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Basic study

Dietary supplements and nutraceuticals in the recovery of COVID-19: A systematic review and meta-analysis



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ABSTRACT

The outbreak of nSARS-CoV2 in December 2019 turned into a global pandemic and is still underway. Infection with nSARS-CoV2 resulted in severe acute respiratory distress syndrome and was named COVID-19. COVID-19 requires the intervention of a series of therapeutics, including antiviral, anti-inflammatory, and immune-modulating molecules. Additionally, studies have demonstrated that nutraceuticals offer a promising impact in fast recovery and boosting immunity. Here, the study aimed to provide a comprehensive synthesis of the scientific evidence examining the effectiveness of nutraceuticals. A detailed search of scientific literature was conducted utilizing the most relevant scientific studies published during 2019–2022 on the intervention of nutraceuticals in the management of COVID-19. PubMed, Cochrane Central Register of Controlled Trials and Scielo databases were explored for the most relevant studies. Meta-analysis was carried out using the MedCalC tool as per PRISMA guidelines for odds ratio among the studies along with risk factor analysis and relative risk. A total of 1,308 original records were identified, where 1,268 studies were collected from different databases, and 40 additional records were obtained from non-pre-defined sources. Odds ratio, risk analysis, and risk difference analysis showed nutraceuticals intervention reported effective ($P < 0.001$) in COVID-19 patient over control. Nutraceuticals-based interventions had improved immunity, short-term duration, and fast recovery of COVID-19 patients.

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R É S U M É

L'épidémie de nSARS-CoV2 en décembre 2019 s'est transformée en pandémie mondiale et est toujours en cours. L'infection par le nSARS-CoV2 a entraîné un syndrome de détresse respiratoire aiguë sévère et a été nommée COVID-19. Le COVID-19 nécessite l'intervention d'une série de thérapeutiques, notamment des molécules antivirales, anti-inflammatoires et immunomodulatrices. De plus, des études ont démontré que les nutraceutiques offrent un impact prometteur sur la récupération rapide et le renforcement de l'immunité. Ici, l'étude visait à fournir une synthèse complète des preuves scientifiques examinant l'efficacité des nutraceutiques. Une recherche détaillée de la littérature scientifique a été menée en utilisant les études scientifiques les plus pertinentes publiées au cours de la période 2019–2022 sur l'intervention des nutraceutiques dans la gestion du COVID-19. Les bases de données PubMed, Cochrane Central Register of Controlled Trials et Scielo ont été explorées pour les études les plus pertinentes. Une méta-analyse a été réalisée à l'aide de l'outil MedCalC conformément aux directives PRISMA pour l'*odds ratio* entre les études, ainsi que l'analyse des facteurs de risque et le risque relatif. Un total de 1308 enregistrements originaux ont été identifiés, où 1268 études ont été collectées à partir de différentes bases de données, et 40 enregistrements supplémentaires ont été obtenus à partir de sources non prédéfinies. Le rapport de cotes, l'analyse des risques et l'analyse des différences de risque ont montré que l'intervention de nutraceutiques était efficace ($p < 0,001$) chez le patient COVID-19 par rapport au groupe témoin. Les interventions basées sur les nutraceutiques ont amélioré l'immunité, la durée à court terme et la récupération rapide des patients COVID-19.

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1. Introduction

An outbreak in December 2019 of novel beta coronavirus (nSARS-CoV2) was reported at Wuhan; China spread as a global pandemic [1]. Since the outbreak of nSARS-CoV2, the world has witnessed multiple waves of infections affecting millions of lives across the world and is still underway. The World Health Organisation (WHO) announced this infection as a global pandemic in February 2020 [2]. Novel SARS-CoV-2 is a new member of the beta coronavirus family that primarily targets the respiratory tract (upper and lower). The nSARS-CoV2 infects via Angiotensin-Converting Enzyme-2 receptor and triggers a massive immune response that causes acute respiratory distress syndrome (ARDS) [3]. The severe infection of nSARS-CoV2 leads to a cytokine storm via the release of inflammatory mediators. Along with the number of non-structural proteins, including the RNA-dependent RNA polymerase (Redrop), the viral RNA encodes four key essential structural proteins, namely the Nucleocapsid (N) protein surrounding the RNA genome and three membrane proteins: the S-glycoprotein, the matrix (M) protein, and the envelope (E) protein [4]. The S-glycoprotein on the surface of CoV can attach to the cellular receptor, Angiotensin-Converting Enzyme 2, on the surface of human cells. ACE-2 is found in the lower respiratory tract of humans and regulates both cross-species and human-to-human transmission. Studies have shown multiple mutations in nSARS-CoV2 result in the emergence of various variants associated with surges in cases from time to time [5]. The new variants of nSARS-CoV2 with altered transmission and pathogenicity, posed the threat of infection and COVID-19 disease to millions of people across the world. The nSARS-CoV-2 and variants with mild, moderate, and severe ARDS, i.e., COVID-19, remain associated with greater difficulty in the treatment and recovery [6]. Since the outbreak of the COVID-19 pandemic, efforts have been made to find therapeutics for the management of the disease.

