Received: 18 January 2022 | Revised: 3 March 2022 | Accepted: 4 March 2022

DOI: 10.1002/ptr.7440

LETTER TO THE EDITOR

WILEY

Quercetin potential effects against SARS-CoV-2 infection and COVID-19-associated cancer progression by inhibiting mTOR and hypoxia-inducible factor-1α (HIF-1α)

Dear Editor,

Globally, the coronavirus disease-2019 (COVID-19) pandemic has spread rapidly, with millions of confirmed cases. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is responsible for this disease (Etemadifar et al., 2021; Zalpoor et al., 2022). Based on the studies, it seems that cancer patients not only are more prone to experience severe complications and death by COVID-19 (Y. Tian et al., 2021) but also cancer progression by COVID-19 (Purcaru et al., 2021).

1 | COVID-19 AND ACTIVATION OF mTOR AND HIF-1α

The activity of SARS-CoV-2 in human organs and the immune system can lead to the activation of some crucial signaling pathways. For instance, in infected cells, SARS-CoV-2 stimulates the mammalian target of the rapamycin (mTOR) signaling pathway in order to facilitate the transcription of viral structural proteins. On the other hand, according to Ramaiah's hypothesis, the nonstructural protein of SARS-CoV-2 in human cells causes the stability of E3 ubiquitin (E3U) ligase ring-finger and CHY zinc-finger domain-containing 1 (RCHY1) leading to P53 degradation. P53 is involved in the transcription of some miRNAs that result in posttranscriptional mTOR gene silencing. Hence, the degradation of P53 is in favor of mTOR signaling pathway (Ramaiah, 2020). After infection, damage-associated molecular patterns (DAMPs) are released from infected cells and bind to toll-like receptors (TLRs) on immune cells, such as dendritic cells (DCs), and activate.

PI3K/Akt/mTOR signaling pathway. Activation of this signaling pathway leads to the release of high levels of inflammatory cytokines (Omarjee et al., 2020). Many types of cancer exhibit aberrant mTOR signaling due to genetic alterations at various levels of the signal cascade. It reveals that mTOR exerts a significant role in cancer progression and in the increase of cell metabolism, cell growth, cell survival, and protein synthesis following upstream signals in cancer (T. Tian, Li, & Zhang, 2019).

Hypoxia-inducible factor-1α (HIF-1α) as a transcription factor is activated in hypoxic conditions. Increasing HIF-1α during SARS-CoV-2 infection increases a disintegrin and metalloprotease 17 (ADAM17) expression. This factor increases the inflammation and processes TNF-α and increases absorption of processed TNF-α by innate immune cells. ADAM17 also cleavages the IL-6/IL-6R/gp130 and converts IL-6R into a pro-inflammatory factor leading to a cytokine storm (Serebrovska, Chong, Serebrovska, Tumanovska, & Xi, 2020). In addition, HIF-1α transcriptional activity can alter genes expression related to cancer progression, autophagy, which can lead to drug resistance, immune-suppression, glucose consumption and metabolic pathways, cell proliferation, angiogenesis, and metastasis (Rashid et al., 2021).

2 | QUERCETIN ANTI-COVID-19 EFFECTS

Quercetin is the major polyphenolic flavonoid that can be naturally received through various fruits and vegetables, including apples, onions, berries, capers, lovage, dill, and cilantro or artificially from supplementary tablets containing quercetin or its synthetic derivatives. Quercetin exhibits significant antiviral, pro-metabolic, and antiinflammatory properties. Recent studies have been suggested that quercetin potentially can exert its role as anti-COVID-19 agent through multiple mechanisms; (a) disrupting the interaction of SARS-CoV-2S protein with its specific receptor ACE2, which can prevent the viral entry to the host cells; it was reported that quercetin tightly bound to S protein with a—7.8 kcal/mol binding affinity at its Gly496, Asn501, Tyr505, and Tyr453 residues. (b) Interfering with SARS-CoV-2 replication. Nguyen et al. and Ryu et al. have revealed that quercetin has inhibitory activity against 3C-like protease (3CLpro), as a vital for the replication of SARS-CoV, with an IC50 of 73 μM. Moreover, it was proved that quercetin has strong interaction with SARS-CoV-2 Mpro, as a protease facilitating the virus RNA translation (Derosa, Maffioli, D'Angelo, & Di Pierro, 2021; Nguyen et al., 2012; Ryu et al., 2010; Vijayakumar, Ramesh, Joji, & Kannan, 2020). (c) Reducing the cytokine storm with its antiinflammatory response (Derosa et al., 2021). As a result of adding quercetin to cultured peripheral mononuclear cells, it induces the production of (Th-1)-derived Interferon-α (IFN-α) and lowers the production of the Th2-derived IL-4 (Tanaka, Furuta, Asano, & Kobayashi, 2020).

