Treatment of COVID-19 Patients with Quercetin: A Prospective, Single - Centre, Randomized, Controlled Trial

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Abstract

Aim The present study aimed to evaluate the effect of quercetin in COVID-19 treatment. Methods This was a single-centre, prospective randomised controlled cohort study. Routine care versus QCB (quercetin, vitamin C, bromelain) supplementation was compared between 447 patients with at least one chronic disease and moderate-to-severe respiratory symptoms. Demographic features, signs, laboratory results and drug administration data of patients were recorded. The endpoint was that QCB supplementation was continued throughout the follow-up period from study baseline to discharge, intubation, or death. Results The most common complaints at presentation were fatigue (62.4%), cough (61.1%), anorexia (57%), thirst (53.7%), respiratory distress (51%) and chills (48.3%). The decrease in CRP, procalcitonin and ferritin levels was higher in the QCB group (all Ps were <0.05). In the QCB group, an increase in platelet and lymphocyte counts were higher (all Ps were <0.05). QCB did not reduce the risk of events during follow-up. Adjustments for statistically significant parameters, including the lung stage, use of favipiravir and presence of comorbidity did not change the results. While there was no difference between the groups in terms of event frequency, QCB group had more advanced pulmonary findings. QCB supplement is shown to have a positive effect on laboratory recovery. Conclusion We suggest that suboptimal bioavailability of QCB may explain this. So, we conclude that if a stable blood level can be achieved for QCB, it may make a difference in the treatment of COVID-19.

Introduction

Scientific research continues on new preventive and therapeutic strategies against severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2). So far, there is no proven curative treatment for the Novel Coronavirus Disease 2019 (COVID-19), and while an effective vaccine is expected, "wild" protocols based on "ancient" anti-inflammatory and anti-viral drugs are being offered. A valid and alternative therapeutic approach needs to be developed.

Affecting the nasopharyngeal cells first, SARS-CoV-2 can target different tissues such as lung, vascular endothelium, kidney and nervous at various degrees and it can cause severe illness and death.[1,2] With the advantage of the lack of systemic toxicity, flavonoids, including quercetin, are proven to potentialise routine drugs against Coronavirus.[3] Flavonoids owe their antioxidant, anti-inflammatory and anti-viral properties, against a wide range of DNA and RNA viruses, to their pleiotropic molecular structure that acts by targeting variable cells on multiple pathways.[4,5] Therefore, this study aimed to determine if quercetin had a curative role in the treatment of COVID-19.

Material and Methods:

Design: This was a single-centre, prospective, randomised controlled cohort study. This study was conducted in the Health Sciences University Kanuni Sultan Suleyman Training and Research Hospital, which was designated as a pandemic hospital. The Ministry of Health and local ethics committee approved the study (Ethics Committee approval number: KAEK/2020.05.50).

Participants: Between March 7 and July 8, 2020, adults who were hospitalised in the pandemic ward with the diagnosis of COVID-19 included upon individual informed written consent. All participants evaluated with a nasopharyngeal swab polymerase chain reaction (PCR) and chest computed tomography (CCT). The treatment protocol recommended by the Ministry of Health was applied for all cases. The recommended treatment regimen is hydroxychloroquine, 400 mg daily for another 5 days, and/or favipiravir, 2 x 600 mg for 4 days following a 2 x 1600 mg loading dose on day one. QCB (1000 mg quercetin, 1000 mg vitamin C and 100 mg bromelain) supplementation was added daily in 2 divided doses to 52/447 patients with at least one chronic disease and moderate-to-severe respiratory symptoms. Computer-generated random numbers used for simple randomisation. Exclusion criteria determined as severe respiratory failure, shock and/or combined failure of other organs that required ICU monitoring and treatment; previous history of allergic reactions against any component of QCB; pregnant or lactating women; women of childbearing age with a positive pregnancy test, breastfeeding, miscarriage, or within 2 weeks after delivery; and participation in another clinical trial against SARS-CoV-2 treatment currently or in the past 28 days.

