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Efficient Control of IL-6, CRP and Ferritin in COVID-19 Patients With Two Variants of Beta-1,3-1,6 Glucans in Combination: An Open-Label, Prospective, Randomised Clinical Trial

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Abstract

Background: Several biomarkers, including C-reactive protein (CRP), ferritin, D-dimer, and Interleukin-6 (IL-6), are established predictors of disease severity and respiratory failure in patients with COVID-19.
Objective: In this randomised clinical study, we evaluated the efficiency of the combination of 2 variants' AFO-202 and N-163 strains of *Aureobasidium pullulans* produced 1,3-1,6 β-glucans in comparison with the control arm on these biomarkers in COVID-19 patients.
Methods: Forty RT-PCR positive COVID-19 patients were divided into 2 groups: control (n = 22) and standard treatment; ii. (n = 18) – Standard treatment + combination of AFO-202 and N-163 beta glucans for 15 days.
Results: IL-6 levels significantly decreased in the treatment group on day 7 ($P = 0.03$) but not by day 15 ($P = 0.30$). CRP levels in the treatment group decreased at day 7 (5.53 ± 8.21 mg/L) compared to baseline but showed no significant difference from the control group (4.91 ± 12.54 mg/L, $P = 0.98$). At day 15, CRP levels remained lower in the treatment group (5.42 ± 10.41 mg/L) but increased in the control group (14.0 ± 37.16 mg/L), with no significant difference ($P = 0.52$). Ferritin levels dropped

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significantly in the treatment group by day 15 (from 560.58 ± 537.30 ng/mL to 127.51 ± 215.91 ng/mL) but increased in the control ($P = 0.98$). D-dimer levels decreased in the treatment group by day 15 but were not significantly different from controls ($P = 0.56$).

Conclusion: These results indicate that while co-supplementation with AFO-202 and N-163 beta-glucans led to improvement in CRP, ferritin, and IL-6 levels in COVID-19 patients, only the reduction in IL-6 levels on day 7 reached statistical significance. Further long-term multicentric clinical research is warranted to validate the potential of these supplements as treatment adjuncts, for addressing inflammation in COVID-19, especially in vulnerable populations infected with emerging SARS-CoV-2 variants.

Keywords

COVID-19, IL-6, ferritin, C-reactive protein, cytokine storm, immuno-modulation, beta glucans, adjunct treatment

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Introduction

COVID-19, caused by the SARS-CoV-2 virus, has led to a global health crisis with severe respiratory implications. Various biomarkers such as C-reactive protein (CRP), ferritin, fibrinogen, D-dimer, and interleukin-6 (IL-6) are well recognised as indicators of disease severity and predictors of respiratory failure in affected patients.[1] These markers are routinely assessed at initial diagnosis to guide treatment decisions. Various therapeutic strategies have been explored for the treatment of COVID-19, including immunomodulators, corticosteroids, statins, angiotensin pathway modulators, macrolides, and hydroxychloroquine. However, many of these approaches have undesirable side effects. With the availability of COVID-19 vaccines, adjuvants can be considered to address potential limitations, such as low immunogenicity and suboptimal protective immunity.[2] Beta-glucans, particularly β-1,3-glucans, are natural immunomodulators with over 20,000 studies supporting their biological efficacy. Structurally classified as pathogen-associated molecular patterns (PAMPs), they activate immune cells through pattern Recognition Receptors (PRRs) like Dectin-1, CR3, and Toll-2.[3] Beta-glucans have been reported to exert beneficial effects on metabolic and gastrointestinal health, reducing blood glucose and cholesterol, and aiding in conditions such as metabolic syndrome and cardiovascular diseases.[4] They also have anti-infective properties against pathogens, such as *Leishmania*, *Candida*, and *Staphylococcus*.[5] Yeast-derived beta-glucans, such as those from *Aureobasidium pullulans*, differ in structure and function.[6] The AFO-202 strain of *A. pullulans* produced beta-glucan has been reported in pre-clinical and clinical studies as a metabolic regulator and enhances the immune response by stimulating anti-inflammatory cytokines and reducing pro-inflammatory cytokines, while the N-163 strain produces beta-glucan as an immune modulator and has anti-inflammatory and antifibrotic effects.[7-9] Unlike traditional beta-glucans that require extraction and have solubility challenges, *A. pullulans*-derived beta-glucans are water-soluble, simplifying oral administration. These beta-glucans can be explored as potential treatments and preventive measures against COVID-19.[10,11] Previous research demonstrated promise for beta-glucans produced by the AFO-202 and N-163 strains of *A. pullulans* in managing COVID-19 severity markers over 30 days.[12] That study reported beneficial effects, including sustained reductions in erythrocyte sedimentation rate (ESR), D-dimer, IL-6, and ferritin levels for up to 30 days. In the control group, an initial decrease in these markers was followed by an increase. Effective immune enhancement and modulation were also observed, as indicated by a decrease in the neutrophil to lymphocyte ratio (NLR) and increases in the lymphocyte-to-CRP ratio (LCR) and leukocyte-to-C-reactive protein ratio (LeCR).

