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GRAPE JUICE MINIMIZES INFLAMMATION AND REDUCES HOSPITALIZATION TIME IN PATIENTS WITH COVID-19

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Crislane de Moura Costa[a], Alexandre Sergio Silva[b], Aislan Erick Pereira de Sousa[a], Rayane Carvalho de Moura[a], Valmir Oliveira Silvino[a], Aline Camarão Telles Biasoto[c], Débora Santos Lula Barros[d], Esmeralda Maria Lustosa Barros[a], Leonardo da Rocha Sousa[e], Joyce Lopes Macedo[a], Lais Lima de Castro Abreu[a]*, Maria do Carmo de Carvalho e Martins[a], Guilherme Loureiro Werneck[f], Davyson de Lima Moreira[f], Regis Bernardo Brandim Gomes[g], Marcos Antonio Pereira dos Santos[a]

Federal University of Piauí – UFPI, Teresina – PI, Brazil[a]
Federal University of Paraíba – UFPB, João Pessoa – PB, Brazil[b]
Brazilian Agricultural Research Company – EMBRAPA, Petrolina – PE, Brazil[c]
University of Brasília – UnB, Brasília – DF, Brazil[d]
Federal Institute of Education, Science and Technology of Piauí – IFPI, Teresina – PI, Brazil[e]
Oswaldo Cruz Foundation, State University of Rio de Janeiro – UERJ, Rio de Janeiro – RJ, Brazil[f]
Oswaldo Cruz Foundation - FIOCRUZ, Immunoparasitology, Eusébio, Ceara, Brazil[g]
****E-mail: lais.castro123@ufpi.edu.br***

ABSTRACT

Inflammation and oxidative stress are the main mortality mechanisms caused by SARS-CoV-19. Grape juice has anti-inflammatory and antioxidant properties, which are believed to be beneficial in treating COVID-19. This randomized clinical trial evaluated the impact of grape juice supplementation in the treatment of patients with COVID-19. Thirty-six patients were randomized to the grape juice supplementation group (GJG, n = 20; 10 ml/kg/day) or the control group (CG, n = 16), which received conventional COVID-19 treatment protocols. Blood samples were collected at admission and discharge for analysis of oxidative stress markers. CBC, C-reactive protein levels, electrolytes and markers of renal function were obtained from medical records. Handgrip strength was also measured to assess muscle strength. The GJG presented significantly lower levels of C-reactive protein compared to the CG (16.35 ± 26.81 vs 56.51 ± 73.29, respectively) with an intragroup decrease in C-reactive protein after the procedures ($p = 0.010$). The strength of the non-dominant hand in the GJG improved in relation to pre-intervention levels and in the CG after the procedures ($p < 0.05$), there was a significantly shorter time of hospitalization for the GJG compared to the CG (6.85 ± 3.16 vs 9.94 ± 5.69 days, respectively). The addition of grape juice during COVID-19 treatment reduced inflammation levels and length of hospital stay, as well as increased upper limb functional strength in COVID-19 patients.
Clinical trial registration: RBR-4bcp54k

Keywords: COVID-19; Inflammation; Oxidative Stress.

INTRODUCTION

The coronavirus disease–2019 (COVID-19) pandemic emerged in Wuhan, China, in late 2019. It had a huge global socioeconomic impact with over 6 million deaths worldwide (JOHN HOPKINS UNIVERSITY, 2023), being the main causes of hospital admissions in 2020 and 2021 (SERAFIM *et al*., 2021). In fact, 15 to 20% of those infected require hospital care due to respiratory difficulties, with 5% necessitating intensive treatment and ventilatory support. This is particularly true for individuals of advanced age or those with underlying health conditions (PASCOAL *et al*., 2020). These patients can be affected by severe dyspnea and hypoxemia, which can rapidly progress to acute respiratory distress syndrome, sepsis, multiple organ failure, and even death (GUAN *et al*., 2021).

COVID-19 progression occurs mainly due to cytokine storm, a powerful inflammatory process caused by an exaggerated response of the immune system (YE; WANG; MAO, 2020). In this process, the virus is spread in large quantities in the infected subject and stimulates the production of CD4+ T cells that release proinflammatory cytokines leading the patient to acute respiratory distress syndrome (HU; HUANG; YIN, 2021). The lack of balance between the generation and counterbalancing of oxidants results in the progression to oxidative stress, which may lead to damage in various tissues, including the kidneys, heart, brain and arteries (HAJAM *et al*., 2022). Additionally, it has been reported that oxidative stress plays a crucial role in cardiovascular disease, and diminishing oxidative stress has been associated with a decrease in both cardiovascular and overall mortality (SENONER; DICHTL, 2019).

Red grape, its juice, and red wine are examples of functional foods and are well known for their antioxidant properties due to high amounts of phenolic and polyphenolic compounds (condensed tannis and proanthocyanidins), which are associated with the reduction of the inflammatory processes, oxidative stress, and protection against cardiovascular diseases (BARBALHO *et al*., 2020). One of the main phenolic compounds present in grapes and their derivatives is the stilbene resveratrol (GOUFO; SINGH; CORTEZ, 2020). Due to its health-related properties, including activity against glycation, oxidative stress, inflammation, neurodegeneration, as well as several types of cancer and aging (GALINIAK; AEBISHER; BARTUSIK-AEBISHER, 2019) resveratrol has been the topic of intense investigation over the last few years (GU *et al*., 2022).

Polyphenols in grape juice, including resveratrol and flavonoids, exhibit potent anti-inflammatory properties through multiple mechanisms. Resveratrol, a polyphenolic compound primarily found in red grapes, acts as an antioxidant by directly scavenging free radicals and targeting pathways that enhance cellular defense. It activates endothelial nitric oxide synthase to boost nitric oxide production and stimulates the Nrf2 pathway, which binds to antioxidant response elements to upregulate protective proteins like heme oxygenase-1 and glutathione reductase, helping to counter oxidative stress and maintain cellular redox balance (CALDEIRA-DIAS *et al*., 2021). Additionally, flavonoids, abundant in grape juice, modulate the activity of immune cells by reducing the production of reactive oxygen species and scavenging free radicals, thus decreasing oxidative stress, which is often elevated in inflammatory states (GEORGIEV; ANANGA; TSOLOVA, 2014). These polyphenols suppress the inflammatory cascade and reduce cellular damage, which may be particularly beneficial in conditions like COVID-19, where excessive inflammation plays a key role in disease severity.

