

The Effects of Probiotic Lactobacillus Acidophilus and Colchicine on The Control of Symptoms, Duration, And Disease Progression of Mild and Moderate Cases of Covid-19: A Randomized Controlled Clinical Trial

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Abstract

Background

Coronavirus disease 2019 (COVID-19) is a newly emerging human disease caused by a novel coronavirus, causing a global pandemic crisis. Probiotics and/or colchicine may be considered as options for treatment since they have anti-viral, anti-inflammatory, and immunomodulatory effects.

Objective

To assess the effectiveness of probiotic supplements (*Lactobacillus acidophilus*) and colchicine on symptoms, duration, and progression of mild and moderate cases of COVID-19 infection.

Methods

A three-arm randomized controlled clinical trial was carried out in the triage clinic of the family medicine department at Ain Shams University Hospitals on 150 participants who had been diagnosed as COVID-19 patients with mild and moderate severity. Patients aged below 18 years or above 65 years with any co-morbidities, pregnant or lactating females, and severe COVID-19 confirmed cases were excluded. Randomization was done by using sealed envelopes containing codes for intervention or control. Patients are followed up for improvement of their symptoms with no development of new symptoms over the course of two weeks.

Results

A total of 150 patients with mild and moderate severity of COVID-19 were enrolled in the study, 50 patients in each arm; around one third (34.7%) of the participants were aged between 29 and 39 years; one-quarter (24.7%) were aged between 18 and 28 years and 40.6% were aged 40 years and above. The mean duration of symptoms improvement was 12, 11 and 12 in the colchicine, probiotic, and control groups, respectively. Improvement of inflammatory markers over time occurred in each of the three groups, with no statistically significant difference between them.

Conclusion

Probiotic *Lactobacillus acidophilus* and colchicine shows no significant effect on the symptoms, duration, and progression of mild and moderate cases of COVID-19.

Keywords: probiotics; colchicine; COVID-19; RCT; ain shams university

Introduction

A novel coronavirus was discovered to be the source of a cluster of pneumonia cases in Wuhan (China), which led to an outbreak throughout China and then to a global pandemic. In February of 2020, the World Health Organization officially recognized COVID-19 (coronavirus disease 2019) [1].

COVID-19 disease frequently manifests as a fever, dry cough, shortness of breath, and breathing difficulties. Some of the less frequent symptoms include anosmia, sore throat, runny nose, vomiting, and diarrhea [2].

Dysbiosis of the gut microbiome, immunological dysregulation, hyperinflammation, and a cytokine storm are hallmarks of COVID-19 illness [3]. Probiotics are defined as "live bacteria that provide health benefits to the host when given in sufficient doses" [4].

Early reports from Wuhan indicate that 2–10% of COVID-19 patients exhibited gastrointestinal symptoms, including diarrhea, vomiting, and abdominal pain. 10% of patients experienced one to two days of nausea and diarrhea prior to the onset of fever and respiratory symptoms [5].

The severity of COVID-19 disease was correlated with the diversity of the gut microbiota, and alterations in the gut microbiota persisted even after the virus eliminated, suggesting that the virus may have a long-lasting negative impact on the homeostasis of the human microbiome [6].

As an intestinal microbe regulator, probiotics help to improve the immune system, lessen allergic reactions, and play a crucial part in antiviral immunomodulation. They also increase the gastrointestinal microbiota's capacity to modulate immunological activity [7].

Infection with SARS-CoV-2 significantly altered the fecal microbiomes of all 15 patients, according to a study of confirmed COVID-19 patients in Hong Kong. This imbalance of intestinal microbiota persisted even after SARS-CoV-2 clearance [8].

Colchicine is an anti-inflammatory drug frequently prescribed for the treatment and prevention of crystals induced arthritis, such as gout, systemic auto-inflammatory illnesses such as Behcet's disease and familial Mediterranean fever [9]. Inhibiting neutrophil chemotaxis and activity in response to vascular damage is its mode of action [10].

One of the clinical trials called COLCORONA 2020 was directed by the Montreal Heart Institute and conducted in Brazil, Canada, Greece, South Africa, Spain, and the United States conducted by Tardif et al. in 2021. The trial revealed that the effect of colchicine on clinical symptoms of COVID-19- community-treated individuals was not statistically significant difference between the colchicine group and controls [11].

