



RESEARCH ARTICLE

REVISED Effect of natural products use prior to infection with COVID-19 on disease severity and hospitalization: A self-reported cross-sectional survey study [version 2; peer review: 2 approved]

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Abstract

Background: Managing coronavirus disease 2019 (COVID-19) using available resources is essential to reduce the health burden of disease. The severity of COVID-19 is affected by nutritional status. In this study the effect of natural product use prior to infection with COVID-19 on disease severity and hospitalization was explored.

Methods: This was a cross-sectional study. Between March and July 2021, a self-administered survey was conducted in Jordan. Individuals who recovered from COVID-19 and were ≥ 18 years old were the study population. Study measures included the use of natural products, COVID-19 severity, and hospitalization status. A multivariate regression model was used for statistical analysis.

Results: The mean age (mean \pm SD) of the study sample (n=2,148) was 40.25 \pm 15.58 years old. Multivariate logistic regression showed that the regular intake of carnation (OR [0.56], CI [0.37–0.85]), onion (OR [0.69], CI [0.52–0.92]), lemon (OR [0.68], CI [0.51–0.90]), and citrus fruits (OR [0.66], CI [0.50–0.89]) before infection were associated with a substantial reduction in COVID-19 severity (P<0.01). Also, the consumption of carnation (OR [0.55], CI [0.34–0.88]), lemon (OR [0.57], CI [0.42–0.78]), and citrus fruits (OR [0.61], CI [0.44–0.84]) were associated with a significant decrease in the frequency of COVID-19-induced hospitalization (P<0.01).







Conclusions: Regular consumption of carnation, lemon, and citrus fruits before infection was associated with better outcomes for COVID-19. Studies on other populations are required to confirm these findings.

Keywords

COVID-19, natural products, carnation, onion, lemon, citrus, hospitalization, severity

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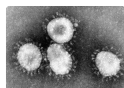
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REVISED Amendments from Version 1

This version was updated based on reviewers' comments.

- All the results expressed as N (%).
- The way of Carnation consumption was included.
- The reference PMID: 33511704 was added.
- The covariates in multivariate logistic regression were incorporated.
- Lemon is kept a separate category from citrus because some studies showed variations in their nutritional values. These studies were incorporated into the new version.
- The inclusion criteria were updated.
- The table is updated based on reviewer comments to express gender, age, and BMI in N% instead of Mean±SD.

Any further responses from the reviewers can be found at the end of the article

Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic due to the SARS-CoV-2 that causes severe acute respiratory syndrome.^{1,2} Since the World Health Organization (WHO) declared the pandemic in March, 2020, the mortality toll from COVID-19 worldwide has passed six million by April 2022.³ SARS-CoV-2 can cause a wide variety of symptoms, from asymptomatic infection to severe acute respiratory syndrome and death.^{4,5}

Maintaining a healthy diet has been suggested as a way to boost immune functions and protect against severe infections.⁶ Certain foods and natural products contain bioactive constituents that have immunomodulating, anti-inflammatory, antioxidant, antibacterial, and antiviral properties. Hence, they can be used for pre- and post-exposure prophylaxis to enhance the activity and quantity of cytokines and different types of white blood cells.⁷ Therefore, natural products may enhance viral infection outcomes by reducing inflammation and respiratory symptoms.⁸

Most people in the Middle East region still consume traditional medicinal herbs, immune-boosting foods, and drinks as part of their diet.^{9–11} During the pandemic, increased demand on medicinal natural products certain foods, drinks, and medicinal herbs such as ginger, garlic, turmeric, and citrus fruits, has been observed.^{12–14}

Several studies have examined the effect of consumption of certain foods, drinks, and medicinal herbs on COVID-19 progression.^{15,16} However, the method of preparing and consuming these natural products may vary for different populations, which may affect the desired benefits of these products. In addition, each geographical area or country may have unique medicinal herbs and immunomodulatory foods. In Jordan, the effect of regular consumption of certain immune-boosting foods and medicinal herbs prior to infection with COVID-19 on the clinical course has not yet been investigated. Due to the seriousness of COVID-19, we hypothesized that an increase in the use of some immune-boosting foods and medicinal herbs would be associated with a less severe form of COVID-19. Therefore, the current study examined the association between the use of many natural products prepared from natural sources at home and foods that boost the immune system (green tea, black caraway, Indian costus, cumin, turmeric, anis, chamomile, propolis, honey, carnation, star anis, onion, garlic, lemon, and citrus fruits) before infection with the risk of COVID-19 severity and hospitalization in Jordan. The selected natural products are the most widely used in Jordan.

Methods**Study design and subjects**

This cross-sectional survey was carried out in Jordan (between March and July 2021) as part of the Jordanian COVID-19 survey project (JCSP).¹⁷ The Institutional Review Board of Jordan University of Science and Technology granted ethical approval for the project (Ref.: 3/139/2021, dated 30/03/2021). Adults (≥18 years old) who recovered from COVID-19 were included in the current investigation. Participants were recruited from public places such as bus stations, parks, religious places, universities, and restaurants. The cover page of the questionnaire outlined the criteria for participation in the study, which included infection with COVID-19 and recovery from illness. Research assistants emphasized to participants that infection should have been confirmed by polymerase chain reaction (PCR). Exclusion criteria included current COVID-19 infection and vaccination prior to contracting the virus. Persons previously vaccinated were excluded since vaccination has a considerable influence on disease severity and may mask the potential benefits of the consumption of medicinal herbs and immune-boosting foods on the dependent variables of the study. This cross-sectional study was designed as recommended by the STROBE checklist.¹⁸

Study instrument

The current study used a self-administered questionnaire in Arabic, which can be found translated into English as *Underlying data*.⁶⁷ Participants were asked about their demographics (age, gender, body mass index (BMI), and education), comorbidities, and consumption of medicinal herbs and immune-boosting foods before infection with COVID-19. Furthermore, infection symptoms and admission to hospital data were gathered. A panel of area specialists validated the questionnaire, which was then piloted on a limited number of participants. The opinions of experts and participants were gathered and utilized to assess and enhance the clarity of the questionnaire. Results of the first draft of the questionnaire were excluded from the final analysis. The principal investigators' involvement in data collection was minimized to reduce sources of bias. Participants were chosen to represent various Jordanian geographical regions, and information was gathered from them through an online questionnaire supplied to participants by trained research assistants. We used specific techniques to reduce response bias as much as possible. First, the researcher did not interpret the questionnaire because it was self-administered. Second, we double-checked the items' clarity by translating them into Arabic. Finally, all duplicate entries were eliminated.

