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Molecular basis of quercetin as a plausible common denominator of macrophage-cholesterol-fenofibrate dependent potential COVID-19 treatment axis

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ABSTRACT

The world's largest randomized control trial against COVID-19 using remdesivir, hydroxychloroquine, lopinavir and interferon-β1a appeared to have little or no effect on hospitalized COVID-19 patients. This has again led to search for alternate re-purposed drugs and/or effective "add-on" nutritional supplementation, which can complement or enhance the therapeutic effect of re-purposed drug. Focus has been shifted to therapeutic targets of severe acute respiratory syndrome coronavirus (SARS-CoV-2), which includes specific enzymes and regulators of lipid metabolism. Very recently, fenofibrate (cholesterol-lowering drug), suppressed the SARS-CoV-2 replication and pathogenesis by affecting the pathways of lipid metabolism in lung cells of COVID-19 patients. A preclinical study has shown synergistic effect of quercetin (a flavonoid) and fenofibrate in reducing the cholesterol content, which might be useful in COVID-19 treatment. Based on the scientific literature, use of quercetin and fenofibrate in COVID-19 seems meaningful in pharmaceutical and biomedical research, and warrants basic, experimental and clinical studies. In this article, we have summarized the contemporary findings about drug fenofibrate and its effect on membrane synthesis of COVID-19 virus along with emphasizing on possible synergistic effects of quercetin with fenofibrate.

Introduction

The world's largest randomized control trial (Solidarity therapeutics trial) on COVID-19 using re-purposed drugs [Remdesivir, Hydroxychloroquine, Lopinavir (fixed-dose combination with Ritonavir) and Interferon-β1a (mainly subcutaneous; initially with Lopinavir)], coordinated by the World Health Organization, apparently revealed to have little or no effect on hospitalized COVID-19 patients, as indicated by overall duration of hospital stay, mortality and initiation of ventilation (under review, preprint) [1]. This has rekindled the search for alternate re-purposed drugs and/or effective "add-on" nutritional supplementation, which can complement or enhance the therapeutic effect of re-purposed drug, while the worldwide efforts are going on for the development of vaccine. For possible therapeutic targets of severe acute respiratory syndrome coronavirus (SARS-CoV-2) [2], the promising focus rests on 3-chymotrypsin-like protease, papain-like protease, RNA-dependent RNA polymerase, spike protein and specific enzymes and regulators of lipid metabolism [3,4].

Macrophage-cholesterol-fenofibrate-SARS-CoV-2 axis

It is well known fact that lipids are the structural foundations of cellular and viral membranes, and play a crucial role in viral replication. Molecules such as cholesterol and sphingolipids could prove effective therapeutic targets to selectively inhibit the viral multiplication [5]. It is pertinent here to note that SARS-CoV-2 infection causes the up-regulation of genes related to lipogenesis and cholesterol synthesis process in primary bronchial epithelial cells. COVID-19 infection differentially up-regulates both HMG-CoA synthase and squalene monooxygenase supporting increased demand for formation of membrane (preprint) [6], and lipid rafts and palmitoylation of viral proteins as essential components of the SARS-CoV-2 replication complex [7]. It is

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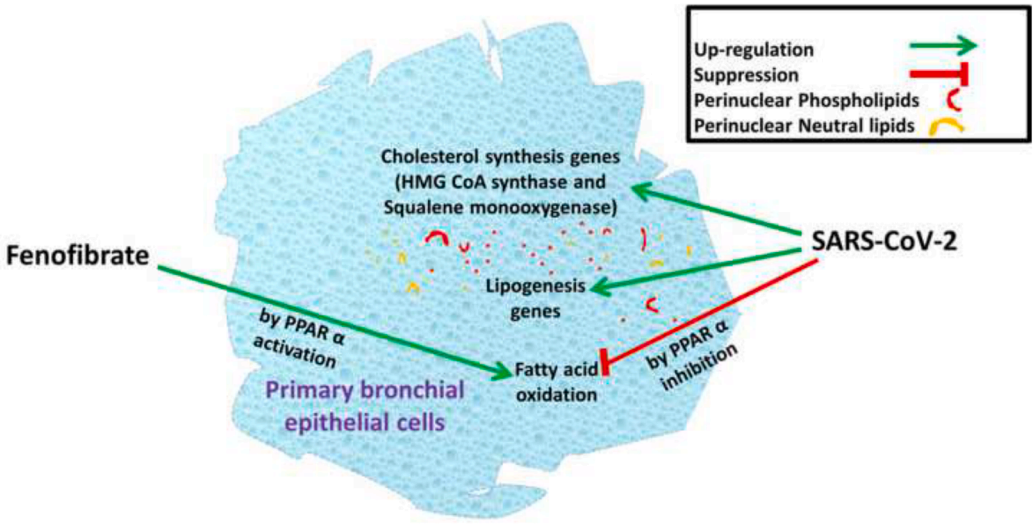

