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QUERCETIN AS AN ANTIVIRAL WEAPON-A REVIEW

Ramen Kalita[1]*, Kunal Bhattacharya [1], Amir Ali[1], Satyasish Sandilya[2]

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ABSTRACT

Antioxidants are substances that can prevent cells from the damage caused by unstable molecules such as free radicals. Quercetin, a plant pigment present in many fruits, vegetables, grains, and one of the most beneficial antioxidants in the diet and plays an important role in helping the body and prevent free radical damage, which is linked to chronic diseases. The antioxidant properties of quercetin may help to reduce inflammation, allergy symptoms, blood pressure. A lot of studies have been done and experiments have been conducted both in vivo and in vitro and it has been found that in cultured cells many respiratory viruses were inhibited by quercetin. At a minimal inhibitory concentration of 0.03 to 0.5µg/ml in WI-38 or Hela cells, Cytopathic effects produced by echovirus type 7,11,12,19, rhinovirus, poliovirus, and coxsackievirus A21 and B1 were inhibited. The plaque formed by DNA and RNA viruses such as Herpes Simplex Virus-1, Polio type 1, and parainfluenza types 3 were effectively reduced demonstrating its anti-replicative properties. This article reviews effect of quercetin on different types of viral infections.

INTRODUCTION

Most of the Plants and it's parts are used for their flavour, scent, and therapeutic uses. It has been proved that the plant extracts and their phytoconstituents showed various biological activities such as antidiabetic, antihyperlipidemic, free-radical scavenging, and anti-inflammatory activities. It has been studied that Quercetin has promising antiviral effects in inhibiting polymerases, proteases, reverse transcriptas, suppressing DNA gyrase, and binding viral capsid protein. Quercetin (3, 3', 4', 5, 7-pentahydroxyflavone) is one of the most promising flavonoids, and it is found in many Chinese herbs, vegetables, and fruits, as well as red wine. A number of experiments have shown that quercetin may be used as an antiproliferative, antioxidative, antibacterial, anticancer, and antiviral agent. It has been found that quercetin could protect patients in severe

[1]*NETES Institute of Pharmaceutical Science, Mirza, Kamrup, Assam-781125, India*
[2]*Pratiksha Institute of Pharmaceutical Science, Panikhaiti, Guwahati-781026, India*

For Correspondence: **ramengips89@gmail.com**

complications associated with the pandemic influenza A (H1N1) virus infection [1]. Although, the details of the anti-influenza mechanism of Quercetin remain to be elucidated. Chlorogenic acid and Quercetin were derived from traditional Chinese medicine and tested in molecular docking against influenza A virus H1N1 (A/PR/8/34). It has been proved that both the compounds showed strong binding abilities (−10.23 and −11.05 kcal/mol for Quercetin and chlorogenic acid, respectively) with Neuraminidases (NA) of this virus which was comparable with oseltamivir (−11.24 kcal/mol).

Quercetin possesses great activity against influenza infection in the early stages by interacting with the HA2 subunit of influenza HA protein and inhibited virus-cell fusion. Quercetin and its derivatives may be tested in future clinical trials to enrich the drug arsenal against coronavirus infections due to its pleiotropic activities and lack of systemic toxicity. A synergistic antiviral action may provide an alternative or additional therapeutic/preventive option due to overlapping antiviral and immunomodulatory properties when quercetin is combined with vitamins C and D [2].

EFFECT OF QUERCETIN IN VIRAL INFECTIONS

Quercetin causing a 67 percent decrease in viral RNA of the Dengue virus which demonstrates the property of quercetin to either inhibits the viral polymerases or prevents the entry of the virus at an IC50 of 35.7μg/mL [3]. On administering quercetin to athletes it was found that upper respiratory tract infections that were induced by stress were not observed [4].

During antiviral treatments, the first choice is to always try to stop the entry of the virus into the cell. It has been studied that administering quercetin in 0-2 hours of viral entry on MDCK cells of H3N2 and H1N1, an in vitro model showed decreased cytopathic effect post 48 hours of infection based on the ability to bind with hemagglutinin proteins. The effect was found maximum when the pretreatment was done using quercetin [5]. Via multiple mechanisms in BEAS-2B cells pretreatment with 10μM quercetin in the in-vitro model inhibited Rhinovirus entry. It retard RV endocytosis by misdirecting EEA1 localization and minimized 3-4old viral load at 24 h, lowering negative-strand RNA and modulating interferon (IFN) and IL- 8 expressions [6]. As an antiviral agent quercetin can reduce HIV viral replication by inhibiting integrase, protease, and transcriptase enzyme [7]. Quercetin has been found to be inhibited Rous-associated virus-2 (RAV-2-RT) and Maloney murine leukemia virus (MMLV-RT) non-HIV-RT activity along with avian myeloblastosis reverse transcriptase (AMV-RT) by *in vitro* experiment [8]. Five hydroxyl groups on 3, 3′, 4′, 5, and 7 were assumed to be responsible for the antiviral effects produced by quercetin when compared to luteolin and baicalein where these groups were not found [9].