Sample size calculation

The sample size for our study was calculated using the online Raosoft sample size calculator (Raosoft Inc., Seattle, WA, USA). According to the world meter elaboration of the most recent United Nations data, Jordan's population is around 10 million people. The confidence level was set at 95%, the margin of error was set at 3%, and the response distribution was set at 50%. With 770,712 confirmed cases, including children, reported by the end of July 2021,¹⁹ the recommended sample size was 1067. Of note, the number of cases under the age of 18 at the time of sample collection, which occurred before the emergence of the Omicron variant, was expected to be small compared to adult cases (no data available). Therefore, if cases under 18 years of age were subtracted from the total, it would lead to a negligible change in the sample size. However, the size of the sample recruited ($n = 2,148$) was larger than what was required to represent the COVID-19 cases in Jordan, even if child cases were taken into consideration.

Recruitment of subjects

A convenient sampling procedure was used in the study. "Google Forms" was used to create and administer the survey. To ensure anonymity, the study did not collect identifying information, such as participants' names and places of work. In addition, the data were saved in encrypted digital format that required a password to access. The first section of the questionnaire sought informed consent and confirmed recovery from COVID-19. All participants provided informed consent. Anyone could opt out and withdraw from the survey by not submitting their answers, so participation was entirely voluntary. To ensure that the Jordanian population is adequately represented, trained researchers recruited participants from various Jordanian governorates. The questionnaire was completed by a total of 2,148 participants.

Classification of COVID-19 severity

Based on symptoms, the severity of COVID-19 infection was classified into two categories; severe and non-severe (asymptomatic, mild symptoms, and moderate), as previously reported.²⁰ Fever, sore throat, body pains, and nausea, with no signs or symptoms of pneumonia, were considered mild cases. Pneumonia (persistent fever and cough) but no hypoxemia (arterial oxygen saturation measured by pulse oximetry ($SpO_2 \leq 92\%$)) were considered moderate cases.²⁰ Confirmed severe pneumonia and hypoxemia were considered severe cases. It is worth noting that during peak COVID-19 waves, several patients were not admitted to hospitals because of the increased burden on hospitals.¹⁷ As a result, such cases received medical care at home through private doctor visits, and some used medical oxygen supply systems in their homes.

Statistical analysis

In this study, the independent variables were the use of natural products (medicinal herbs, immune-boosting foods), whereas the dependent variables were COVID-19 severity and hospitalization. All data with missing values were excluded from the analysis. For different variables, percentages, frequencies, means, and standard deviations (SD), were used as appropriate. The Chi-squared test was utilized to determine any differences in severity/hospitalization between users of natural products. Multivariate logistic regression was applied to examine the impact of natural food use on the severity/hospitalization while controlling for different confounders. The adjusted odds ratios (OR) and 95% confidence interval (CI) were presented. $P < 0.05$ indicates statistical significance. The data were analyzed using IBM SPSS Statistics v23 (RRID:SCR_016479).

Results

Demographic characteristics of the participants

The questionnaire was completed by 2,148 participants. The demographics of the sample are summarized in [Table 1](#).⁶⁷ Women comprised 58.2% of participants. The participants' mean age was 40.25 ± 15.58 years. The majority of

Table 1. Demographics of the sample.

Characteristics	n (%)
Reported age (years)	
18-40	1203 (56.0)
41-60	684 (31.8)
More than 60	261 (12.2)
Sex	
Male	903 (42.0)
Female	1245 (58.0)
Body mass index	
≤24.9	723 (33.7)
25-29.9	786 (36.6)
≥30	639 (29.7)
Tobacco use	362 (16.85)
Chronic diseases	496 (23.09)
COVID-19* infection status	
Severe disease	260 (12.10)
Non-severe disease	1,888 (87.89)
Admitted to hospital	219 (10.19)

*COVID-19, coronavirus disease 2019. Total n=2148.

participants had non-severe COVID-19 infection and were not admitted to hospitals (87.9% and 89.8%, respectively). Among the participants, 16.9% were smokers, and 23.1% had at least one comorbidity (Table 1).

Association of natural products use with COVID-19 severity and hospitalization

COVID-19 severity/hospitalizations were investigated in relation to the use of medicinal herbs and immune-boosting foods (Table 2). Lemon and citrus fruits were associated with lower incidence of severe COVID-19 and hospitalization ($P<0.01$). Moreover, intake of ginger and green tea was associated with reduced disease severity ($P=0.018$ and $P=0.036$, respectively). However, no significant effects on severe COVID-19 and hospitalization outcomes were observed due to consumption of anise, chamomile, propolis, honey, onions, garlic, carnation, star anise, black caraway, Indian costus, and turmeric, prior to infection.

Regression model

The multivariate logistic regression model was performed to account for potential confounders and comorbidities. The data are shown in Table 3 for two outcomes: COVID-19 severity and hospitalization status with the use of each natural product. After controlling for covariates (age, gender, BMI, cigarette smoking status, and the number of comorbidities), the findings (Table 3) showed that consumption of carnation ($P<0.01$), onion ($P<0.01$), lemon ($P<0.01$), and citrus fruits ($P<0.01$) were predictors of lower disease severity. In addition, the consumption of carnation ($P<0.01$), lemon ($P<0.001$), and citrus fruits ($P<0.01$), were predictors of reduced hospitalizations due to COVID-19 infection (Table 3).

Discussion

COVID-19 can show a spectrum of clinical symptoms from mild to severe respiratory distress and death. It is suggested that the nutritional status of people may influence COVID-19 clinical severity.²¹ In the current study, the effects of using natural products prior to infection with COVID-19 on disease severity and hospitalization were examined. Previous studies have examined the associations between the severity of infection with the intake of immune-boosting foods and medicinal herbs.^{12,22,23} According to the literature, there is no evidence that natural products and medicinal herbs impart protection from or cure COVID-19.²⁴ However, consumption of natural products before becoming infected with COVID-19 may boost the immune system and lead to favored disease outcomes. The current study found that regular consumption of carnation, lemon, and citrus fruits, before infection was associated with better outcomes for COVID-19.

Table 2. Severe COVID-19 and hospitalization cases based on natural product use prior to infection.

