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Comparison of Nutraceuticals Use and Outcomes in COVID-19 Patients Vs Non-COVID-19 Population

Original Research

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ABSTRACT

Background: Nutraceuticals, representing a synergy between nutrition and pharmaceuticals, are gaining traction due to increasing awareness of their health benefits. As dietary supplements become integrated into pharmacological treatments, their role in managing health conditions, including COVID-19, is of significant interest.

Objective: This study aims to explore the use of nutraceuticals among individuals who have recovered from COVID-19 compared to those who have never contracted the virus, focusing on the patterns of usage and associated side effects.

Methods: A cross-sectional online survey was conducted from April to June 2023, targeting a diverse population of COVID-19 survivors and non-infected individuals. The survey captured data on demographics, vaccination status, nutraceutical use, and any adverse effects experienced. A total of 250 participants were recruited to provide a broad perspective on the dietary supplementation habits among these groups.

Results: Of the total participants, 65.1% (n=163) were non-COVID-19 individuals, and 34.9% (n=87) had recovered from COVID-19. Nutraceuticals were more commonly used by non-COVID-19 individuals, with multivitamins and folates being the most frequently consumed supplements. Notably, 77% of non-COVID-19 individuals reported side effects, predominantly an unpleasant taste, compared to 23% of COVID-19 survivors experiencing similar issues.

Conclusion: The findings indicate a higher utilization of nutraceuticals among non-COVID-19 individuals, with multivitamins and folates being predominant. Side effects were more prevalent in non-COVID-19 participants. Future research should further investigate the specific benefits and risks of nutraceuticals to better understand their role in health management and recovery post-COVID-19.

Keywords: COVID-19, Dietary Supplements, Folates, Multivitamins, Nutraceuticals, Side Effects, Survey Studies.

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INTRODUCTION

COVID-19, officially termed coronavirus disease has rapidly emerged as a predominant global health crisis due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Manifesting symptoms akin to flu, the disease primarily challenges public health with its potential for severe respiratory complications and the lingering aftermath in recovered patients, often referred to as "post-COVID syndrome" (1). This condition is characterized by a spectrum of symptoms including fatigue, cognitive disruptions termed "brain fog," difficulty in breathing, and joint pain, which markedly diminish the quality of life and impede daily functions (2). As the pandemic has unfolded, about 40% of adults in the United States have been infected with the virus at some point, with nearly one in five experiencing persistent symptoms, underscoring the virus's long-term impact on public health (2). This scenario has not only intensified the burden on healthcare systems but has also shifted the focus towards integrative approaches combining modern medicine with dietary modifications to manage and mitigate the diverse manifestations of the disease.

In response to this health crisis, the role of nutraceuticals—products derived from food sources with extra health benefits—has gained significant attention. These products are increasingly viewed as a pivotal component of dietary strategies aimed at enhancing immune responses and managing symptoms associated with chronic diseases, including COVID-19 (3). Nutraceuticals such as zinc, vitamin D, vitamin C, and selenium play critical roles in strengthening the immune system, which is paramount in combating COVID-19 and minimizing the risk of severe outcomes (1, 3, 8). Zinc, for example, is essential for immune function and has antiviral properties that are particularly effective against respiratory illnesses. Zinc supplementation has been found to reduce the duration of cold-like symptoms, which are similar to those experienced by many COVID-19 patients (8). Similarly, vitamin D plays a crucial role in immune modulation and reducing inflammation, making it vital for protecting against respiratory tract infections that can be severe in COVID-19 cases (8).

Moreover, the antioxidant properties of vitamin C support immune cell function, helping to prevent and treat upper respiratory infections, thereby offering a dual function in both prevention and recovery phases of the disease (8). Selenium, a micronutrient found in various foods, enhances antioxidant defense in the lungs, which is crucial for managing the inflammatory responses typical of COVID-19 (8). The emerging research not only supports the beneficial impacts of these nutraceuticals in managing COVID-19 symptoms but also highlights their broader potential in addressing post-COVID conditions that affect a significant portion of the population. These conditions often involve prolonged fatigue, joint pain, and neurological symptoms, which can be ameliorated through targeted nutritional support (1, 8). In addition to these micronutrients, compounds like curcumin and piperine have also demonstrated significant anti-inflammatory and antioxidant properties. Curcumin, for instance, has shown potential in blocking the entry and replication of viruses at the cellular level, while piperine, extracted from black pepper, has been effective in reducing inflammation, a common complication in severe COVID-19 cases (8).

