, having a hieroglyph for the disease, and prescribed “the administration of milk of one who has borne a male child and fragrant gum” [1]. Other ancient remedies included bleeding patients, and kissing the muzzle of a mouse [2].

Despite our growth in medical knowledge and understanding, modern treatments for the common cold have advanced little. No known cure for the common cold exists, yet the disease imposes costs of around \$40 billion per year in the United States, and is the leading cause for doctor visits and missed school days [3,4]. Respiratory infections are the leading causes of death for children under age 5, and recurring viral infections during infancy may lead to the development of asthma later in life [4,5]. In patients with chronic lung diseases including asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis, 40-60% of exacerbations are associated with respiratory viruses, imposing tremendous burdens on healthcare costs and sometimes accelerating progression of lung disease in these patients [5-8]. Respiratory viral infections also increase the risk of acquiring secondary bacterial infections requiring antibiotics.

Rhinoviruses are small non-enveloped single-stranded RNA viruses and belong to the family Picornaviridae. Rhinoviruses are responsible for the majority of common colds [9,10] and are also associated with between 25% to over 50% of exacerbations in patients with chronic lung diseases. Recently, experimental rhinovirus infection in COPD patients was shown to cause prolonged lower respiratory symptoms including wheezing, shortness of breath, increased sputum production, and increased bacterial burden in the lungs [11,12]. Rhinovirus infection may enhance susceptibility to bacterial infection by impairing innate immune defense mechanisms of the respiratory tract, such as enhancing paracellular permeability of airway epithelium, degrading antimicrobial peptides expressed in the airways,

and inhibiting protective innate immune responses to subsequent bacterial infections [13-16].

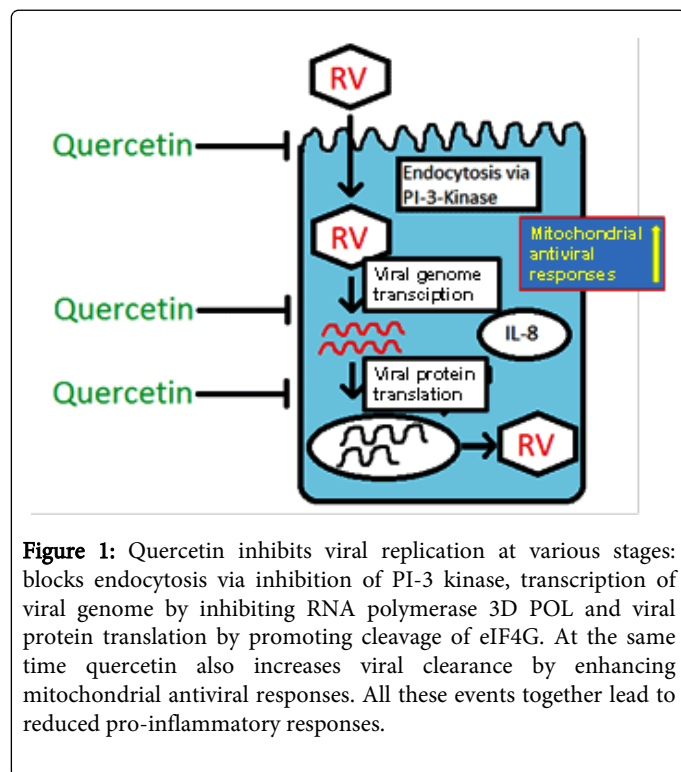
Although numerous preparations are available to treat the symptoms of the common cold, only a few of these agents have been shown to reduce symptoms and/or to shorten the duration of illness. An effective vaccine or antiviral drug against common cold causing viruses does not exist. Since ancient times, extracts from various herbal products have been used to reduce symptoms of the common cold in adults and children. Recent studies have identified active compounds in these herbal mixtures that exhibit antiviral activity and/or modulate innate immunity [17]. In addition, Vitamin C, an antioxidant, is also believed to prevent or reduce duration of the common cold.

Quercetin, a plant flavonol found in various foods including blue berries, red onions, kale, cranberries, broccoli, and green tea. The physiologist Albert Szent Gyorgyi first discovered flavonoids in 1930, and they were soon found to be important in a variety of plant processes, from pigmentation to protection against bacteria and fungi [18]. More than 4000 flavonoids have been described, and their activity in humans is diverse; from scavenging free radicals and modulating enzyme activities, to modifying gene expression and even inducing cellular apoptosis. Quercetin itself has poor water solubility, and is therefore often found stabilized by sugars. Although intestinal absorption is in the range of 30-50%, Quercetin's long half-life of 25 hours suggests high plasma levels are maintainable with proper diet [18]. Moreover, vitamin C has been shown to improve quercetin absorption by the intestine and enhances plasma quercetin levels [19].

Quercetin is a well-known antioxidant with antiviral and anti-inflammatory properties. Reactive Oxygenated Species (ROS) produced during viral infection although is required for effective clearance of virus and induce beneficial inflammation, excessive production or persistently increased ROS generation may cause tissue damage. Administration of antioxidants may therefore attenuate oxidative damage and susceptibility to secondary bacterial infection. Experiments suggest that quercetin not only scavenges free radicals to prevent tissue damage, but also decreases inflammatory markers such as IL-8, and exerts antiviral effects [19].

Recent in vitro studies have demonstrated that quercetin acts as a potent antiviral agent by inhibiting viral replication of several

respiratory viruses, including influenza virus, parainfluenza virus, respiratory syncytial virus, adenovirus, and rhinovirus [18,20-23]. Although the quercetin's antiviral mechanisms are not well understood, a number of possibilities have been proposed and is summarized in (Figure 1).



**Figure 1:** Quercetin inhibits viral replication at various stages: blocks endocytosis via inhibition of PI-3 kinase, transcription of viral genome by inhibiting RNA polymerase 3D POL and viral protein translation by promoting cleavage of eIF4G. At the same time quercetin also increases viral clearance by enhancing mitochondrial antiviral responses. All these events together lead to reduced pro-inflammatory responses.

Quercetin increases skeletal muscle mitochondrial biogenesis, and so could exert its antiviral effects through enhanced mitochondrial antiviral signaling [24]. Quercetin has been shown to inhibit PI-3-kinase, an enzyme required for viral endocytosis, and RNA polymerase 3DPOL which is required for negative-strand RNA production. Finally, there is also evidence that quercetin cleaves eIF4G to inhibit viral genome translation, and may inhibit PI-4-kinases required for viral replication in specialized lipid organelles of the cell [24].

Additionally, quercetin reduces rhinovirus-induced expression of pro-inflammatory cytokines and lung inflammation in mice [23,24]. Quercetin was also found to reduce viral load and improve lung function in a mouse model of chronic obstructive pulmonary disease [24]. Interestingly, quercetin supplementation was demonstrated to reduce susceptibility to influenza A virus infection and the severity of the disease in mice [25], and reduce symptoms of upper respiratory infections in athletes post- stressful exercise [26]. Despite mounting evidence, no clinical trials have been performed examining the effects of quercetin on the common cold.

**Future directions:** Because the common cold is caused by several respiratory viruses, vaccination against any single virus may not be effective in preventing the common cold. Instead, an antiviral agent such as quercetin, which inhibits viral infection and replication at various stages without being specific to a single virus, and with no serious side effects, may be more promising in the treatment of the common cold.

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