Two interventional clinical trials (ClinicalTrial. gov identifiers: NCT04377789 and NCT04468139) suggested a daily dose of 1,000 mg quercetin alone and its 500 mg concomitant use with zinc, bromelain, and vitamin C in COVID-19 patients, respectively. In

addition, another study on 152 COVID-19 patients, indicated that 1,000 mg of quercetin for 30 days significantly reduced length of hospitalization, in need of noninvasive oxygen therapy, in progression to intensive care units, and in number of deaths (Di Pierro et al., 2021).

3 | QUERCETIN ANTICANCER EFFECTS

Quercetin has been demonstrated to have anticancer properties in numerous in vitro and in vivo studies with various cell lines and animal models. Quercetin inhibits the spread of malignancies such as lung, prostate, liver, breast, colon, pancreatic, bladder, gastric, bone, blood, brain, head and neck, skin, eye, thyroid, ovarian, kidney, mesothelioma, and cervical cancers. However, quercetin appears to be free of side effects or harm to normal cells, despite its high toxicity to cancer cells. Various mechanisms can exert these anticancer properties, including the cellular signaling pathway and the ability to inhibit enzymes that activate carcinogens (Rauf et al., 2018) **(Table 1)**. Refolo et al. have shown that quercetin increases the expression of the endocannabinoid receptor (CB1R) and reduces PI3K/Akt/mTOR in human colon cancer cells (Refolo et al., 2015). Moreover, other researchers found that the quercetin-induced apoptosis involves the sestrin 2/AMPK/mTOR pathway by regulating increased intracellular ROS in colon cancer cell lines (Kim, Lee, & Kim, 2013). Quercetin suppresses cell proliferation and promotes death in U937 human leukemia cells via reducing the Bcl2-to-Bax ratio. It significantly reduces tumor cell penetration as well as the expression of angiogenesis-related proteins HIF-1 and VEGF. The expression of 2Notch 1 and the phosphorylation stages of the downstream signaling proteins Akt and mTOR are significantly lowered by quercetin (Rauf et al., 2018). In addition, Granato et al. have shown that quercetin decreases c-Myc expression and inhibits PI3K/Akt/mTOR activity in EBV-negative Burkitt's lymphoma cells (Granato et al., 2016). The researchers further suggested quercetin might be used as a treatment for glioblastoma multiforme (GBM). In terms of molecular interactions, quercetin has been found to interact with proteins involved in GBM cell growth and signal transduction pathways, including PI3K/Akt/mTOR (Tavana et al., 2020).

4 | QUERCETIN POTENTIAL EFFECTS IN INHIBITION OF mTOR AND HIF-1α

Quercetin, as a flavonol with antiinflammatory and antioxidant properties, promisingly exerts antitumor roles by regulating a variety of cancer signaling pathways, affecting the activity of mTOR and HIF-1 in particular (Bruning, 2013; Samec et al., 2021) (Figure 1). It has been demonstrated that quercetin inhibits the mTOR signaling pathway and that it also interferes with AMP-dependent protein kinase (AMPK) activity, PI3K-dependent Akt stimulation, and hamartin upregulation. As a dual-specific mTOR/PI3K inhibitor, quercetin is able to suppress both mTOR activity and PI3K activation. Cell growth, protein biosynthesis, and autophagy are crucial processes controlled by the mTOR complex, which is often hyperactive in cancer (Bruning, 2013). It has been reported that quercetin inhibits the accumulation of HIF-1α, in addition to HIF-1α protein expression during hypoxic conditions in various cancer cell lines, such as SkBr3 breast cancer cells, LNCaP prostate cancer cells, and CX-1 colon cancer cells (18). Surprisingly, it has been reported that quercetin has the same effect on HIF-1α expression as cycloheximide (a HIF-1α inhibitor drug) (Lee & Lee, 2008).

Consequently, the potential of quercetin in inhibiting mTOR and HIF-1α activity and expression by multiple pathways is the reason that this bioflavonoid is an attractive therapeutic candidate for various cancers and other diseases involved with mTOR activity.

TABLE 1 Anticancer effects of quercetin

Pathway–factor	Cancer	Mechanism–function	References
PI3K/Akt/mTOR	Colon cancer	Upregulation of the endocannabinoid receptor (CB1R) and PI3K/Akt/mTOR modulation	Refolo et al. (2015)
	Colon cancer cell lines	Apoptosis induction via sestrin induction of 2/AMPK/mTOR pathway and increasing intracellular ROS in cancer cells	Kim et al. (2013)
	U937 human leukemia cells	Suppresses cell proliferation and promotes death by reducing the Bcl2-to-Bax ratio	Rauf et al. (2018)
	EBV-negative Burkitt's lymphoma cells	Attenuating c-Myc expression and inhibition of PI3K/Akt/mTOR activity	Granato et al. (2016)
	Glioblastoma multiforme (GBM)	Interacting with signal transduction pathways, including PI3K/Akt/mTOR and its downstream proteins playing role in GBM cell growth	Tavana et al. (2020)
	P388 leukemic cells, and U937 human leukemia cells	Decrease 2Notch 1 expression and phosphorylation of its downstream signaling proteins Akt and mTOR	Rauf et al. (2018)
HIF-1α and VEGF	Human prostate cancer LNCaP, colon cancer CX-1, and breast cancer SkBr3 cell lines	Downregulating the angiogenesis factors of HIF-1α and VEGF	Rauf et al. (2018); Refolo et al. (2015)

