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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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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 that cholesterol-lowering drug, fenofibrate (Peroxisome proliferator-activated receptor (PPAR)-α agonist) [11], suppressed the SARS-CoV-2 replication as well as pathogenesis by affecting the pathways of lipid metabolism in 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-hydroxylase required 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 anti-inflammatory 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 angiotensin 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 an 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 mainstream 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.

References

[1] WHO Solidarity Trial Consortium, H. Pan, R. Petö, et al., Repurposed Antiviral Drugs for Covid-19-Interim WHO Solidarity Trial Results, N. Engl. J. Med. 384 (6) (2021) 497-511, https://doi.org/10.1056/NEJMoa2023184.

[2] M. Rogomszty, E. Berkowitz, A.R. Jadad, Delivering benefits at speed through real-world repurposing of off-patent drugs: The COVID-19 Pandemic as a case in point, EMIR Public Health Surveill. 6 (2) (2020), e19199, https://doi.org/10.1186/s12991-019-19199.

[3] M. Abu-Farha, T.A. Thananjay, M.G. Qaddoumi, A. Hashem, J. Abubakar, F. Al-Mulla, The role of lipid metabolism in COVID-19 virus infection and as a drug target, Int. J. Mol. Sci. 21 (10) (2020) 3544, https://doi.org/10.3390/ijms21103544.

[4] V. Parvathaneyi, V. Gupta, Utilizing drug repurposing against COVID-19: efficacy, limitations, and challenges, Life Sci. 259 (2020), 118275, https://doi.org/10.1016/j.lfs.2020.118275.

[5] M. Lorizate, H.G. Krausslich, Role of lipids in virus replication, Cold Spring Harb. Perspect. Biol. 3 (10) (2011), a004820, https://doi.org/10.1101/cshperspect.a004820.

[6] A. Ehrlich, S. Uhl, K. Ioannidis, M. Hofree, B.R. tenOever, Y. Nahmias, The SARS-CoV-2 Transcriptional Metabolic Signature in Lung Epithelium, SSRN Electron J. (2020) DOI:10.2139/ssrn.3650499.

[7] B. Yan, H. Chu, D. Yang, et al., Characterization of the lipidomic profile of human coronavirus-infected cells: implications for lipid metabolism remodeling upon coronavirus replication, Viruses 11 (1) (2019) 73, https://doi.org/10.3390/v11010072.

[8] L. Plantier, V. Besnard, Y. Xu, et al., Activation of sterol-response element-binding proteins (SREBP) in alveolar type II cells enhances lipogenesis causing pulmonary lipotoxicity, J. Biol. Chem. 287 (13) (2012) 10099–10114, https://doi.org/10.1074/jbc.M111.303669.

[9] K.M. Gowdy, M.B. Fensler, Emerging roles for cholesterol and lipoproteins in lung disease, Pulum Pharmacol Ther. 26 (4) (2013) 430–437, https://doi.org/10.1016/j.jpt.2012.06.002.

[10] A.R. Tall, L. Yvan-Charvet, Cholesterol, inflammation and innate immunity, Nat. Rev. Immunol. 15 (2) (2015) 104–116, https://doi.org/10.1038/nri3792.

[11] G. Sidhu, J. Tripp, Fenofibrate. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559219/.

[12] C. Aguiar, E. Alegría, R.C. Bonadonna, et al., A review of the evidence on reducing macrovascular risk in patients with atherogenic dyslipidaemia: a report from an expert consensus meeting on the role of fenofibrate-statin combination therapy, Atherosclerosis. Suppl. 19 (2015) 1–12, https://doi.org/10.1016/j.am J. 2016.12.005.

[13] R. Ferrari, C. Aguiar, E. Alegría, et al., Current practice in identifying and treating cardiovascular risk, with a focus on residual risk associated with atherogenic dyslipidaemia, Eur. Heart J. Suppl. 18 (Supp C) (2016) C2–C12, https://doi.org/10.1093/eurheartj/ehw009.

[14] Z. Reiner, M. Hatamipour, M. Banach, et al., Statins and the COVID-19 main protease: in silico evidence on direct interaction, Arch. Med. Sci. 16 (3) (2020) 490–496, https://doi.org/10.5114/ams.2020.94655.

[15] M. Banach, P.E. Benson, Z. Fras, et al., Brief recommendations on the management of adult patients with familial hypercholesterolemia during the COVID-19 pandemic, Pharmacol. Res. 158 (2020), 104891, https://doi.org/10.1016/j.phrs.2020.104891.