Functional foods, have gained attention as adjunct therapies for managing COVID-19 due to their bioactive compounds with anti-inflammatory and immune-supportive properties. It has been proposed that the natural compounds in functional foods primarily offer anti-inflammatory, antioxidant, antihistamine, bronchodilator, immunomodulatory, and mucoactive effects, along with central or peripheral antitussive properties (MOSLEH *et al*., 2021). Furthermore, ingredients commonly found in functional foods, such as polyphenols, flavonoids, propolis, curcumin, prebiotics, probiotics, and supplements like zinc and vitamins C, D, and E, are often regarded as natural immune boosters (OMER *et al*., 2022). These foods offer a natural complement to conventional treatments by potentially reducing inflammation and enhancing immune resilience, contributing to improved outcomes in patients.

In this study, the hypothesis was tested that the addition of daily doses of grape juice to the hospital treatment protocol for COVID-19 could increase antioxidant capacity, combat inflammation, and enhance recovery. Thus, this study aimed to analyze the impact of adding whole red grape juice supplementation on inflammation, oxidative stress, and time of hospitalization in COVID-19 patients.

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MATERIAL AND METHODS

Study design and subjects

This randomized clinical trial was carried out in a public hospital. The study was conducted between October 2020 and February 2021with patients with COVID-19. The sample size was calculated using the Gpower 3.1 software. We considered a previous study which observed that the adjunct propolis treatment decreased in 3.03 days the time of hospitalization of adult patients with COVID-19 (DUARTE SILVEIRA *et al*., 2021), resulting in an effect size of 1.03. Adopting a statistical power of 0.90 and an α error of 0.05, a minimum sample size of 16 participants in each group was found to be required.

We initially recruited 95 patients admitted to the premises of the hospital with the COVID-19. 52 patients were not able to participate in the research because they did not meet the inclusion criteria (Participants had to be 18 years or older, have a confirmed COVID-19 diagnosis, and possess adequate functional capacity to perform the evaluation tests). Patients with chronic diseases or those unable to perform the evaluation tests were not included. Thus, 43 patients agreed to participate and signed the consent form according to the resolution 466/12 of the National Health Council. Seven patients did not complete the procedures as they presented difficulties in food intake during the study, did not undergo the final exams at the time of hospital discharge, or passed away.

Participants were randomly assigned to two groups based on a predefined randomization model (www.randomizer.org). Therefore, thirty-six patients were analyzed. Sixteen were assigned to the control group (CG) and twenty to the grape juice treatment group (GJG) (Figure 1). This study was approved by the Research Ethics Committee of the Federal University of Piauí under the protocol number 4.287.623 and was performed in accordance with relevant guidelines and regulations by the Declaration of Helsinki for human research. This study was registered at The Brazilian Registry of Clinical Trials (ReBEC), under protocol number RBR-4bcp54k available at https://ensaiosclinicos.gov.br/rg/RBR-4bcp54k/. The primary outcome expected was a clinical improvement in patients hospitalized with COVID-19 who were supplemented with grape juice during traditional treatment.

During hospitalization, all patients were subjected to the same treatment protocol, which consisted of the interventions following the guidelines of the clinical management protocol for patients suspected and diagnosed with COVID-19 protocol number (EBSERH, 2021a). The entire procedure was supervised by a physician, for supportive measures and prevention of complications.

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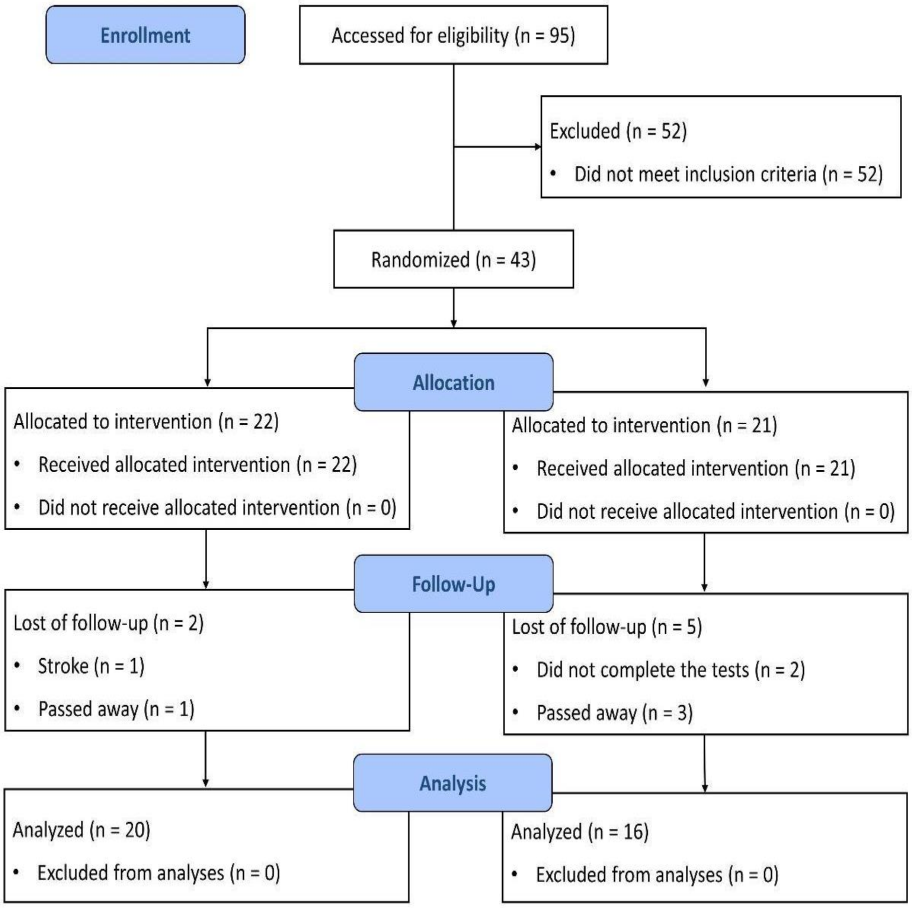
Figure 1. CONSORT flow diagram.



Experimental Protocol

The diet offered to the patients with COVID-19 followed the recommendations proposed by the diet manual of the hospital, under the protocol 23524.032612/2020-18-11262836 (EBSERH, 2021b). The manual stated that the necessary intake of calories and nutrients must be assured to all patients insuring recovery and preservation of nutritional status. Therefore, the diet offered followed a pattern, with a total energy value of approximately 2,500 kcal, considering the patient's pathophysiological status, provided as total fat (20-35%), carbohydrates (45-65%), and proteins (10-35%). The individual and clinical characteristics of the patient, such as type of pathology, food history, nutritional assessment, and identification of nutritional needs were considered by the nutritionists during the dietary prescription. Necessary changes applied in the diet included food consistency, type of food consumed, increase or decrease in the energy value, and adjustment in the proportion of fats, proteins, and carbohydrates (EBSERH, 2021b).