	COVID-19 classification						Hospitalized					
	Non-severe			Severe			No			Yes		
	n	%		n	%		n	%		n	%	
Did you consume anise before COVID infection to boost your immune system	No	1,029	87.4%	148	12.6%	0.43	1,053	89.5%	124	10.5%	0.40	
	Yes	827	88.5%	107	11.5%		846	90.6%	88	9.4%		
Did you consume chamomile before COVID infection to boost your immune system	No	1,229	87.7%	173	12.3%	0.44	1,263	90.1%	139	9.9%	0.85	
	Yes	628	88.8%	79	11.2%		635	89.8%	72	10.2%		
Did you consume propolis before COVID infection to boost your immune system	No	1,714	87.9%	235	12.1%	0.78	1,755	90.0%	194	10.0%	0.30	
	Yes	101	87.1%	15	12.9%		101	87.1%	15	12.9%		
Did you consume honey before COVID infection to boost your immune system	No	1,023	88.3%	135	11.7%	0.69	1,050	90.7%	108	9.3%	0.27	
	Yes	840	87.8%	117	12.2%		854	89.2%	103	10.8%		
Did you consume onions before COVID infection to boost your immune system	No	993	87.1%	147	12.9%	0.21	1,023	89.7%	117	10.3%	0.78	
	Yes	863	88.9%	108	11.1%		875	90.1%	96	9.9%		
Did you consume garlic before COVID infection to boost your immune system	No	1,075	88.2%	144	11.8%	0.78	1,100	90.2%	119	9.8%	0.57	
	Yes	784	87.8%	109	12.2%		799	89.5%	94	10.5%		
Did you consume carnation before COVID infection to boost your immune system	No	1,515	87.5%	217	12.5%	0.12	1,552	89.6%	180	10.4%	0.21	
	Yes	320	90.4%	34	9.6%		325	91.8%	29	8.2%		
Did you consume star anise before COVID infection to boost your immune system	No	1,580	87.6%	224	12.4%	0.20	1,619	89.7%	185	10.3%	0.40	
	Yes	251	90.3%	27	9.7%		254	91.4%	24	8.6%		
Did you consume ginger before COVID infection to boost your immune system	No	1,157	86.9%	175	13.1%	0.02*	1,189	89.3%	143	10.7%	0.10	
	Yes	708	90.3%	76	9.7%		717	91.5%	67	8.5%		
Did you consume green tea before COVID infection to boost your immune system	No	1,450	87.3%	211	12.7%	0.04*	1,486	89.5%	175	10.5%	0.08	
	Yes	393	91.0%	39	9.0%		399	92.4%	33	7.6%		
Did you consume lemons before COVID infection to boost your immune system	No	674	86.1%	109	13.9%	0.02*	687	87.7%	96	12.3%	0.003*	
	Yes	1,194	89.6%	139	10.4%		1,223	91.7%	110	8.3%		
Did you consume citrus fruits before COVID infection to boost your immune system	No	574	84.8%	103	15.2%	0.001*	587	86.7%	90	13.3%	<0.001*	
	Yes	1,299	89.7%	149	10.3%		1,327	91.6%	121	8.4%		

Table 2. *Continued*

	COVID-19 classification						Hospitalized						
	Non-severe			Severe			No			Yes			
	n	%	P-value	n	%	P-value	n	%	n	%	n	%	P-value
Did you consume black caraway before COVID infection to boost your immune system	No	1,503	87.8%	208	12.2%	0.44	1,537	89.8%	174	10.2%	1,537	89.8%	0.65
	Yes	333	89.3%	40	10.7%		338	90.6%	35	9.4%	338	90.6%	
Did you consume Indian costus before COVID infection to boost your immune system	No	1,736	87.9%	238	12.1%	0.56	1,773	89.8%	201	10.2%	1,773	89.8%	0.53
	Yes	97	89.8%	11	10.2%		99	91.7%	9	8.3%	99	91.7%	
Did you consume cumin before COVID infection to boost your immune system	No	1,502	88.1%	202	11.9%	0.70	1,533	90.0%	171	10.0%	1,533	90.0%	0.98
	Yes	341	87.4%	49	12.6%		351	90.0%	39	10.0%	351	90.0%	
Did you consume turmeric before COVID infection to boost your immune system	No	1,554	88.0%	211	12.0%	0.91	1,586	89.9%	179	10.1%	1,586	89.9%	0.46
	Yes	289	87.8%	40	12.2%		300	91.2%	29	8.8%	300	91.2%	

COVID-19, coronavirus disease 2019.

*P ≤ 0.05.

Table 3. Logistic regression analyses for medicinal herbals, natural products, and immune-boosting foods used with COVID-19 severity and hospitalization as the output.

Substance consumed before COVID-19	Total number of users	Severity			Hospitalization		
		P-value	Odds ratio (OR)	95% CI of OR	P-value	Odds ratio (OR)	95% CI of OR
Green Tea	432	0.13	0.75	0.51-1.10	0.26	0.78	0.52-1.19
Black caraway	373	0.07	0.70	0.48-1.04	0.11	0.71	0.47-1.08
Indian costus	108	0.09	0.55	0.27-1.09	0.08	0.50	0.24-1.08
Cumin	390	0.90	0.98	0.68-1.40	0.56	0.89	0.60-1.33
Turmeric	329	0.47	0.86	0.58-1.28	0.08	0.67	0.42-1.04
Anis	934	0.32	0.86	0.65-1.15	0.29	0.84	0.62-1.16
Chamomile	707	0.11	0.78	0.57-1.06	0.54	0.90	0.65-1.25
Propolis	116	0.54	0.83	0.45-1.51	0.99	1.00	0.54-1.85
Honey	957	0.33	0.87	0.65-1.16	0.78	0.96	0.70-1.31
Carnation	354	0.01*	0.56	0.37-0.85	0.01*	0.55	0.35-0.87
Star Anis	278	0.06	0.65	0.41-1.03	0.15	0.70	0.43-1.13
Onion	971	0.01*	0.69	0.52-0.92	0.07	0.75	0.55-1.02
Garlic	893	0.25	0.84	0.63-1.13	0.31	0.85	0.62-1.16
Lemon	1333	0.01*	0.68	0.51-0.90	<0.001*	0.57	0.42-0.78
Citrus fruits	1448	0.01*	0.66	0.50-0.89	0.002*	0.61	0.44-0.84

Each independent variable was adjusted for confounders, and comorbidities. COVID-19, coronavirus disease 2019. *P≤0.05.