Diagnosed patients require the intervention of antiviral, anti-inflammatory, and immunotherapy for the management of COVID-19. The treatment strategy depends on the severity of nSARS-CoV2 infections; however, therapeutics, dietary supplements, and nutraceuticals have been used in several interventions. Zhang and Liu, 2020, demonstrated the potential of PUFAs against the nSARS-CoV2 infection and COVID-19 disease [7]. The study had shown that the omega-3 fatty acids, Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) trigger resolution of inflammation and decrease ARDS via regulating cytokine storm. Earlier, Halide et al., 2018, had shown that EPA and DHA remain key PUFAs in the biosynthesis of endogenous lipid mediators called specialised pro-resolving mediators (SPM) [8]. There is growing research evidence demonstrated that n-3 PUFAs mediate inflammation by influencing processes such as leukocyte chemotaxis, adhesion molecule expression, and the production of eicosanoid [9]. In a randomized clinical trial, DoAA et al., 2021, demonstrated that the intervention of n-3 PUFAs improves renal and hepatic function and improves the rapid recovery of COVID-19 patients [10]. Similarly, multivitamins remain key nutraceuticals in various interventions for COVID-19 management. Shakoor et al., 2021, had shown that vitamins D, C, E, zinc, and selenium offer an immune-boosting role and improve COVID-19 patients' illnesses [11]. In a similar study, Bae and Kim, 2020, advocated that supplementation of multivitamins attenuates excessive inflammatory responses and hyperactivation of immune cells [12]. Previous studies have shown that vitamin C increases antiviral cytokines and free radical formation, decreasing viral yield in the case of nSARS-CoV2 and other viral infections such as influenza [13].

Probiotics use in clinical inventions demonstrated potential immunomodulation in COVID-19 infection management. Probiotics represent selected microbes; primarily useful bacteria that improve not only immunity but also restore gut microbial

ecology [14]. Gut microbial ecology is linked with gut immunity, and it has been reported during nSARS-CoV2 infections, a massive paradigm shift in gut microbiota [15]. Gut microbiota via Gut-Lung Axis affects lung microbial ecology and causes dysbiosis [16]. Gut microbiota is also involved in the pathogenesis of sepsis and acute respiratory distress syndrome (ARDS), mainly in gut dysbiosis [17]. Probiotics improve the colonisation of useful gut microbes and boost immunity, including intestinal and systemic [18]. There has been tremendous development in diagnostics, therapeutics, and vaccines. Various therapeutic approaches are available to combat COVID-19 however; still, there is no precise medication to treat COVID-19. Apart from approved therapeutics, the use of nutraceuticals has shown significant benefits not curing COVID-19 patients but in case of early recovery and narrowing disease time [19]. These nutraceuticals include a combination of vitamins, i.e., Vit C, B, D, and PUFAs. Additionally, probiotics have shown a significant role in recovery and boosting native immunity [20]. The study attempted to provide a scientific basis for the role of different nutraceuticals in the early recovery of COVID-19 patients. Here, we aim to structure a scientific finding based on available clinical data for different nutraceuticals. The study estimated the efficacy of listed nutraceuticals based on forest and funnel plot analysis using MedCalc tools for meta-analysis as per PRISMA guidelines.

2. Methods

A comprehensive search of literature published in PubMed, Embase, Cochrane library, and China National Knowledge Infrastructure (CNKI) was carried out to identify the most relevant studies during 2019–2022. The studies were screened based on inclusion and exclusion criteria. The eligible studies were subjected to a meta-analysis, and the MedCalc tool (<https://www.medcalc.org/>) was used for statistical determinants as per the PRISMA statement. The analysis was carried out using the Odds ratio, continuous measures, relative risk/risk difference, and correlation. Meta-analysis was done with forest plots and funnel plots. Confidence interval (CI) and relative risk was determined for each class of nutraceuticals based on available clinical data.

The most relevant studies were searched independently in various databases PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), and the Cochrane Central Register of Controlled Trials. A search of clinical findings (clinical trials, Animal studies, and meta-analysis) was carried out from Cochrane Library database (<https://www.cochranelibrary.com/>). Additionally, the NCBI database was used to explore for the most relevant articles. Search was done using specific keywords including “nutraceuticals and COVID-19”, “Vitamin C and COVID-19”, “Vitamin D and COVID-19”, “PUFAs and COVID-19,” and “Probiotics and COVID-19”. Further, more keywords were used for additional search in selected databases, including “safety and efficacy of nutraceuticals in COVID-19”, “Clinical use of nutraceuticals in COVID-19”, “Nutraceuticals, COVID-19 and recovery rate”, “Nutraceuticals, and duration of COVID-19”. The selection of studies was based on inclusion and exclusion criteria. Publication bias analysis was also done for study selection. The clinical data and effect on patients infected with nSARS-CoV2 were retrieved from eligible studies. Here, in the present study, three major classes of nutraceuticals as PUFAs, vitamins, and probiotics were examined in clinical interventions for effectiveness in COVID-19; efficacy and recovery of patients. The clinical data were retrieved and segregated for all three categories and analysed.