Patients included in the GJG initiated ingestion of 10 ml/kg/day (TOSCANO *et al*., 2015) of commercial grape juice divided into two doses during the period of hospitalization, one in the morning and one in the afternoon. According to the juice manufacturer, 200 ml of the juice contains: 130 kcal; 32 g of carbohydrates; total phenolic content of 1293.25 ± 29.93 mg/L; total anthocyanin content of 33.89 ± 0.40 mg/L. The juice, as specified by the manufacturer, was a natural, pure (100% grape juice) and non-alcoholic beverage, containing no added sugar, water, flavorings, or preservatives.

Study variables

Sociodemographic variables (age, weight, height, body mass index (BMI), education level, marital status, and living conditions) were investigated, as well as variables related to health conditions (smoking and referred comorbidities). Blood was collected at the admission and discharge of the patients to assess oxidative stress parameters, including malondialdehyde, myeloperoxidase, and peroxynitrite. Additional data such as blood count, C-reactive protein, electrolytes, and renal function markers were collected from medical records.

Systolic (SBP) and diastolic (DBP) blood pressure, as well as heart rate were measured at the time of their routine activities. The methodological rigor of using only one device for measuring in all patients could not be fulfilled due to the safety protocol. The monitoring device PORTAL DX 2020 (DIXTAL®) was used. The evaluations were conducted in accordance with the guidelines recommended by the Brazilian Guidelines on Arterial Hypertension (NOBRE *et al*., 2010).

The hand grip strength was verified to assess muscle strength using a manual dynamometer (Crown® 100 Kgf/1 Kgf). Patients performed the test at rest in horizontal position, with their arms extended at their sides, and forearms and wrists in a neutral position. They were instructed to perform three maximal isometric contractions, with 30 s between measurements. The values of the handgrip strength measurement were grouped as dominant (right for right-handed, and left for left-handed) and nondominant (left for right-handed, and right for left-handed) hands (SOSTISSO *et al*., 2020).

Statistical analysis

Normality and homogeneity of the data were evaluated with the Shapiro-Wilk and Levene tests, respectively. Variables that did not meet normality assumptions were transformed to improve distributional characteristics before conducting statistical analyses. Specifically, log transformation was applied to skewed data, to reduce skewness and achieve approximate normality. Transformed data were then used in parametric tests, ensuring assumptions of normality and homogeneity of variance were met. Results obtained were shown as mean and standard deviation of the mean. Time of hospitalization was also presented as median and interquartile range (IQR). Independent *t* test was used to compare the characteristics of the participants between groups. In order to compare the effect of grape juice on the study variables, analysis of variance (ANOVA) for repeated measures was performed, with Bonferroni's post-hoc test. Linear regression analysis was used to evaluate the association between supplementation with grape juice and time of hospitalization and improvement of specific health parameters controlling for pre-intervention values. A significance level of $p < 0.05$ was adopted. The entire statistical analyses were performed using the Statistical Packages for the Social Sciences software for Windows (SPSS version 21.0).

RESULTS

Patients' characterization

The characteristics of the participants are presented in Table 1. The patients recruited for this study were middle-aged, with no statistical difference between the intervention and control groups. The GJG participants had significantly higher body weight (p = 0.010) and BMI (p = 0.009) compared to the CG. The number of hypertensives, diabetic and smoking patients was statistically similar in the groups. Before the evaluations, both groups had values compatible with normotensive individuals regarding both systolic and diastolic pressure, with no statistical differences observed between them. In the CG, the SBP was 4.12% higher compared to the GJG.

Table 1. Description of the participants.

Variables	Control group	Grape juice group	p value
Men	12	12	
Women	4	8	
Age (years)	58.81 ± 11.92	50.70 ± 13.62	0.06
Body mass (kg)	67.56 ± 14.669	81.46 ± 15.561	0.01*
BMI (kg/m^2)	25.50 ± 5.064	30.46 ± 5.57	0.01*

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Hypertensive	9 (56.3%)	6 (30%)	0.11
Diabetic	9 (56.3%)	6 (30%)	0.10
Smokers	5 (31.3%)	2 (10%)	0.10

Legends: Data presented as mean and standard deviation of the mean or frequency and percentage. Independent t test and chi square were used to compare groups. BMI = body mass index.

Specific health parameters

As shown in Table 2, patients supplemented with grape juice had a significant reduction in SBP by 9.79% (p = 0.03). The analysis of time *vs.* group interaction did not show statistical differences between groups after the evaluation tests. However, although not significantly, SBP showed a reduction of 4 mm/Hg with grape juice supplementation when controlled by baseline values in linear regression. At baseline, both groups had similar oxygen saturation level, which remained after the evaluations, with a slight nonsignificant increase in the GJG. Furthermore, heart rate at rest was significantly higher in the CG compared to the GJG (~8.9%), and a slight nonsignificant reduction was observed in both groups at the end of the investigation.

Table 2. Health-related parameters pre and post the evaluation tests in patients hospitalized with COVID-19.

Variables	Control group		Grape juice group		p value
	Pre	*Post*	*Pre*	*Post*	
HR at rest (bpm)	83.50 ± 14.25	83.06 ± 14.39	76.05±8.62	73.40±10.87 *	0.03
SBP (mm/Hg)	129.31 ± 8.70	117.10±13.10	123.97±10.28	111.83±14.42#	0.01
DBP (mm/Hg)	74.19 ± 10.87	69.74 ± 8.24	76.13±8.60	72.75 ± 10.77	n.s.
SpO_2 (%)	94.88 ± 3.13	94.44 ± 3.61	94.41±2.81	94.60 ± 3.23	n.s.
Blood glucose (mg/dl)	131.75 ± 50.83	150.69±30.17	118.90±36.34	119.90 ± 34.31	n.s.
Hb (g/dl)	11.63 ± 2.62	11.41±2.22	12.96 ±1.31*	13.41 ± 1.733*	0.04/ 0.01
Leukocytes ($x10^3/mm^3$)	10.31 ± 3.15	11.12 ± 10.70	8.02±4.21*	11.60 ± 6.49#	0.02/ 0.01
Segmented neutrophils ($x10^3/mm^3$)	73.21 ± 40.42	80.57 ± 38.50	235.71±260.2	511.57±533.82	n.s.
Lymphocytes ($x10^3/mm^3$)	21.14 ± 23.48	15.36 ± 8.27	44.14±48.70	56.14 ± 56.30	n.s.
Monocytes ($x10^3/mm^3$)	5.54 ± 2.76	5.71 ± 3.68	12.86±10.51	32.14 ± 38.61*	0.02
NLR ($x10^3/mm^3$)	642.86 ± 442.29	719.57 ± 503.22	686.71±771.1	877.57±438.76	n.s.
Platelets ($x10^3/mm^3$)	275.69 ±118.41	351.19 ± 127.09	295.30±13.21	356.25±159.12	n.s.
Sodium (mmol/L)	135.94 ± 2.81	133.19 ± 2.85#	136.72±2.73	133.40 ± 3.37#	0.01/ 0.01