Fig. 1. Schematic representation of increased lipogenesis and cholesterol synthesis in primary bronchial epithelial cells upon infection with SARS-CoV-2. Specifically, SARS-CoV-2 infection induces increased cholesterol synthesis, achieved by differential up-regulation of HMG-CoA synthase and squalene monooxygenase enzymes (enzymes catalyzing the rate-limiting steps in cholesterol synthesis) ultimately leading to significant perinuclear accumulation of neutral lipids and phospholipids. In addition, SARS-CoV-2 infection also causes suppression of fatty acid oxidation *via* inhibition of PPAR-α. Fenofibrate inhibits cholesterol synthesis and lipogenesis by activating PPAR-α. PPAR-α Peroxisome proliferator-activated receptor; SARS-CoV, Severe acute respiratory syndrome coronavirus.

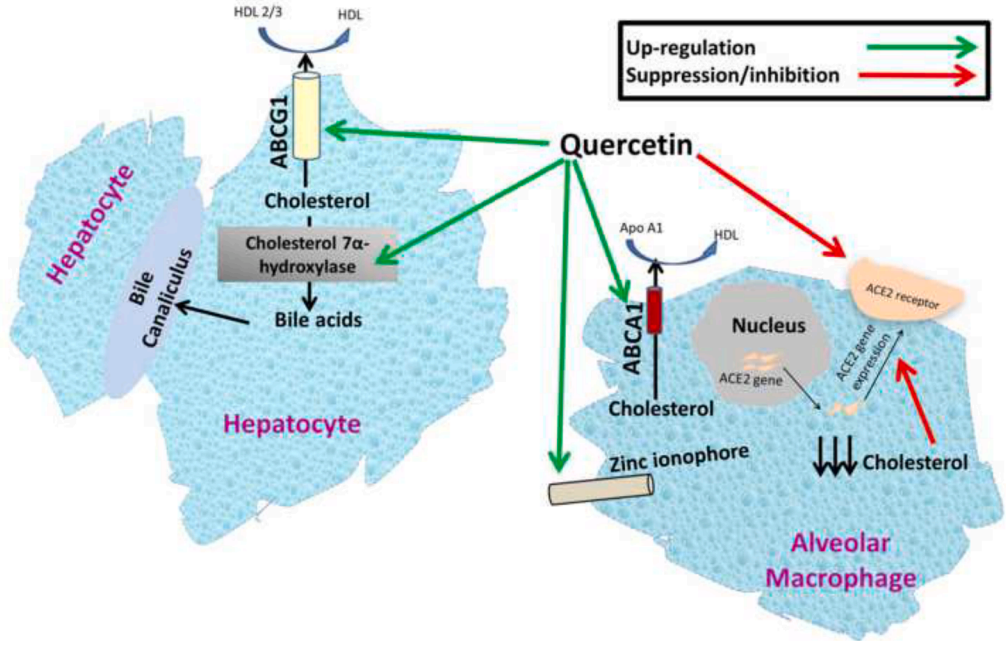

Fig. 2. Schematic representations of various anti-hypercholesterolemic and anti-SARS effects of quercetin. Quercetin exerts its anti-hypercholesterolemic effects by increasing cholesterol 7-α hydroxylaseactivity and increasing the expression of ABCG1in hepatocytes resulting in conversion of cholesterol in to bile and efflux of cholesterol, respectively. Further, quercetin also up-regulates ABCA1 in alveolar macrophages, which also causes cholesterol efflux from cells. Reduced intracellular cholesterol has been shown to reduce the expression of ACE2 gene. Quercetin also acts as a zinc ionophore, thereby increasing intracellular zinc concentration causing inhibition of SARS-CoV-1 genome transcription by inhibiting viral RdRp in a dose dependent manner. Furthermore, quercetin also suppresses the ACE2 gene expression thereby impeding the entry of SARS-CoV-2 virus inside the cell. ACE2, Angiotensin-converting enzyme 2; RdRp, RNA-dependent RNA polymerase; SARS-CoV-2, Severe acute respiratory syndrome coronavirus-2.

contextual to emphasize here that lipogenesis is poorly tolerated in thin epithelial tissue, and can lead to pulmonary lipotoxicity [8]. Hypercholesterolaemia stimulates inflammation and consequent lung disease through various pathways by accumulating cholesterol inside macrophages, pneumocytes and other immune cells in lung tissue [9,10].

In a recent study, Ehrlich et al. [6] observed thatcholesterol-lowering drug, fenofibrate (Peroxisome proliferator-activated receptor (PPAR)-αagonist) [11], suppressed the SARS-CoV-2 replication as well as pathogenesis by affecting the pathways of lipid metabolismin lung cells of COVID-19 patients (Fig. 1). There are reports of favorable role of fenofibrate either alone or in combination in combating cardiometabolic risk associated with dyslipidemia [12,13]. Anticoagulant and cardiovascular protective effects of fenofibrate along with its capacity of lowering the plasma fibrinogen levels to a statistically significant degree, can provide significant therapeutic advantage (reviewed in [2]), which might also prove beneficial in COVID-19 patients. In this context, it is interesting to note that conventional anti-cholesterol drug, statin has been shown to specifically target the COVID-19 proliferation process [14,15].