The present study specifically investigates the effects of the combination of these beta-glucans on COVID-19 patients in the earlier stages of the illness (7 and 15 days).

Materials and Methods

The present study was an open-label, prospective, comparative, two-arm, randomised pilot clinical study conducted between October 2021 and March 2022 (the CONSORT Checklist is available as supplemental information).

This study was designed as a pilot clinical trial to evaluate the effects of food supplement on COVID-19 patients. Based on the preliminary data and feasibility, the target sample size was set at 100 participants to provide an initial understanding of the efficacy and safety of the intervention.

The study enrolled 100 participants; however, only 40 were ultimately included (Figure 1). Participants were recruited from patients who presented to the hospital after an initial triage assessment. Forty participants were randomised to the study group after meeting the eligibility criteria and agreeing to participate. Recruitment challenges were compounded by the study's focus on treating COVID-19 with a food supplement, which, despite being noninvasive, led to hesitancy among patients unfamiliar with the novel approach. Additionally, the urgency of initiating treatment during the early stages of

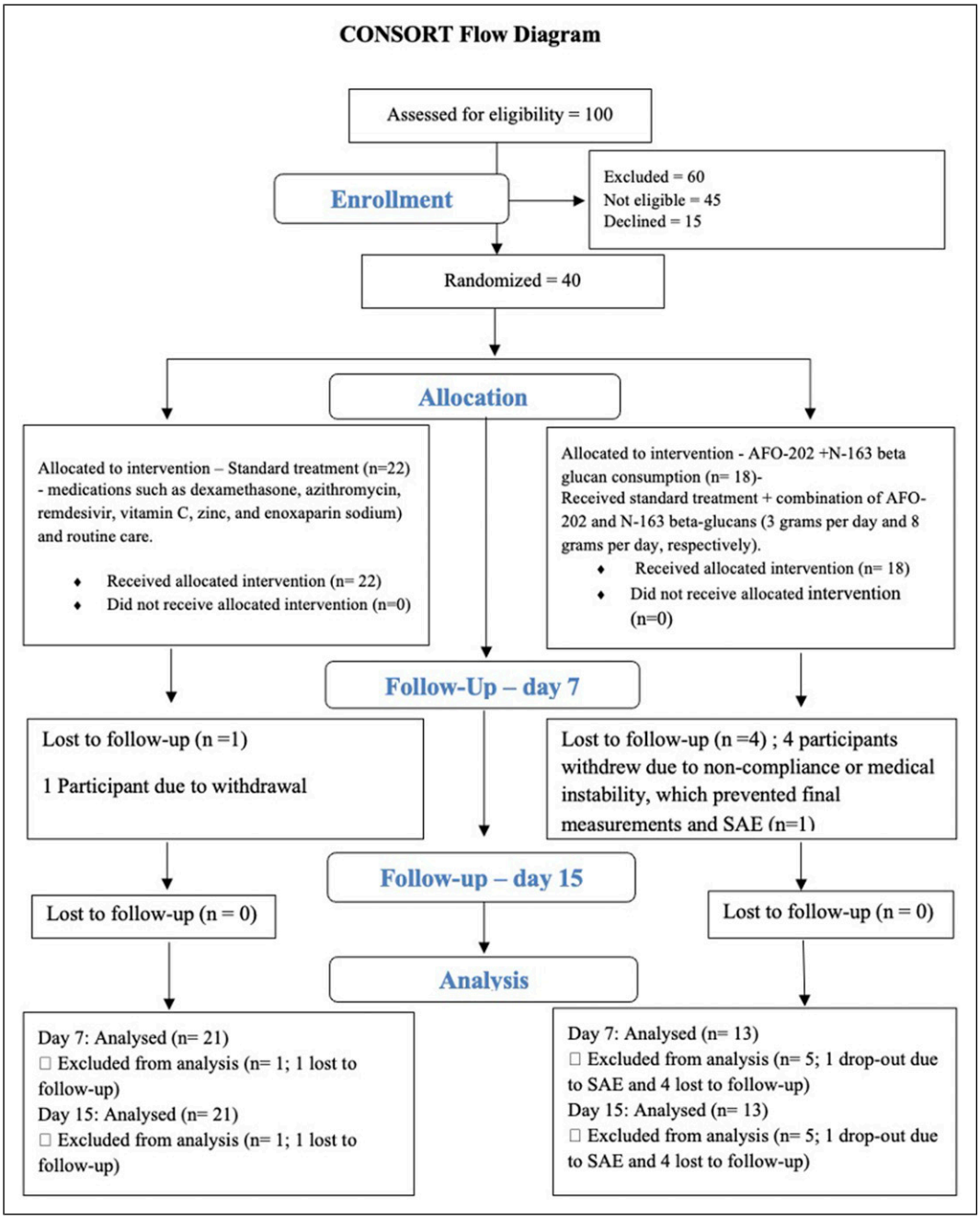

Figure 1. CONSORT flow diagram illustrating the enrolment, allocation, follow-up, and analysis stages of the trial.

infection further constrains the recruitment process, resulting in a smaller sample size than initially planned.

This study included adult subjects aged 18-70 years (inclusive) diagnosed with SARS-CoV-2 infection via RT-PCR testing. Both sexes and individuals with or without co-morbidities were eligible for enrolment, and hospitalisation was required. Patients with severe COVID-19 requiring intensive care, children, and pregnant women were excluded from the study. Written informed consent was obtained from all the participants.

Two groups (Gr.) were assigned by computer generated randomisation:

