



Oral Quercetin in Adult Patients as a Potential Nutraceutical against Coronavirus Disease 2019 (COVID-19)

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Authors' contributions

This work was carried out in collaboration among all authors. All listed authors have made a substantial, direct and intellectual contribution to the work and have approved it for publication. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To establishing the use of oral Quercetin as a potential nutraceutical against Coronavirus Disease 2019.

Methods: A descriptive, prospective longitudinal study was carried out on 52 patients treated at the ECOMED-LAMB Clinic, in the period from the onset of Covid-19 in our country, March 3, 2020 to January 2021.

Results: Were studied 52 patients COVID-19 positive, 20 (38.4%) were in preventive treatment and 32 patients (61.5%) was administered biological therapy once the diagnosis, no difference was found between female or male sex and the predominant age was those over 60 years. Twenty-four patients (70.6%) have presented at least one comorbidity.

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The association of hospitalization with preventive treatment was not significant ($p=0.166$), we observed difference in the evolution of the patients ($p= 0.084$).

Conclusions: Quercetin could prevent and decrease the duration of SARSCoV-2 infections, it is plausible to propose the prophylactic use of this flavonoid in order to achieve clinical benefits.

Keywords: Clinical benefits; flavonoid; biological therapy; quercetin.

1. INTRODUCTION

The COVID-19 disease, caused by the novel coronavirus SARS-CoV-2, has challenged the health systems and the economy of all countries affected by the pandemic that worldwide until December 2020 has been diagnosed in 93 million individuals and claimed the lives of 2 million people, the most affected countries have been the United States of America, India and at the regional level Brazil [1] with 45% of all cases.

Mortality estimates vary according to the country and the data reported ranges from less than 0.1% to more than 25% [2], these data have mobilized many researchers in the identification of drugs against this pathology, either as therapeutic or prophylactic for the treatment, or control of viral infection.

In this race against COVID-19, the reuse of numerous drugs has been implemented, with different mechanisms of action, as well as the use of drugs with applications other than antiviral action [3], in this line, some research groups have reported the promising therapeutic effects of hydroxychloroquine / chloroquine, remdesivir, lopinavir, and ritonavir against severe COVID-19 [4].

In the fight against diseases and more when we speak of a pandemic, we have the option of starting a preventive or prophylactic treatment in

order to reduce the incidence or severity of the disease and the public expenditure of the disease [5]. However, drug prophylaxis is still controversial, without considering the possible adverse effects in some cases such as hydroxychloroquine / chloroquine [6], then the use of biochemicals is an alternative that is imposed in these cases as COVID-19 chemoprophylaxis.

Quercetin (also known as 3-, 3'-, 4'-, 5-,7-pentahydroxyflavone) is a plant flavonoid found in various vegetables, leaves, seeds, and grains, where it conjugates with residual sugars to form quercetin glycosides [7] has action known as an antioxidant with anti-inflammatory and antiviral bioactive that acts by inhibiting the entry of viruses and the fusion of viral cells [8] and reduces the expression of pro-inflammatory cytokines and lung inflammation induced by rhinovirus in mice [9], studies in which lowercase models were applied, it has been seen that Quercetin binds to the S protein of SARS-CoV-2 in the host receptor region or to the interface of the human S-ACE2 protein, which interferes with the entry of the virus into the cells, this reveals its therapeutic potential [10] and supports the idea that it inhibits infection by the SARS-CoV virus [11]. Other studies have also found that quercetin in combination with vitamin C induces synergistic antiviral and immunomodulatory effects against COVID-19 [12] (Fig. 1).

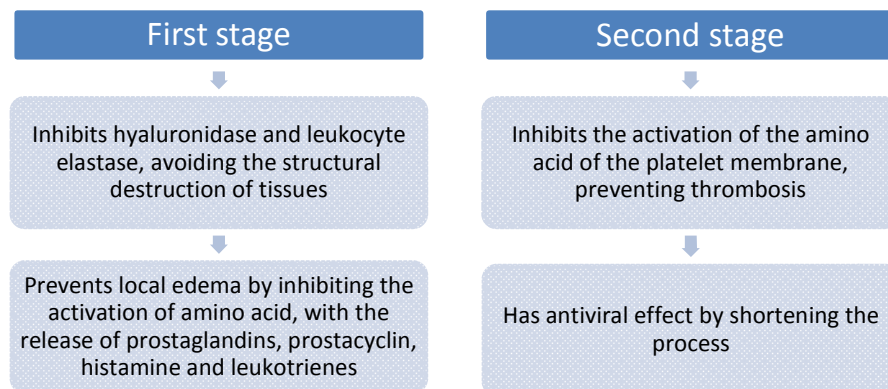


Fig. 1. Diagram of action mode of quercetin

The mode of action of vitamin C as an antiviral is supported by the activity of lymphocytes, increasing the production of interferon- α , modulating cytokines, reducing inflammation, improving endothelial dysfunction and restoring mitochondrial [13] and viricidal function [13,14].