The study was reported according to the *Consolidated Standards of Reporting Trials* guidelines and registered on ClinicalTrials.gov (number: NCT04377789) on March 20, 2020. The primary endpoint of the study was determined as QCB supplementation was continued throughout the follow-up period from study baseline to discharge, intubation, or death. Demographic features, vital signs, laboratory test results during follow-up, drug administration data, past and current diagnoses of the patients were recorded. CCT findings of the cases were evaluated in 5 stages: stage 0 is the lung being completely normal, stage 1; light one-sided ground glass image, stage 2; multifocal double-sided ground glass image, stage 3; multifocal bilateral ground glass and stage 4; opacity, air bronchogram, bilateral ground glass and opacity, respectively.

Statistical Analysis

The quantitative data were described as the mean ± standard deviation (SD), or as the median (min-max). A sample size calculation was performed based on our observed results by using a one-sided McNemar's test. A sample size of 447 individuals, at least 49 in each arm, is found to be sufficient to detect a clinically significant difference between groups with 80% power and a 5% level of significance. The qualitative data were described by the number of cases (proportion, %). Patient characteristics were compared using the χ^2 test or Fisher's exact test for categorical data and the Mann Whitney U test for continuous data. Cox proportional-hazards regression models were used to estimate the association between QCB use and the composite endpoint of intubation or death. Statistical significance was accepted when the probability (P) value was <0.05 and changes were referred to as significant at this P-value.

Results

A total of 447 adult covid patients hospitalised in the COVID ward were included in the study between March 7 and July 8, 2020. Flow chart of the study was demonstrated as Figure-1 (Figure 1). None of the adverse effects related to QCB supplement was observed in participants.

The most common symptoms at presentation were fatigue (62.4), cough (61.1%), anorexia (57%), thirst (53.7%), respiratory distress (51%) and chills (48.3%; Table 1).

There was no significant difference in gender and age distribution between the standard treatment group and the standard treatment plus QCB group ($p = 0.30$; $p = 0.19$). In terms of comorbid diseases, the standard treatment plus QCB group had a significantly higher number of chronic obstructive pulmonary disease (COPD) and tuberculosis infection cases ($p = 0.02$; $p = 0.07$), though there was no significant difference in terms of other diseases. Both groups did not differ in terms of smoking ($p = 0.34$; Table 2). Pulmonary findings in the standard therapy plus QCB group were significantly more severe than in the

standard therapy group (p = 0.04; Table 2). The proportion of patients with an oxygen saturation <93 mmHg at admission and/or follow-up was significantly higher in the group receiving standard therapy plus QCB (p = 0.021; Table 2). Nasopharyngeal swab SARS CoV2 PCR result was positive in 40-50% of cases for both groups (p = 0.84; Table 2).

The decrease in the levels of C-reactive protein, procalcitonin and ferritin were significantly higher in the group that received standard treatment plus QCB compared to the other group (Pcrp = 0.001; Pprocalcitonin = 0.004; Pferritin = 0.021; Table 3, Figure 2). Also, the increase in thrombocyte and lymphocyte count was significantly higher in the group receiving standard therapy plus QCB (Pplatelet = 0.009, Plymphocyte = 0.014; Table 3). It was found that the addition of QCB to the standard therapy/routine care did not reduce the risk of events during the service follow-up period (Omnibus tests of model coefficients p = 0.028, Hazard Ratio: 0.180, p = 0.094, (0.024–1.34); Table 4).

After adjustment for the conditions (CCT lung stage, oxygen saturation, favipiravir use, presence of comorbid chronic disease), similar results were observed between the groups (statistically significantly different values were persisted same as the previous). Therefore, QCB supplement found to be effective in the treatment of COVID-19.

