

Quercetin: Antiviral Significance and Possible COVID-19 Integrative Considerations

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Pawan K. Agrawal¹ , Chandan Agrawal¹, and Gerald Blunden²

Abstract

Quercetin, a naturally occurring dietary flavonoid, is well known to ameliorate chronic diseases and aging processes in humans, and its antiviral properties have been investigated in numerous studies. *In silico* and *in vitro* studies demonstrated that quercetin can interfere with various stages of the coronavirus entry and replication cycle such as PLpro, 3CLpro, and NTPase/helicase. Due to its pleiotropic activities and lack of systemic toxicity, quercetin and its derivatives may represent target compounds to be tested in future clinical trials to enrich the drug arsenal against coronavirus infections. There is evidence that quercetin in combination with, for example, vitamins C and D, may exert a synergistic antiviral action that may provide either an alternative or additional therapeutic/preventive option due to overlapping antiviral and immunomodulatory properties. This review summarizes the antiviral significance of quercetin and proposes a possible strategy for the effective utilization of natural polyphenols in our daily diet for the prevention of viral infection.

Keywords

Quercetin, flavonoids, antiviral, COVID-19, integrative considerations

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Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) represents an emergent global threat which is straining worldwide healthcare capacity. A coronavirus such as SARS-CoV-2 can be deadly because of its ability to stimulate a part of the innate immune response called the inflammasome, which can cause the uncontrolled release of proinflammatory cytokines, namely, interleukin (IL)-1B and IL-18, leading to cytokine storm and severe, sometimes irreversible, damage to the respiratory epithelium.^{1,2} The SARS-CoV-2 virus has been shown to activate the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome.^{3,4}

Among various polyphenolic natural products, quercetin (3,3',4',5,7-pentahydroxyflavone, Figure 1), a flavonoid, found abundantly in fruits and vegetables, including onions, broccoli, buckwheat, capers, peppers, Brassica vegetables, apples, grapes, berries, tea, and wine, as well as many nuts, seeds, barks, flowers, leaves, and spices,⁵⁻⁸ has been reported as one of the potent inhibitors of NLRP3 inflammasome-mediated IL-1 β production, typically acting at more than one element of the involved pathways.⁹ However, it is worthwhile to note that dietary intake of flavonoids ranges from 5 to 100 mg/day (quercetin [Que] and its glycosides account for about 75%), mostly depending on the consumption of fruits and vegetables and the intake of tea.^{10,11} Que is largely metabolized in the intestine and liver^{12,13} so that its plasma level is normally low. However, after consuming Que-rich foods, the plasma level of this flavonoid increases to different ranges.

In nature, Que predominantly occurs in *O*-glycosidic form, having either a monosaccharide moiety, such as glucose, galactose, and/or rhamnose, or a disaccharide, usually rutinose (3-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 6)- β -D-glucopyranoside), linked to the 3, 7, and 4'-positions. The sugar moiety is usually *O*-linked to Que, but it can be *C*-linked as well. The OH at C-3 is the most common position, but *O*-glycosylation may occur on carbons 4' and 7.¹⁴ The 4'-*O*-glucoside is considered the major representative of Que glycosides in onion.¹⁵

Epidemiological studies suggested tight links between the intake of flavonoid-rich diets and a decreased incidence of various chronic age-related diseases.¹⁶ From a dietary point of view, Que glycosides are mostly found in food with a negligible portion of Que itself,^{12,13} with the exception of some red wine.¹⁷ The excess consumption of flavonoids is possibly toxic as flavonoids act as mutagens, pro-oxidants, and inhibitors of vital enzymes responsible for metabolism.¹⁸ As a dietary

¹Natural Product Inc., Westerville, OH, USA

²School of Pharmacy and Biomedical Science, University of Portsmouth, Portsmouth, UK

Corresponding Author:

Pawan K. Agrawal, Natural Product Inc., 7963 Anderson Park Lane, Westerville, OH 43081, USA.
Email: agrawal@naturalproduct.us



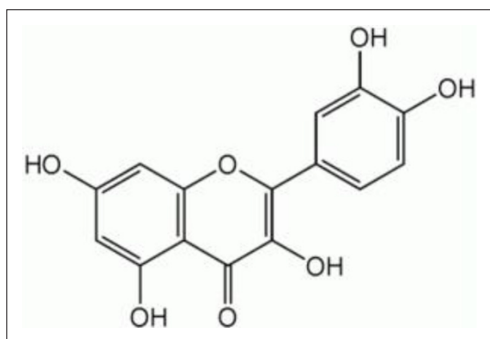


Figure 1. Structure of quercetin (Que).