In this study were collected scientific evidence of the use of quercetin and vitamin C, vitamin B2B3B5 and ZINC for ATP formation, the use of copper as an iron stabilizer for the prevention and treatment of the SARS-CoV-2 / COVID-19 Pandemic with the objective of establishing the use of Quercetin as a nutraceutical potential against coronavirus disease 2019 (COVID-19).

2. MATERIALS AND METHODS

A descriptive, prospective longitudinal work was carried out.

Total of 75 patients followed up by biweekly or monthly consultation until the disappearance of the clinical and radiological findings in the ECOMED-LAMB Clinic, 52 patients were selected, in the period from the beginning of Covid-19 in our Country, March 3, 2020 to January 2021.

As inclusion criteria, patients of legal age, with a diagnosis confirmed by PCR or symptomatic direct contact with COVID-19 in the period studied, were taken into consideration, and patients with incomplete data were considered as exclusion criteria.

Age, sex, underlying disease and hospitalization requirement were studied.

In addition, the start of treatment before, at or after the diagnosis of COVID-19 and the time of improvement were specified. Preventive treatment requires at least 4 days to start the

protective effects, the dose consists of 1 capsule daily, before breakfast, (300 mg of quercetin and 300 mg of Vitamin 5 and 5 mg of zinc and 0.2 mg of copper), in patients who started treatment after acquiring COVID-19, the dose was 2 or 3 capsules according to the weight of the patient.

A descriptive analysis of the variables was made utilizing frequency distribution and percentages. The Chi-Square test was used to establish possible associations between evolution and biological treatment.

This research was endorsed by the research ethics committee of the Institute of Tropical Medicine and the information obtained was kept confidential and used only for scientific purposes.

3. RESULTS

In this study, patients with preventive treatment of quercetin, vitamin C, zinc and copper were initially included, in addition to a vitamin revitalizer composed of Vitamin B1, B2, B3, B5, B9 and B12, Mg, zinc and copper (tablet), finally they were studied 52 patients diagnosed with COVID-19, 20 patients (38.4%) who were in preventive treatment and 32 patients (61.5%) who were administered biological therapy once the diagnosis was obtained, the demographic characteristics are demonstrated in Table 1.

Regarding comorbidity, which includes: cancer, heart disease, diabetes, obesity, respiratory, puerperal, 24 patients (70.6%) have presented at least one comorbidity and 10 patients (29.4%) two of those mentioned, with a total of 34 patients (65%) with some risk factor.

In relation to biological treatment, preventive treatment and the beginning of it, we can see in Table 2 the details of the same, as well as the observed evolution.

Table 1. Demographic characteristics of adult patients with oral Quercetin administration as a potential nutraceutical against coronavirus disease 2019 (COVID-19)

Demographic characteristics	N°= 52	%
Gender		
Female	24	46.15
Male	28	53.85
Grouped age		
20 - 29 years	4	7.69
30 - 39 years	9	17.31
40 - 49 years	12	23.08
50 - 59 years	9	17.31
> 60 years	18	34.62

Table 2. Administration of oral Quercetin in adult patients as a potential nutraceutical against coronavirus disease 2019 (COVID-19)

Variables	N°= 52	%
Biological treatment		
Immunocu	43	84.69
Immunocu + Revitalizer	4	7.69
Immunocu + Revitalizadorcu	3	5.77
Revitalizing	1	1.92
Vitamin C, Zinc and D3		
Start of treatment	20	38,4
Before the diagnosis of COVID-19	32	61,5
After the COVID-19 diagnosis	14	26.92
With other preventive treatment		
Evolution	1	1.92
Asthma	2	3.85
Pneumonia	4	7.69
24-hour oxygen requirement	6	11.54
Asymptomatic	39	75.00
Improved	4	7.69

The association of hospitalization with respect to preventive treatment was not significant ($p = 0.156$), if we have observed a difference in terms of the evolution of the patients with a $p = 0.035$ (Table 3).

Regarding the evolution of the patients, we have observed that preventive treatment before contracting Covid-19 causes patients to present mild symptoms, those who started treatment between days 1 to 6 of the confirmation of the Covid-19 diagnosis, had symptoms mild to moderate and improved within 48 hours to mild symptoms.

Patients who had Covid-19 and started treatment on day 7 or 8 of the symptoms improved after 4 to 6 days, two of them were hospitalized.

All received outpatient treatment except for two of them who began treatment with moderate to severe symptoms and required hospitalization.

4. DISCUSSION

Nutraceuticals include any food or part of food that provides health benefits, including the prevention or treatment of disease. Quercetin is a nutraceutical compound with a well-known preventive activity against viral respiratory infections. Importantly, Quercetin has low toxicity and its oral use is considered safe [15]. In 1998, the International Agency for Research on Cancer evaluated the carcinogenic effect of Quercetin and assigned it to Group 3 mutagenicity, suggesting the absence of carcinogenicity in humans at safe doses (500 mg twice daily for 12 weeks) [16].