Of note, lemon was kept as a separate category from citrus because some studies have shown differences in their nutritional values.^{25,26}

This study found that carnation use by the participants reduced COVID-19 hospitalizations and disease severity. Due to its therapeutic uses, carnation is nominated as a candidate for the management of COVID-19.^{27–30} During the COVID-19 pandemic, the consumption of carnation as an additive to food or drink to relieve throat pain has increased.³¹ A randomized clinical trial of a blend that contains carnation buds demonstrated a boost in energy levels among post-COVID-19 female patients.³² In addition, carnation has antibacterial, antiviral, and antifungal effects, and is used to kill germs in dental creams, toothpaste, mouthwash formulations, and throat sprays.^{23,33} The mechanism by which carnation may reduce the severe form of COVID-19 involves interference of SARS-CoV-2 S1-protein binding to the angiotensin-converting enzyme 2 (ACE2) receptor.³⁴ Moreover, carnation has been shown to increase the availability of oxygen by improving blood supply to both the heart and the brain.³⁵ Carnation has also been reported to be beneficial for the management of chronic coughs, shortness of breath, and maintaining a normal heart rate.³⁶

The current study also showed a significant decrease in the frequency of the severe form of COVID-19 and hospitalization due to the consumption of lemon and citrus. Citrus fruits are known to contain a variety of bioactive constituents, including vitamin C, anthocyanin, and flavanones,³⁷ which offer a variety of health benefits, such as the normalization of oxidants and inflammation.^{38,39} Furthermore, citrus fruits, such as oranges and grapefruits, are grown in Jordan, making them a readily available natural source of vitamin C.⁴⁰ Citrus fruits are commonly used by Jordanians to improve the body's immunity against COVID-19 infection.¹¹ Similar to carnation, active ingredients in citrus fruits can interfere with binding of SARS-CoV-2 to the ACE2 receptor.^{41,42} Moreover, naringin of citrus fruits has been shown to suppress the expression of proinflammatory cytokines during the inflammatory response.^{41,43} Furthermore, hesperidin, a biologically active molecule in orange fruit, was shown to inactivate the SARS-CoV-2 RNA polymerase complex.^{44,45} The antioxidant components of citrus fruits can also protect against oxidative stress associated with COVID-19 infection.⁴⁶

Onion has been shown to significantly reduce the frequency of severe illness among participants who consumed it regularly. Onion has antiviral, antifibrotic, antioxidant, and anti-inflammatory bioactive compounds, such as quercetin, apigenin, and selenium.^{39,47} In several studies, onion and its bioactive components reduced inflammation in the lungs and protected against various respiratory illnesses.^{48–50} It is suggested that phytochemicals derived from onions can interfere with the function of the main protease of SARS-CoV-2.^{51–53} In addition, anti-inflammatory diets that incorporate onions were recommended to reduce the severity of COVID-19.^{12,54,55}

Although honey and ginger were among the most consumed natural products for the prevention or mitigation of COVID-19 symptoms in Jordan,¹¹ results showed no impact of ginger and honey on the rate of hospitalization and disease severity. Ginger is suggested as a natural product for the management of COVID-19.⁵⁶ In contrast to the current findings, Aldwihi *et al.*, showed that patients who consumed ginger were less likely to be hospitalized.⁵⁷ Moreover, a decrease in COVID-19 severity was observed among patients who consumed ginger as treatment.⁵⁸ According to clinical trials, honey (propolis), a resinous substance made by bees, may help reduce viral clearance time and improve clinical COVID-19 outcomes by interfering with viral replication and entry.^{59–61} However, the effects of honey were observed in a limited number of studies involving small sample sizes.⁶² Thus, more investigations are required to confirm the role of bee products in the management of COVID-19.

According to the logistic regression analysis, no associations were observed due to consumption of green tea, black caraway, Indian costus, cumin, turmeric, anis, chamomile, star anis, and garlic with COVID-19 hospitalizations and severity. While several studies have revealed the anti-inflammatory and antiviral effects of many of these natural products,^{63–65} their contribution toward reducing COVID-19 severity is highly controversial, and requires preclinical and clinical trial evaluations, and validation using models of the disease.^{8,66} Among the study's limitations is that the total number and quantity of natural products used by the subjects were unknown. In addition, the method of consuming carnation, the most active natural product to protect against severe COVID-19, was not investigated.

Furthermore, data on the duration of COVID-19 and hospitalization were not collected. Finally, since the study collected retrospective data, the data may be subject to recall bias. As a result, more studies are required to verify the study findings.

Conclusions

The study findings showed that the regular consumption of lemon, citrus fruits, and carnation lowers the rates of COVID-19 severity and hospitalization. Studies in other populations are required to confirm these findings.

Data availability

Underlying data

Figshare: Natural Products Raw Data. <https://doi.org/10.6084/m9.figshare.19758820>.⁶⁷

This project contains the following underlying data:

- Natural products Raw Data.xlsx (survey responses from all participants)
- Questionnaire in English.docx