Potassium (mmol/L)	4.24 ± 0.65	4.52 ± 0.47	4.03 ± 0.31	4.34 ± 0.53	n.s.
Urea (mg/dl)	34.80 ± 12.96	32.95 ± 12.64	32.91±13.27	38.74 ± 11.16#	0.02
Magnesium (mg/dl)	2.18 ± 0.29	2.18 ± 0.26	2.40±0.33	2.36±0.17*	0.01
Creatinine (mg/dl)	0.90 ± 0.19	0.82 ± 0.22	0.96±0.30	0.93±0.19	n.s.
CRP (mg/l)	85.38 ± 66.13	56.51 ± 73.29#	57.66±56.38	16.35 ± 26.81#	0.03/ 0.01
MDA (µM)	9.421 ± 0.19	9.71 ± 0.67	9.45±0.10	9.18±1.84	n.s.
MPO (U/µl)	9.13 ± 0.46	9.30 ± 0.41	8.89±0.31	9.29±0.53#	0.02
Peroxynitrite (µM)	8.91 ± 0.13	8.87 ± 0.48	8.89±0.10	8.99 ± 0.25	n.s.

Legends: Data presented as mean and standard deviation of the mean. *, statistical difference between groups at the same timepoint; #, statistical intragroup difference before and after the tests. CRP, C-reactive protein; DBP, diastolic blood pressure; Hb, hemoglobin; HR, heart rate; MDA, malondialdehyde; MPO, myeloperoxidase; NLR, neutrophils and lymphocytes ratio; n.s., not significant; SBP, systolic blood pressure; SpO_2%, peripheral oxygen saturation.

The glycemic index of patients in both groups did not change significantly, but it increased in the CG by 12.70%, while only 1.08% in the GJG. The blood glucose reduction in the group supplemented with grape juice was around 23 mg/dl. Regarding blood count, there was no significant difference in all the different types of cells for the groups. It was found a statistical intragroup difference before and after the tests for the GJG regarding leukocytes, sodium, urea, and MPO. Additionally, between groups differences after the addition of grape juice supplementation were found regarding monocytes and magnesium. C-reactive protein was higher in the CG (with a difference of 32.23%) when compared to the GJG, suggesting an unfavorable clinical condition (Figure 2). Linear regression analysis demonstrated a significant reduction of C-reactive proteins in the GJG comparing to that observed in the CG, controlling for baseline values (p=0.05) (Table 3).

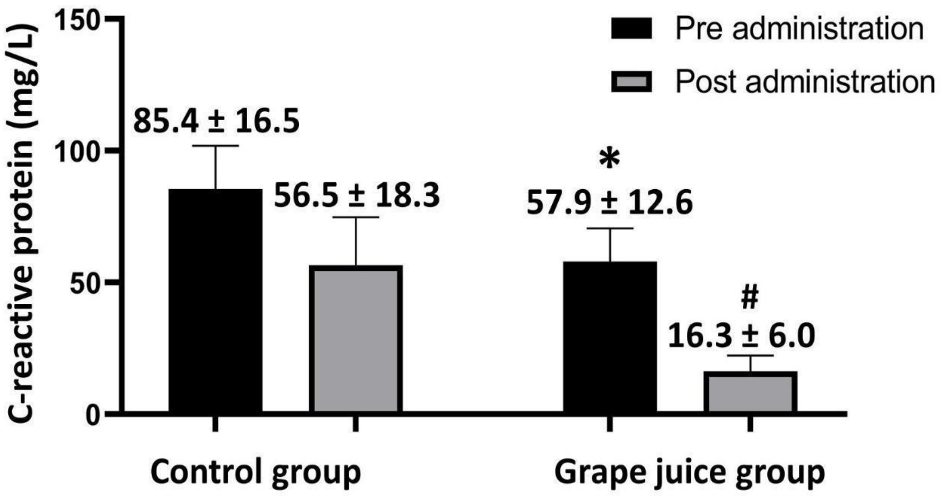
Table 3. Linear regression analysis between grape juice supplementation and length of stay, hand grip strength and health parameters among hospitalized patients with COVID-19.

Variables	Controlled results	Confidence intervals	p values
Time of hospitalization (days)	-3.08	-6.13 – -0.04	0.04
HR (bpm)	-5.57	-1-13.49 – 2.35	0.16
SBP (mm/Hg)	-4.08	-15.04 – 6.87	0.45
DBP (mm/Hg)	0.58	-6.88 – 8.05	0.87
SpO_2 (%)	0.25	-1.59 – 2.10	0.78
Blood glucose (mg/dl)	-23.84	-57.36 – 9.68	0.15
Hb (g/dl)	0.84	0.00 – 1.69	0.04
Leukocytes ($x10^3/mm^3$)	1.88	-1.59 – 5.35	0.27
Segmented neutrophils ($x10^3/mm^3$)	1.59	-1.36 – 4.54	0.28
Lymphocytes ($x10^3/mm^3$)	-0.32	-0.76 – 0.12	0.15

Monocytes (x10³/mm³)	0.13	-0.29 – 0.57	0.51
NLR (x10³/mm³)	2.43	-1.54 – 6.41	0.22
Platelet (x10³/mm³)	-10.58	-89.22 – 68.06	0.78
Sodium (mmol/L)	0.13	-2.01 – 2.28	0.90
Potassium (mmol/L)	0.01	-0.34 – 0.34	0.99
Urea (mg/dl)	0.44	-6.73 – 7.63	0.90
Magnesium (mg/dl)	0.10	-0.03 – 0.24	0.13
Creatinine (mg/dl)	0.04	-0.08 – 0.17	0.47
CRP (mg/l)	-35.26	-71.89 – 1.36	0.05
Handgrip test DH (Kgf)	3.01	-1.24 – 7.26	0.15
Handgrip test NDH (Kgf)	2.11	-1.75 – 5.98	0.27
MDA (µM)	0.14	-0.71 – 1.00	0.72
MPO (U/µl)	-0.26	-0.82 – 0.28	0.32
Peroxynitrite (µM)	1.18	-4.87 – 7.24	0.69

Legends: CRP: C-reactive protein; DBP: diastolic blood pressure; DH: dominant hand; Hb: hemoglobin; HR: heart rate; MDA: malondialdehyde; MPO: myeloperoxidase; NDH: nondominant hand; NLR: neutrophils and lymphocytes ratio; SBP: systolic blood pressure; SpO_2%: peripheral oxygen saturation.