constituent, Que has unique biological properties that may improve mental/physical performance and reduce infection risk.¹⁹ It is worthwhile to note that dietary supplements differ but often contain the free form of Que—under the FDA national drug code numbers 65448-3085, 65448-3005.²⁰

Que acts as a free radical scavenger, donating 2 electrons via o-quinone/quinone methide²¹; both in vitro and in vivo^{22,23} studies implicate Que as a potent antioxidant. Que has been shown to exert anticancer, anti-inflammatory, antiallergic, antioxidant, antidiabetic, vasoprotective, antihypertensive, hypolipidemic, antithrombotic, and psychostimulant activities, as well as having the ability to inhibit lipid peroxidation, platelet aggregation, capillary permeability, and to stimulate mitochondrial biogenesis.^{14,24-51}

Beneficial Effects of Que in Viral Infections

There is a tremendous amount of literature supporting the antiviral properties of Que, in both in vitro and in vivo experiments. Early in vivo studies showed that oral treatment with Que displayed a beneficial effect in immunocompetent mice infected with the Mengo virus.^{52,53} Que also demonstrated a dose-dependent antiviral activity against herpes simplex virus, HSV-1 and HSV-2, in cell cultures.^{54,55} Que inhibits several respiratory viruses in cultured cells.^{56,57} It inhibits the cytopathic effects provoked by many serotypes of rhinovirus, echovirus (type 7, 11, 12, and 19), coxsackievirus (A21 and B1), and poliovirus (type 1 Sabin).⁵⁸ Que exhibits antiviral activity against Canine Distemper Virus as it decreases viral expression and improves cellular viability.⁵⁹

In mice infected with rhinovirus, Que treatment decreased viral replication and attenuated virus-induced airway cholinergic hyper-responsiveness.⁶⁰ In silico analysis revealed that Que may be a potential inhibitor of the neuraminidase of influenza A H1N1 and H7N9 viruses.^{61,62} Molecular docking analysis also found that Que may interact with HCV NS3 helicase, NS5B polymerase, and p7 proteins.^{63,64} These results correlate with experimental studies showing the anti-HCV activity of Que through inhibition of NS3 helicase and heat-shock proteins.⁶⁵⁻⁶⁷

A phase I trial investigated the potential antiviral effect of Que among patients with hepatitis C virus (HCV).⁶⁸ The results showed that the compound was safe in all patients as

there were no changes in liver enzymes (aspartate transaminase and alanine transaminase), and about 25% of patients showed a “clinically meaningful” decrease in viral load.⁶⁸ An herbal formula containing Que was evaluated for its effects in patients with oral herpes, caused by the HSV.⁶⁹

In an animal study of influenza (H3N2), the onset of infection was associated with a significant decrease in the pulmonary concentrations of catalase, reduced glutathione, and superoxide dismutase (antioxidants); supplementation with Que given at the same time as inoculation with the virus produced significant increases in the pulmonary concentrations of these antioxidants.⁷⁰ A similar study showed that Que exerted a mild to moderate protective effect on lung morphology and a significant decrease in the number of infiltrating cells.⁷¹

A randomized, double-blinded, placebo-controlled trial suggested significantly lower upper respiratory tract infection (URTI) severity (36% reduction, $P = 0.020$) and URTI total sick days (31% reduction, $P = 0.048$) in individuals (>40 years) of the Que 1000 mg group compared with placebo.⁷² The use of an herbal formula containing 1000 mg Que and some other natural products in obese individuals reflects upregulation of genes related to interferon-induced antiviral activity.⁷³