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

References

1. Wu F, Zhao S, Yu B, *et al.*: **A new coronavirus associated with human respiratory disease in China.** *Nature*. 2020; **579**: 265–269. [PubMed Abstract](#) | [Publisher Full Text](#)
2. Zheng J: **SARS-CoV-2: an emerging coronavirus that causes a global threat.** *Int. J. Biol. Sci.* 2020; **16**: 1678–1685. [PubMed Abstract](#) | [Publisher Full Text](#)
3. (WHO) WHO: **WHO Coronavirus (COVID-19) Dashboard 2022.** [Reference Source](#)
4. Sagnelli C, Celia B, Monari C, *et al.*: **Management of SARS-CoV-2 pneumonia.** *J. Med. Virol.* 2021; **93**: 1276–1287. [PubMed Abstract](#) | [Publisher Full Text](#)
5. Wiersinga WJ, Rhodes A, Cheng AC, *et al.*: **Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review.** *JAMA*. 2020; **324**: 782–793. [Publisher Full Text](#)
6. Wu D, Lewis ED, Pae M, *et al.*: **Nutritional modulation of immune function: analysis of evidence, mechanisms, and clinical relevance.** *Front. Immunol.* 2019; **9**: 3160. [PubMed Abstract](#) | [Publisher Full Text](#)
7. Sengupta S, Bhattacharyya D, Kasle G, *et al.*: **Potential Immunomodulatory Properties of Biologically Active Components of Spices Against SARS-CoV-2 and Pan β -Coronaviruses.** *Front. Cell. Infect. Microbiol.* 2021; **11**: 11. [Publisher Full Text](#)
8. Panyod S, Ho C-T, Sheen L-Y: **Dietary therapy and herbal medicine for COVID-19 prevention: A review and perspective.** *J. Tradit. Complement. Med.* 2020; **10**: 420–427. [PubMed Abstract](#) | [Publisher Full Text](#)
9. Almahasheer H: **Nutrition in herbal plants used in Saudi Arabia.** *Scientifica*. 2020; **2020**: 1–9. [PubMed Abstract](#) | [Publisher Full Text](#)
10. Alghamdi M, Mohammed AA, Alfahaid F, *et al.*: **Herbal medicine use by Saudi patients with chronic diseases: A cross-sectional study (experience from Southern Region of Saudi Arabia).** *Journal of Health Specialties*. 2018; **6**: 77–77. [Publisher Full Text](#)
11. Thiab SH, Nassar RI, Thiab S, *et al.*: **Medications and natural products used in Jordan for prevention or treatment of COVID-19 infection during the second wave of the pandemic: A cross-sectional online survey.** *Saudi Pharm. J.* 2022. [PubMed Abstract](#) | [Publisher Full Text](#)
12. Pieroni A, Vandebroek I, Prakofjewa J, *et al.*: **Taming the pandemic? The importance of homemade plant-based foods and beverages as community responses to COVID-19.** Springer; 2020; 1–9.
13. Khabour OF, Hassanein SF: **Use of vitamin/zinc supplements, medicinal plants, and immune boosting drinks during COVID-19 pandemic: A pilot study from Benha city, Egypt.** *Heliyon*. 2021; **7**: e06538. [PubMed Abstract](#) | [Publisher Full Text](#)
14. Singh NA, Kumar P, Jyoti KN, *et al.*: **Spices and herbs: Potential antiviral preventives and immunity boosters during COVID-19.** *Phytother Res.* 2021 May; **35**(5): 2745–2757. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
15. Hamulka J, Jeruszka-Bielak M, Górnicka M, *et al.*: **Dietary supplements during COVID-19 outbreak. results of google trends analysis supported by PLifeCOVID-19 online studies.** *Nutrients*. 2020; **13**: 54. [PubMed Abstract](#) | [Publisher Full Text](#)
16. Nuertey BD, Addai J, Kyei-Bafour P, *et al.*: **Home-Based Remedies to Prevent COVID-19-Associated Risk of Infection, Admission, Severe Disease, and Death: A Nested Case-Control Study.** *Evid. Based Complement. Alternat. Med.* 2022; **2022**: 4559897.
17. Nimer RM, Khabour OF, Swedan SF, *et al.*: **The impact of vitamin and mineral supplements usage prior to COVID-19 infection on disease severity and hospitalization.** *Bosn. J. Basic Med. Sci.* 2022. [PubMed Abstract](#) | [Publisher Full Text](#)
18. Vandenbroucke JP, Von Elm E, Altman DG, *et al.*: **Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration.** *PLoS Med.* 2007; **4**: e297. [PubMed Abstract](#) | [Publisher Full Text](#)
19. Worldometer: **Worldometer 2021 [updated May 22, 2022].** [Reference Source](#)
20. Parasher A: **COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment.** *Postgrad. Med. J.* 2021; **97**: 312–320. [PubMed Abstract](#) | [Publisher Full Text](#)
21. Gasmi A, Chirumbolo S, Peana M, *et al.*: **The Role of Diet and Supplementation of Natural Products in COVID-19 Prevention.** *Biol. Trace Elem. Res.* 2022; **200**: 27–30. [PubMed Abstract](#) | [Publisher Full Text](#)
22. Abedi F, Ghasemi S, Farkhondeh T, *et al.*: **Possible potential effects of honey and its main components against covid-19 infection.** *Dose-Response*. 2021; **19**: 155932582098242. [Publisher Full Text](#)
23. Dorsch W, Ring J: **Anti-inflammatory substances from onions could be an option for treatment of COVID-19 - a hypothesis.** *Allergo Journal: interdisziplinäre Zeitschrift für Allergologie und Umweltmedizin: Organ der Deutschen Gesellschaft für Allergie- und Immunitätsforschung*. 2020; **29**: 30–31.
24. Abdullah Alotiby A, Naif A-HL: **Prevalence of using herbs and natural products as a protective measure during the COVID-19 pandemic among the Saudi population: an online cross-sectional survey.** *Saudi Pharm. J.* 2021; **29**: 410–417. [PubMed Abstract](#) | [Publisher Full Text](#)
25. Denkova-Kostova R, Teneva D, Tomova T, *et al.*: **Chemical composition, antioxidant and antimicrobial activity of essential oils from tangerine (*Citrus reticulata* L.), grapefruit (*Citrus paradisi* L.), lemon (*Citrus lemon* L.) and cinnamon (*Cinnamomum zeylanicum* Blume).** *Z. Naturforsch. C. J. Biosci.* 2020 Nov 23; **76**(5-6): 175–185. [PubMed Abstract](#) | [Publisher Full Text](#)
26. Wallis CM, Gorman Z, Rattner R, *et al.*: **Amino acid, sugar, phenolic, and terpenoid profiles are capable of distinguishing Citrus tristeza virus infection status in citrus cultivars: Grapefruit, lemon, mandarin, and sweet orange.** *PLoS One*. 2022 May 10; **17**(5): e0268255. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
27. Bahramsoltani R, Rahimi R: **An Evaluation of Traditional Persian Medicine for the Management of SARS-CoV-2.** *Front. Pharmacol.* 2020; **11**: 571434. [PubMed Abstract](#) | [Publisher Full Text](#)