Discussion

Quercetin, as a common component of many fruits and vegetables such as high capers, lovage, and tea (Camellia sinensis), is a flavonoid.[6] There is a wealth of literature supporting the anti-viral properties of quercetin in both in vitro and in vivo experiments. Quercetin is proven to inhibit several respiratory viruses in cell cultures.[7, 8] Viral S-protein of SARS-CoV-2 is known to infect the human cell via binding angiotensin-converting enzyme-2 (ACE-2) receptor. This mechanism of the virus emerged as a target for several anti-viral therapies. Hence, in silico studies demonstrated that a variety of small molecules which bind to either the isolated SARS-CoV-2 Viral S-protein at its host receptor region or to the S protein-human ACE-2 interface.[9] Quercetin is pointed one of those top five small molecules. Having that advantage of sharing the same receptor (ACE-2) and the accessory protease FURIN with SARS-CoV to bind the cell, quercetin is suggested to be an effective drug against COVID-19.[11,12] Besides, quercetin, due to its similar biochemical structure, was reported as a competitive inhibitor of SARS-CoV-2 for entry into human cells like luteolin It, therefore, has the ability to prevent SARS-CoV-2 infection.[10] Several natural polyphenolic compounds like quercetin and kaempferol are revealed as anti-viral in virtual studies.[13]

Shukor et al. (1999) showed that flavonoids which include a catechol group, enact better inhibitory capacity on ACE.[14] Thus, quercetin seems to be the most effective inhibitory flavonoid against ACE. Elimination of quercetin in humans is relatively low, with a half-life ranging from 11 to 28 hrs.[13] In parallel with this data, the bioavailability of oral quercetin widely varies, ranging from 0 to 50%.[14] Mostly depending on the individual features, an average terminal half-life of 3.5 hrs is defined for 500 mg oral quercetin.[17] Isoquercetin (glycosylated quercetin) is reported to be more absorbable than quercetin in the aglycone form, and the concomitant ingestion of quercetin with vitamin C, folate and additional flavonoids improves bioavailability.[13,15] Quercetin has the ability of spontaneous oxidation to O-semiquinone (antioxidant) or O-quinone/quinone methide (QQ; prooxidant), and this can result in the process of "quercetin paradox."[18] Consequently, inadequate ascorbate or glutathione levels may cause quercetin to convert to QQ, which has prooxidant effects. Since its co-administration with vitamin C is crucial.[19,20] Therefore, a combination of quercetin and vitamin C would not only provide a viral blockade of SARS-CoV-2 but also strengthen the immune response.

US Food and Drug Administration described quercetin as GRAS status (generally recognised as safe).[6] Besides, the European Food Safety Authority (EFSA) claimed several beneficial physiological effects of quercetin, including the protection of DNA, proteins and lipids from oxidative damage (EFSA, 2011). Bromelain is a crude extract of the pineapple that is considered as a food supplement and is freely available to the general public in health food stores and pharmacies around the world.[22] Bromelain is also demonstrated to improve oral bioavailability of quercetin up to 80% similar to vitamin C.[22]