By *in vitro* experiments of quercetin against adenoviruses (ADV-3−8−11) and herpesviruses (HSV-1, 2), viral replication was seen at an early stage in a dose-dependent manner. At 60mg/L 100 percent inhibition was observed [12-13]. At 10μM concentration of 3-methyl quercetin, 1-2 hours post-infection showed beneficial effects on embryonic kidney cells inoculated with poliovirus which demonstrates the delay in the binding of the heat shock elements and heat shock factor required for transcription of the stress genes.

EFFECT OF QUERCETIN ON HCV LIFE CYCLE

Quercetin being a natural flavonoid has shown great activity on various steps of the HCV life cycle in Huh-7.5 cells and primary human hepatocytes (PHH) infected with HCVcc. It has been studied that quercitin mainly decreases the viral genome replication along with the production of infectious HCV particles and the specific infectivity of the newly produced viral particles (by 85% and 92%, Huh7.5 and PHH respectively) [12-13]. It has been proved that Cell culture media of Huh-7.5 cells infected with JFH1 have collected 72 h after treatment with 50 μM quercetin for quantification of HCV RNA by a viral load assay, which provides a short overview of the assembly of physical viral particles regardless of whether they are infectious or not, and determination of infectivity titers by focus-formation assay, which reflects the assembly of infectious viral particles. It's been observed that a decrease of the viral load by 52.08% ± 22.6% ($p = 0.016$) within the medium of cells treated with quercetin compared to DMSO-treated cells, which can be a consequence of the quercetin-induced inhibition of HCV genome replication [13].

PROTEASE INHIBITION

Quercetin was successfully studied and found that it can inhibit the protease catalytic activity of the Hepatitis C virus in a dose-dependent manner. At 1.25 mg/mL 95 percent NS3 inhibition was observed. At 72 hours post-infection replication of the virus was delayed by 70 percent of the initial rate and along with that

blockage in RNA production of the virus was also observed [14]. When quercetin is added on the cultured blood peripheral mononuclear cells, Interferon-gamma production from the helper T-cells is promoted by quercetin [15]. Lytic activity of NK cells, the proliferation of lymphocytes, and neutrophil chemotaxis were observed in mice during immunonutrition studies when they were administered quercetin along with polyphenols [16-17].

EFFECT OF QUERCETIN ON SARS COV-2

In 1990, the possible antiviral effect of quercetin has been investigated on different members of the family of Corona virus; the first research came out indicating the possible antiviral effects of quercetin against bovine NCDCV and human OC43 Coronaviruses when it was administered at 60µg/mL. With a cytotoxicity concentration of 50% and half maximal inhibitory concentration of 0.014 µg/mL in Vero cells, quercetin inhibited the replication of PEDV [18]. With a half-maximal inhibitory concentration of 73M, Pichia pastoris which contains quercetin prohibits 3CL-like protease. With a cytotoxicity concentration of 3.32mM and half-effective concentration of 83.4 µM coronavirus entry was prohibited by quercetin in the Vero E6 cells. As described by Ling Yi and colleagues, "quercetin offers great potency in the clinical treatment of SARS". In 2003, SARS coronavirus was described as a single-stranded RNA virus [19] consisting of 29,700 nucleotides that encodes two glycoproteins PP1a and PP1b by using the ribosomes for replication of the virus. 3C-like protease upon the synthesis of precursor glycoproteins causes a lytic release of replicates [20].

On administration of quercetin, it binds with SARS-CoV 3CL protease and inhibits its proteolytic activity with an IC50 of 42.79 ± 4.95µM [21]. In Vero E6 cells with an EC50 of 83.4µM Quercetin can block the entry of SARS Coronavirus producing minimal cytotoxicity [22]. Like SARS CoV which infects the type -II pneumocytes with the help of receptor angiotensin-converting enzyme II, SARS CoV-2 which is responsible for the current pandemic also infects in a similar manner [23]. The hydroxyl group present in the quercetin binds with the same binding site to which the SARS CoV-2 virus binds that is the Gln189 site. With binding energy of 5.6 kcal/mol to 3CL pro, docking studies suggest it bound very well to each target. Quercetin binds to ACE2, Spike protein, PLpro, and RdRp properly which suggested Quercetin has a good potential to act as an antiviral agent against SARS CoV-2 [24].

