

Synergistic Effect of Quercetin and Vitamin C Against COVID-19: Is A Possible Guard for Front liners?

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Summary

Background While waiting for vaccine, hygiene measures, social distance and personal protective equipment are the only basic protection against Novel Coronavirus. However, these are not sufficient to protect healthcare workers. This study aimed to evaluate if quercetin and vitamin C could be protective against Novel Coronavirus.

Methods In prophylaxis group supplementation containing 500mg of quercetin, 500mg of vitamin C and 50mg of bromelain (QCB) was initiated daily in 2 divided doses for 71 healthcare workers working in areas with high risk of COVID-19, whereas 42 were determined as control group without using supplements. A maximum period of follow-up was determined as 120 days. Termination of use of QCB earlier or having a Coronavirus infection was considered as final point. At the end rapid diagnostic test used to detect immunoglobulin positivity.

Results A total of 113 persons included. No significant difference detected between groups in terms of other features. Mean age of QCB group was 39.0 ± 8.8 years and control group was 32.9 ± 8.7 . Average follow-up period for the QCB group was 113 days, and for the control group, 118, during follow-up period, 1 healthcare worker in QCB group and 9 out of 42 in control group had COVID-19. One of cases was asymptomatic, while others were not. Transmission risk hazard ratio whose did not receive QCB was 12.04 (95% Confidence interval= 1.26-115.06, $P = 0.031$). No significant effect of gender, smoking, antihypertensive medication exposure and having chronic disease on rate of transmission.

Conclusion This study revealed that QCB was protective for healthcare workers.

Trial registration NCT04377789

Key Words: COVID-19, healthcare workers, prophylaxis, quercetin, vitamin C

Introduction

Quercetin, is a flavonoid found in fruits and vegetables (1). Quercetin is also a component of a variety of human food such as red onion, grape, apple, berries, cherry, broccoli, citrus fruit, tea (*Camellia sinensis*) and, particularly high caper and lovage (2) .

Human subjects can absorb significant amounts of quercetin from food or supplements, and its elimination is quite slow, with a reported half-life ranging from 11 to 28 h (3). The bioavailability of oral quercetin is extremely variable, achieving values from 0 to 50% (4). The average terminal half-life of 500 mg oral quercetin is 3.5 h. The total recovery of C-quercetin in urine, faeces and exhaled air is highly variable, depending on the individual (5). Additional literature suggests that isoquercetin (glycosylated quercetin) is more completely absorbed than quercetin in the aglycone form, and that the simultaneous ingestion of quercetin with vitamin C, folate and additional flavonoids improves bioavailability (3, 6).

Quercetin has GRAS status (generally recognised as safe) according to criteria established by the U.S. Food and Drug Administration (FDA) (1). Not only is quercetin accepted as safe, but the European Food Safety Authority has published a number of health claims finding that quercetin has beneficial physiological effects in the protection of DNA, proteins and lipids from oxidative damage (EFSA 2011). Supplements may also include other substances, such as bromelain or vitamin C, which may help the body absorb quercetin more effectively. Bromelain is a crude extract from the pineapple that contains, Bromelain is considered as a food supplement and is freely available to the general public in health food stores and pharmacies in the USA and Europe (7).

Oral supplementation with quercetin up to 1 g/day for 3 months has not resulted in significant adverse effects (6). The safety of quercetin-based oral supplementation during pregnancy and breastfeeding has not been established.

Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) emerged in December 2019 and spread overseas causing the pandemic with a heavy burden of mortality and morbidity. Currently, an effective form of treatment has not yet been developed to prevent Novel Coronavirus Disease 2019 (COVID-19) after exposure to the virus or to prevent worsening of symptoms after confirmed infection. Healthcare workers are under high level of COVID-19 risk while fighting against virus all over the world. Therefore, present study has the hypothesis of that healthcare workers can be protected against COVID-19 infection with quercetin, vitamin C and bromelain (QCB) supplementation.