Oral supplementation with quercetin up to 1 g/day for 3 months has not resulted in significant adverse effects.[15] The safety of quercetin-based oral supplementation during pregnancy and breastfeeding has not been established. None of the adverse effects related to QCB supplement was observed in participants. SARS CoV2 can affect many other systems along with the lung, and its effect may last after the acute period of infection resolves. It can cause endothelial dysfunction, hypercoagulability and cytokine storm.[24] In the case of significant blood levels achieved for quercetin, the adverse effects of SARS CoV2, in both acute and chronic periods, can be overcome. Inhibitory effect of quercetin on the xanthine dehydrogenase/xanthine oxidase system is another mechanism to decrease oxidative injury due to the pathological conditions.[24,25] As the most potent scavenger of reactive oxygen species, quercetin also reduces ischemia reperfusion injury in experimental models.[25,26] Moreover, quercetin provides antihypertensive effects and improves endothelial function by inhibiting endothelin-1.[27,28] Depending on its structural relation to disodium cromoglycate, quercetin is a potent antihistamine that can prevent allergic and asthma attacks.[29,30] Several studies demonstrated that quercetin causes a down-regulation of histidine decarboxylase mRNA in the human mast cell line; it also inhibits the production of leukotriene B4 in leukocytes.[33-35] Besides, it suppresses TNFa and nitric oxide release from macrophages.[31,32] Regardless of its antioxidant properties, quercetin noted to have a positive impact on endothelial function by PDE5A inhibition.[36,37] Quercetin has the ability to regulate platelet function by inhibiting thrombin-induced and collagen-induced platelet activation.[37] Possible impacts of quercetin on platelet functions may include down-regulation of CD40L on platelets and interference with adhesion molecules.[38,39] In the current study, although the lung involvement was more advanced and significantly comorbid COPD was present in the group with QCB supplement, a significant decrease was achieved in the acute phase reactants (APRs). Besides, QCB supplement is suggested to have a role on the elevation of the thrombocyte and lymphocyte count. The exaggerated release of the pro-inflammatory cytokines from 'hyper-reactive' monocytes, thought to be the reason for the increase of APRs in COVID-19.[41] Therefore, those findings may be explained by the immune-modulatory properties of flavonoids on macrophages via contributing their transformation from pro- to anti-inflammatory phenotypes.[42] Variable bioavailability, high bio-transformations due to adsorption in the gut, and complexity of the gut microbiota make it unlikely for flavonoids and their metabolites to reach micromolar blood concentrations.[43] We tried to overcome this problem with vitamin C and bromelain supplements. Although the lung findings are more advanced in the patient group receiving QCB, it has a positive effect in terms of improvement in laboratory markers/results. We suggest that a similar event rate between groups is due to the non-optimal bioavailability of quercetin. Furthermore, the possible effect of hydroxychloroquine which is included in the standard treatment, on the bioavailability of QCB has not been well described.

Conclusion We suggest that QCB has a positive effect in addition to routine treatment against COVID-19 even for patients with more advanced lung involvement, still further studies with isoquercetin, a different form of quercetin with higher bioavailability, are needed as a light of hope.

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Figure Legends

Figure-1: Flow chart of the study was demonstrated.

Figure-2: Alterations in acute phase reactants and complete blood count parameters during the follow-up

Table 1. Symptoms of all patients at the time of admission

Table 2. Comparison of demographic characteristics of the groups

Table 3. Comparison of groups in terms of laboratory parameters

Table-4 Average time of hospital follow-up, discharge rate and rate of events of the groups

Table 1. Symptoms of all patients at the time of admission

Symptoms	N=447 (%)
Cough	273 (61.1)
Fever	160 (35.8)
Sore throat	135 (30.2)
Respiratory distress	228 (51)
Fatigue	279 (62.4)
Poor appetite	255 (57.0)
Loss of smell	90 (20.1)
Loss of taste	123 (27.5)
Thirst	240 (53.7)
Nausea	168 (37.6)
Vomiting	107 (23.9)
Diarrhae	129 (28.9)
Muscle pain	100 (22.4)
Joint pain	174 (38.9)
Chest pain	129 (28.9)
Back pain	161 (36)
Headache	213 (47.7)
Vertigo	134 (30)
Syncope	15 (3.4)
Chill	216 (48.3)
Insomnia	159 (35.6)

Table 2. Comparison of demographic characteristics of the groups

		Standard treatment Group n (%)	Standard treatment plus QCB Group n (%)	
N		395	52	P
Standard therapy				
Hydroxychloroquine		387 (98)	49 (94.2)	0.12
Favipiravir		45 (11.4)	14 (26.9)	0.004
Sex				0.30
	Male	220 (55.7)	33 (63.5)	
	Female	175 (44.3)	19 (36.5)	
Age				0.19