28. Kaplan A: **The nanocomposites designs of phytochemicals from medicinal and aromatic plants: promising anticancer-antiviral applications.** *Beni. Suef. Univ. J. Basic Appl. Sci.* 2022; **11**: 17.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. Koyama S, Kondo K, Ueha R, *et al.*: **Possible Use of Phytochemicals for Recovery from COVID-19-Induced Anosmia and Ageusia.** *Int. J. Mol. Sci.* 2021; **22**.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Vicidomini C, Roviello V, Roviello GN: **Molecular Basis of the Therapeutical Potential of Clove (*Syzygium aromaticum* L.) and Clues to Its Anti-COVID-19 Utility.** *Molecules.* 2021; **26**.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Malabadi RB, Meti NT, Chalannavar RK: **Role of herbal medicine for controlling coronavirus (SARS-CoV-2) disease (COVID-19).** *International Journal of Research and Scientific Innovations.* 2021a; **2021**(8): 135–165.
32. Hawkins J, Hires C, Keenan L, *et al.*: **Aromatherapy Blend of Thyme, Orange, Clove Bud, and Frankincense Boosts Energy Levels in Post-COVID-19 Female Patients: A Randomized, Double-Blinded, Placebo Controlled Clinical Trial.** *Complement. Ther. Med.* 2022; **67**: 102823.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Milind P, Deepa K: **Clove: a champion spice.** *Int. J. Res. Ayurveda Pharm.* 2011; **2**: 47–54.
34. Paidi RK, Jana M, Raha S, *et al.*: **Eugenol, a Component of Holy Basil (Tulsi) and Common Spice Clove, Inhibits the Interaction Between SARS-CoV-2 Spike S1 and ACE2 to Induce Therapeutic Responses.** *J. Neuroimmune. Pharmacol.* 2021; **16**: 743–755.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Chaieb K, Hajlaoui H, Zmantar T, *et al.*: **The chemical composition and biological activity of clove essential oil, *Eugenia caryophyllata* (*Syzygium aromaticum* L. Myrtaceae): a short review.** *Phytother. Res.* 2007; **21**: 501–506.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Rafiqul Islam ATM, Ferdousi J, Shahinozaman M: **Previously published ethno-pharmacological reports reveal the potentiality of plants and plant-derived products used as traditional home remedies by Bangladeshi COVID-19 patients to combat SARS-CoV-2.** *Saudi J. Biol. Sci.* 2021; **28**: 6653–6673.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Antonio AS, Wiedemann LSM, Galante EBF, *et al.*: **Efficacy and sustainability of natural products in COVID-19 treatment development: opportunities and challenges in using agro-industrial waste from Citrus and apple.** *Heliyon.* 2021; **7**: e07816.
[PubMed Abstract](#) | [Publisher Full Text](#)
38. Barreca D, Mandalari G, Calderaro A, *et al.*: **Citrus flavones: An update on sources, biological functions, and health promoting properties.** *Plan. Theory.* 2020; **9**: 288.
39. Zhu C, Zhou X, Long C, *et al.*: **Variations of flavonoid composition and antioxidant properties among different cultivars, fruit tissues and developmental stages of citrus fruits.** *Chem. Biodivers.* 2020; **17**: e1900690.
[Publisher Full Text](#)
40. Bayer AGCS-jfhwjcbceCCaBayer AG: **Crop Science- Jordan.** 2022.
[Reference Source](#)
41. Liu W, Zheng W, Cheng L, *et al.*: **Citrus fruits are rich in flavonoids for immunoregulation and potential targeting ACE2.** *Nat. Prod. Bioprospect.* 2022; **12**: 4.
[PubMed Abstract](#) | [Publisher Full Text](#)
42. Khan J, Sakib SA, Mahmud S, *et al.*: **Identification of potential phytochemicals from Citrus Limon against main protease of SARS-CoV-2: molecular docking, molecular dynamic simulations and quantum computations.** *J. Biomol. Struct. Dyn.* 2021; **1**–12.
[Publisher Full Text](#)
43. D'Amore A, Gradogna A, Palombi F, *et al.*: **The Discovery of Naringenin as Endolysosomal Two-Pore Channel Inhibitor and Its Emerging Role in SARS-CoV-2 Infection.** *Cells.* 2021; **10**.
[Publisher Full Text](#)
44. Naidu SAG, Mustafa G, Clemens RA, *et al.*: **Plant-Derived Natural Non-Nucleoside Analog Inhibitors (NNAIs) against RNA-Dependent RNA Polymerase Complex (nsp7/nsp8/nsp12) of SARS-CoV-2.** *J. Diet Suppl.* 2021; **1**–30.
[Publisher Full Text](#)
45. Cheng FJ, Huynh TK, Yang CS, *et al.*: **Hesperidin Is a Potential Inhibitor against SARS-CoV-2 Infection.** *Nutrients.* 2021; **13**.
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Magurano F, Sucameli M, Picone P, *et al.*: **Antioxidant Activity of Citrus Limonoids and Investigation of Their Virucidal Potential against SARS-CoV-2 in Cellular Models.** *Antioxidants (Basel).* 2021; **10**.
[Publisher Full Text](#)
47. Kumar S, Pandey AK: **Chemistry and biological activities of flavonoids: an overview.** *Sci. World J.* 2013; **2013**: 1–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
48. Ghorani V, Marefati N, Shakeri F, *et al.*: **The effects of *Allium cepa* extract on tracheal responsiveness, lung inflammatory cells and phospholipase A2 level in asthmatic rats.** *Iran. J. Allergy Asthma Immunol.* 2018; **17**: 221–231.
[PubMed Abstract](#)
49. Zaki SM: **Evaluation of antioxidant and anti-lipid peroxidation potentials of *Nigella sativa* and onion extract on nicotine-induced lung damage.** *Folia Morphol. (Warsz).* 2019; **78**: 554–563.
[PubMed Abstract](#) | [Publisher Full Text](#)
50. El-Hashim AZ, Khajah MA, Orabi KY, *et al.*: **Onion Bulb extract downregulates EGFR/ERK1/2/AKT signaling pathway and synergizes with steroids to inhibit allergic inflammation.** *Front. Pharmacol.* 2020; **11**.
[Publisher Full Text](#)
51. Bondhon TA, Fatima A, Jannat K, *et al.*: **In silico screening of *Allium cepa* phytochemicals for their binding abilities to SARS and SARS-CoV-2 3C-like protease and COVID-19 human receptor ACE-2.** *Trop. Biomed.* 2021; **38**: 214–221.
[PubMed Abstract](#) | [Publisher Full Text](#)
52. Sen D, Debnath P, Debnath B, *et al.*: **Identification of potential inhibitors of SARS-CoV-2 main protease and spike receptor from 10 important spices through structure-based virtual screening and molecular dynamic study.** *J. Biomol. Struct. Dyn.* 2022; **40**: 941–962.
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Sharma P, Shanavas A: **Natural derivatives with dual binding potential against SARS-CoV-2 main protease and human ACE2 possess low oral bioavailability: a brief computational analysis.** *J. Biomol. Struct. Dyn.* 2021; **39**: 5819–5830.
[PubMed Abstract](#) | [Publisher Full Text](#)
54. Vahid F, Rahmani D: **Can an anti-inflammatory diet be effective in preventing or treating viral respiratory diseases? A systematic narrative review.** *Clin. Nutr. ESPEN.* 2021; **43**: 9–15.
[PubMed Abstract](#) | [Publisher Full Text](#)
55. Dorsch W, Ring J: **Anti-inflammatory substances from onions could be an option for treatment of COVID-19—a hypothesis.** *Allergo J. Int.* 2020 Dec; **29**(8): 284–285.
[Publisher Full Text](#)
56. Jafarzadeh A, Jafarzadeh S, Nemati M: **Therapeutic potential of ginger against COVID-19: Is there enough evidence?.** *J. Tradit. Chin. Med. Sci.* 2021; **8**: 267–279.
[Publisher Full Text](#)
57. Aldwihli LA, Khan SI, Alamri FF, *et al.*: **Patients' Behavior Regarding Dietary or Herbal Supplements before and during COVID-19 in Saudi Arabia.** *Int. J. Environ. Res. Public Health.* 2021; **18**: 5086.
[PubMed Abstract](#) | [Publisher Full Text](#)
58. Wannas WA, Tounsi MS: **Can medicinal plants contribute to the cure of Tunisian COVID-19 patients.** *J. Med. Plant.* 2020; **8**: 218–226.
59. Guler HI, Tatar G, Yildiz O, *et al.*: **Investigation of potential inhibitor properties of ethanolic propolis extracts against ACE-II receptors for COVID-19 treatment by Molecular Docking Study.** *Arch. Microbiol.* 2021; **203**: 3557–3564.
[PubMed Abstract](#) | [Publisher Full Text](#)
60. Refaat H, Mady FM, Sarhan HA, *et al.*: **Optimization and evaluation of propolis liposomes as a promising therapeutic approach for COVID-19.** *Int. J. Pharm.* 2021; **592**: 120028.
[PubMed Abstract](#) | [Publisher Full Text](#)
61. Elwakil H, Shaaban MM, Bekhit AA, *et al.*: **Potential anti-COVID-19 activity of Egyptian propolis using computational modeling.** *Futur. Virol.* 2021; **16**: 107–116.
[Publisher Full Text](#)
62. Dilokthornsakul W, Kosiyaporn R, Wuttipongwaragon R, *et al.*: **Potential effects of propolis and honey in COVID-19 prevention and treatment: A systematic review of in silico and clinical studies.** *J. Integr. Med.* 2022; **20**: 114–125.
[PubMed Abstract](#) | [Publisher Full Text](#)
63. Bettuzzi S, Gabba L, Cataldo S: **Efficacy of a polyphenolic, standardized green tea extract for the treatment of COVID-19 syndrome: A proof-of-principle study.** *Covid.* 2021; **1**: 2–12.
[Publisher Full Text](#)
64. Cheng K, Yang A, Hu X, *et al.*: **Curcumin attenuates pulmonary inflammation in lipopolysaccharide induced acute lung injury in neonatal rat model by activating peroxisome proliferator-activated receptor γ (PPAR γ) pathway.** *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research.* 2018; **24**: 1178–1184.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
65. Sengupta R, Sheorey SD, Hinge MA: **Analgesic and anti-inflammatory plants: an updated review.** *Int. J. Pharm. Sci. Rev. Res.* 2012; **12**: 114–119.