- Group 1 (Control): Patients received standard care consisting of dexamethasone, azithromycin, remdesivir, vitamin C, zinc, and enoxaparin sodium. In addition, routine medications for preexisting co-morbidities and supportive care measures were administered as required.

- Group 2 (treatment): Patients received standard treatment (as described in Group 1) plus a combination of AFO-202 beta-glucan at a dose of 3 g per day (administered as 1 gram granules in a sachet with each meal × 3 times per day) and N-163 beta-glucan at a dose of 8 gram per day (administered as a gel in a 8 g sachet with 1 meal per day).

We present a CONSORT flow diagram (Figure 1) detailing the participant enrolment process. The diagram summarises the reasons for the loss to follow-up, with 5 participants lost in the intervention group and 1 in the control group. These dropout rates may have influenced the study outcomes.

The primary outcome measures of this clinical trial were key immunological and clinical parameters. Immunological markers, including IL-6, were monitored to evaluate the immune responses. Hospitalisation parameters such as mortality, duration of hospital stay, and the need for oxygen or life-support interventions were assessed. Comprehensive blood tests including complete blood count (CBC), D-dimer, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fasting blood glucose (FBG), post-prandial blood glucose (PPG), HbA1c, lipid profile, liver function, and ferritin levels were conducted. Secondary outcome measures included evaluating COVID-19 clinical symptoms, recording the time taken for improvement, complete recovery, and any recurrence of symptoms, such as pyrexia, respiratory distress, cephalic pain (headache), and malaise. These outcomes were measured at 3 key time points: day zero (baseline), day 7, and day 15.

Statistical Analysis

Statistical analysis was performed using Prism10 software. Continuous, normally distributed data are presented as mean ± standard deviation. Unpaired t-tests were used for the comparisons. Statistical significance was set at $P < 0.05$.