For meta-analysis, MedCalc tool (<https://www.medcalc.org/>) was used for statistical determinants (multiple variables alone and or in combination) as per PRISMA statement (<http://prisma-statement.org/prismastatement/Checklist.aspx>).

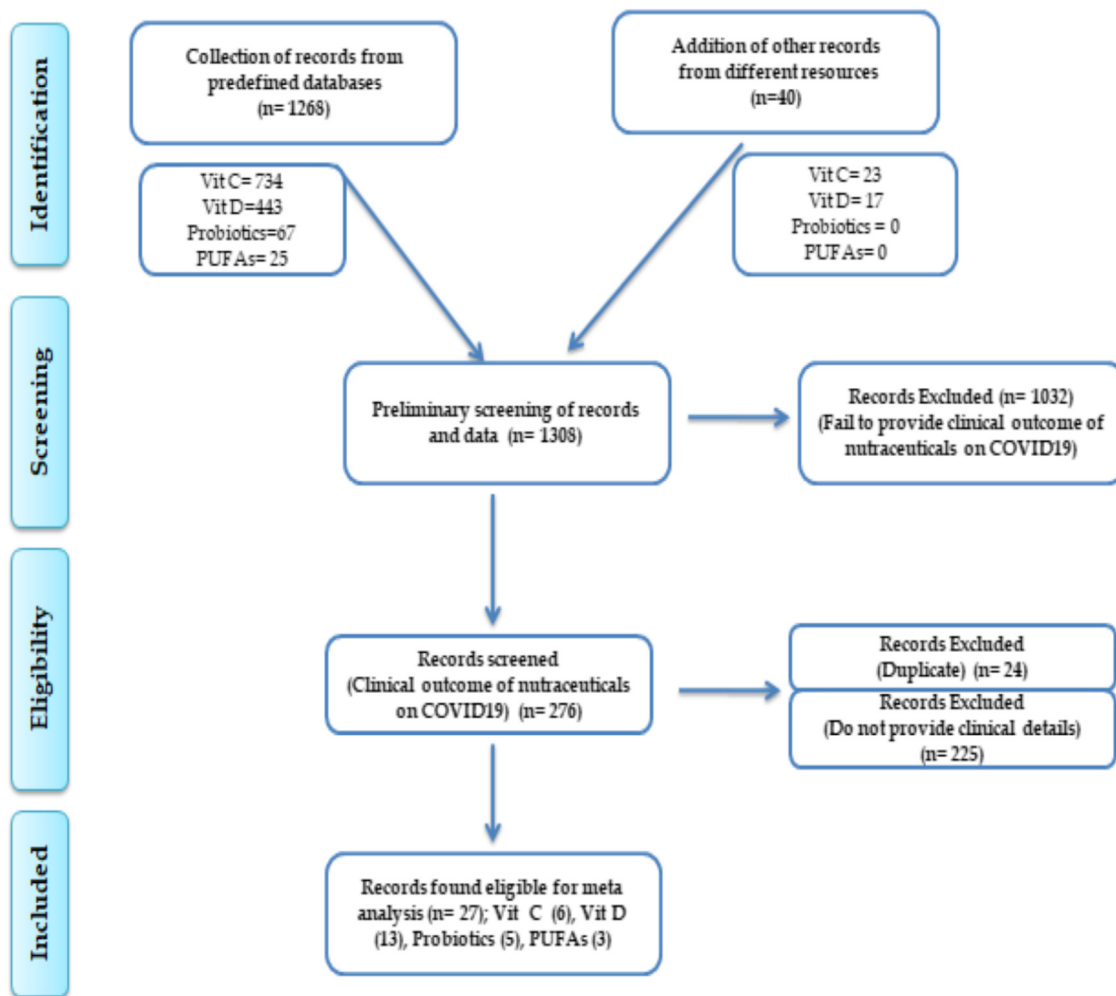


Fig. 1. Flow chart for study selection and screening [21].

The analysis was carried out using the Odds ratio, continuous measures, relative risk/risk difference, and correlation. Meta-analysis was done with forest plots and funnel plots. Confidence interval (CI) and relative risk were determined for each class of nutraceuticals based on available clinical data. The overall impact of nutraceuticals in the management of COVID-19 analysed (based on available data) in both categories of COVID-19 patients provided gone through standard COVID-19 test. In the present study, multiple analyses were carried out for PUFAs, vitamins, and probiotic interventions in COVID-19 patients.