Colchicine may lessen mortality and the need for mechanical ventilation in mild-to-moderate COVID-19 patients, according to a systematic review and meta-analysis conducted by Siemieniuk et al. in 2020 [12].

Consequently, probiotics and/or colchicine may be viable treatment options for COVID-19 patients. To examine the efficacy of probiotics and colchicine in the treatment of COVID-19, it is necessary to conduct additional clinical trials and provide clinicians with evidence, as there are currently insufficient studies to support this conclusion.

The aim of the current study was to assess the effectiveness of probiotic supplements (*Lactobacillus acidophilus*) and colchicine on symptoms,

duration, and progression of mild and moderate cases of COVID-19 infection.

Patients And Methods

Study design and setting

A three-arm randomised controlled clinical trial was done as part of the investigation over the course of a year at the Triage Clinic of the Family Medicine Department at Ain Shams University Hospitals.

Inclusion criteria

Patients with mild and moderate COVID-19 severity, aged 18 to 64.

Exclusion criteria

Patients with COVID-19 who are under 18 or over 65, have co-morbid conditions, are pregnant or lactating mother, or have severe confirmed COVID-19 were excluded from the trial.

Participants in the research and sampling

A total of 150 individuals who satisfied the inclusion criteria had their data gathered between the beginning of July 2021 and the end of August 2022.

Patients were chosen from the Triage/COVID-19 Outpatient Clinic, and each one had the following procedures: Sociodemographic information was gathered for the clinical history, including age, gender, marital status, place of residence, smoking history, etc. Medical information included weight, current medications, symptoms (onset, course, and duration), and the presence of co-morbidities. The temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation are all measured during a thorough general examination.

Patients who met the CDC's criteria for suspicion had radiographic and laboratory confirmation using the tests PCR-COVID-19, Complete Blood Count, CRP, Ferritin and D-Dimer, as well as High-resolution CT chest.

Patients were categorised as mild and moderate based on laboratory and radiographic results once the diagnosis was confirmed.

The participants were divided into 3 groups:

Group A (Colchicine group) consisted of COVID-19 patients with mild to moderate disease who received the recommended course of care in accordance with the protocol established by the Egyptian Supreme Council of University Hospitals, as well as Colchicine tablets (0.5 mg) three times per day for three days and subsequently twice per day for four days [13].

Patients in Group B (Probiotic group) with mild and moderate COVID-19 severity got probiotics in the form of oral sachets once daily for two weeks in addition to protocol prescribed by the Egyptian Supreme Council of University Hospitals.

Group C (Control group) consists of COVID-19 patients with mild and moderate severity who received the recommended course of care in accordance with the protocol established by the Egyptian Supreme Council of University Hospitals (yet to be published) (Vitamin C 500

mg twice daily, Vitamin D3 2000–4000 IU/day, Zinc 75 mg once daily for two weeks, and necessary protocol of management based on case assessment and severity).

Randomization

To distribute intervention or control codes, the researcher utilised sealed envelopes.

Follow-up

Participants were contacted twice a week by phone to assess their symptoms (increase or decrease, duration, and development of new symptoms), compliance with treatment, daily temperature, oxygen saturation, need for oxygen inhalation, need for hospital admission, need for ICU admission, need for mechanical ventilation, and improvement in inflammatory markers level (CBC, CRP, ferritin, and D-dimer).

Final assessment

Release from isolation 10 days after start of symptoms or 10 days after the patient's first positive swab [14].

14 days after the initiation of therapy, individuals were polled about whether their symptoms had improved or remained the same, and Complete Blood Count, CRP, Ferritin, and D-Dimer were retested.

End point

The trial lasted until the sample size was reached, the patient's symptoms had improved, and no new symptoms had appeared. It also continued until there was no longer a requirement for hospitalization or ICU admissions or the occurrence of adverse events (AES) or severe adverse events (SAEs) during the course of the study.

Ethical Considerations:

Administrative and ethical committee board approvals (no. MD 88/2020) to carry out the study at Ain Shams University Hospitals were obtained (Approval date 19/6/2021). An informed consent was obtained from the patients which addressed all the steps of the study as well as their right to withdraw from the study at any time. Privacy and confidentiality of data was also assured. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Data Analysis:

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test, Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test was used for comparison between groups. For comparison of Lab investigation before and after the treatment Mc Nemar test was used for qualitative binary variables, While Marginal Homogeneity test was used for nominal variables. P value ≤ 0.05 was statistically significant.