Results

The study initially aimed to enrol 100 evaluable participants; however, only 40 eligible patients were enrolled. Of them, 22 were assigned to the control group and 18 to the AFO-202+N163 treatment group (Figure 1). Notably, the treatment group had a higher proportion of patients with diabetes mellitus (DM), which is known to influence the severity of SARS-CoV-2 infection (Table 1). Four patients in the treatment group and 1 patient in the control group withdrew from the study. Two patients in the treatment group required mechanical ventilation and intensive care unit (ICU) admission, with 1 succumbing to the illness 7 days later.

Randomisation achieved similar age distributions in each group, with the control group ranging from 29 to 70 years (mean ± SD = 45.04 ± 11.5 years) and the treatment group ranging from 23 to 65 years (mean ± SD = 43.0 ± 9.26 years). Baseline characteristics, including body weight, body mass index (BMI), and blood pressure, were comparable between the groups. All the participants presented with mild-to-moderate COVID-19 upon admission. Oxygen supplementation (2-8 L/min) was administered to 4 patients in the control group and 3 patients in the treatment group.

While no significant differences were observed in hospitalisation duration, symptom resolution, oxygen saturation on days 7 and 15, temperature, or heart rate between the 2 groups, it is important to note that the 4 patients lost to follow-up in the treatment group remained hospitalised on day 15, but did not participate in the final measurements because of reasons related to their medical conditions and care. The specific reasons for their failure to follow up included noncompliance and medical instability.

We evaluated the effects of the treatment on key inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), ferritin, and D-dimer (Table 2).

The baseline CRP levels were identical in the treatment and control groups (33.95 mg/L). At day 7, CRP decreased to 5.53 ± 8.21 mg/L in the treatment group and to 4.91 ± 12.54 mg/L in the control group, resulting in a between-group mean difference of 0.62 mg/L ($P = 0.98$; 95% CI: −34.40 to 35.14). By day 15, CRP levels decreased further to 5.42 ± 10.41 mg/L in the treatment group and 14.0 ± 37.16 mg/L in the control group, with a between-group mean difference of −8.58 mg/L ($P = 0.52$; 95% CI: −37.65 to 19.40) (Figure 2).

IL-6 levels in the treatment group showed a significant decrease from baseline (25.67 ± 24.9 pg/mL) to day 7 (8.62 ± 13.95 pg/mL), with a between-group mean difference of −17.05 pg/mL ($P = 0.03$; 95% CI: −67.40 to −2.93). However, by day 15, the differences between groups were no longer statistically significant, with a between-group mean difference of −14.73 pg/mL ($P = 0.30$; 95% CI: −45.88 to 16.83) (Figure 2).

Ferritin levels decreased steadily in the treatment group, from 560.58 ± 537.30 ng/mL at baseline to 127.51 ± 215.91 ng/mL on day 15. The control group experienced an initial decrease from 535.24 ± 605.21 ng/mL to 108.18 ± 265.72 ng/mL on day 7, followed by an increase to 250.40 ± 356.47 ng/mL on day 15. The between-group mean differences were not statistically significant at either time point (day 7:19.33 ng/mL, $P = 0.64$; 95% CI: −338.2 to 531.2, and day 15: −122.89 ng/mL, $P = 0.98$; 95% CI: −371.1 to 376.6) (Figure 2).

D-Dimer levels in the treatment group declined from 0.37 ± 0.51 FEU/L at baseline to 0.29 ± 0.25 FEU/L on day 15. In the control group, D-dimer levels decreased from 0.91 ± 3.10 FEU/L to 0.38 ± 0.45 FEU/L. The between-group mean differences were not statistically significant (day 7: −0.15 FEU/L, $P = 0.73$; 95% CI: −0.8059 to 1.108, and day 15: −0.09 FEU/L, $P = 0.56$; 95% CI: −1.592 to 2.856) (Figure 2).

HbA1c and IgA levels remained stable in both groups, with no significant changes from baseline to day 15.

Table 1. Baseline Characteristics of Study Subjects.