Table: Nutraceuticals and Their Health Benefits in Supporting Immunity and Combating Infections

NUTRACEUTICALS	USES
Zinc	Antiviral and antioxidant properties
	Speeds healing process
Vitamin D	Defend against respiratory infections
Vitamin C	Prevent infections
	Aids immune system
Selenium	Boosts innate immunity
	Improves lung antioxidant state
Piperine	Decrease the production of pro inflammatory cytokines
Iron	Lowers inflammation and enhancing the immune response
Probiotics	Promote production of immunoglobulins
Vitamin E	Promote T Cells proliferation
Curcumin	Boosts production of antioxidant enzymes

The integration of nutraceuticals into daily dietary practices not only supports the management of existing health conditions but also acts as a preventive measure against the development of new symptoms or the exacerbation of existing ones. The dietary approaches such as the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet have been proven to positively influence overall health outcomes, particularly in reducing high blood pressure, a common comorbidity in COVID-19 patients (5). This comprehensive approach to health maintenance through dietary and supplemental interventions reflects a shift towards a more holistic understanding of health and disease management. It acknowledges the complex interplay between diet, immunity, and disease outcomes and underscores the importance of nutritional strategies in the broader context of health care and disease prevention. As the global community continues to grapple with COVID-19 and its consequences, the role of nutraceuticals is increasingly recognized as part of a multifaceted strategy to enhance immune resilience and improve long-term health outcomes. This approach not only helps in managing the immediate challenges posed by the pandemic but also contributes to the ongoing efforts to improve public health in the face of evolving viral threats. Emerging from Wuhan, China, in December 2019, COVID-19 has been identified as a global pandemic by the World Health Organization, with a wide range of symptoms from mild respiratory issues to severe acute conditions (11). The response to the pandemic has been swift, with significant research into the virus's biology, transmission, and potential treatments. Despite these efforts, the pandemic has significantly impacted mental health, increasing the prevalence of psychological distress across various demographics worldwide (12).

The long-term health complications for COVID-19 survivors, often termed 'Long COVID', include persistent symptoms such as breathlessness, fatigue, and neurological impairments, which highlight the virus's capacity to affect health well beyond initial recovery (13). This post-recovery phase can significantly reduce quality of life, impeding the return to pre-disease daily activities and thus becoming a focal point for ongoing medical research and healthcare support. The concept of nutraceuticals, introduced by Stephen DeFelice in 1979, has gained prominence in this context. Defined as food or food components that provide medicinal benefits, nutraceuticals offer a complementary approach in the fight against COVID-19 by potentially enhancing the immune response and ameliorating symptoms associated with the virus (14). Nutraceuticals range from isolated nutrients like vitamins and minerals to more complex herbal products and diets, all aimed at disease prevention and health promotion. Given the nutritional deficiencies observed in severely ill COVID-19 patients, which often exacerbate the disease's progression, there is a significant emphasis on the nutritional management of patients. For instance, interventions such as the intravenous administration of milk proteins, vitamins, and minerals have been explored to mitigate the effects of reduced food intake due to anorexia or severe inflammatory responses in hospitalized patients (15). The biological underpinnings of such nutritional interventions are supported by substantial evidence indicating the antiviral and immunomodulatory properties of various nutraceuticals. For example, compounds like luteolin and quercetin have shown promise in inhibiting the SARS-CoV-2 virus through different mechanisms, such as binding to viral proteins and disrupting their function (16, 21, 24). This has extended the potential utility of nutraceuticals beyond mere nutritional supplementation to that of a tactical component in managing viral infections, including COVID-19.

Table: Nutraceuticals with potential benefits for COVID-19 patients are given in the table.