3. Results

PUFAs, vitamins (C and D) and probiotics 1,308 original records were retrieved from different predefined databases. Among them, records, 1,268 studies were collected from PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Scielo databases and 40 additional records were obtained from non-predefined sources. Screening of most relevant studies was segregated from the pool. For the multivitamins, vitamin C, and D, a total of 19 studies (13 associated with vitamin D and 6 with vitamin C) were found eligible for meta-analysis. Here, for vitamin D, the deficiency was criteria to the correlative risk of infection of nSARS-CoV2 while in the case of vitamin C, a supplementation to both intervention and control group for different doses and time period. For probiotics intervention to the COVID-19 patient's based studies, only five

were found eligible for the meta-analysis based on the inclusion and exclusion criteria. For PUFAs, only three studies were found eligible for the meta-analysis. A detailed search strategy and study selections are shown in Fig. 1 [21]. Online material Tables S1 and S2 provide information on clinical data from the most relevant studies for vitamin C and D. Here, Table 1 demonstrated the level of vitamin D in the study group and the risk of infection leading to COVID-19. Table 2 provides a comprehensive summary of studies with the clinical intervention of vitamin C in the case and control at different doses for varying time period. Clinical data and outcome from probiotics and PUFAs is shown in Tables 3 and 4, respectively.

Vitamins may pivotal role in host immunity and offer protection against infections. Vitamin C and D reported significant against respiratory pathogen where a low level of vitamin D remained associated with a higher risk of nSARS-CoV2 infection. In the present study, as shown in Table 1, the level of vitamin D reported significantly low in all the studies compared to control (30–50 ng/mL). In the COVID-19 patients, vitamin D level ranges 14–30 ng/mL and is one of the major risk factors for poor immunity and a higher infection rate. The Odds ratio analysis clearly demonstrates that the serum level of Vitamin D in COVID-19 patients remains low ($P < 0.001$) (Online material Table S1 and Fig. 2). The significant variation in 95% CI and % weight is primarily due to the strength of the study group. All the studies shown populations with lower vit D remained associated with a higher risk of COVID-19 ($P < 0.001$) (Online material Table S1 and Fig. S1). A total random effect lied

Table 1
Clinical data table of vitamin D interventions in COVID-19 management with control [22–34].

| Study | Study design | Serum level of vitamin D | Sample size | Case; nSARS-CoV2 positive group | Control; nSARS-CoV2 negative group |
|------------------------------|----------------------------------|--------------------------|-------------|---------------------------------|------------------------------------|
| Abdollahi et al., 2020 | Case-control study | 20–28 ng/mL | 402 | 201 | 201 |
| Alguwalhes et al., 2021 | Retrospective study | < 20 ng/mL | 222 | 150 | 72 |
| Al-Daghri et al., 2021 | Multi-center case-control study | 14–20 ng/mL | 220 | 138 | 82 |
| Baktash et al., 2020 | Prospective cohort study | 20–30 ng/mL | 105 | 70 | 35 |
| D'Avolio et al., 2020 | Retrospective study | 20–30 ng/mL | 107 | 27 | 80 |
| Hernández et al., 2020 | Retrospective case-control study | 15–20 ng/mL | 413 | 216 | 197 |
| Im et al., 2020 | Prospective cohort study | < 20 ng/mL | 200 | 150 | 50 |
| Livingston et al., 2021 | Prospective cohort study | 20–30 ng/mL | 104 | 47 | 57 |
| Mardani et al., 2020 | Case-control study | 20–30 ng/mL | 123 | 63 | 60 |
| Merzon et al., 2020 | Population-based study | 15–20 ng/mL | 1807 | 782 | 1025 |
| Raisi-Estabragh et al., 2020 | Prospective cohort study | < 20 ng/mL | 4510 | 1326 | 3184 |
| Sulli et al., 2021 | Case-control study | 15–20 ng/mL | 130 | 65 | 65 |
| Ye et al., 2020 | Case-control study | < 20 ng/mL | 142 | 62 | 80 |

Table 2
Clinical data table of vitamin C interventions in COVID-19 management with control [35–40].

| Study | Study design | Intervention dose and duration | Sample size | Case; nSARS-CoV2 positive group | Control; nSARS-CoV2 negative group |
|---------------------------|--|--------------------------------|-------------|---------------------------------|------------------------------------|
| Zhang J et al., 2021 | Multicenter, randomized trial | 168 gm for 7 days | 56 | 27 | 29 |
| Kumari P et al., 2020 | Prospective, open-label RCT | 24 gm for 7 days | 150 | 75 | 75 |
| Siahkali S et al., 2021 | Open-label, non-blinded, randomized controlled trial | 30 gm for 5 days | 60 | 30 | 30 |
| Hakamifard A et al., 2021 | Randomized controlled clinical trial | 10 days | 72 | 38 | 34 |
| Darban M et al., 2021 | Pilot single-center randomized, controlled, open-label, parallel-group trial | 10 days | 20 | 10 | 10 |
| Thomas S et al., 2021 | Multicenter, single health system factorial randomized open-label trial | 10 days | 214 | 48 | 50 |

Table 3
Clinical data table of probiotics interventions in COVID-19 management with control [41–45].

| Study | Study design | Sample size | Case; nSARS-CoV2 positive group | Control; nSARS-CoV2 negative group |
|-----------------------|----------------------------------|-------------|---------------------------------|------------------------------------|
| Gu S, et al., 2020 | Prospective cohort study | 184 | 84 | 100 |
| Zuo T, et al., 2020 | Prospective cohort study | 25 | 15 | 10 |
| Gou W, et al., 2020 | Multi-methodological study | 667 | 366 | 301 |
| Liu F, et al., 2021 | Prospective interventional study | 20 | 11 | 10 |
| Yeoh YK, et al., 2021 | Prospective cohort study | 215 | 165 | 50 |