Results

Of the participants in the present clinical trial, around one-third (34.7%) were between the ages of 29 and 39, one-quarter (24.7%) were between the ages of 18 and 28, and 40.6% were older than 40. 68% of people live in cities, 57% in rural regions, and 25% in urban slum. 23 percent of them smoked, 92% were married, 49% had graduate degrees, and 71% were housewives. Regarding demographic information, there was no statistically significant difference between the three groups (**Table 1**).

Variable		Total		Treatment groups						P-value
				Control group		Colchicine group		Probiotic group		
		N	%	N	%	N	%	N	%	0.870
Age	18–28 Y	37	24.7%	9	18.0%	15	30.0%	13	26.0%	0.780
	29–39 Y	52	34.7%	19	38.0%	16	32.0%	17	34.0%	
	40–50 Y	30	20.0%	10	20.0%	9	18.0%	11	22.0%	
	51–60 Y	31	20.7%	12	24.0%	10	20.0%	9	18.0%	
Sex	Male	66	44.0%	20	40.0%	23	46.0%	23	46.0%	0.490
	Female	84	56.0%	30	60.0%	27	54.0%	27	54.0%	
Smoking	No	115	76.7%	41	82.0%	38	76.0%	36	72.0%	0.740
	Yes	35	23.3%	9	18.0%	12	24.0%	14	28.0%	
Marital status	Single	36	24.0%	8	16.0%	14	28.0%	14	28.0%	0.760
	Married	92	61.3%	33	66.0%	29	58.0%	30	60.0%	
	Divorced	5	3.3%	2	4.0%	1	2.0%	2	4.0%	
	Widow	17	11.3%	7	14.0%	6	12.0%	4	8.0%	
Education	Illiterate	22	14.7%	8	16.0%	8	16.0%	6	12.0%	0.760

	Read and write	10	6.7%	5	10.0%	3	6.0%	2	4.0%	
	Primary	9	6.0%	1	2.0%	5	10.0%	3	6.0%	
	Preparatory	7	4.7%	3	6.0%	3	6.0%	1	2.0%	
	Secondary	12	8.0%	4	8.0%	4	8.0%	4	8.0%	
	Intermediate institute	40	26.7%	15	30.0%	12	24.0%	13	26.0%	
	University graduate	49	32.7%	14	28.0%	14	28.0%	21	42.0%	
	Postgraduate	1	0.7%	0	0.0%	1	2.0%	0	0.0%	
Occupation	Non-working/housewife	71	47.3%	26	52.0%	25	50.0%	20	40.0%	0.610
	unskilled manual worker	4	2.7%	1	2.0%	3	6.0%	0	0.0%	
	skilled manual worker/farmer	14	9.3%	4	8.0%	4	8.0%	6	12.0%	
	Trades/business	9	6.0%	4	8.0%	3	6.0%	2	4.0%	
	semi-professional	30	20.0%	10	20.0%	8	16.0%	12	24.0%	
	Professional	22	14.7%	5	10.0%	7	14.0%	10	20.0%	
Residence	Urban slum	25	16.7%	7	14.0%	6	12.0%	12	24.0%	0.550
	Rural	57	38.0%	20	40.0%	20	40.0%	17	34.0%	
	Urban	68	45.3%	23	46.0%	24	48.0%	21	42.0%	

Table 1: Comparisons between the three treatment groups regarding the sociodemographic characteristics.

Test of Sig, Chi-square test.

Table 2 summarizes clinical information, such as the number of new residual symptoms with no difference between the three groups. symptoms, their duration, and their persistence after two weeks. In the Hospitalization rate was 14%, 2% and 10% in the colchicine, probiotic, colchicine, probiotic, and control groups, the mean symptom duration was and control groups respectively, with no statistically significant differences. 12, 11 and 12, respectively, with no statistically significant differences. After two weeks, the majority of patients (54%, 46% and 56%) had

Variable		Total		Control group		Colchicine group		Probiotic group		P-value
Duration of symptoms improvement (post)	Mean (SD)	12	(4)	12	(3)	12	(4)	11	(4)	0.837**
	Min-Max	(5-30)		(5-21)		(7-30)		(5-25)		
residual symptoms (post)	NO	72	48%	22	44%	23	46%	27	54%	0.57
	Yes	78	52%	28	56%	27	54%	23	46%	
Hospitalization (post)	NO	137	91.3%	45	90%	43	86%	49	98%	0.09
	Yes	13	8.7%	5	10%	7	14%	1	2%	

Table 2: Comparisons between the three treatment groups regarding the clinical data.