SR	Molecule	Target	Type of Study/Techniques Used	Results
1	Luteolin	SARS-CoV S2 protein	Frontal-affinity chromatography-mass spectrometry, HIV-luc/SARS pseudotype virus assay, MTT assay with wild-type SARS-CoV	Luteolin inhibited SARS-CoV infection in a dose-dependent manner. EC50: 10.6 μM, CC50: 0.155 mM, LD50 in mice: 232.2 mg/kg.
2	Quercetin	SARS-CoV S2 protein	HIV-luc/SARS pseudotype virus assay	EC50: 83.4 μM, CC50: 3.32 mM.
3	GCG (gallocatechin gallate)	SARS-CoV 3CLPro	Expression of recombinant 3CLPro in Pichia pastoris and its inhibition, Molecular docking	91% inhibition at 200 μM. IC50: 47 μM. Binding energy: –14 kcal/mol.
4	EGCG	SARS-CoV 3CLPro	Expression of recombinant 3CLPro in Pichia pastoris and its inhibition, Molecular docking	85% inhibition at 200 μM. IC50: 73 μM. Binding energy: –11.7 kcal/mol.
5	Resveratrol	MERS-CoV NP	MTT assay using Vero-E6 cell line, Nucleocapsid protein staining	Effective in the 125–250 μM range on viral titre and viral RNA amount. Inhibits caspase 3 cleavage.
6	Hesperetin	SARS-CoV 3CLPro	Cell-free and cell-based cleavage assays	IC50: 60 μM (cell-free assay), IC50: 8.3 μM (cell-based assay), CC50: 2718 μM.

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Moreover, the immune system's role in combating COVID-19 cannot be overstated. Nutraceuticals contribute to immune support by supplying bioactive ingredients like probiotics, polysaturated fatty acids, and phytoconstituents with known immunomodulatory properties. These components not only support the body's natural defenses but also help manage inflammation, a critical aspect of severe COVID-19 cases characterized by cytokine storms and hyperinflammation (17). Respiratory health remains a primary concern in the management of COVID-19, given the virus's target of the respiratory system. Nutraceuticals such as vitamins C and E play critical roles in maintaining respiratory integrity and function. Their antioxidant properties help mitigate oxidative stress, a common pathway through which the virus exacerbates lung damage (19, 20).

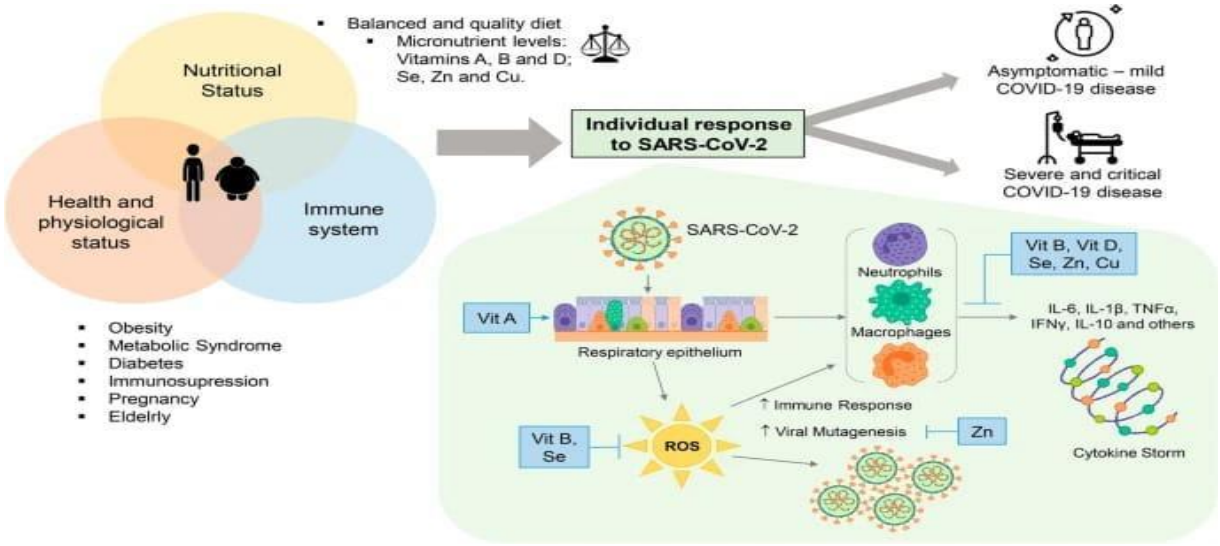

Figure 1: Micronutrient regulation of individual response in SARS-CoV-2 infection.