		Standard treatment Group n (%)	Standard treatment plus QCB Group n (%)	
	18-30	21 (5.3)	0 (0)	
	30-40	40 (10.1)	1 (1.9)	
	40-50	81 (20.5)	10 (19.2)	
	50-60	96 (24.3)	17 (32.7)	
	60-70	81 (20.5)	13 (25.0)	
	70-80	41 (10.4)	8 (15.4)	
	80-90	29 (7.3)	3 (5.8)	
	90-100	6 (1.5)	0 (0)	
Comorbidities				
	COPD	20 (5.1)	7 (13.5)	0.02
	Asthma	52 (13.2)	10 (19.2)	0.28
	Cardiac disease	85 (21.6)	16 (30.8)	0.16
	Hypertension	149 (37.7)	24 (46.2)	0.29
	Diabetes Mellitus	110 (27.8)	16 (30.8)	0.74
	Malignity	14 (3.6)	2 (3.8)	0.91
	Obesity	3 (0.8)	1 (1.9)	0.39
	Rheumathologic Disease	22 (5.6)	3 (5.8)	0.95
	Chronic liver disease	3 (0.8)	0 (0)	0.52
	Chronic renal disease	0 (0)	1 (1.9)	0.11
	Tuberculose	6 (1.5)	3 (5.8)	0.07
Smoking				0.34
	-	229(58)	27 (51.9)	
	+	36 (9.1)	8 (15.4)	
	Past history of smoking	130 (32.9)	17 (32.7)	0.04
CCT at admission				
0: Totally normal 1: Slight, one-sided ground-glass 2-Multifocal two-sided ground-glass 3-Multifocal two-sided ground-glass and opasity 4- Air bronchogram, bilateral ground-glass and opacity	0	25 (6.4)	2 (3.8)	
	1	46 (11.7)	0 (0)	
	2	123 (31.3)	14 (26.9)	
	3	166 (42.2)	30 (57.7)	
	4	33 (8.4)	6 (11.5)	

		Standard treatment Group n (%)	Standard treatment plus QCB Group n (%)	
Partially Oxygen saturation				0.021
	>93	263 (66.6)	26 (50)	
	<93	132 (33.4	26 (50)	
SARS-CoV-2 test result				0.84
	Positive	180 (45.6)	23 (44.2)	
	Negative	199 (50.4)	26 (50.0)	
	Test result not yet known	16 (4.1)	3 (5.8)	

Table 3. Comparison of groups in terms of laboratory parameters

		Standard treatment	Standard treatment plus QCB
		Median (min-max)	Median (min-max)
C-reactive protein (mg/liter)			
	1.measurement	20.15 (0.1-352.9)	49.18 (4.6-339)
	2.measurement	15.27 (0.1-326.0)	22.23 (0.4-88.8)
	Difference between the results (2-1)	-2.21	-34.64
Procalsitonin (ng/ml)			
	1.measurement	0.09 (0.02-305.7)	0.15 (0.04-10.5)
	2.measurement	0.06 (0.00-39)	0.06 (0.02-55)
	Difference between the results (2-1)	-0.00	-0.06
LDH (U/liter)			
	1.measurement	265.5 (20-1247)	309 (140-556)
	2.measurement	242 (41-972)	233.5 (37-566)
	Difference between the results (2-1)	-33	-47.5
Hgb			
	1.measurement	13.5 (4.8-17.5)	13.3 (8.9-16)
	2.measurement	12.5 (4.2-20.5)	12.4(8.5-16)
	Difference between the results (2-1)	-0.7	-0.8
Leukocyte count per mm3			
	1.measurement	6.73 (0.4-39.3)	7.16 (3.1-43)
	2.measurement	5.94 (1.8-21.6)	6.81 (4.0-18.9)
	Difference between the results (2-1)	-0.69	-0.5
Neutrophil count per mm3			
	1.measurement	4.36 (0.01-79)	4.20 (0.9-40)
	2.measurement	3.57 (1.0-40.8)	4.64 (2.3-17.91)
	Difference between the results (2-1)	-0.52	-0.08
Lymphocyte count per mm3			
	1.measurement	1.50 (0.00-26.8)	1.30 (0.5-3.80)
	2.measurement	1.40 (0.2-21.5)	1.55 (0.4-3.5)
	Difference between the results (2-1)	-0.10	0.10
Platelet count per mm3			
	1.measurement	214.5 (9-768)	232 (114-471)
	2.measurement	242 (4-698)	309.5 (64-687)