Table 4
Clinical data table of PUFAs interventions in COVID-19 management with control [46–48].

| Study | Study design | Intervention dose and duration | Sample size | Case; nSARS-CoV2 positive group | Control; nSARS-CoV2 negative group |
|-------------|---------------------------|--|-------------|---------------------------------|------------------------------------|
| NCT04647604 | Randomized clinical trial | Omegaven® (2 mL/kg/day, equivalent to 6 g (DHA)+ (EPA) once daily for 5 days Sodium chloride (NaCl) 2 mL/kg/day) once daily for 5 days | 46 | 23 | 23 |
| NCT04495816 | Randomized clinical trial | 1000 mg of omega-3 fatty acid blend including 683 mg EPA and 252 mg DHA Supplement drug: placebo/control | 167 | 117 | 50 |
| NCT04828538 | Randomized clinical trial | 4000 IU vitamin D vs. placebo factorial 2 (F2): 1000 mg omega DHA/EPA vs. placebo factorial 3 (F3): combination 1000 mg vitamin C, vitamin B complex and Zinc Acetate, 100 mg/day vs. placebo | 1800 | 1000 | 800 |

in the range 0.7–0.9 for risk difference. On the contrary, relative risk showed a variation (3.1–37.5) in the different studies selected for the meta-analysis, primarily due to different sample sizes of the intervention and control group (Online material Table S3 and Fig. S2). In the test for heterogeneity under Odds ratio analysis, inconsistency (I²) remained 94.31% while 95% CI for I² range

91.87–96.02. A similar pattern was primarily reported for heterogeneity under relative risk (I² = 96.10%; 95% CI for I² 94.64–97.16) and risk difference (I² = 95.32%; 95% CI for I² 93.45–96.55) analysis. The significance level for risk difference under Egger test showed a P-value of 0.0004 while non-significant in the case of Odds ratio and risk difference.

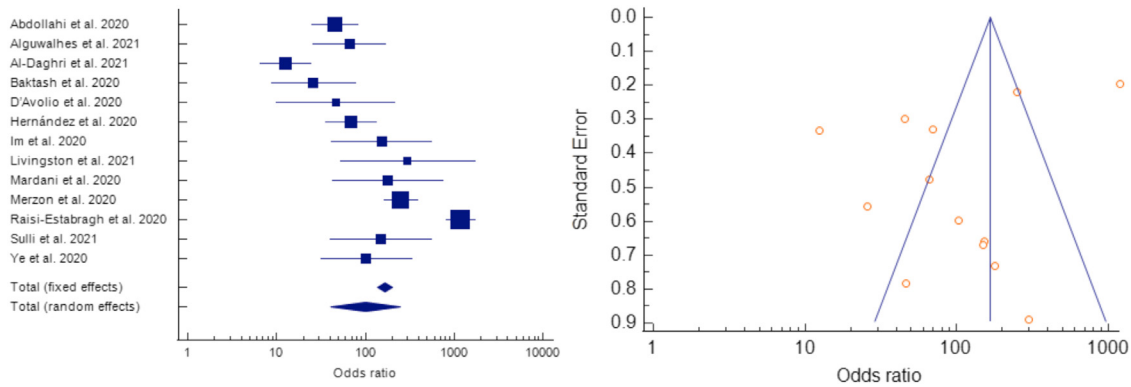


Fig. 2. Figure demonstrates forest and funnel plot for Odds ratio analysis among intervention and control group under vitamin D interventions.

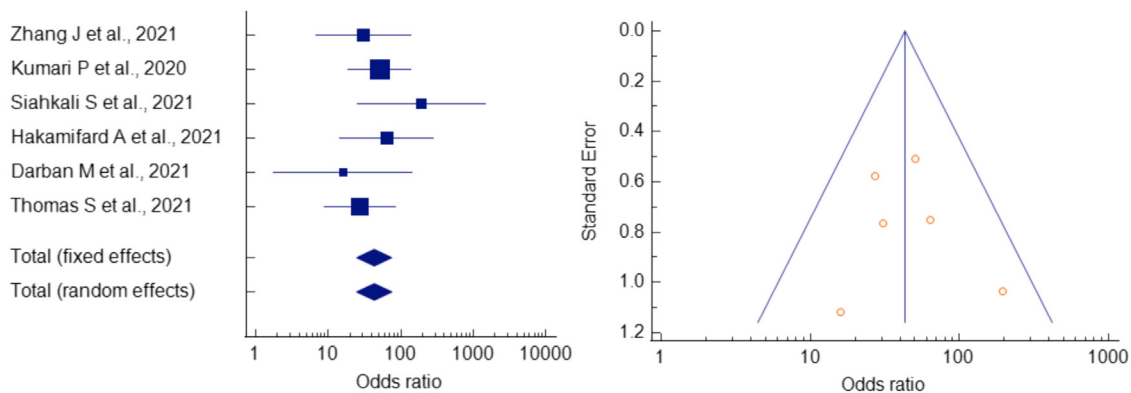


Fig. 3. Figure demonstrates forest and funnel plot for Odds ratio among intervention and control under vitamin C interventions.