Nutritional support is thus a critical pillar in the management and recovery of COVID-19 patients. Ensuring adequate intake of key micronutrients like vitamins A, C, D, and essential minerals can fortify the immune system and potentially reduce the severity of the infection. The role of these micronutrients in immune function has been well-documented, underscoring their importance in a balanced diet (22, 26). The objective rationale behind integrating nutraceuticals into COVID-19 management is grounded in both their preventive and therapeutic potentials. As the pandemic continues to evolve, with new variants emerging, the role of nutrition and dietary supplements becomes ever more critical in supporting immune function and overall health resilience. This approach not only aims to mitigate the immediate effects of the virus but also addresses the long-term health consequences faced by COVID-19 survivors. As we advance in our understanding of COVID-19 and its broad impacts, the integration of nutraceuticals into therapeutic regimens offers a promising adjunct to conventional medical treatments. By enhancing immune defenses and supporting recovery, nutraceuticals embody a proactive approach to health maintenance and disease prevention in the face of ongoing and future viral threats. This strategy aligns with a broader perspective on health care that emphasizes preventive care and holistic management as foundational to combating not only COVID-19 but also other potential viral epidemics.

METHODS

The study was ethically approved by the Ethical Committee of Akhtar Saeed College of Pharmaceutical Sciences, Lahore, ensuring adherence to research ethics throughout the process. No incentives were offered, and informed written consent was obtained from all participants, guaranteeing the authenticity and voluntary nature of their participation. The research did not involve any deceptive practices. Conducted over three months from April to June 2023 in Pakistan, the study aimed to assess the utilization of nutraceuticals among individuals who had recovered from COVID-19, as well as those who had not contracted the virus. It included survivors of all ages, with a focus on both COVID-19 and non-COVID-19 populations who utilized dietary supplements. Participants were recruited using convenience sampling through various platforms such as WhatsApp, Facebook, and threads where the online survey link was shared. To ensure a comprehensive analysis, only fully completed surveys were included, with incomplete responses being excluded from the study.

The sample size, calculated using the Raosoft Calculator®, was determined to be 250 participants, factoring in a 95% confidence level and a margin of error of ±2.52%. To accommodate a potential dropout rate of 10%, the target was initially set to gather 300 responses. The actual data collection was facilitated through an online questionnaire distributed across multiple social media platforms, including Instagram and Twitter, ensuring a broad reach. The inclusion criteria specified that participants were to be divided into three age groups: 20-40, 40-60, and over 60 years. Eligibility was limited to those who were either COVID-19 positive or negative but were consuming

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any form of dietary supplements. Exclusion criteria ruled out anyone under the age of 18, those not using dietary supplements, and any duplicate responses.

The questionnaire was meticulously developed to ensure clarity and relevance to the study's objectives. Initially drafted after a thorough review of the existing literature on nutraceutical use among both patient groups, the questionnaire underwent a pre-test to validate its effectiveness. Following approval from a supervisory body, the questionnaire was made available to participants through Google Forms in English. It comprised 18 questions divided into two sections; the first section collected demographic data and the second detailed the nutraceutical consumption patterns, including type, dosage, duration, and any side effects experienced by the respondents. Statistical analysis was performed using the IBM SPSS software, version 26.0. Descriptive statistics, such as frequencies and percentages, were utilized to analyze the collected data, providing insights into the patterns and impacts of nutraceutical use among the surveyed populations. It is important to note that while the study employed convenience sampling, which may limit the generalizability of the findings, this method was suitable given the practical constraints and the specific nature of the population studied.

RESULTS

In the recent study conducted over three months, a total of 250 participants were approached to examine the use of nutraceuticals among individuals who had recovered from COVID-19, and those who had not contracted the virus. The demographic distribution revealed a predominant participation of females, constituting 77% of the total sample. The majority of the participants were non-COVID-19 survivors, making up 63.5% of the sample, while the average age primarily ranged between 20 to 40 years, accounting for 94.4% of the participants. Notably, 89.6% of the participants reported being vaccinated.

Table: Frequency Distribution of Socio-demographic Variables Among COVID and Non-COVID Patients.