Studies have shown that ATP binding cassette transporter A1 (ABCA1) and ATP-binding cassette sub-family G member 1 (ABCG1) by stimulating the efflux of cholesterol from macrophage suppress the inflammatory responses *via* toll like receptors (TLR) 2, TLR3 and TLR4 [16,17].

Potential therapeutic role of quercetin

Intriguingly, quercetin as a natural flavonoid also exhibits the anti-hypercholesterolemic property by modulating the expression of ABCA1, a major regulator of reverse cholesterol transport, and may also reduce the accumulation of cholesterol in macrophages. Quercetin therapy reduced the foam cell formation by improving the dysregulated cholesterol metabolism and chronic inflammation during early phases of atherosclerosis [18]. Moreover, Zhang et al. [19] (2016) also unraveled the role of quercetin in regulation of hepatic cholesterol metabolism

through induction of hepatic cholesterol 7α-hydroxylaserequired in the conversion of cholesterol to bile acids for its disposal and also by the efflux of cholesterol by increasing the ABCG1 expression in rat model (Fig. 2). Quercetin has pleotropic beneficial effects in terms of antihypertensive and antioxidant properties [20].

With increasing age and higher extent of inflammation, elevated level of cholesterol is associated with upsurge in viral entry points on cell surface. Cholesterol augments the binding and entry of SARS-CoV-2 into the cell by interfering with the localization as well as association of SARS-CoV-2 with angiotensinogen converting enzyme (ACE2) in GM1 lipid rafts (under review, preprint [21]). Methyl-β-cyclodextrin (MβCD), an antiviral drug reduced the SARS-CoV multiplication by depleting cholesterol and reduction of the ACE2 receptor expression in a dose-dependent manner in *in vitro* cell models [22]. Quercetin also interferes with the expression of ACE2 [23] thereby blocking the entry of COVID-19 inside the cell and hence can provide dual protection against SARS-Cov-2. Moreover, being P-glycoprotein inducer, quercetin can inhibit the cytokine storm like effects of pro-inflammatory cytokines [which suppress the expression and activity of P-glycoprotein in severely ill COVID-19 patients (reviewed in [24]).

Various systematic reviews and meta-analysis have recorded the potential of quercetin as anti-inflammatory, anti-obesity, anti-diabetic, anti-hypertensive, anti-fibrinogen agent along with its role in regulating cholesterol metabolism [25–27]. Various seminal studies (*in silico*, pre-clinical and clinical studies) have demonstrated the possible usefulness of quercetin in COVID-19 [28,29]. A growing body of evidence (experimental as well as predictive studies) supported the usefulness of quercetin not only as an "add-on" but also as a mainstay in the COVID-19 therapy. Moreover, quercetin acts as zinc ionophore, and it has been demonstrated that exogenous zinc inhibits RNA dependent RNA polymerase activity of SARS-CoV in dose dependent manner (reviewed in [30]). Quercetin improves ER stress as well [6]. Currently, there are 4 clinical trials going on worldwide using quercetin and its derivatives alone or in combination with other drugs/nutritional supplements against COVID-19 (Supplementary material 1). In addition, there are clinical evidences of usefulness of quercetin against COPD, and it is also a FDA approved drug against inflammation (reviewed in [24]).

However, how or whether quercetin will affect the fenofibrate distribution inside the cells is not known. Nonetheless, preclinical *in vivo* study has shown synergistic effect of quercetin and fenofibrate in reducing the cholesterol content, which might be useful in COVID-19 treatment [31]. It should be taken into consideration that safety and efficacy of fenofibrate drug is well established only for geriatric population but not for pediatrics population and pregnant women [11]. Previously, there have been concerns over the poor oral bioavailability profile of quercetin, but this problem is obviated with the advent of quercetin phytosomes. Pharmacokinetics studies in humans have demonstrated an increased bioavailability rate by about 20-fold for total quercetin by using such quercetin phytosomes [32].

Conclusion

Given its wide range of therapeutic effects, quercetin holds promise as broad-spectrum"add-on"anti-cholesterol as well as an anti-inflammatory agent for COVID-19 patients (however due to known possibility of interactions with several drugs, quercetin shouldn't be taken without medical prescription). Therefore, definite evidence is required to be gathered from ongoing and future prospective randomized clinical trials (RCT's). This hypothesis is an attempt to reveal untapped potential of quercetin's therapeutic properties, and provide the possible pathophysiological rationale of its use alone or in combination with other drugs in prospective RCT's. The risk to reward ratio is clearly in favor of encouraging therapeutic prospect of quercetin in COVID-19 patients, and hence the results of ongoing clinical trials are being meticulously followed and eagerly awaited.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rechem.2021.100148.

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