EFFECT OF QUERCITIN IN RESPIRATORY INFECTION

It has been observed that when influenza virus A/Udorn/317/72(H3N2) was instilled in the mice intranasally, it results in a significant decrease in the pulmonary concentrations of catalase, reduced glutathione, and superoxide dismutase [25]. The study also showed a decrease in vitamin E levels. All these effects were observed on the 5th day after viral instillation. Oral administration with quercetin simultaneous with viral instillation produced significant increases in the pulmonary concentrations of catalase, reduced glutathione, and superoxide dismutase. The study concluded that during influenza virus infection, there is 'oxidative stress.' Because quercetin restored the concentrations of many antioxidants, it is proposed that it may be useful as a drug to protect the lung from the harmful effects of oxygen-derived free radicals released during influenza virus infection [25].

EFFECT OF QUERCETIN IN COMMON COLD

Quercitin has some promising effects on the common cold such as running at the nose and discharge from the nostrils because of its well-known antioxidant with antiviral and anti-inflammatory properties.

TOXIC SIDE EFFECTS OF QUERCETIN

Quercetin is reported as a mutagen based on the Ames test; at the same time, most in vivo creature contemplates have shown that quercetin might be a safe compound without any harmful neoplastic infection impacts. Its cost taking note of that in 1999, the International Agency for examination on Cancer (IARC) express that quercetin might not be recorded as a human carcinogen compound [26]. There's no distinct evidence of quercetin teratogenic action on embryonic development; in any case, in vitro examines suggest that quercetin will adversely affect fetal development [27].

In vivo tests have shown that quercetin brought about an exceptionally increase in the prevalence of threatening tumors to the young offspring of mice lacking DNA repair [28]. An *in-vitro* experiment was performed on a four-week rodent showed the increased ratio of liver and kidney in rodents weighing greater than 314 mg and 157 mg quercetin/kg body weight/day, severally. Besides, greater than the dose of 157 mg quercetin/kg body weight/day, a prooxidant efficacy was observed [29]. Quercetin was once in a while all around endured in human clinical examinations.

Eminently, the use of quercetin on several days at a dose of greater than 1,000 mg/day didn't show any impacts on natural liquid electrolytes, kidney, liver function, parameters of blood, and hematology. As of now, a high quercetin portion with digitalis glycoside is perceived to be the best purpose for poisonousness; thus, the utilization of quercetin in digoxin-treated patients should be confined before extra information on appropriate dose levels is possible. Underneath bound circumstances, quercetin shows every revolutionary rummaging and supportive of oxidant movement [30].

Quercetin shows mutagenicity *in vitro* inside the Ames test, and reports of mutagenicity in the 1970s have semiconductor diode to issues concerning its wellbeing [31]. Most *in vivo* tests have shown that quercetin isn't a substance and will be ensuring against Geno poisons. Dietary quercetin, round-confronted with the main pass digestion inside the digestive system and liver, is kind of completely processed, lessening the potential for poisonousness. At oral supplemental dosages over 1,000 mg each day taken for up to a couple of months, no evidence of poisonousness has been discovered; but, information on semipermanent security at high portions is missing [31].

CONCLUSION

On the administration of Quercetin, virus assembly, replication, and enzyme activity may be inhibited along with blockage of virus entry leading to a strengthened immune system causing early production of IFNs, interleukins, T cell maturation, and phagocytic activity. Not only for the SARS virus. Quercetin has been found very useful for almost various respiratory tract infections producing minimal side effects. Quercetin stops the viral replication by inhibiting the reverse transcriptase enzyme and acting on the polymerase.

Broad-spectrum anti-viral properties are demonstrated by Quercetin which has the potential to stop viral infection at different levels mainly by stopping the entry of the virus, inhibiting the replication of the virus, and assembly of the proteins. They also interfere with DNA and RNA polymerases. As quercetin is being used as a supplement form it is found economical and does not shows severe side effects. Therefore, we suggest and recommend the use of Quercetin as a Prophylaxis and Treatment for COVID-19 patients and people suffering from upper respiratory tract infections.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Ramen Kalita designed the work, corrected and made necessary revisions in the manuscript. Kunal Bhattacharjee collected the contents and performed the literature survey. Amir Ali and Satyasish Sandilya contributed to drafting the manuscript. All the authors framed the final manuscript

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