		Standard treatment	Standard treatment plus QCB
	Difference between the results (2-1)	14	69
D-dimer (μg/dl)			
	1.measurement	0.68 (0.16-48.0)	0.94 (0.19-7.1)
	2.measurement	0.76 (0.17-14.5)	0.81 (0.17-35.2)
	Difference between the results (2-1)	-0.03	0.08
Ferritin (ng/ml)			
	1.measurement	199.6 (3.9-15029)	370 (65.9-2166)
	2.measurement	257 (3.3-80503)	375.3 (23.5-1621)
	Difference between the results (2-1)	25.7	-8.1

Table-4 Average time of hospital follow-up, discharge rate and rate of events of the groups

		Standard treatment	Standard treatment and QCB
		Median (min-max)	Median (min-max)
Outcomes			
Follow-up (days)		6 (2-57)	8 (2-30)
Discharge		371 (93.9)	51 (98.1)
Events			
	Need for intensive care	14 (3.5%)	0 (0)
	Death in the ward	10 (2.5%)	1 (1.9%)

Figure 1. Flow diagram of the study

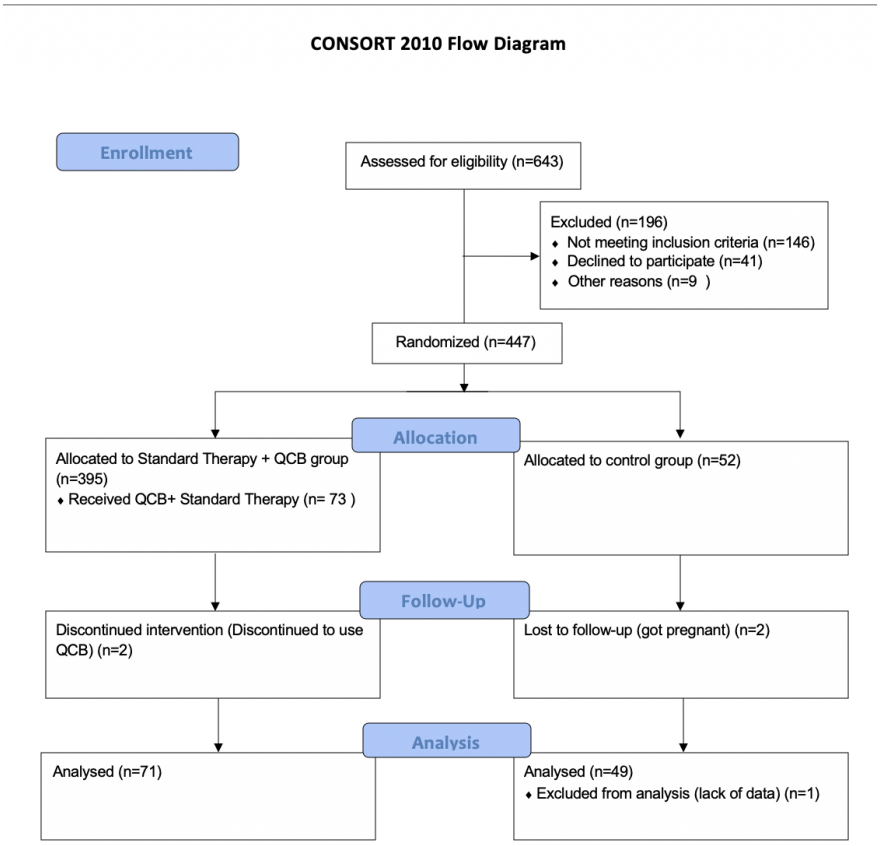

Figure-2: Alterations in acute phase reactants and complete blood count parameters during the follow-up