Figure 2. C-reactive protein levels decreased after the procedures within the GJG. Additionally, C-reactive protein levels were significantly smaller in the GJG compared to controls after the procedures. Data are presented as means ± standard deviation of the mean. GJG, grape juice group; * $p < 0.05$.



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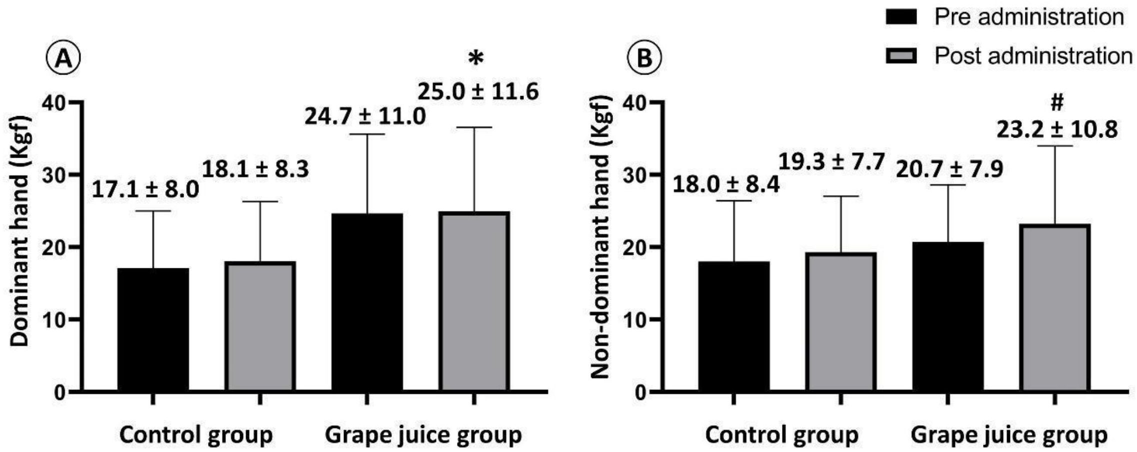
Handgrip Strength

There was a significant increase in strength of the nondominant hand after the grape juice supplementation when compared to the values before the intervention ($p < 0.05$). Additionally, the strength of the dominant hand was significantly greater in the GJG after the procedures when compared to the CG ($p < 0.05$). No significant differences were found regarding pre and post procedures for the dominant hand in the grape juice group and between groups after the procedure for the nondominant hand (Figure 3).

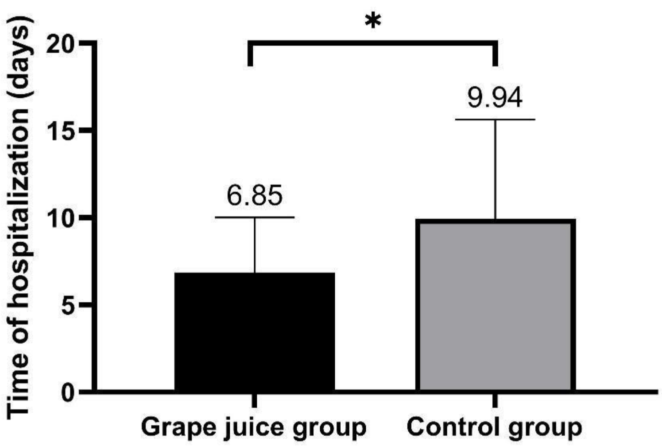
Figure 3. Handgrip strength of the dominant hand was significantly greater for the GJG compared to controls after the procedures (Panel A). Additionally, handgrip strength of the nondominant hand was significantly greater after the procedures within the GJG (Panel B). Data are presented as means ± standard deviation of the mean. GJG, grape juice group; * $p < 0.05$.



Time of hospitalization

As seen in Figure 4, the time of hospitalization for the GJG was 6.85 days (median 5.5 (IQR 4.5 – 9.0)) while for the CG was 9.94 days (median 9.5 (IQR 7.0 – 10.0)). This result was reinforced by linear regression analysis adjusted for age, reinforcing the reduction found in the GJG (Table 3).

Figure 4. Time of hospitalization comparison between grape juice group and control group.



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DISCUSSION

The results of the present study showed a significant decrease in systolic blood pressure, sodium, and C-reactive protein (CRP), as well as an increase in isometric strength for the nondominant hand after the addition of grape juice in patients hospitalized with COVID-19. Additionally, the GJG presented higher levels of magnesium and monocytes than the control group after the procedures.

Systemic inflammation and oxidative stress are directly linked to the increase in hospitalizations and deaths in patients affected by COVID-19 (GONZALEZ CAÑAS *et al*., 2020). Elevated plasma levels of interleukine-1 (IL-1) and interleukine-6 (IL-6) are associated with cardio-cerebrovascular diseases (SU *et al*., 2021), cerebral hemorrhage (LIN *et al*., 2021), and multiple organ failure (ANDRUSZKOW *et al*., 2014). Additionally, it has been recently reported that high plasma IL-6 and CRP levels are associated with adverse clinical outcomes and death in COVID-19 patients at critical conditions (LAVILLEGRAND *et al*., 2021).

The CRP is one of the acute phase proteins produced in the liver in response to the production of pro-inflammatory cytokines. Thus, it is linked to several high-incidence diseases and is commonly detected for the evaluation of inflammatory processes. We observed that CRP levels significantly decreased in the GJG. In fact, it has been reported that grape-based products, such as grape extract, juice and raisins, have significant effects on CRP levels especially when administered at high doses (>500 mg/d) and longer intervention periods (≥12 weeks) (SARKHOSH-KHORASANI; HOSSEINZADEH, 2021). Elevated serum CRP is associated with a poor outcome in COVID-19 as it is the most frequent laboratory alterations in patients, with an increase of 75-93% (XAVIER et al., 2020).