Test of Sig: ANOVA**: *Sig P value ≤ 0.05.

The proportion of adverse effects in the colchicine group is shown in Figure 1. In the present trial, 44% of the patients in the colchicine group had gastrointestinal side effects.

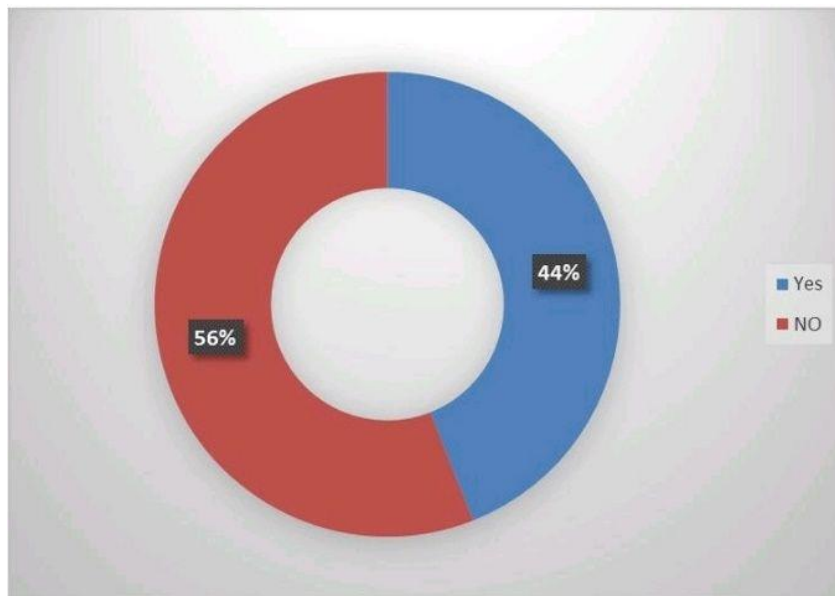


Figure 1 shows the percentage of side effects in the Colchicine group

Figure 1: See image above for figure legend.

In terms of laboratory results, all the parameters before and after the intervention were statistically significantly (Table 3).

Variable		Pre		Post		P-value
		N	%	N	%	
Neutrophil	Normal	96	64%	120	80%	0.05*#
	Neutropenia	36	24%	11	7.3%	
	Neutrophilia	18	12%	19	12.7%	
Lymphocytes	Normal	80	53.3%	104	69.3%	0.02*#
	Lymphopenia	55	36.7%	29	19.3%	
	Lymphocytosis	15	10%	17	11.3%	
CRP	Normal	39	26%	91	60.7%	< 0.001*\$
	Increase	111	74%	59	39.3%	
D-dimer	Normal	64	42.7%	114	76%	< 0.0001*\$
	Increase	86	57.3%	36	24%	
S. ferritin	Normal	52	34.7%	111	74%	< 0.001*\$
	Increase	98	65.3%	39	26%	

Table 3: Comparison between the treatment groups regarding the laboratory data before and after intervention.

*Sig P value; # test of Sig Marginal Homogeneity Test; \$ test of sig McNamar Test.

Each of the three groups had improvements in inflammatory markers over time, with no statistically significant differences between them except lymphocyte count post intervention.