Characteristic	Control Group (n = 22)	Treatment Group (n = 18)
Age Range (years)		
18-25	0 (0%)	1 (5.6%)
26-30	5 (22.7%)	3 (16.7%)
31-35	2 (9.1%)	0 (0%)
36-40	4 (18.2%)	4 (22.2%)
41-45	3 (13.6%)	2 (11.1%)
46-50	4 (18.2%)	6 (33.3%)
51-55	2 (9.1%)	1 (5.6%)
56-60	1 (4.5%)	1 (5.6%)
61-65	1 (4.5%)	0 (0%)
66-70	0 (0%)	0 (0%)
Gender		
Male	13 (59.1%)	9 (50%)
Female	9 (40.9%)	9 (50%)
Co-morbidities		
Diabetes mellitus	8 (36.4%)	8 (44.4%)
Hypertension	5 (22.7%)	3 (16.7%)
Other Co-morbidities	1 (4.5%)	1 (5.6%)
None	8 (36.4%)	6 (33.3%)
BMI (mean ± SD)	28.0 ± 5.4	27.6 ± 4.6
Blood pressure (mm/Hg) (mean ± SD)	124/80 ± 15/10	127/82 ± 12/8

Table 2. Key Findings of Effects on Inflammatory Markers: C-Reactive Protein (CRP), Interleukin-6 (IL-6), Ferritin, and D-dimer.

Marker	Groups	Baseline (Mean ± SD)	Day 7 (Mean ± SD)	*P*-value (Day 7)	95% CI (Day 15)	Day 15 (Mean ± SD)	*P*-value (Day 15)	95% CI (Day 15)
CRP mg/L	Control	33.95 ± 52.89	4.91 ± 12.54	0.36	−34.40 to 35.14	14.0 ± 37.16	0.52	−37.65 to 19.40
	Treatment	33.95 ± 61.44	5.53 ± 8.21			5.42 ± 10.41		
IL-6 pg/mL	Control	19.48 ± 33.62	10.32 ± 22.493	0.03	−67.40 to −2.930	14.23 ± 29.49	0.3	−45.88 to 16.83
	Treatment	25.67 ± 24.9	8.62 ± 13.95			5.50 ± 7.28		
Ferritin ng/mL	Control	535.24 ± 605.21	108.18 ± 265.72	0.64	−338.2 to 531.2	250.40 ± 356.47	0.98	−371.1 to 376.6
	Treatment	560.58 ± 537.30	278.94 ± 326.35			127.51 ± 215.91		
D-dimer FEU/L	Control	0.91 ± 3.10	0.52 ± 0.39	0.73	−0.8059 to 1.108	0.38 ± 0.45	0.56	−1.592 to 2.856
	Treatment	0.37 ± 0.52	**0.65 ± 1.05**			0.29 ± 0.25		

Serious Adverse Events

Two patients in the treatment group required mechanical ventilation and admission to the intensive care unit (ICU), and 1 patient succumbed to the illness 7 days later. Notably, the adverse events were attributed to COVID-19-related complications and were determined to be unrelated to the food supplements administered as part of the intervention.

Dropout Rates

The dropout rate was significantly higher in the intervention group (n = 5) than in the control group (n = 1). This significant difference in retention may have affected the overall study results and warrants further consideration when interpreting the findings.

Discussion

This study investigated the effects of the AFO-202 and N-163 beta-glucan combination on the acute phase of COVID-19. Considering the need for rapid intervention against the rapidly progressing SARS-CoV-2 pathogenesis, the combination of AFO-202 and N-163 beta-glucan from the previous study[12] was tested for a shorter duration of 7 and 15 days.

The treatment group demonstrated a decrease of biomarkers, including IL-6, CRP, ferritin and D-dimer levels, by day 7, with these reductions persisting through day 15. In contrast, some markers, such as ferritin, decreased in the control group by day 7 but showed an increased by day 15. Nonetheless, the findings confirm the safety of beta-glucans as an adjuvant in COVID-19 treatment. The decrease observed in the control group may also be part of the natural