Supplementation of Vit C to COVID-19 patients and control were examined under Odds ratio analysis where total random effect and fixed effect remained the same with P -value < 0.001 (Online material Table S4 and Fig. 3) [46–48]. The analysis showed a variation in the 95% CI range 6.8–25.77 and primarily due to the sample size, dose of vitamin C, route of administration, and duration of intervention. On the contrary, the Risk difference remained the same for the intervention and control group range 0.68–0.86 with 95% CI 0.2–0.67 (Online material Table S5 and Fig. S3). The P -value remained significant ($P < 0.001$) for risk difference with marginal difference in % weight. Under relative risk analysis, maximum variation between intervention and control group was evaluated as total random and fixed effect remain significant ($P < 0.001$) showed in Online material Table S6 and Fig. S4. In the test for heterogeneity under Odds ratio analysis for Vit C, inconsistency (I^2) remained 00.00% while 95% CI for I^2 range 00.00–96.02. A similar pattern was reported for heterogeneity under relative risk ($I^2 = 3.75\%$; 95% CI for I^2 00.00–76.28) and risk difference ($I^2 = 24.29\%$; 95% CI for I^2 00.00–67.96) analysis. The significance level for risk difference under Egger test showed non-significant in the case of Odds ratio, relative risk, and risk difference ($P > 0.05$).

In COVID-19, gut dysbiosis is one of the major clinical outcomes in the majority of patients. The results concerning probiotics are shown in Online material Table S7 intervention group with probiotics supplements effectively restoring gut microbial ecology; 95% CI 6.5–11.448 for Odds ratio ($P < 0.001$). There was not any difference in weight percentage under Odds ratio analysis for all five studies associated with probiotic intervention (Online material Table S8 and Fig. 4). The test for heterogeneity showed inconsistency 16% with 95% CI 0.00–83.55 where significance level $P = 0.3126$. Under the risk difference between intervention and control group received probiotics it showed 95% CI (0.44–0.58)

($P < 0.001$) (Online material Table S9 and Fig. S5). The inconsistency I^2 reported 23.94 with 95% CI range 0.00–69.01 ($P = 0.2612$). Interestingly, the relative risk was reported at 2.99 with 95% CI (2.5–3.5) ($P < 0.001$) between interventional and control groups that received probiotics. Overall, the total effect of probiotic supplements in COVID-19 and control showed a similar pattern. A slight variation in the results is due to a difference in control against the treatment group. All the study under the narrowed funnel, and hence standard error remained minimal for relative risk analysis compared to Odds ratio and risk difference.

In the study, three clinical trial studies were analysed for the impact of PUFAs on the treatment of COVID-19 (Table 4). The Odds ratio analysis of three clinical trials is shown in Online material Table S9 and Fig. 5. The Odds ratio was reported 84.7 with 95% CI 62.96–114.14. The Odds ratio analysis showed a significant outcome ($P < 0.001$) weight % 100 (Online material Table S10 and Fig. S6). There was no significant variation in the risk difference in the intervention and control group with risk difference 0.80 and 95% CI (0.77–0.83) (Online material Table S11 and Fig. S7). A similar pattern was reported for relative risk, where relative risk was 8.9 with 95% CI (7.35–10.93). The weight % remained 100% for both risk difference and relative risk (Online material Table S12 and Fig. S8). For heterogeneity test, significance level for Odds ratio reported $P = 0.96$ with inconsistency 0.00%. Test for heterogeneity for risk analysis and relative risk reported insignificant where P -value 0.96 and 0.89 respectively.

4. Discussion

In the present meta-analysis, several dietary supplements and nutraceuticals were examined for their role in COVID-19 treatment. While existing evidence suggesting potential benefits of n-3 PUFA

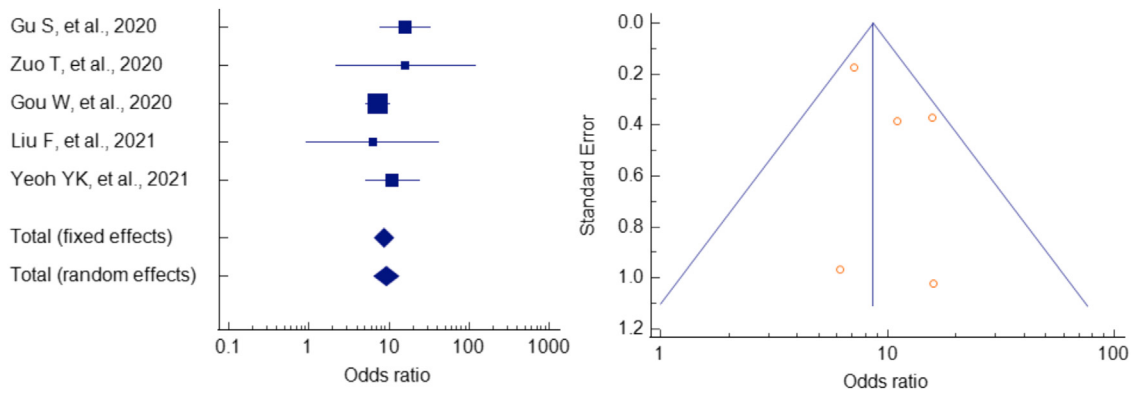


Fig. 4. Figure demonstrates forest and funnel plot for Odds ratio among intervention and control under vitamin probiotics interventions.