The widely recognized biological effects of polyphenols in grape juice are associated with their antioxidant, anti-inflammatory, anticancer, anti-aging, antimicrobial, and cardioprotective attributes (BENDAALI *et al*., 2022). Additionally, grape juice is well known for reducing inflammation (BLUMBERG; VITA; CHEN, 2015), prevent membrane oxidation (MORENO-MONTORO *et al*., 2015), improving blood pressure regulation (BLUMBERG; VITA; CHEN, 2015), and helping prevent diabetes and obesity (TOSCANO *et al*., 2017). Moreover, it has been observed that its Phenolic compounds enhance antioxidant activity by scavenging reactive oxygen and nitrogen molecules, binding to redox-active transition minerals, working in combination with other antioxidants, activating antioxidant enzymes and proteins, suppressing pro-oxidant enzymes, and regulating redox-sensitive transcription factors (BLUMBERG; VITA; CHEN, 2015). This study demonstrated that the protective effects of grapes also extend to cases of infectious diseases, such as COVID-19. It can provide systemic improvement mainly due to its high content of phenolic compounds and polyphenols, such as resveratrol, condensed tannins and proanthocyanidins, which show antioxidant and anti-inflammatory properties (FILARDO *et al*., 2020).

The anti-inflammatory action of grapes resulted in improvements in two important outcomes for COVID-19 hospitalized individuals, namely, increased handgrip strength and reduced hospitalization time. Muscle strength is one of the most important components of health-related physical fitness and it is positively linked to a better quality of life and general health. The handgrip strength test is a simple and reliable method of assessing muscle function, which is an important indicator of functional capacity, muscle mass conditioning, inflammatory state, and nutritional status (MONTIEL ROJAS *et al*., 2018). We observed an increase in the GJG handgrip test values for the nondominant hand after the procedures and an increase for the dominant hand when compared to the control group. It has been verified that the level of pro-inflammatory cytokines increases about 2.4 times and tumor necrosis factor-a can double in people at an older age, which increases 2 to 3 times the risk of muscle strength loss by around 40% (TIELAND; TROUWBORST; CLARK, 2018). High levels of CRP and IL-6 in are associated with lower handgrip strength, since inflammation can cause damage to muscle fibers (SOSTISSO *et al*., 2020).

We observed that the addition of grape juice to COVID-19 treatment resulted in a decrease of 31.1% in hospitalization time. This is an important finding of our study, considering that lower time of hospitalization for COVID-19 patients can have several positive impacts, including lower healthcare costs for both patients and healthcare providers, increased bed availability and reduced risk of hospital-acquired infections (BAEK *et al*., 2018). Using a similar approach to the one of this investigation, a recent study in patients with COVID-19 evaluated the effect of propolis supplementation, well known for its anti-inflammatory and antioxidant properties (DUARTE SILVEIRA *et al*., 2021). The

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authors found a significant reduction in the time of hospitalization for the patients supplemented with propolis compared to the patients with traditional treatment in the control group (6.85 *vs* 9.94 days). Numerous investigations prompted by COVID-19 have been revealing new insights, indicating that specific nutrients possess significant potential not only in preventing and treating chronic diseases but also in addressing infectious diseases.

Regarding hemodynamic parameters, the inclusion criteria for the admission to the intensive care unit is when the patient requires the use of a nasal catheter ($NCO_2 > 3L/min$) to maintain peripheral oxygen saturation above 94% or respiratory rate ≤ 24 rpm (CORRÊA et al., 2020). In our investigation, we observed that the patients from both groups maintained their SpO2 levels stable during the hospital stay, probably due to the use of supplemental oxygen during the treatment. Thus, no differences between groups were observed regarding oxygen saturation levels.

Additionally, we observed a significant improvement in the strength of the nondominant hand following grape juice supplementation compared to baseline values, indicating a positive effect on physical recovery. The strength of the dominant hand was notably higher in the grape juice group compared to the control group after the intervention, suggesting a potential role of grape juice in enhancing overall physical function. While no significant differences were observed in the dominant hand strength within the grape juice group pre- and post-procedure, and between groups for the nondominant hand strength post-procedure, these findings collectively support the notion that grape juice may contribute to inflammation reduction and expedited recovery in COVID-19 patients. This is in accordance with a similar study which observed that greater handgrip strength was correlated with reduced severity of COVID-19 and fewer subsequent complications in older adults (SEVILLA; SÁNCHEZ-PINTO, 2022).

COVID-19 is considered as systemic disease that affects several systems of the body, including the hematopoietic and hemostasis systems (SATHLER, 2020). For instance, lymphopenia can serve as an adverse prognostic indicator for individuals afflicted by this illness (NIKOLICH-ZUGICH *et al*., 2020). As the severity of the COVID-19 symptoms increase and clinical manifestations are more present, there is an increase in production of inflammatory cytokines, known as cytokine storm, and a significant decrease in the absolute and relative lymphocytes count (ZHU *et al*., 2020). In our study, there was no significant difference in lymphocyte reduction in both groups, inferring that supplementation with grape juice did not interfere in the lymphocyte reduction process. It is noteworthy that few patients progressed to a more severe outcome of the disease in this investigation, which supports the hypothesis that low lymphocyte counts is more frequently observed in patients who needed intensive treatment compared to those who did not (BERHANE *et al*., 2019).

Renal function is one of the parameters that indicate severity of COVID-19 infection and its assessment is critical to prevent further morbidity (TORAIH *et al*., 2021). A recent meta-analysis study suggested that resveratrol treatment was significantly associated with positive renal function outcomes by inhibiting inflammation (CAO *et al*., 2022). Our study did not show a significant change in renal function parameters, suggesting that supplementation with grape juice at the used dosage may not have an influence on kidney functioning.

Although COVID-19 is no longer classified as a pandemic, virus mutations and inadequate vaccination continue to lead to cases worldwide (YÜCE; FILIZTEKIN; ÖZKAYA, 2021). Our data suggest that grape juice could be used as an adjunct strategy, both in hospital settings and at home, to help reduce inflammation and hospitalization time. In addition to COVID-19, other influenza syndromes, such as those caused by H2N2 and H1N1 viruses, also contribute to current mortality rates. Therefore, we recommend that future studies explore the effects of grape juice not only in patients with SARS-CoV-2 but also in those with various influenza infections.

The limitations of this study include its relatively small sample size, which may limit the generalizability of the findings. Additionally, the study did not control for varied comorbidities of the participants, which could influence inflammatory and oxidative stress markers. Another limitation is the short duration of grape juice supplementation, as longer intervention periods may result in different outcomes. Furthermore, while the study shows associations between grape juice supplementation and improved outcomes in COVID-19 patients, it cannot definitively establish causation due to potential confounding factors.