Que and isoquercitrin (quercetin-3-O- β -D-glucopyranoside) were the bioactive compounds in the ethyl acetate fraction of *Elaeocarpus sylvestris* that effectively inhibited human herpes virus replication.⁷⁴ Que inhibits the infection by HSV-1, HSV-2, and acyclovir-resistant HSV-1 mainly by blocking viral binding and penetration to the host cell, and also suppresses NF- κ B activation, which is essential for HSV gene expression.^{75,76} *Epimedium koreanum* Nakai, which contains Que as its major active component, has been shown to induce secretion of type I interferon (IFN), reducing the replication of HSV, Newcastle disease virus, and vesicular stomatitis virus in vitro, as well as influenza A subtypes (H1N1, H5N2, H7N3, and H9N2) in vivo.⁷⁷ Que inhibits the replication of cytomegalovirus inoculated HeLa cells at a half inhibitory concentration (IC_{50}) of $3.2 \pm 0.8 \mu\text{M}$ and with a selectivity index of 22.⁷⁸ Dengue virus type 2 (DENV-2) replication in Vero cells is inhibited by Que at an IC_{50} of $35.7 \mu\text{g/mL}$, causing a DENV-2 ribonucleic acid (RNA) reduction of 67%. This is attributed to Que's ability to either block virus entry or inhibit viral replication enzymes such as viral polymerases.⁷⁹ Que and fisetin inhibited DENV-2 and DENV-3 infection in the absence or presence of enhancing antibody (>90%, $P < 0.001$).⁸⁰ Athletes supplemented with Que are protected from stress-induced susceptibility to upper respiratory tract infection,⁸¹ which is not related to immunomodulation.^{82,83}

In vitro data suggest that Que may inhibit viral replication of the influenza virus, via interfering with 3 stages of viral replication^{31,84}: (1) blocks endocytosis (uptake of the virus into the host cell) via inhibition of phosphatidylinositol 3-kinase; (2) blocks transcription of the viral genome by inhibiting RNA polymerase and viral protein translation by promoting cleavage of eukaryotic translation initiation factor 4G, and (3) increases viral clearance by enhancing the mitochondrial antiviral response.⁸⁴

Antiviral activity of Que against a wide spectrum of influenza virus strains has been demonstrated via its interactions with influenza hemagglutinin protein, thereby inhibiting viral cell fusion.⁸⁵ Que has been documented for its efficacy against human T-lymphotropic virus 1, as well as the Japanese encephalitis virus (JEV), a mosquito-borne disease.⁸⁶ Furthermore, Que has been reported to suppress DENV-2 and HCV by suppressing the nonstructural protein 3 protease activity.^{65,79,80}

Other Que formulations, such as quercetin-3-O- β -D-glucuronide, Que-enriched lecithin formulations, and quercetin-7-rhamnoside have been reported for their efficacy against the porcine epidemic diarrhea virus (PEDV) and influenza A virus (IAV).⁸⁷⁻⁸⁹

Studies on the extracts of *Zanthoxylum armatum* and *Hibiscus sabdariffa* led to the identification of Que as an antiviral constituent against norovirus as it was able to considerably reduce the viral titer.⁹⁰ Based on a comparative study of the antiviral activity of flavonoids against murine norovirus and feline calicivirus, Que has been identified as one of the active compounds.⁹¹

Que has been studied in various types and models of viral infection due to its promising antiviral effects in inhibiting polymerases,⁹² proteases,⁶⁵ reverse transcriptase,⁹³ suppressing deoxyribonucleic acid gyrase, and binding viral capsid proteins.^{56,94} Similarly, 25 μ M Que blocked IL-1 β , IL-6, IFN- γ , and tumor necrosis factor- α (TNF- α) secretion in human whole blood induced by lipopolysaccharide (LPS).³³ Que can also inhibit proinflammatory cytokines. A 6-week regimen of 150 mg of Que taken daily by human subjects significantly lowered cytokine TNF- α serum concentrations.³³ In addition, Que uniquely blocked endocytosis by dendritic cells (DCs) and LPS-induced DC migration.⁹⁵ Que has been shown clinically to block human mast cell cytokine release, possibly inhibiting the clinical manifestation of cytokine storm.⁹⁶ Among various flavonoids, Que has been found, *in vitro*, to reduce NLRP3 inflammasome signaling, and consequently nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), TNF- α , IL-6, IL-1 β , and IL-18 expression; IL-1 β production was inhibited at 10 μ M.⁹⁷

Thus, studies have shown that Que exhibits antiviral properties against a variety of viruses, including respiratory syncytial virus, polio type 1, parainfluenza type 3, HSV-1, IAV, hepatitis B virus, IAV H1N1, Epstein-Barr virus, enterovirus 71, ADVs, arthropod-borne Mayaro virus, porcine reproductive and respiratory syndrome virus, canine distemper virus, JEV, DENV-2, PEDV, and equid herpesvirus 1.⁹⁸⁻¹¹²