Demographics	N	COVID-19	Non- COVID-19	P value
Gender				
Male	55 (22%)	17 (30.9)	38 (69.1%)	0.451
Female	195 (77%)	71 (36.4%)	124 (63.6%)	
Age				
20-40	236 (94.4%)	81 (34.3%)	155 (65.7%)	0.272
40-60	13 (5.2%)	6 (46.2%)	7 (53.8%)	
>60	16 (4%)	1 (100%)	0 (0%)	
Nationality				
Pakistani	246 (98.4%)	85 (34.6%)	161 (65.4%)	0.172
Non-Pakistani	4 (1.6%)	3 (75%)	1 (25%)	
Socio-economic status				
Upper	27 (10.8%)	14 (51.9%)	13 (48.1%)	
Middle	220 (88%)	74 (33.6%)	146 (66.4%)	0.076
Lower	3 (1.2%)	0 (0%)	3 (100%)	

Data presented as frequency (%); p-value from chi-squared tests.

The socioeconomic status showed that 88% of the participants belonged to the middle class, while COVID-19 incidence was higher among upper-class participants, with no cases reported among the lower-class participants. In terms of nationality, 98.4% of the participants were Pakistani. When analyzing nutraceutical usage, 58.5% of non-COVID-19 patients reported using nutraceuticals compared to 41.5% of COVID-19 patients. This difference was statistically significant. Chronic illnesses were less prevalent among non-COVID-19 participants at 68.2%, whereas 63% of COVID-19 participants suffered from chronic conditions, predominantly diabetes.

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Table: Frequency Distribution of Variables with Regards to COVID-19 & Non-COVID-19 Patients.

VARIABLE	N	COVID-19	NON- COVID-19	P -VALUE
Have you used any nutraceuticals?				0.016*
Yes	142 (56.8%)	59 (41.5%)	83 (58.5%)	
No	108 (43.2%)	29 (26.9%)	79 (73.1%)	
Chronic illness				0.001*
Yes	27 (10.8%)	17 (63%)	10 (37%)	
No	223 (89.2%)	71 (31.8%)	152 (68.2%)	
If yes				0.027*
Asthma	6 (2.4%)	3 (50%)	3 (50%)	
Diabetes	3 (1.2%)	3 (100%)	0 (0%)	
Hypertension	10 (4%)	6 (60%)	4 (40%)	
Other	5 (2%)	3 (60%)	2 (40%)	
Dietary supplements used:				
Probiotic	13 (5.2%)	5 (38.5%)	8 (61.5%)	0.80
Multivitamins	148 (59.2%)	61 (41.5%)	86 (58.5%)	0.013*
Folate	9 (3.6%)	4 (44.4%)	5 (55.6%)	0.554
Vitamin B- complex	13 (5.2%)	5 (38.5%)	8 (61.5%)	0.382
Zinc	7 (2.8%)	2 (28.6%)	5 (71.4%)	0.710
Omega 3	2 (0.8%)	1 (33.3%)	2 (66.7%)	0.946
Other	57 (22.8%)	9 (15.5%)	49 (84.5%)	<0.001
Who suggested you take nutritional supplements?				
Pharmacist	70 (28.0%)	11 (15.7%)	59 (84.3%)	<0.001
Physician	87 (34.8%)	41 (47.1%)	46 (52.9%)	
Relative	17 (6.8%)	9 (52.9%)	8 (47.1%)	
Self-medication	76 (30.4%)	27 (35.5%)	49 (64.5%)	
Dose of nutraceuticals per day.				0.659
One time/day	183 (73.2%)	64 (35%)	119 (65%)	
Two times/day	30 (12%)	13 (43.3%)	17 (56.7%)	
Once a week	32 (12.8%)	10 (31.3%)	22 (68.8%)	
Twice a week	5 (2%)	1 (20%)	4 (80%)	