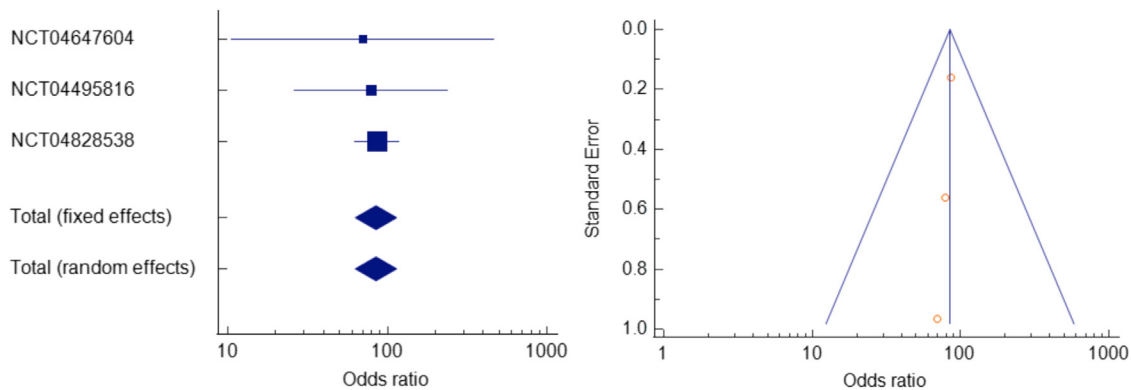


Fig. 5. Figure demonstrates forest and funnel plot for Odds ratio among intervention and control under PUFAs interventions.

and probiotic supplementation for COVID-19 treatment and prophylaxis, clinical data are lacking, although trials are underway. Both vitamin D and vitamin C supplementation in hospitalised patients seemed to be associated with positive outcomes; however, further clinical trials are required. In any case, both vitamin C and D intake are part of a healthy diet, and both likely present minimal risk when supplemented, though their potential prophylactic or therapeutic effects against COVID-19 are yet to be determined [49]. On the other hand, mounting evidence from observational studies indicated an association between vitamin D deficiency and COVID-19 incidence [50]. Increased levels of inflammatory cytokines triggered by SARS-CoV-2 in the peripheral blood cause an uncontrolled systemic inflammation, referred to as cytokine release syndrome or “cytokine storm.” The PUFAs especially, DHA and EPA have shown promising results in resolving inflammation [10]. At the same time, the use of probiotics remained associated with improved immunity via restoring gut microbial ecology and gut immunity subsequently [15].

The potential role in the prevention of a severe course of COVID-19 was further strengthened by the identification of calcitriol (the active form of vitamin D) as the regulator of the renin-angiotensin system (RAS), of which an over activation is associated with poor prognosis. Szarpak et al., 2021, demonstrated that low serum vitamin D levels were associated with low serum vitamin D levels are statistically significantly associated with the risk of COVID-19 infection. Supplementation of vitamin D, especially in the deficiency risk groups, might improve host immunity and reduce the risk of infection [51]. Vit D is an essential hormone preventing infection of nSARS-CoV2; however, its role in COVID-19 patients for recovery from hospital is poorly studied. An interaction between 25(OH)D and viral infections is a subject of increasing concern, and lessons from previous similar epidemics may offer insights as to

why vitamin D supplementation may be protective against COVID-19. SARS-CoV was observed to down-regulate type 1 interferon (IFN) receptors which negatively affect innate immunity [52]. In a recent study, Alguwaihes et al., 2021, showed deficiency of Vit D is not associated with infection of nSARS-CoV2, but increases the risk of higher mortality during the hospital stay [53]. The findings clearly showed that a lower serum level of Vit D may be associated with higher comorbidity and higher mortality. A meta-analysis of 13 different clinical trials showed a higher risk of infection in those who have been diagnosed with lower serum Vit D levels compared to control.