Que and SARS-COV-2

Que has been investigated for its possible antiviral effect on several members of the Coronaviridae family. To the best of our knowledge, one of the first reports exploring the antiviral effect of Que on coronaviruses appeared in 1990 suggesting that it reduced infectivity of human and bovine coronaviruses, OC43 and NCDCV, respectively, by 50% at a concentration of 60 μ g/mL.⁵⁶ On a different Coronaviridae of veterinarian

interest, PEDV, quercetin 7-O-rhamnoside inhibited PEDV replication in Vero cells with an IC₅₀ of 0.014 μ g/mL and a 50% cytotoxicity concentration (CC₅₀) of 100 μ g/mL.¹¹³ Luteolin and Que showed the capacity to block the entry of SARS-CoV into host cells.¹¹⁴ Luteolin inhibited, in a dose-dependent manner, SARS-CoV infection of Vero E6 cells with a half-effective concentration (EC₅₀) value of 10.6 μ M (CC₅₀ = 155 μ M), while Que antagonized HIV-luc/SARS pseudo-type virus entry with an EC₅₀ of 83.4 μ M.¹¹⁴ Thus, Que offers great promise as a potential drug in the clinical treatment of SARS.¹¹⁴

SARS coronavirus, described in 2003,¹¹⁵ is a single-stranded RNA virus, which uses ribosome sites to encode 2 replicase glycoproteins, PP1a and PP1b, which mediate viral replication.^{115,116} Once these precursor glycoproteins are synthesized, 3C-like protease (3CLpro) plays a critical role in the lytic release of its replicates.¹¹⁷

Que, identified as one of the constituents of *Pichia pastoris* displayed good inhibition toward 3CLpro with an IC₅₀ value of 73 M.¹¹⁸ Quercetin-3-O- β -galactoside binds to SARS-Cov 3 Cl protease and inhibits its proteolytic activity with an IC₅₀ of 42.79 $\pm$ 4.95 μ M.¹¹⁹ This inhibitory action on 3CLpro is dependent on the hydroxyl group of Que which, as shown through molecular modeling and Q189A mutation, recognizes Gln189 as a crucial site on 3CLpro responsible for the binding of Que.¹²⁰ Que was also identified as being able to block SARS-coronavirus entry into Vero E6 cells with a half-effective concentration (EC₅₀) of 83.4 μ M and with low cytotoxicity (CC₅₀ 3.32 mM).¹¹⁴ SARS-CoV-2, the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic,¹²⁰ belongs to the genus *Betacoronavirus* and subgenus *Sarbecovirus* and, due to its similar receptor-binding domain, it is assumed, similarly to SARS-CoV, to infect type II pneumocytes entering via the angiotensin-converting enzyme-2 (ACE2) receptor.¹²¹ SARS-Cov-2 protease 3 Cl maintains the same Gln189 site¹²² of SARS-Cov 3CLpro, which previously was identified as the binding site for the hydroxyl groups of Que and its derivatives. Interestingly, an *in vitro* study of ascorbic acid treatment on chick-embryo ciliated tracheal organ cells promoted resistance to coronavirus infection but did not show any effect on either orthomyxovirus or paramyxovirus.¹²³ Docking studies of Que to 3CLpro, as well as other key targets, suggested that it bound well to each target, with a binding energy of -5.6 kcal/mol to 3CLpro. Surprisingly, it has also been found that Que binds better to Spike protein, ACE2, RdRp, and PLpro, indicating good potential against SARS-CoV-2.¹²⁴ SARS-CoV 3CLpro shares some features with SARS-CoV2; therefore, Que might exert some protective or curative role against COVID-19, particularly considering its antioxidant¹²⁵ and anti-inflammatory³⁶ properties, as well as the effects of Que observed against other viruses described above. It also modulates the cellular unfolded protein response (UPR). As coronaviruses can utilize the UPR to complete their entire replication cycle, Que may have anti-coronavirus effects through its modulation of this pathway.¹²⁶

Coronavirus appears to be susceptible to the inhibitory actions of zinc, which may prevent viral entry into cells¹²⁷ and

appears to reduce coronavirus virulence.¹²⁸ Que also functions as a zinc ionophore and has been shown to facilitate the transport of zinc across lipid membranes.¹²⁹ This could, theoretically, enhance the antiviral actions of zinc.¹³⁰