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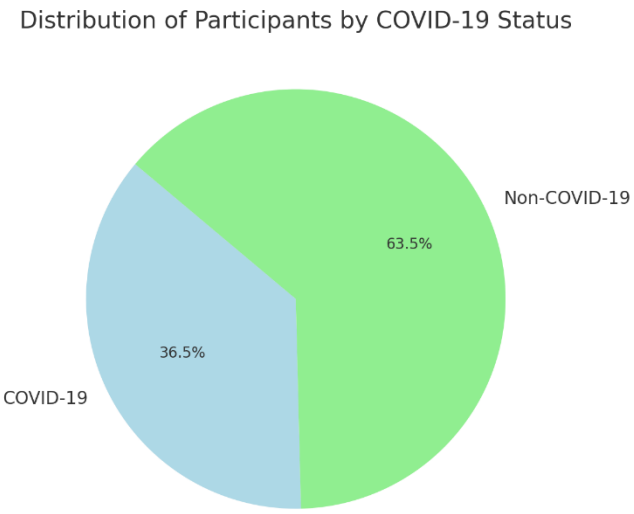
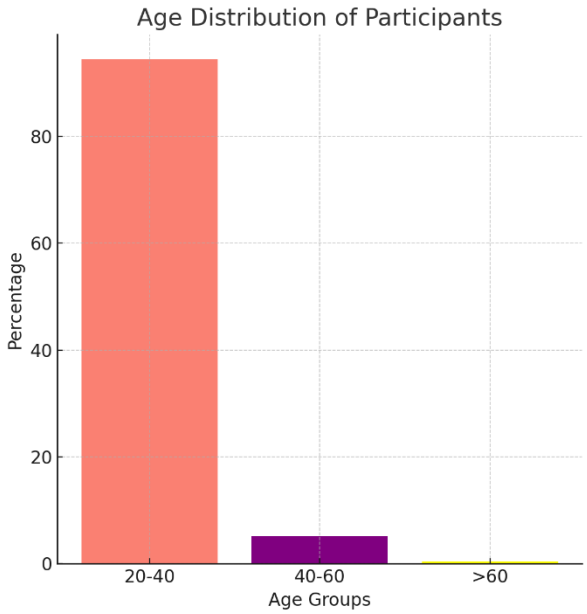
How long did you continue taking nutraceuticals?				
1-2 week	102 (40.8%)	44 (43.1%)	58 (56.9%)	0.106
1month	100 (40%)	29 (29%)	71 (71%)	
2-3month	26 (10.4%)	10 (38.5%)	16 (61.5%)	
more than 3 months	22 (8.8%)	5 (22.7%)	17 (77.3%)	
After taking nutraceuticals did you suffer any other complications?				
Yes	26 (10.4%)	11 (42.3%)	15 (57.7%)	0.42
No	224 (89.6%)	77 (34.4%)	147 (65.6%)	
Have you noticed any of these symptoms while taking nutraceuticals?				
Nausea	34 (13.6%)	12 (35.3%)	22 (64.7%)	0.990
Vomiting	6 (2.4%)	3 (50%)	3 (50%)	0.292
Diarrhea	15 (6%)	3 (20%)	12 (80%)	0.204
Headache	64 (25.6%)	18 (28.1%)	46 (71.9%)	0.169
Unpleasant taste	91 (36.4%)	37 (40.7%)	54 (59.3%)	0.172
GI disturbance	40 (16%)	15 (37.5%)	25 (62.5%)	0.740
Did you feel after taking nutraceuticals your body weight increased?				
Yes	55 (22%)	17 (30.9%)	38 (69.1%)	0.443
No	189 (75.6%)	70 (37%)	119 (63%)	
How satisfied are you with the benefits of using nutritional supplements?				
Very satisfied	27 (10.8%)	13 (48.1%)	14 (51.9%)	0.395
Satisfied	127 (50.8%)	44 (34.6%)	83 (65.4%)	
Neutral	86 (34.4%)	29 (33.7%)	57 (66.3%)	
Dissatisfied	8 (3.2%)	1 (12.5%)	7 (87.5%)	
Very dissatisfied	2(0.8%)	1 (50%)	1 (50%)	

Data presented as frequency (%); p-value from chi-squared tests.