In conclusion, the addition of grape juice supplementation to COVID-19 treatment reduced hospitalization time and resulted in favorable changes in glycemic index, blood count parameters, and C-reactive protein levels compared to the control group. Moreover, the GJG showed a significant reduction in systolic blood pressure by 9.79%, with a suggestive but nonsignificant decrease of 4 mm/Hg when adjusted for baseline values. The strength of both dominant and nondominant hands increased significantly in the GJG, and patients in this group experienced a shorter hospital stay by three days. These findings collectively suggest potential cardiovascular and metabolic benefits associated with the addition of grape juice supplementation in the COVID-19 treatment.

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The authors have no acknowledgments to declare.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

ANDRUSZKOW, Hagen *et al*. Interleukin-6 as inflammatory marker referring to multiple organ dysfunction syndrome in severely injured children. **Scandinavian journal of trauma, resuscitation and emergency medicine**, v. 22, p. 1-8, 2014. DOI: https://doi.org/10.1186/1757-7241-22-16.

BAEK, Hyunyoung *et al*. Analysis of length of hospital stay using electronic health records: A statistical and data mining approach. **PloS one**, v. 13, n. 4, 2018. DOI: https://doi.org/10.1371/journal.pone.0195901.

BARBALHO, Sandra Maria *et al*. Grape juice or wine: which is the best option? Critical **Reviews in Food Science and Nutrition**, v. 60, n. 22, p. 3876-3889, 2020.

BENDAALI, Yasmina *et al*. Contribution of grape juice to develop new isotonic drinks with antioxidant capacity and interesting sensory properties. **Frontiers in Nutrition**, v. 9, p. 890640, 2022. DOI: https://doi.org/10.3389/fnut.2022.890640.

BERHANE, Muruts *et al*. The role of neutrophil to lymphocyte count ratio in the differential diagnosis of pulmonary tuberculosis and bacterial community-acquired pneumonia: a cross-sectional study at Ayder and Mekelle Hospitals, Ethiopia. **Clinical laboratory**, v. 65, n. 4, 2019. DOI: https://doi.org/10.7754/Clin.Lab.2018.180833.

BLUMBERG, Jeffrey B.; VITA, Joseph A.; CHEN, C.-Y. Oliver. Concord grape juice polyphenols and cardiovascular risk factors: Dose-response relationships. **Nutrients**, v. 7, n. 12, p. 10032-10052, 2015. DOI: https://doi.org/10.3390/nu7125519.

CALDEIRA-DIAS, M. *et al*. Resveratrol and grape juice: Effects on redox status and nitric oxide production of endothelial cells in in vitro preeclampsia model. **Pregnancy Hypertension**, v. 23, p. 205–210, 2021. DOI: https://doi.org/10.1016/j.preghy.2021.01.001.

CAO, Shangmei *et al*. The anti-inflammatory activity of resveratrol in acute kidney injury: a systematic review and meta-analysis of animal studies. **Pharmaceutical Biology**, v. 60, n. 1, p. 2088-2097, 2022. DOI: https://doi.org/10.1080/13880209.2022.2132264.

CORRÊA, Thiago Domingos *et al*. Intensive support recommendations for critically-ill patients with suspected or confirmed COVID-19 infection. **Einstein** (Sao Paulo), v. 18, p. eAE5793, 2020. DOI: https://doi.org/10.31744/einstein_journal/2020CE5931.

DUARTE SILVEIRA, Marcelo Augusto *et al*. Efficacy of propolis as an adjunct treatment for hospitalized COVID-19 patients: a randomized, controlled clinical trial. **medRxiv**, p. 2021.01. 08.20248932, 2021. DOI: https://doi.org/10.1016/j.biopha.2021.111526.

EBSERH. Manejo clínico de pacientes suspeitos e diagnosticados com COVID-19. **Hosp Univ Da Univ Fed Do Piauí**, p. 1-19, 2021a. https://acrobat.adobe.com/id/urn:aaid:sc:VA6C2:e1da1436-565f-4ca0-9d44-4cf7d093ea94.

revista interfaces Artigos Originais
V. 12, N. 4 (2024) | ISSN 2317-434X

EBSERH. Manual de dietas hospitalares do HU-UFPI. Teresina: HU-UFPI; 2021b.

FILARDO, Simone *et al*. Therapeutic potential of resveratrol against emerging respiratory viral infections. **Pharmacology & therapeutics,** v. 214, p. 107613, 2020. DOI: https://doi.org/10.1016/j.pharmthera.2020.107613.

GALINIAK, Sabina; AEBISHER, David; BARTUSIK-AEBISHER, Dorota. Health benefits of resveratrol administration. **Acta Biochimica Polonica**, v. 66, n. 1, p. 13-21, 2019.

GEORGIEV, V.; ANANGA, A.; TSOLOVA, V. Recent advances and uses of grape flavonoids as nutraceuticals. **Nutrients**, v. 6, n. 1, p. 391–415, 2014. DOI: https://doi.org/10.3390/nu6010391.

GONZALEZ CAÑAS, E. *et al*. Acute peripheral arterial thrombosis in COVID-19. Role of endothelial inflammation. **Journal of British Surgery**, v. 107, n. 10, p. e444-e445, 2020. DOI: https://doi.org/10.1002/bjs.11904.

GOUFO, Piebiep; SINGH, Rupesh Kumar; CORTEZ, Isabel. A reference list of phenolic compounds (including stilbenes) in grapevine (Vitis vinifera L.) roots, woods, canes, stems, and leaves. **Antioxidants**, v. 9, n. 5, p. 398, 2020. DOI: https://doi.org/10.3390/antiox9050398.

GU, Wei *et al*. Effects of Resveratrol on Metabolic Indicators in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. **International Journal of Clinical Practice**, v. 2022, n. 1, p. 9734738, 2022. DOI: https://doi.org/10.1155/2022/9734738.

GUAN, Wei-jie *et al*. Clinical characteristics of coronavirus disease 2019 in China. **New England journal of medicine**, v. 382, n. 18, p. 1708-1720, 2020. DOI: https://doi.org/10.1016/j.jemermed.2020.04.004.

HAJAM, Younis Ahmad *et al*. Oxidative stress in human pathology and aging: molecular mechanisms and perspectives. **Cells**, v. 11, n. 3, p. 552, 2022. DOI: https://doi.org/10.3390/células11030552.

HU, Biying; HUANG, Shaoying; YIN, Lianghong. The cytokine storm and COVID-19. **Journal of medical virology**, v. 93, n. 1, p. 250-256, 2021. DOI: https://doi.org/10.1002/jmv.26232.

JOHN HOPKINS UNIVERSITY. COVID-19 Dashboard by the Center for Systems Science and Engineering 2023. 2023. Available in: https://coronavirus.jhu.edu/map.html. Accessed in March 6, 2023.