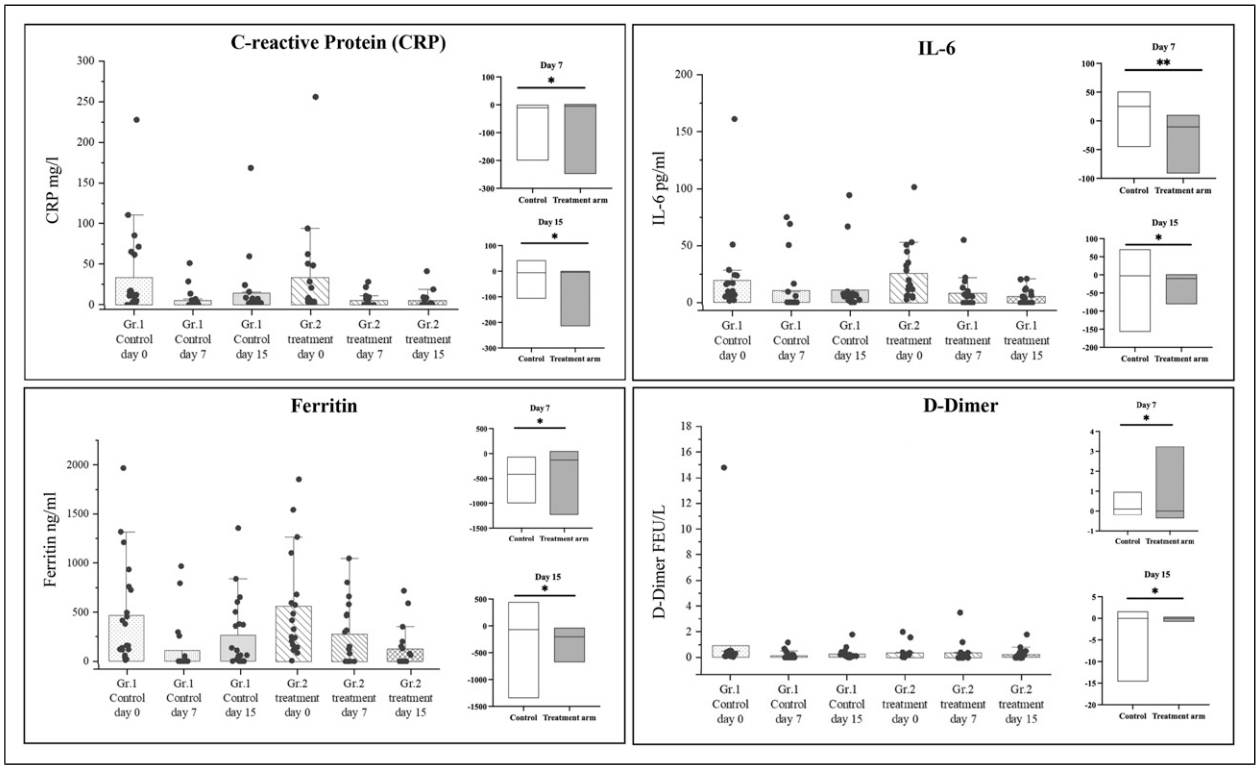

Figure 2. CRP levels in the treatment groups compared to the control group. CRP levels showed a decrease until day 7, followed by an increase by day 15. IL-6 levels in the treatment groups compared to the control group, showing a consistent decrease over time. Ferritin levels in the treatment groups compared to the control group. Levels decreased until day 7 and increased by day 15. D-Dimer levels in the treatment groups compared to the control group. Similar to CRP and ferritin, D-Dimer levels decreased until day 7 and increased by day 15. For each parameter, the difference in values from baseline to day 7 and day 15 is shown in separate graphs, with median values represented by plot lines within floating bars. (*Not significant; **$p < 0.05$ indicates statistical significance).

course of COVID-19 and may be associated with immunologic responses or medication-related reductions in viral load, rather than solely due to the supportive care received during hospitalisation. In contrast, the treatment group maintained the beneficial effects even after discharge.