Animal coronavirus models¹³¹ have shown that mast cells residing in the respiratory submucosa may play a mixed role, including the generation of Th2 proinflammatory cytokines under the influence of viral stimulation and immunoglobulin E, an antibody type associated with Th2 style immune reaction. Que has been shown in many human studies to modulate mast cell degranulation.¹³² Que is also important as one of the multiple flavonoids shown in vitro to block the activity of MERS-CoV 3CLpro, a critical enzyme for coronavirus replication. Animal studies are limited at this time but support efficacy.¹³³

In silico modeling of the interaction between the SARS-CoV-2 Viral Spike Protein and ACE2 protein identified Que, from a database of known drugs, metabolites, and natural products, as one of the top 5 most potent compounds for binding to the interface site and potentially disrupting the initiating infection process.¹³⁴ In support of this hypothesis, Que was active against infection in a model of virus cell entry and also inhibited the 3C-like protease of SARS-CoV in vitro.^{118,124} Que modulates NF- κ B upregulation, which is useful to counteract the COVID-19 hyperinflammation.¹³⁵ Que has a pleiotropic role as an antioxidant and anti-inflammatory, modulating signaling pathways that are associated with post-transcriptional modulators affecting postviral healing.¹³⁶

Proteases play essential roles in viral replication, and specifically, 6LU7 was determined to be the main protease (Mpro) found in SARS-CoV-2. In vitro molecular docking studies between Que and viral protease suggest that Que forms H-bonds with the 6LU7 amino acids His164, Glu166, Asp187, Gln192, and Thr190, with all of the H-bonds interacting with amino acids in the virus Mpro active site.¹³⁷ The genome of SARS-CoV-2 is approximately 79% identical to that of SARS-CoV-1.¹³⁸ It is, therefore, not surprising that Que showed an IC₅₀ of $8.6 \pm 3.2 \mu\text{M}$ against SARS-CoV-1 PLpro.¹³⁹

Que has been investigated as a pneumolysin (PLY) inhibitor that protects mice against *Streptococcus pneumoniae* infection. PLY is the pore-forming cytotoxin and the major virulence determinant that belongs to the cholesterol-dependent cytolysin family (CDC) and is found in infections with *S. pneumoniae*. Hemolysis tests were used to confirm that Que can inhibit PLY activity. Que significantly reduced PLY-induced hemolytic activity and cytotoxicity suggesting that Que may be a new potential drug candidate in the treatment of clinical pneumococcal infections.¹⁴⁰ The senolytic property of Que¹⁴¹ has also been considered as one of the important factors for its use for the prevention of coronavirus.¹⁴²

In any case, based on the strong inflammatory cascade and the blood-clotting phenomena triggered during SARS-CoV-2 infection, the multifaceted aspect of Que, which has been well described as exerting both anti-inflammatory (Que dose-dependently decreases the messenger RNA and protein levels of intercellular adhesion molecule-1, IL-6, IL-8, and monocyte

chemoattractant protein-1) and thrombin-inhibitory actions,¹⁴³⁻¹⁴⁵ should be taken into consideration.

Synergistic Therapy and Integrative Considerations

There is a high level of interest in integrative strategies to augment public health measures to prevent COVID-19 infection and associated pneumonia. Unfortunately, no integrative measures have been validated in human trials as effective specifically for COVID-19. Using available in vitro evidence and an understanding of the virulence of COVID-19, as well as data from similar, but different, viruses, as mentioned above, the use of Que seems to be appealing.

Que and Vitamin C

Vitamin C is an essential vitamin with known antiviral properties¹⁴⁶ which is under investigation for its beneficial effects during the stress response in sepsis and critically ill patients.¹⁴⁷ Co-administration of Que (12.5 mg/kg/week) and vitamin C and B3 in a murine model of exercise-induced susceptibility to influenza H1N1 prolonged time-to-death (median time to death: placebo 9.0 ± 0.33 vs Que 16.5 ± 1.2) and improved survival (mortality: placebo 74% vs Que 52%) when compared with mice receiving only vitamins B3 and C.¹⁰² An older, small clinical trial identified the combination of flavonoids and ascorbic acid (1:1 ratio) as beneficial for respiratory infection (200 mg thrice a day).¹⁴⁸ There is evidence that vitamin C and Que co-administration exerts a synergistic antiviral action due to overlapping antiviral and immunomodulatory properties and the capacity of ascorbate to recycle Que, increasing its efficacy. Safe, cheap interventions which have a sound biological rationale should be prioritized for experimental use in the current context of a global health pandemic. The use of vitamin C and Que has also been suggested both for prophylaxis in high-risk populations and for the treatment of COVID-19 patients as an adjunct to promising pharmacological agents such as Remdesivir or convalescent plasma.¹⁴⁹