66. Nugraha RV, Ridwansyah H, Ghozali M, *et al.*: **Traditional Herbal Medicine Candidates as Complementary Treatments for COVID-19: A Review of Their Mechanisms, Pros and Cons.** *Evid. Based Complement. Alternat. Med.* 2020; **2020**: 2560645.
67. Nimer R, Khabour O, Swedan SF, *et al.*: **Natural Products Raw Data.** [figshare. \[Dataset\]](#). 2022. [Publisher Full Text](#)

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Version 2

Reviewer Report 18 July 2022

<https://doi.org/10.5256/f1000research.135778.r143818>

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Caterina Vicidomini

Istituto di Biostrutture e Bioimmagini IBB-CNR, Naples, Italy

The changes made are satisfactory. I have no further comments to add. The paper is approved.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Environmental chemistry & human health. Computational studies. Synthesis of small molecules

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 13 July 2022

<https://doi.org/10.5256/f1000research.135778.r143817>

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Fatin Y. Atrooz

Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX, USA

Approved.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Behavioral neuroscience, cytogenetics, public health research.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 28 June 2022

<https://doi.org/10.5256/f1000research.133852.r140506>

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Caterina Vicidomini

Istituto di Biostrutture e Bioimmagini IBB-CNR, Naples, Italy

In this paper, the authors retrospectively explored the effect of a series of natural products use prior to infection with COVID-19 on disease severity and hospitalization. The authors hypothesized that an increase in the use of some immune-boosting foods and medicinal herbs would be associated with a less severe form of COVID-19 infection. Study measures included the use of selected natural products, COVID-19 severity, and hospitalization status. A multivariate regression model was used for statistical analysis.

In my opinion, this paper has some limitations including those the authors have described in the text. The total number and quantity of natural products used by the subjects were unknown, and also, I didn't find any information on whether the participants consumed these natural products as commercial supplements, or if they prepared them from natural sources at home, for example.

In any case, the work seems interesting and provides ideas for research insights. In my opinion it is therefore worthy of indexing.

I have just a few suggestions:

- Provide some information on the recruitment method adopted.
- Specify, at least for the most active products such as carnation, how it is usually consumed.
- Reading the questionnaire, I saw that the authors collected data on potential confounders and comorbidities, but they didn't specify anything on this aspect. Please, add what they considered confounders. If possible, it would be interesting to evaluate whether, for example, the cigarette smoking modified the beneficial effect of natural substances intake.
- I know that there are other natural substances traditionally used to boost the immune system, but they were not mentioned or considered in the study. Please add a comment in the text and cite at least the following reference.¹

References

1. Singh NA, Kumar P, Jyoti, Kumar N: Spices and herbs: Potential antiviral preventives and immunity boosters during COVID-19. *Phytother Res.* 2021. [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Environmental chemistry & human health. Computational studies. Synthesis of small molecules

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 02 Jul 2022

Refat Nimer, Jordan University of Science and Technology, Irbid, Jordan

We would like to thank the reviewers for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which helped to improve the quality of this manuscript.