Research in context

Evidence before this study

Quercetin and vitamin C were proven to be beneficent for Coronavirus diseases other than COVID-19, previously. A literature search was done through MEDLINE to March 17, 2020, using the keywords “coronavirus disease 2019”, “COVID-19”, “SARS-CoV-2”, “healthcare workers”, “quercetin”, and “vitamin C”, without language restrictions. Although there are a couple of work on the effects of quercetin and vitamin C for Coronavirus disease, the only research on the combination of both is owned by Colunga Biancatelli RML et al. Therefore, present study is unique with evaluating the possible protective effect of combination of quercetin, vitamin C and bromelain on healthcare workers against COVID-19.

Added value of this study

Our study was a singlecentre randomized-controlled trial that assessed the effectiveness of the combination of quercetin and vitamin C in the prophylaxis of COVID-19. We recruited 113 participants consisted of healthcare workers from a large pandemic hospital. We found that quercetin, vitamin C and bromelain in combination was protective against COVID-19.

Implications of all the available evidence

This study revealed that QCB supplementation was significantly protective for healthcare workers in a 3-month period. This finding is partially consistent with another trial of Colunga Biancatelli RML et al, which found quercetin and vitamin C significantly effective in treatment and prevention of COVID-19. Therefore, combination supplement should be considered as protective agents for healthcare workers who work under high risk of COVID-19. Further studies including large number of participants are required to place QCB in regular prophylaxis.

Methods:

This was a single center, prospective randomized controlled cohort study.

Participants: The first COVID-19 case was seen in Istanbul on March 11, 2020. Study center was determined as one of the pandemic hospitals. Whole healthcare workers, serving within boundaries of hospital, were equipped by taking appropriate protective measures and equipments. On March 13, 2020, all healthcare professionals were informed about the study protocol via an announcement on local weblines of hospital. A total of 113 healthcare professionals who worked actively in the study hospital accepted to participate in the study with a written informed consent. Figure-1 demonstrates the flow diagram of the study (Figure-1). Healthcare professionals (aged between 20-60 years) working in areas of high exposure and high risk of transmission of SARS-CoV-2 (COVID areas, Intensive Care Unit (ICU), Emergency Department, Anesthesia Inpatient and Outpatient Clinics, Dialysis Units and healthcare frontiers who perform all those aerosol-generating procedures) were included. Exclusion criteria determined such as previous infection with SARS CoV2 (positive SARS-CoV-2 PCR or IgG serology), pregnancy or lactation, any kind of contraindication to quercetin and vitamin C or evidence of unstable systemic disease. Ministry of Health and local ethics committee approved the study (Ethics Committee approval number: KAEK/2020.05.50). This study was registered on March 20nd 2020 at ClinicalTrials.gov with the number of

NCT04377789. The intention-to-treat population included 113 patients (71 in the QCB group and 42 in the control group). Computer-generated random numbers used for simple randomization. In prophylaxis group supplementation (QCB) containing 500 mg of quercetin, 500 mg of vitamin C and 50 mg of bromelain was initiated daily in 2 divided doses for 71 healthcare workers working in areas with high risk of COVID, whereas 42 healthcare workers were determined as the control group without using any supplements. Demographic features of the participants such as age, gender, smoking, chronic disease and antihypertensive medication were all recorded.

A maximum period of follow-up was determined as 120 days during study. Termination of the participant's use of the QCB supplement earlier than 120 days or having an active Coronavirus infection was considered as the final point. At the end of the follow-up period, COVID-19 rapid diagnostic tests (RDT) were used to detect COVID-19 IgG and M positivity in all cases. While computerized axial tomography (CAT) scan is being used for diagnosis of COVID-19, accurate diagnosis is established by reverse transcriptase chain reaction (RT-PCR).

Statistical Analysis

Clinical data are presented as means $\pm$ SD and study data as means $\pm$ SEM. Comparisons were performed with the student's t test or Chi-Square test. A sample size calculation was performed based on our observed results by using a one-sided McNemar's test. A sample size of 113 infants, at least 42 in each arm, is found to be sufficient to detect a clinically important difference between groups with 80% power and a 5% level of significance.