Que, Vitamin D, and Estradiol

Using Gene Set Enrichment Analyses, vitamin D and Que have been identified as putative COVID-19 mitigation agents. Que alters the expression of 98 of 332 (30%) human genes encoding protein targets of SARS-CoV-2, thus potentially interfering with functions of 23 of 27 (85%) of the SARS-CoV-2 viral proteins in human cells. Similarly, vitamin D may interfere with functions of 19 of 27 (70%) of the SARS-CoV-2 proteins by altering the expression of 84 of the 332 (25%) human genes encoding protein targets of SARS-CoV-2. Significantly, numerous observational studies suggest that age-associated vitamin D insufficiency and/or deficiency may contribute to the high mortality of older adults and elderly individuals during the COVID-19 pandemic. Consequently,

vitamin D supplementation may mitigate the severity of the disease. Considering the potential effects of both Que and vitamin D, the inference could be made that functions of 25 of 27 (93%) SARS-CoV-2 proteins in human cells may be altered. Estradiol also affects the expression of the majority of human genes (203 of 332; 61%) encoding SARS-CoV-2 targets, thus potentially interfering with functions of 26 of 27 SARS-CoV-2 viral proteins. A hypothetical tripartite combination consisting of Que/vitamin D/estradiol may affect the expression of 244 of 332 (73%) human genes encoding SARS-CoV-2 targets.¹⁵⁰

Que, Zinc, Bromelain, and Vitamin C

A quadruple therapy consisting of zinc, Que, bromelain, and vitamin C has been suggested to show a promising positive therapeutic effect in patients.¹⁵¹

Others

However, Que has low bioavailability and, therefore, requires special formulations to achieve clinically effective blood levels. A trial with a phytosomal Que formulation has been started for COVID-19 patients.¹⁵²⁻¹⁵⁴ Considering bioavailability issues, a nasal spray of dilute Que has been suggested to be a suitable vehicle, administered regularly at low doses during the early stages of infection, as it could attenuate entry of the virus into cells and so halt progress of the infection, possibly leading to a reduced need for hospitalization.¹⁵⁵

Concluding Remarks

Viruses causing respiratory diseases invade their host via the nasopharyngeal, oropharyngeal, and tracheal mucosa. At present, there are no specific antiviral drugs or vaccines against SARS-CoV2 infection for potential therapy of humans. Identifying methods able to either reduce or prevent colonization, viral adhesion, and promote virus shedding on mucous membranes or have the ability to inactivate pathogens and thus reduce virus dose and/or increase immune response would be useful.¹⁵⁶ Waiting for the generation of vaccines and for proven, safe, and effective treatments, any therapy shown to be safe and capable of mitigating the effects of the disease on the body should be welcomed. Que displays a broad range of antiviral properties which can interfere at multiple steps of pathogen virulence-virus entry and virus replication. According to researchers at the Montreal Clinical Research Institute “A cell has a lock, and the virus has a key [to enter and infect the cell];” Chrétien said, “But quercetin puts glue in the lock.”¹⁵⁷ Therefore, we anticipate that Que could be a therapeutic tool to be assayed against COVID-19, either alone or in combination with other nutritional substances, antivirals, or other drugs. Que may affect medications metabolized by CYP2C8, CYP2D6, CYP3A4, and P-glycoprotein substrates, and this is a concern for its use that has to be taken into consideration.¹⁵² As Que can inhibit coronavirus enzymes, which are essential

for virus replication and infection, therefore it provides a potential key for designing antiviral therapies for inhibiting viral proteases. With well-known pharmacokinetic and absorption, distribution, metabolism and excretion-toxicity (ADMET) properties,¹⁵⁸ Que can be considered as a good candidate for further optimization and development or repositioned for COVID-19 therapeutic treatment. Furthermore, the known pharmacophore structures of bioactive substances can be useful in the elaboration of new anti-COVID-19 formulations.

Declaration of Conflicting Interests

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ORCID ID

Pawan K. Agrawal  <https://orcid.org/0000-0002-7149-8358>

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