LAVILLEGRAND, Jean-Remi *et al*. Elevated plasma IL-6 and CRP levels are associated with adverse clinical outcomes and death in critically ill SARS-CoV-2 patients: inflammatory response of SARS-CoV-2 patients. **Annals of Intensive Care**, v. 11, p. 1-10, 2021. DOI: https://doi.org/10.1186/s13613-020-00798-x.

LIN, Jianjian *et al*. Interleukin-1 and Interleukin-6 Polymorphisms Might Influence Predisposition to Hemorrhagic Cerebral Vascular Diseases: A Meta-Analysis. **Neuroimmunomodulation**, v. 28, n. 4, p. 222-228, 2021. DOI: https://doi.org/10.1159/000506990.

MONTIEL ROJAS, Diego *et al*. Short telomere length is related to limitations in physical function in elderly European adults. **Frontiers in Physiology**, v. 9, p. 1110, 2018. DOI: https://doi.org/10.3389/fphys.2018.01110.

MORENO-MONTORO, Miriam *et al*. Phenolic compounds and antioxidant activity of Spanish commercial grape juices. **Journal of Food Composition and Analysis**, v. 38, p. 19-26, 2015. DOI: https://doi.org/10.1016/j.jfca.2014.10.001.

MOSLEH, G. *et al*. Potentials of Antitussive Traditional Persian Functional Foods for COVID-19 Therapy†. **Frontiers in Pharmacology**, v. 12, 2021. DOI: https://doi.org/10.3389/fphar.2021.624006.

NIKOLICH-ZUGICH, Janko *et al*. SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. **Geroscience**, v. 42, p. 505-514, 2020. DOI: https://doi.org/10.1007/s11357-020-00186-0.

NOBRE, Fernando *et al*. VI Diretriz Brasileira de Hipertensão. **Arquivos Brasileiros de Cardiologia** (Impresso), 2010.

OMER, A. K. *et al*. A Review on the Antiviral Activity of Functional Foods Against COVID-19 and Viral

Respiratory Tract Infections. **International Journal of General Medicine**, v. 15, p. 4817–4835, 2022. DOI: https://doi.org/10.2147/IJGM.S361001.

PASCOAL, D. B. *et al*. Acute Respiratory Syndrome: an exacerbated immune response to COVID19. **Braz. J. Hea. Rev**, v. 3, n. 2, p. 2978-2994, 2020. DOI: https://doi.org/10.34119/bjhrv3n2-138.

SARKHOSH-KHORASANI, Sahar; HOSSEINZADEH, Mahdieh. The effect of grape products containing polyphenols on C-reactive protein levels: a systematic review and meta-analysis of randomised controlled trials. **British Journal of Nutrition**, v. 125, n. 11, p. 1230-1245, 2021. DOI: https://doi.org/10.1017/S0007114520003591.

SATHLER, Plinio C. Hemostatic abnormalities in COVID-19: A guided review. Anais da **Academia Brasileira de Ciencias**, v. 92, p. e20200834, 2020.
SENONER, Thomas; DICHTL, Wolfgang. Oxidative stress in cardiovascular diseases: still a therapeutic target?. **Nutrients,** v. 11, n. 9, p. 2090, 2019. DOI: https://doi.org/10.3390/nu11092090.

SERAFIM, Rodrigo B. *et al*. Clinical course and outcomes of critically ill patients with COVID-19 infection: a systematic review. **Clinical Microbiology and Infection**, v. 27, n. 1, p. 47-54, 2021. DOI: https://doi.org/10.1016/j.cmi.2020.10.017.

SEVILLA, Guillermo García Pérez de; SÁNCHEZ-PINTO, Beatriz. Associations between muscle strength, dyspnea and quality of life in post-COVID-19 patients. **Revista da Associação Médica Brasileira**, v. 68, p. 1753-1758, 2022. DOI: https://doi.org/10.1590/1806-9282.20220974.

SOSTISSO, Caroline Finger *et al*. Handgrip strength as an instrument for assessing the risk of malnutrition and inflammation in hemodialysis patients. **Brazilian Journal of Nephrology**, v. 42, p. 429-436, 2020. DOI: https://doi.org/10.1590/2175-8239-JBN-2019-0177.

SU, Jian-Hui *et al*. Interleukin-6: a novel target for cardio-cerebrovascular diseases. **Frontiers in pharmacology**, v. 12, p. 745061, 2021. DOI: https://doi.org/10.3389/fphar.2021.745061.

TIELAND, Michael; TROUWBORST, Inez; CLARK, Brian C. Skeletal muscle performance and ageing. **Journal of cachexia, sarcopenia and muscle**, v. 9, n. 1, p. 3-19, 2018. DOI: https://doi.org/10.1002/jcsm.12238.

TORAIH, Eman A. *et al*. Multisystem inflammatory syndrome in pediatric COVID-19 patients: a meta-analysis. **World journal of pediatrics**, v. 17, p. 141-151, 2021. DOI: https://doi.org/10.1007/s12519-021-00419-y.

TOSCANO, Lydiane Tavares *et al*. Potential ergogenic activity of grape juice in runners. **Applied Physiology, Nutrition and Metabolism**, v. 40, n. 9, p. 899–906, 2015. DOI: https://doi.org/10.1139/apnm-2015-0152.

TOSCANO, Lydiane Tavares *et al*. Phenolics from purple grape juice increase serum antioxidant status and improve lipid profile and blood pressure in healthy adults under intense physical training. **Journal of Functional Foods**, v. 33, p. 419-424, 2017. DOI: https://doi.org/10.1016/j.jff.2017.03.063.

XAVIER, Analucia R. *et al*. COVID-19: clinical and laboratory manifestations in novel coronavirus infection. **Jornal Brasileiro de Patologia e Medicina Laboratorial**, v. 56, p. e3232020, 2020. DOI: https://doi.org/10.5935/1676-2444.20200049.

YE, Qing; WANG, Bili; MAO, Jianhua. The pathogenesis and treatment of the Cytokine Storm in COVID-19. **Journal of infection**, v. 80, n. 6, p. 607-613, 2020. DOI: https://doi.org/10.1016/j.jinf.2020.03.037.

YÜCE, Meral; FILIZTEKIN, Elif; ÖZKAYA, Korin Gasia. COVID-19 diagnosis—A review of current methods. **Biosensors and Bioelectronics**, v. 172, p. 112752, 2021. DOI: https://doi.org/10.1016/j.bios.2020.112752.

ZHU, Lihua *et al*. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. **Cell metabolism**, v. 31, n. 6, p. 1068-1077. e3, 2020. DOI: https://doi.org/10.1016/j.cmet.2020.04.021.