SPSS version 21.0 (SPSS, Chicago, IL) was used for statistical analysis. Statistical significance was accepted when the probability (P) value was <0.05 and changes were referred to as significant at this P value. For the primary outcome, the hazard ratio (HR) of transmission risk was evaluated by Cox regression method to estimate the infection contagion rate ratio.

Findings

There was no statistically significant difference between the QCB group and the control group in terms of gender, smoking and antihypertensive medication use, and presence of chronic disease. The mean age of the QCB group was 39.0 ± 8.8 years, the mean age of the control group was 32.9 ± 8.7 years, and the ages of the subjects in the study group were statistically significantly higher (Table-1).

Outcomes

During the follow-up period between March 20 and June 20, 1 out of 71 healthcare workers using QCT and 9 out of 42 healthcare workers in the control group had COVID-19 (Figure-2). While one of the cases was asymptomatic in the form of silent infection, the others were symptomatic and were followed up at home for 15 days. None of the patients required hospitalization. Table-2 demonstrates characteristics of 10 cases who had COVID-19 (Table-2).

Protective potential of QCB against COVID-19 was investigated by using the Cox proportional risk model, among healthcare workers whose receiving QCB supplementation ($n = 48$). In control group who did not receive QCB, the risk of having COVID-19, COVID-19 transmission HR pointed 12.04 that was statistically higher than those who did not receive QCB support (95% Confidence interval [CI] = 1.26-115.06, $p = 0.031$). There was no statistically significant difference between the QCB group and the control group in terms of gender, smoking and antihypertensive medication use, and presence of chronic disease (Table-1).

Discussion

Marik et al. suggested that the synergistic effect of quercetin and vitamin C can be effective in the prevention and treatment of the SAR-CoV-2 virus, firstly in the literature (8).

To the best of our knowledge, this is the first study that elucidates the protective role of QCB against COVID-19 in healthcare workers. However, there is a large body of literature supporting the antiviral properties of quercetin in both in vitro and in vivo experimental studies (9-12). Quercetin was shown to have inhibitory effects on several respiratory viruses in cell cultures (9, 10). Besides, it was proven to prevent cytopathic effects caused by Rhinovirus Echovirus (types 7, 11, 12 and 19), Coxsackievirus (A21 and B1) and Poliovirus (type 1 Sabin) serotypes (11). Quercetin also significantly reduces plaque formation by RNA and DNA viruses [such as Respiratory Syncytial Virus (RSV), Polio type 1, Parainfluenza type 3 and Herpes Simplex Virus-1 (HSV-1)], which have anti-infective and anti-replicative properties (12). It inhibits replication of Cytomegalovirus (CMV) and Dengue virus type 2 (DENV-2) (10). Many of the small molecules were nominated for binding to either the specific SARS-CoV-2 Viral S-protein at its host receptor region or to the S protein-human ACE2 interface in a supercomputer modeling study using the world's most powerful supercomputer, SUMMIT (13). Quercetin was pointed as a high scoring ligand for viral S-protein-human ACE2 receptor interface. This enables Quercetin to be a promising candidate molecule that may interfere with SARS-CoV-2 in binding to human cells. Previous experiments also proved that Quercetin could prevent SARS-CoV to enter into human cells (14). Considering SARS-CoV-2 uses the same receptor (ACE2) and the accessory protease *FURIN* as the key to enter human body cells, Quercetin is thought to provide antiviral activity against SARS-CoV-2 as well. Along with quercetin, luteolin was also designated among the top five ligands for the viral S-protein–human ACE2 receptor interface–ligand-binding complex (13). Upon this finding, these highly structurally similar molecules were considered and studied to inhibit SARS-CoV-2 infection (14).

Likewise, Zhang et al. (2020) virtually screened 115 components of Chinese traditional medicines, highlighted 13 including quercetin and kaempferol for further studies (16).

In a study of Shukor and colleagues (17), showed that quercetin and epicatechin were able to form an interaction with ACE via both the zinc ion of ACE and amino acids of ACE. The study also demonstrated the presence of a catechol group on the flavonoid, seemed to increase the potency to inhibit ACE. Therefore, Quercetin seemed to own the highest inhibitory capacity against ACE receptors among the other flavonoids all (17).