Please find attached a point-by-point response to reviewers' concerns. We hope that you find our responses satisfactory and that the manuscript is now acceptable for publication.

Reviewer #2 (Comments to the Author):

In my opinion, this paper has some limitations including those the authors have described in the text. The total number and quantity of natural products used by the subjects were unknown,..

Authors' response: We agree with the reviewer that the rate of consumption of these

natural products was unknown. However, this point was mentioned in the limitations (highlighted in red).

And also, I didn't find any information on whether the participants consumed these natural products as commercial supplements, or if they prepared them from natural sources at home, for example.

Authors' response: This study focuses on natural products, not commercial supplements. However, the point raised by the reviewer is now incorporated in the revised manuscript.

Provide some information on the recruitment method adopted.

Authors' response: More information was added at "Study design and subjects" section.

Specify, at least for the most active products such as carnation, how it is usually consumed.

Authors' response: Your suggestion is now incorporated in the updated version of the manuscript.

Reading the questionnaire, I saw that the authors collected data on potential confounders and comorbidities, but they didn't specify anything on this aspect. Please, add what they considered confounders. If possible, it would be interesting to evaluate whether, for example, the cigarette smoking modified the beneficial effect of natural substances intake.

Authors' response: COVID-19 was reported to be more severe in people having high BMI or comorbidities. However, the aim of this study was to explore the effect of using natural products on the severity of the disease, regardless of the confounding factors. Therefore, multivariate regression analysis was applied to control for possible confounding factors such as age, gender, cigarette smoking, and the number of comorbidities (Table 3). The analysis without adjusted confounding factors is shown in Table 2.

The point raised by the reviewer is now discussed in the revised manuscript.

I know that there are other natural substances traditionally used to boost the immune system, but they were not mentioned or considered in the study. Please add a comment in the text and cite at least the following reference. PMID: 33511704

Authors' response: We agree with the reviewer's comment. However, this study covered the broadest range of natural products used by the Jordanian population.

The point raised by the reviewer is now incorporated in the revised manuscript (the last sentence in the introduction) and the proposed reference was added (ref no. 14).

Competing Interests: No competing interests were disclosed

Reviewer Report 22 June 2022

<https://doi.org/10.5256/f1000research.133852.r140507>

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Fatin Y. Atrooz

Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX, USA

Summary: The study explored the association between using specific natural products prior to COVID-19 infection and the severity of the disease and hospitalization status in a sample of Jordanian adults.

Title: This is a retrospective study, the study design included a survey about prior COVID-19 infection and natural products consumption prior to infection.

Methods:

- Recruitment method is not clear, how the investigators reached out to the potential participants is not stated. The study suggests that only people who were previously infected with COVID-19 were included in the study. This assumption should be discussed in the inclusion criteria.
- Calculation of the study sample assumed that the total population is the number of COVID-19 infected people as reported by the end of July 2021. Does this report include only adults or total confirmed cases? As the survey targeted only adults, the authors should identify precisely the study population as a reference for sample size calculation.

Results:

- Why is lemon considered a separate category from citrus? I suggest including all citrus fruit, including lemon as one category.
- In table 1, the results were expressed in a different format, I suggest having all the results expressed as N (%). For this purpose, age can be categorized into 2-3 categories, and same for BMI.
- In the multivariate logistic regression, the authors mentioned that after controlling for covariate, the findings...
What are the covariates? The authors should list the covariates here, and if that includes controlling for age and gender.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Behavioral neuroscience, cytogenetics, public health research.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 02 Jul 2022

Refat Nimer, Jordan University of Science and Technology, Irbid, Jordan

We would like to thank the reviewers for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which helped to improve the quality of this manuscript.

Please find attached a point-by-point response to reviewers' concerns. We hope that you find our responses satisfactory and that the manuscript is now acceptable for publication.

Reviewer #1 (Comments to the Author):

- Recruitment method is not clear, how the investigators reached out to the potential participants is not stated. The study suggests that only people who were previously infected with COVID-19 were included in the study. This assumption should be discussed in the inclusion criteria.

Authors' response: The recruitment method has now been illustrated in the revised manuscript. In the cover page for the questionnaire, we outlined the criteria for participation in the study, which includes infection with COVID-19 and recovery from illness. The research assistance emphasized that participants' infection should have been confirmed by polymerase chain reaction (PCR). Participants were approached in public places such as bus stations, parks, religious places, universities and restaurants.

- Calculation of the study sample assumed that the total population is the number of COVID-19 infected people as reported by the end of July 2021. Does this report include only adults or total confirmed cases? As the survey targeted only adults, the authors should identify precisely the study population as a reference for sample size calculation.

Authors' response: The sample size for our study was calculated using Raosoft Online Sample Size Calculator (Raosoft Inc., Seattle, WA, USA). 770,712 is the total confirmed cases reported by the end of July 2021, and the recommended sample size was 1067. However, this calculation is to check whether the sample size in our study is sufficient and representative. The number of cases under 18 years of age during the time of sample collection (before the emergence of the Omicron variant) was expected to be small

compared to the adult cases (no data available). Therefore, if patients under 18 years are subtracted from the total cases, this would lead to a negligible change in the sample size. Nonetheless, the study sample size was larger than required ($n= 2,148$) even if child cases are considered. This point is now clarified in the Method section.

- Why is lemon considered a separate category from citrus? I suggest including all citrus fruit, including lemon as one category.

Authors' response: Thank you for your comment. We prefer to keep lemon as a separate category from citrus because some studies showed variations in their nutritional values. This was clarified in the revised manuscript.

- In table 1, the results were expressed in a different format, I suggest having all the results expressed as N (%). For this purpose, age can be categorized into 2-3 categories, and same for BMI.

Authors' response: Done as suggested.

- In the multivariate logistic regression, the authors mentioned that after controlling for covariate, the findings...

What are the covariates? The authors should list the covariates here, and if that includes controlling for age and gender.

Authors' response: The point raised by the reviewer is now incorporated in the revised manuscript.

Competing Interests: No competing interests were disclosed

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