SARS-CoV-2 infection triggers a cytokine storm and the uncontrolled release of inflammatory mediators, leading to tissue damage[1] Elevated levels of interleukin-6 (IL-6) are associated with severe COVID-19 and increased mortality,[13] and are considered a hallmark biomarker occupying the centre stage of the cytokine storm.[14] Therefore, controlling inflammation and modulating immune responses are critical therapeutic strategies. In earlier studies in healthy volunteers, a combination of AFO-202 and N-163 beta-glucans demonstrated beneficial effects, including reduced D-dimer levels, improved NLR, and increased lymphocyte-to-CRP ratio (LCR) and leukocyte-to-CRP ratio (LeCR).[15] This combination also exhibits anti-fibrotic and anti-inflammatory properties in non-alcoholic steatohepatitis (NASH) models.[8] Another study showed that this beta-glucan combination significantly decreased inflammatory and hyperimmune response markers (IL-6, NLR, ESR, and D-dimer) for 30 days, whereas the control group displayed increased levels of these markers on day 15.[12] These beta-glucans, having been used as adjuvants in vaccines like influenza,[6] may serve as unique nutritional supplements that complement conventional COVID-19 treatments. Having previously demonstrated the potential to manage the cytokine storm in COVID-19 in a 30-day study, the present study highlighted the potential of AFO-202 and N-163 beta-glucan combination interventions in tackling COVID-19 in the acute phase.[16]

This study had several limitations. First, the sample size was smaller than expected; although the study aimed to recruit 100 participants, only 40 were ultimately enrolled because of challenges in recruitment during the COVID-19 pandemic. These challenges include hesitancy toward novel treatments and logistical difficulties. Second, the follow-up duration was shortened from the intended 60 to 15 days, as many participants were unwilling to continue the supplement after discharge. This limits the ability to assess the long-term outcomes and sustained effects of treatment beyond the acute phase of infection. The second limitation was the lack of a placebo control group. Finally, the dropout rates related to patient follow-up post-discharge represent another limitation, as they restricted further data collection in the later stages of recovery. These factors suggest that, while the findings are promising, they should be interpreted with caution, and larger, longer-term studies are necessary to confirm these results.

Furthermore, fasting blood glucose levels are associated with severe SARS-CoV-2 infection.[17] While our study did not show significant differences in clinical outcomes such as hospitalisation duration or inflammatory markers between the groups, the presence of a higher proportion of DM patients in the treatment group (Table 1) may have influenced the results. DM exacerbates inflammation and other COVID-19-related complications, which may have contributed to the greater variability in the response to treatment within the treatment group. Previous human clinical studies have demonstrated that AFO-202 beta-glucan exhibits metabolic regulatory effects, including reduction in HbA1c levels and regulation of dyslipidaemia.[18,19] Additionally, when combined with N-163 beta-glucan in a NASH mouse model, it showed further metabolic regulation and immune modulation.[5] Therefore, it is plausible that the beta-glucan treatment, particularly its metabolic-regulating properties, may contribute to more pronounced immune modulation in patients with diabetes mellitus (DM). However, the current study was not designed to analyse specific subgroups, and we did not perform an analysis stratified by comorbidities, such as DM. Future studies focusing on patients with DM alone could provide valuable insights into whether beta-glucan supplementation offers additional benefits for managing COVID-19 in patients with diabetes. We recommend this as an area for further research.

Conclusion

The present study demonstrated that co-supplementation with AFO-202 and N-163 exopolysaccharide beta-glucans from *Aureobasidium pullulans* significantly reduced interleukin-6 (IL-6) levels, a hallmark biomarker of cytokine storms, compared to the control group. Although an additional reduction of other biomarkers, including C-reactive protein (CRP) and ferritin, was evident in the treatment group over this short duration, further validation in long-term multicentric clinical studies is required to confirm their statistical significance and establish the potential of these beta-glucan supplements in managing inflammation in COVID-19, its emerging variants, and other acute inflammatory conditions, especially in vulnerable populations.

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Author Contributions

S.U.P and S.A. contributed to conception and design of the study. E.T and D. S helped with data collection. S.A and S.P. drafted the manuscript. K.R, S.S, V. D, N.I and M. I performed critical revision of the manuscript. All the authors read, and approved the submitted version. All the authors meet the criteria for authorship as per the ICMJE criteria

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Author Samuel Abraham is a shareholder in GN Corporation, Japan which in turn is a shareholder in the manufacturing company of novel beta glucans using different strains of Aureobasidium pullulans.

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Ethical Statement

Ethical Approval

The study was registered in Clinical trials registry of India, CTRI/2021/10/037380. The study was approved by the Institutional Ethics Committee (IEC) of Madras Medical College, India on 15th September, 2021.

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Supplemental Material

Supplemental material for this article is available online.

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