[16] L. Yvan-Charvet, M. Ranalletta, N. Wang, et al., Combined deficiency of ABCA1 and ABCG1 promotes foam cell accumulation and accelerates atherosclerosis in mice, J. Clin. Invest. 117 (12) (2007) 3900–3908, https://doi.org/10.1172/JCI33172.
[17] L. Yvan-Charvet, C. Welch, T.A. Pagler, et al., Increased inflammatory gene expression in ABC transporter-deficient macrophages: free cholesterol accumulation, increased signaling via toll-like receptors, and neutrophil infiltration of atherosclerotic lesions, Circulation 118 (18) (2008) 1837–1847, https://doi.org/10.1161/CIRCULATIONAHA.108.793869.

[18] A.C. Li, C.K. Glass, The macrophage foam cell as a target for therapeutic intervention, Nat. Med. 8 (11) (2002) 1235–1242, https://doi.org/10.1038/nn1102-1235.

[19] M. Zhang, Z. Xie, W. Gao, L. Pu, J. Wei, C. Guo, Quercetin regulates hepatic cholesterol metabolism by promoting cholesterol-to-bile acid conversion and cholesterol efflux in rats, Nutr. Res. 36 (3) (2016) 271–279, https://doi.org/10.1016/j.nutres.2015.11.019.

[20] L. Mirsafaei, Ž. Reiner, R. Shafabakhsh, Z. Asemi, Molecular and biological functions of quercetin as a natural solution for cardiovascular disease prevention and treatment, Plant Foods Hum. Nutr. 75 (3) (2020) 307–315, https://doi.org/10.1007/s11130-020-00832-0.

[21] H. Wang, Z. Yuan, M.A. Pavel, S.B. Hansen, The role of high cholesterol in age-related COVID19 lethality, bioRxiv [Preprint] (2020) 2020.05.09.086249, doi: 10.1101/2020.05.09.086249.

[22] S.A. Sanchez, G. Gunther, M.A. Tricerri, E. Gratton, Methyl-β-cyclodextrins preferentially remove cholesterol from the liquid disordered phase in giant unilamellar vesicles, J. Membr. Biol. 241 (1) (2011) 1–10, https://doi.org/10.1007/s00232-011-9348-8.

[23] L. Yi, Z. Li, K. Yuan, et al., Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells, J. Virol. 78 (20) (2004) 11334–11339, https://doi.org/10.1128/JVI.78.20.11334-11339.2004.

[24] A. Pawar, A. Pal, Molecular and functional resemblance of dexamethasone and quercetin: a paradigm worth exploring in dexamethasone-nonresponsive COVID-19 patients, Phytother. Res. 34 (12) (2020) 3085–3088, https://doi.org/10.1002/ptr.6896.

[25] A. Sahebkar, Effects of quercetin supplementation on lipid profile: a systematic review and meta-analysis of randomized controlled trials, Crit. Rev. Food Sci. Nutr. 57 (4) (2017) 666–676, https://doi.org/10.1080/10408398.2014.948695.

[26] R. Tabrizi, O.R. Tamtaji, N. Mirhosseini, et al., The effects of quercetin supplementation on lipid profiles and inflammatory markers among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials, Crit. Rev. Food Sci. Nutr. 60 (11) (2020) 1855–1868, https://doi.org/10.1080/10408398.2019.1604491.

[27] H. Huang, D. Liao, Y. Dong, R. Pu, Effect of quercetin supplementation on plasma lipid profiles, blood pressure, and glucose levels: a systematic review and meta-analysis, Nutr. Rev. 78 (8) (2020) 615–626, https://doi.org/10.1093/nutrit/nuz071.

[28] G. Derosa, P. Maffioli, A. D Angelo, F. Di Pierro, A role for quercetin in coronavirus disease 2019 (COVID-19), Phytother. Res. 35 (3) (2021) 1230–1236, https://doi.org/10.1002/ptr.6887.

[29] R.M.L. Colunga Biancatti, M. Berrill, J.D. Catravas, P.E. Marik, Quercetin and vitamin C: an experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19), Front. Immunol. 11 (2020) 1451, https://doi.org/10.3389/fimmu.2020.01451.

[30] M.T. Rahman, S.Z. Idid, Can Zn Be a critical element in COVID-19 treatment? Biol. Trace Elem. Res. 199 (2) (2021) 550–558, https://doi.org/10.1007/s12011-020-02394-9.

[31] J. Donaldson, M. Ngema, P. Nkomozepi, K. Erlwanger, Quercetin administration post-weaning attenuates high-fructose, high-cholesterol diet-induced hepatic steatosis in growing, female Sprague Dawley rat pups, J. Sci. Food Agric. 99 (15) (2019) 6954–6961, https://doi.org/10.1002/jsfa.9984.

[32] F. Di Pierro, A. Khan, A. Bertuccioli, et al., Quercetin Phytosome® as a potential candidate for managing COVID-19, Minerva Gastroenterol. Dietol. 67 (2) (2021) 190–195, https://doi.org/10.23736/S1221-421X.20.02771-3.