Variable		Total		grouping						P-value
				Control group		Colchicine group		Probiotic group		
		N	%	N	%	N	%	N	%	
Neutrophil (pre)	Normal	96	64%	33	66%	33	66%	30	60%	0.950
	Neutropenia	36	24%	12	24%	11	22%	13	26%	
	Neutrophilia	18	12%	5	10%	6	12%	7	14%	
Lymphocytes (pre)	Normal	80	53.3%	26	52%	31	62%	23	46%	0.210
	Lymphopenia	55	36.7%	16	32%	16	32%	23	46%	
	Lymphocytosis	15	10%	8	16%	3	6%	4	8%	
Neutrophil (post)	Normal	120	80%	39	78%	41	82%	40	80%	0.820
	Neutropenia	11	7.3%	3	6%	3	6%	5	10%	
	Neutrophilia	19	12.7%	8	16%	6	12%	5	10%	
Lymphocytes (post)	Normal	104	69.3%	34	68%	38	76%	32	64%	0.01*
	Lymphopenia	29	19.3%	10	20%	12	24%	7	14%	
	Lymphocytosis	17	11.3%	6	12%	0	0.0%	11	22%	

Table 4: Comparison between the three treatment groups regarding laboratory data (CBC parameters) before and after the intervention.

Test of Sig Chi-square test; *Sig P value < 0.05.

Variable		Total		Grouping						P-value
				Control group		Colchicine group		Probiotic group		
		N	%	N	%	N	%	N	%	
CRP (pre)	Normal	39	26%	13	26%	15	30%	11	22%	0.660
	increase	111	74%	37	74%	35	70%	39	78%	
D-dimer (pre)	Normal	64	42.7%	15	30%	20	40%	29	58%	0.016*
	increase	86	57.3%	35	70%	30	60%	21	42%	
S. ferritin (pre)	Normal	52	34.7%	16	32%	17	34%	19	38%	0.814
	increase	98	65.3%	34	68%	33	66%	31	62%	
CRP (post)	Normal	91	60.7%	34	68%	26	52%	31	62%	0.254
	increase	59	39.3%	16	32%	24	48%	19	38%	
D-dimer (Post)	Normal	114	76%	40	80%	33	66%	41	82%	0.125
	increase	36	24%	10	20%	17	34%	9	18%	
S. ferritin (post)	Normal	111	74%	40	80%	35	70%	36	72%	0.483
	increase	39	26%	10	20%	15	30%	14	28%	

Table 5: Comparison between the three treatment groups regarding laboratory data (CRP, D-Dimer and Ferritin parameters) before and after the intervention.

Test of Sig Chi-square test; *Sig P value < 0.05.

Discussion

Coronavirus disease 2019 (COVID-19) is an extremely contagious viral infection caused by the SARS-CoV-2 virus, which results in severe acute respiratory syndrome. It has had a catastrophic effect on the demography of the globe. It is now the most crucial aspect of global health. In late December 2019, the first cases of this predominantly respiratory viral illness were reported in Wuhan, Hubei Province, China. SARS-CoV-2 rapidly spread across the globe. On March 11, 2020, the World Health Organization (WHO) had to declare it as a global pandemic.

The 150 COVID-19 non-hospitalized patients in the current trial, which is a three-arm randomized interventional study, ranged in severity from mild to moderate. The participants were randomly assigned to receive the standard treatment protocol alone, the standard treatment protocol plus colchicine, or the standard treatment protocol plus probiotics.

The study's findings regarding the sociodemographic characteristics of the participants show that approximately one third (34.7%) of them are between the ages of 29 and 39 years, one-quarter (24.7%) are between the ages of 18 and 28 years, and forty percent (40.6%) are over the age of 40 years. Of the 150 participants, 84% were female and 66% were male, which is consistent with Doerre and Doblhammer [15] finding that infection rates are highest among the young and Sex ratios show that women at working ages have greater infection risks than males.

In addition, the smoking rate among study participants was 23% which is comparable to that of Farsalinos et al. [16], who discovered that hospitalized COVID-19 patients had a smoking prevalence that was roughly one-fourth of what was predicted.

Notably, there is no statistically significant difference in the sociodemographic features of the three groups, suggesting good matching.

In line with Hakki et al. [17] who found that peak RNA viral load and peak infectious viral load occurred a median of 3 days after symptom onset, the current study revealed that the average duration of symptom onset is the fourth day. As a result, the majority of the study participants sought medical attention at the peak of symptom onset.

Further subgroup analysis revealed that the mean duration of symptoms improvement after intervention is 9.8 days in mild cases and 13 days in moderate cases, with a statistically significant difference between them, which is consistent with Faiq et al. [19] who found the median survival time was 12 days in moderate hospitalized patients. The mean duration of symptoms improvement after intervention is 12 days, and there is no statistically significant difference between the three groups.