At the fight against COVID-19, monocytes play a critical role in the inflammatory response of human body. Activated monocytes display relevant immunomodulatory activities, including the secretion of pivotal cytokines, such as pro-inflammatory cytokines interleukin (IL)-6, IL-1, IL-8, and tumor necrosis factor alpha (TNF-alpha). Variable mechanisms may be involved in the abnormal activation of monocytes in chronic diseases (18). Flavonoids may induce macrophages from pro- to anti-inflammatory cells, probably helping the scavenging/terminating of ongoing inflammatory cascades (19).

Considering the variable characteristics of COVID-19 on host preference, ways of infecting the body, immune system and other body systems, investigators/we suggest that multi-drug and combination options will come to the fore in treatment. With this perspective, Quercetin and vitamin C seemed to play an important role on both prophylaxis and treatment of COVID-19 by preventing virus entry, ACE activity and supporting intrinsic immun response of body (14). By forwarding early IFNs secretion, regulating interleukins, promoting T cell maturation, and phagocytic activity, Quercetin and ascorbic acid/ vitamin C combination was found to be beneficial at protection and recovery of several respiratory viruses including Coronavirus in experimental studies (14). For this reason, the supplement containing Quercetin and vitamin C

was preferred in this study. With the explanatory evidence depending all these data, it is not surprising that in present study, QCB prophylaxis group affected less from COVID-19.

In conclusion, this study revealed that QCB supplementation was significantly protective for healthcare workers in the 3-month period and provides hope for further studies on this subject.

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Table 1. Baseline Demographic and Clinical Characteristics of the Patients

	QCB Group (n=71)	Control Group (n=42)	P
Characteristic			
Age	39.0±8.8	32.9±8.7	0.001
Sex-no(%)			0.24
Male	17 (23.9)	6 (14.3)	
Female	54 (76.1)	36 (85.7)	
Previous coexisting disease			0.14
None	54(76.1)	37(88.1)	
Yes	17 (23.9)	5 (11.9)	
-Other	53 (74.6)	37 (88.1)	
-Asthma	2 (2.8)	1 (2.4)	
-Hashimoto thyroiditis	4 (5.6)	3 (7.1)	
-Malignity	3 (4.2)	0 (0)	
-Migraine	1 (1.4)	0 (0)	
-Diabetes	0 (0)	1 (2.4)	
-Obesity	2 (2.8)	0 (0)	
-Otoimmune disease	6 (8.5)	0 (0)	
Antihypertensive medication	5 (7)	2 (4.8)	1
Smoking	10 (14.1)	3 (7.1)	0.36

SARS COV test result			
Positive	1 (1.4)	9 (21.4)	<i>0.001</i>
Negative	70 (98.6)	33 (77.5)	

Table-2. Characteristics of 10 cases with COVID-19

	n / (%) Mean±SD
n	10
Age	30.7 ± 8.2
Sex (%)	
Male	2 (20)
Female	8 (80)
Occupation	
Doctor	3 (30)
Nurse	6 (60)
Other(Non-medical hospital staff)	1 (10)
QCB prophylaxis	
+	1 (10)
-	9 (90)
Previous coexisting disease	
Any	0(0)
None	10 (100)

Antihypertensive medication use	
+	1 (10)
-	9 (90)
Smoking	
+	1 (10)
-	9 (90)
SARS COV test result	
Positive IgG	10 (100)
Positive PCR	3 (30)
Abnormalities on chest CT-scan	7 (70)

Table-3 Cox proportional risk model

Omnibus Tests of Model			
Coefficients			
-2 Log Likelihood	Overall (score)		
	Chi-square	df	P
69.97	13.465	6	.036
Variables in the Equation			