The clinical interventions of Vit C in COVID-19 patients shorten the duration of hospital stay, including ICU, compared to control. Jude et al., 2021, reported deficiency of Vit D might cause a higher rate of hospitalisation after nSARS-CoV2 infection [49]. The Vit C intervention does not cause any progressive health outcome in COVID-19 patients compared to the control. In the pooled analysis, several reports have demonstrated that Vit C clinical outcome depends on the dose, duration, and co-morbidity conditions of COVID-19 patients. It also remained challenging to enumerate the impact of Vit C on COVID-19 patients for early recovery and shortening the disease duration due to co-administration of therapeutics. Speakman et al., 2021, also demonstrated that a high dose of Vit C reduced hospital stay, including ICU [54]. In a controlled randomised clinical trial, Beigmohammadi et al., 2020, showed that intervention of Vit C reduced mortality and promoted speedy recovery compared to the control group [55]. The study also advocated that the combination of Vit A, D E with C provided promising results in COVID-19 management; however, the therapeutic intervention outcome was not included. For example, one study involving high-dose vitamin C in the setting of COVID-19 demonstrated a significantly longer hospital stay than

the non-vitamin C group. Additionally, there were no significant differences in mortality or ICU length of stay. Vitamin C, alone and in combination with zinc, showed no significant decreases in COVID-19-related symptoms compared to no study intervention.

Cytokine storm is the major clinical manifestation of severe infection of nSARS-CoV-2 associated with the release of macrophage-related cytokines like interleukin (IL)-1 β , IL-6, and tumor necrosis factor- α (TNF- α) [56]. The use of anti-inflammatory therapeutics in COVID-19 management primarily seeks control over cytokine storms. Omega 3 PUFAs are precursors of endogenous bioactive lipid mediators called Specialised Pro Resolving Mediator (SPM) implicated in the resolution of inflammation [8]. The EPA and DHA are promising exogenous PUFAs and promote COX/LOX-driven biosynthesis of Protectins, Resolvins, and Maresins. These endogenous bioactive lipid molecules are a key regulator of eicosanoid and cytokine storms. The use of EPA and DHA, showed a decline in inflammatory response [50]. SPMs do not reduce the expression of IL and TNF- α but reverse the inflammatory cascade. Meta-analysis finding clearly showed that EPA and DHA effectively control the inflammatory response in the COVID-19 patients over control [57]. Additionally, the intervention of EPA and DHA reduced the intake of anti-inflammatory therapeutics in COVID-19 patients. Doaei et al., 2021, reported that omega 3 PUFAs supplementation intervention improved the levels of several respiratory and renal function parameters in critically ill patients with COVID-19 [10].

Gut microbial ecology severely changed during nSARS-CoV2 infection, and COVID-19 patients reported shedding of virus in faecal matter. Gut dysbiosis is the main clinical manifestation of nSARS-CoV2 infection and alters gut immunity [58]. The gut dysbiosis remains associated with altered functioning of Gut Lung Axis essential for the ling microbial ecology. The probiotics supplementation was reported beneficial in two aspects in COVID-19 management, one in restoring gut microbial ecology and the second boosting immunity [59]. Several studies have demonstrated that dietary intake of probiotics and clinical intervention of probiotics shortens the duration of disease and early hospital discharge. Diarrhea is one of the clinical manifestations of moderate to severe COVID-19 and is primarily due to gut dysbiosis [60]. Oral probiotics strains have been used to prevent or treat infections caused by influenza A, influenza H1N1, and respiratory syncytial viruses by minimising the infectious symptoms, shortening the duration of infection, reducing the virus levels in the lungs or nasal washings, producing antiviral components, promoting immune activity, and enhancing health by reducing body weight loss during infection [61]. Probiotics might also have an excellent potential effect against COVID-19 by enhancing probiotics' growth and survivability. Furthermore, probiotics could have a direct effect on GI symptoms caused by COVID-19 via blocking the ACE enzymes. Yeh et al., 2018 systematically reviewed 12 studies that investigated the impact of probiotics and probiotics supplementation on influenza infection [62].

5. Conclusion

The use of nutraceuticals, multivitamins (Vit C and D), PUFAs, and probiotics in the management of COVID-19 disease alone are not effective in controlling the disease. On the contrary, the intervention of nutraceuticals alone or along with therapeutics boosts host immunity that reduces hospital stay, including ICU requirement. Multivitamins such as Vit C and Vit D supplementations remain part of clinical intervention in the COVID-19 patients. The clinical use of PUFA, precisely EPA, and DHA reduces inflammation via pro resolving activity shown beneficial impact to fight against cytokine storm. Similarly, probiotics are natural immune boosters

and restore host gut microbial ecology key player gut immunity. Multiple clinical studies and meta-analyses based on clinical trials demonstrated intervention of nutraceuticals remained beneficial in the management of COVID-19 and did not have any unwanted effect on patient health.

Study limitations

One major limitation was to find out specific interventions for vitamins, PUFA, and probiotics. Most clinical interventions nutraceuticals for COVID-19 management remain associated with therapeutics; hence finding the accurate impact of nutraceuticals remains critical. Additional limitation reported here in the study was an analysis of COVID-19 patients with and without comorbidity gone for the intervention of nutraceuticals.

Human and animal rights

The author declares that the work described has not involved experimentation on humans or animals.

Informed consent and patient details

The author declares that the work described does not involve patients or volunteers.

Disclosure of interest

The author declares that he has no competing interest.

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Author contributions

The author attests that he meets the current *International Committee of Medical Journal Editors* (ICMJE) criteria for Authorship. FKA conceptualized the study and carried out work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.nupar.2022.07.001>.

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