Tardif et al. and Dorward et al. [20] trials, which were conducted on 4,488 and 4,997 non-hospitalized participants while Recovery [21] trial was carried out on 19,423 hospitalized participants, found no statistically significant difference between the colchicine and usual care protocol for time of improvement and hospitalizations in the group treated with the standard protocol and colchicine.

The results of the current study, however, did not agree with a meta-analysis conducted by Hariyanto et al. [22] who sought to investigate the impact of colchicine as a treatment option for COVID-19 on January 29, 2021. It was revealed that a total of eight studies involving 5778 COVID-

19 patients were included in this meta-analysis. Colchicine treatment was linked to better COVID-19 results.

Abdelfattah et al. [23] conducted a retrospective study of 100 patients hospitalized at the Ain Shams University Field Hospital and concluded that colchicine has a significant effect on the participants in terms of duration of symptom improvement and hospitalization.

However, additional clinical trials are required to validate the findings, as they are based on observational studies.

The current study found that 44% of the colchicine group participants experienced gastrointestinal adverse events, particularly at the beginning of the regimen on dose 0.5 mg three times per day for three days, then twice daily for four days. This is consistent with Terkeltaub et al. [24] and Robert et al. [24] studies, which found that 36.5% of participants who took colchicine developed diarrhea.

In addition to clinical improvement, the recent trial evaluated the alternation in hematological parameters of individuals with mild to moderate severity before and after the intervention which was statistically significant and indicates that CBC, CRP, ferritin, and D-dimer may be employed as prognostic and follow-up tools for both disease severity and outcomes. which agrees with Yasmin et al. meta-analysis of five RCTs concluded that CRP and D-dimer levels are crucial in determining the severity of COVID-19 because elevated levels are linked to a poor prognosis. Other studies have also used these parameters to monitor disease severity and outcomes. [25]

Additionally, Qin et al. [26] study revealed that lymphopenia, the most well-known hematological abnormality in patients affected by COVID-19 infection, is seen in up to 85% of severe cases with the severity of lymphopenia linked to outcome. Soraya et al.'s [27] study revealed that leukocytes and neutrophils were significantly higher in severe than in non-severe COVID-19 infected patients. Leukocyte and neutrophil counts also increased as the COVID-19 disease progressed in the severe groups, which is in line with the findings of our study, which show that there is a statistically significant difference between mild and moderate cases with regard to CBC parameters (neutrophils and lymphocytes levels).

Further subgroup analysis revealed no statistically significant difference in inflammatory biomarker levels between the colchicine group and controls, and these results concur with those of Deftereos et al. [28] who found no significant differences in CRP level between the control and colchicine groups.

As opposed to Sarwar et al. [29] who reported from a meta-analysis of six RCTs that Colchicine is effective in decreasing inflammatory biomarkers seen in moderate-to-severe COVID-19 patients. According to Sandhu et al. [30], patients in the colchicine group also had a more pronounced decline in the inflammatory marker's ferritin ($P = 0.012$), D-dimer ($P = 0.037$), and CRP.

On the other hand, the group that received probiotics and the standard of care of treatment shows no statistically significant difference from the controls regarding the time of improvement and for hospitalizations due to COVID-19. In addition, there is no statistically significant difference between the two groups with regard to of biochemical outcomes, which opposes Wischmeyer et al. [31] who claimed that LGG is well-tolerated and is associated with a longer time to COVID-19 development.

The majority of clinical trials on the use of probiotics during COVID-19 use small sample sizes. Most of them have relied on subjective conclusions. In addition, there has been considerable variation among these studies. Most of the studies and meta-analyses were limited to healthy young adults and excluded the elderly as this population is frequently polymedicated and frequently has multiple comorbidities. Additional clinical trials are required to adequately validate this conclusion. [32].

Conclusion

Probiotic *Lactobacillus acidophilus* and colchicine shows no significant effect on the symptoms, duration, and progression of mild and moderate cases of COVID-19. Colchicine causes more gastrointestinal adverse effects in the participants. CBC, CRP, ferritin, and D-dimer may be used as prognostic and follow-up tools for both disease severity and outcomes. Further randomised controlled trials with a larger sample size could be conducted to confirm these results.

Declarations

Author contributions:

Each author declares having participated in the activities.

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None.

Conflict of interest:

None.

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