Table 3. Relation of hospitalization and evolution of patients with oral quercetin administration as a potential nutraceutical against coronavirus disease 2019 (COVID-19)

Variables	Previous biological treatment		p
	No N°=32 (61.5%)	Yes N°=20 (38.4%)	
Internment			
Yes	4 (12.5)	6 (30)	0.156
No	28 (87.5)	14 (70)	
Evolution			
Improved	24 (75)	15 (75)	0.035
Oxygen requirement	4 (12.5)	0	
Pneumonia	2 (6.25)	0	
Asymptomatic	1 (3.1)	5 (25)	
Asthma	1 (3.1)	0	

Studies have shown that Quercetin is active against several viruses, including human immunodeficiency virus (HIV) [17], herpes simplex virus (type 1 and 2) [18], poliovirus (type 1) [19], parainfluenza (type 3) [20], hepatitis C virus [21], respiratory syncytial virus Sindbis virus, vaccinia virus and coronavirus (SARS-CoV) [22]. Furthermore, the use of Quercetin as a prophylactic agent against infections caused by respiratory viruses, such as avian influenza (H5N1) and rhinovirus (US\$ 7,671,086 and US\$ 7,479,498) has been described in two patents [17].

COVID-19 causes more fatalities in patients with advanced chronological age [5], as reflected in our study where the highest proportion of affected is among those over 60 years of age, in terms of sex, we have not found any relevant difference.

Coronary heart disease and diabetes are common comorbidities in patients with COVID-19, just as it was with SARS and MERS. In SARS, the prevalence of Diabetes mellitus and cardiovascular disease was 11% and 8%, respectively, and the presence of either of the two comorbidities increased the risk of death 12 times [23-24]. Several studies have shown that diabetes mellitus and hypertension were prevalent in approximately 50% of MERS cases [24]; on the other hand, cardiovascular disease was present in approximately 30% of the patients [24]. The more significant of cardiovascular comorbidities is also valid for COVID-19, especially among those with more severe disease. In a cohort study of 191 patients from Wuhan, China, there was at least one comorbidity in 48% (67% of non-survivors), hypertension in 30% (48% of non-survivors), DM in 19 % (31% of non-survivors) and CVD in 8% (13% of non-survivors) [25], in our study the presence of at least one comorbidity was presented in 70.6%, well above that reported by lowercase authors.

Quercetin inhibits the entry of SARS-CoV into the host cell. Because this is the initial stage of viral infection, Quercetin is a promising drug for COVID-19 chemoprophylaxis [17]. In the study carried out by Wang D and collaborators recently [26] they demonstrated that the concentration of quercetin required to inhibit 50% of SARS-CoV (EC50) was 83.4 μ M, which is considerably lower than the concentration reached in the human blood (418 μ M for a daily dose of 500 mg for 12 weeks) [21], the biological treatment

administered to our patients consists of 300 mg of Quercetin, 300 mg of vitamin C, 5 mg of zinc and 0.2 mg copper (Immunocu®), 53.8% of the patients received this biological compound at the time of confirmation of the diagnosis of COVID-19, without preventive treatment, and an improvement has been seen in 75% of the patients, only 3 (5.7%) manifested some respiratory symptoms such as asthma (1 patient) and pneumonia, and 4 (7.7%) required oxygen only for 24 hours and therefore hospitalization, the other patients were treated on an outpatient basis.

No deaths have been recorded in our study group and the time to improvement once the treatment has started and the manifestation of symptoms is 3 days.

These Reverse Transcriptase Enzymes and 3CL are essential for viral replication and have become a molecular target in the development of anti-SARS-CoV-2 drugs, (quercetin blocks two enzymes that are involved in viral replication, one of them reverse transcriptase, and 3CLpro which is a protease). In addition, due to glycosylated Quercetin is more soluble and highly bioavailable in the lumen of the intestine [23], its use could be more beneficial than the use of the aglycone form, the best intestinal absorption of Quercetin is obtained if it is combined with Vitamin C or Bromelain. There is currently a clinical trial recruited in Turkey, NCT04377789, titled Quercetin for the prophylaxis and treatment of COVID-19. This study justifies that COVID-19 accompanies an excessive immune reaction of the human body in severe cases, and due to the strong antioxidant and anti-inflammatory activity of quercetin it can be effective both in the prophylaxis and in the treatment of COVID-19 cases.

5. CONCLUSION

Due to the results obtained, we can say that quercetin could prevent and decrease the duration of SARSCoV-2 infections, so it is plausible to propose the prophylactic use of this flavonoid in order to achieve clinical benefits. Although these tests are preliminary due to the size of the sample, it would be interesting to confirm them through in vitro tests and subsequently in a randomized clinical trial.

Despite this, given the clinical evidence of this study and the improvement results of patients with positive Covid-19, treated early or at the

time of acquiring the disease, initial positive Covid-19 symptomatic patients without symptoms of severe hypoxia, we see that Quercetin therapy and revitalizing vitamin compounds can be used on an outpatient basis.

The use of Quercetin reduced the symptoms in seriously ill patients and also reduced the use of oxygen from 72 to 24 hours with better saturation. These results make it possible to use Quercetin as a preventive treatment and a good co-adjuvant in severe cases, reducing hospitalization time.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

The research has received an ethical clearance from the Tropical Medicine Institute in Asuncion – Paraguay number: 042/ 2020.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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