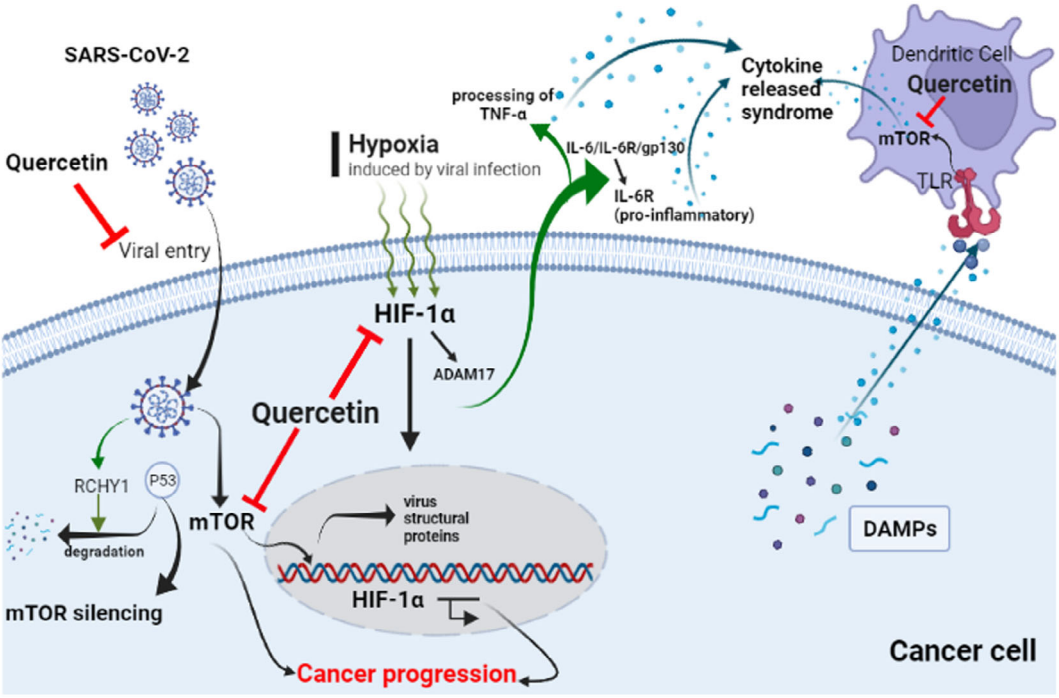

FIGURE 1 Quercetin potential effects against SARS-CoV-2 infection and COVID-19-associated cancer progression by inhibiting mTOR and hypoxia-inducible factor-1α (HIF-1α). COVID-19, coronavirus disease-2019; mTOR, mammalian target of rapamycin; SARS-CoV-2, severe acute respiratory syndrome Coronavirus 2

5 | CONCLUSION

Due to the susceptibility of cancer patients to COVID-19, we suggested that using drugs with few or no adverse effects that have therapeutic effects against COVID-19 and cancer could be very beneficial. We hypothesize that quercetin, as a safe flavonoid that exists in various fruits and vegetables, not only can be used as an anti-COVID-19 component with potential effects on interfacing the viral entry, replication, and its inflammatory activity but also can disrupt the signaling pathways stimulated and upregulated factors by SARS-CoV-2 infection (e.g., mTOR, HIF-1α, etc.), which may lead to cancer progression. Thus, quercetin therapy may be a potential strategy to decrease SARS-CoV-2 infection and improve its desirable effects particularly, in susceptible cancerous patients with severe complications or who passed their chemotherapy–radiotherapy period. We hope that this study will draw more attention to the use of quercetin in clinical research and treatments for COVID-19 patients, especially cancer patients with COVID-19 infection.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Hamidreza Zalpoor: Study design and concept; writing-original draft; manuscript revision. **Maryam Bakhtiyari**: Writing-original draft; figure creation; manuscript revision. **Mahsa Liaghat**: Writing-original draft. **Mohsen Nabi-Afjadi**: Writing-original draft; manuscript revision. **Mazdak Ganjalikhani-Hakemi**: Study Supervision. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Data derived from public domain resources.

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