The types of nutraceuticals consumed varied, with multivitamins being the most commonly used supplement, followed by other types such as probiotics, folate, vitamin B-complex, zinc, and omega-3. Nutraceuticals were predominantly recommended by pharmacists, especially for non-COVID-19 patients, who also reported higher levels of satisfaction with the benefits of these supplements. Complications from nutraceutical use were more frequently reported by COVID-19 patients at 42.3%. Among all participants, there was a notable perception of increased body weight after using nutraceuticals, especially among non-COVID-19 patients. Despite the thorough collection of demographic and nutraceutical usage data, the study did not delve into the specific impact of nutraceuticals on the health outcomes of COVID-19 versus non-COVID-19 patients, which could provide more direct insights into their efficacy and safety.





DISCUSSION

The findings of this study provide valuable insights into the use of nutraceuticals and dietary supplements among individuals affected by and recovered from COVID-19 as well as those uninfected. Nutritional supplementation, known for its potential to boost the immune system and protect against acute respiratory viral infections, has been widely discussed. However, there remains a notable gap in clinical evidence supporting the efficacy of these supplements for preventing or treating COVID-19 or other chronic illnesses (27). This research revealed a higher prevalence of nutraceutical consumption among non-COVID-19 participants, particularly those aged 20-40, which aligns with patterns observed during the COVID-19 pandemic where increased supplement use was reported in similar demographic groups in other studies, such as one conducted in Lithuania (28). The predominant use of multivitamins, often under physician supervision, underscores a proactive approach towards health maintenance during the pandemic period. This is consistent with emerging evidence suggesting potential therapeutic applications of specific supplements like zinc, vitamin C, and omega-3 fatty acids in the context of COVID-19 (27).

Despite the positive reception and usage patterns observed, this study also highlighted some challenges associated with supplement consumption. The majority of participants reported an unpleasant taste as a side effect, which may detract from the usability and acceptability of these products. This sensory attribute of supplements, noted in both COVID-19 and non-COVID-19 groups, suggests a need for improved formulation to enhance patient compliance. Interestingly, while a significant portion of participants followed healthcare professional advice in supplement use, contrasting findings from another study indicated that only a minority consulted healthcare experts, with many relying on advice from social media or family (29). This disparity points to the potential influence of cultural and regional differences in health-related behaviors.

Participants in this study expressed satisfaction with the use of nutritional supplements, reflecting a widespread belief in their protective and immune-boosting properties, a sentiment also observed in recent studies conducted in the Middle East (30). Such perceptions may drive the continued use of these products beyond the pandemic, suggesting a long-term trend towards self-managed health care practices. Several limitations were identified in the study, including the unbalanced representation between COVID-19 and non-COVID-19 patients and reliance on a cross-sectional survey design which restricts the ability to establish causal relationships. The small sample size and geographical concentration limit the generalizability of the findings. Additionally, the use of an online survey may have introduced bias through self-reported data, potentially affecting the accuracy of the results. Future research should aim to address these limitations by incorporating a larger, more diverse population and longitudinal study designs to better understand the long-term effects and efficacy of nutraceutical use. Collecting data on the quantity and frequency of supplement intake could also provide deeper insights into consumption patterns and their health outcomes.

CONCLUSION

This study has highlighted the differential patterns of nutraceutical use among COVID-19 and non-COVID-19 patients, revealing a higher prevalence of use and satisfaction among those not affected by COVID-19. These non-COVID-19 participants also reported a greater incidence of side effects, particularly the unpleasant taste associated with these supplements. The role of physicians in guiding

the use of nutraceuticals emerged as significant, underscoring the importance of professional oversight in the administration of these products. The findings underscore the potential of certain nutritional supplements, which merit further investigation to validate their efficacy and safety in broader therapeutic contexts. Ultimately, this study contributes to the ongoing dialogue on the role of dietary supplements in health management, suggesting avenues for future research to explore their full potential in enhancing well-being among diverse patient populations.

Author	Contribution
Anza Ahmad	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Validation, Supervision
Ahmad Ibne Yousaf	Methodology, Investigation, Data Curation, Writing - Review & Editing
Neelam Bibi	Investigation, Data Curation, Formal Analysis, Software
Momina Akram	Software, Validation, Writing - Original Draft
Maida Khalid	Formal Analysis, Writing - Review & Editing
Faiza Jamshaid	Writing - Review & Editing, Assistance with Data Curation
Azzah Khadim Hussain	Formal Analysis, Writing - Review & Editing
Saleha Hameed	Writing - Review & Editing, Assistance with Data Curation

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