	P	HR	95.0% CI	
			Lower	Upper
QCB supplement	<i>0.031</i>	12.04	1.26	115.06
Sex	0.52	0.52	0.58	0.11
Age	0.33	0.33	0.96	0.88
Smoking	0.33	2.84	0.34	23.85
Antihypertensive medication	0.31	2.94	0.35	24.2
Chronic disease	0.97	0.0	0.0	0.0

Figure-1: Flow diagram of the study

CONSORT 2010 Flow Diagram

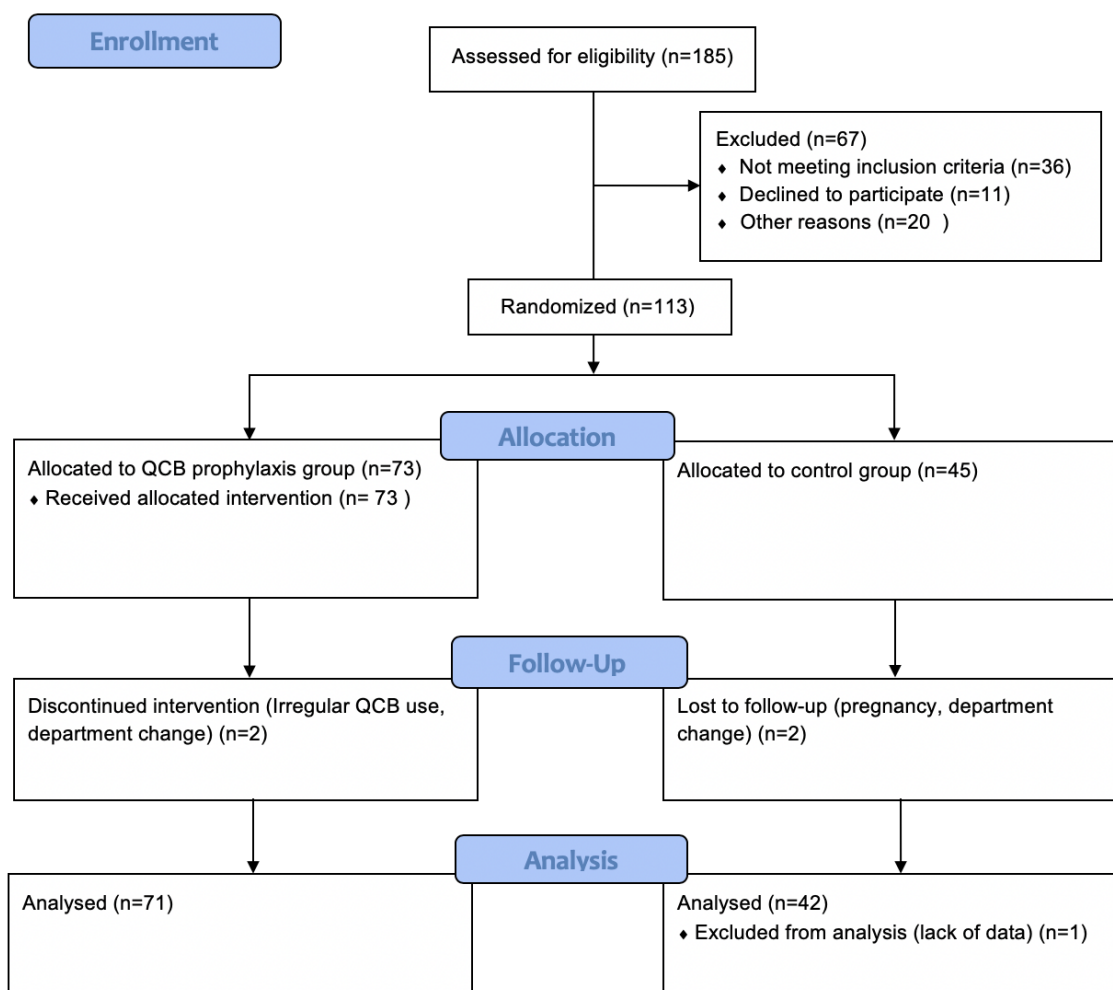


Figure-2: Graphic demonstrated survival without COVID-19 during follow up time between groups

