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Evaluation of Add-On Individualized Homeopathic Medicines Products in the Treatment of Symptomatic COVID-19 Managed at Home: A Double Blind, Placebo-Controlled, Randomized, Exploratory Clinical Trial

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Abstract

Homeopathy has shown promise in fighting epidemics, leading to potential applications in the COVID-19 clinical cases. To assess the impact of add-on individualized homeopathic medicinal products (IHMP) on improving clinical outcomes and time to medical discharge in COVID-19 patients, a prospective, double-blind, randomized, placebo-controlled, parallel-group exploratory clinical trial was conducted in a São Paulo state municipality, Brazil, between February and July 2021. 82 (unvaccinated) patients with confirmed SARS-CoV-2 infection and manageable mild to moderate COVID-19 symptoms were randomly assigned to placebo or IHMP groups. Utilizing unique global COVID-19 symptom scores, a symptom assessment was performed. Statistical analysis involved 68 patients (36 IHMP; 32 placebo). No significant initial disparity existed in total COVID-19 symptom scores between the groups. The IHMP group exhibited a significantly shorter mean time from initial appointment to medical discharge compared to placebo ($p < 0.05$: IHMP 74.5 hours (+/- 57.47, 95% CI: 55.73-93.27); placebo

137.42 hours (+/- 87.85, 95% CI: 106.98-167.86)). Employing the chi-square trend test at selected time points (74.5 and 137.42 hours, corresponding to mean discharge times), COVID-19 scores demonstrated sustained IHMP-associated reductions ($p < 0.05$). COVID-19 symptom scores and time to medical discharge were significantly reduced by treatment with IHMP compared to placebo, suggesting a potential role for IHMP in managing mild to moderate COVID-19 symptoms at home.

Keywords
Coronavirus; clinical trial; homeopathy; COVID-19

1. Introduction

Most people who become ill from COVID-19 have mild to moderate symptoms and recover without special treatment. However, some develop a severe condition and need medical attention [1]. The clinical features of COVID-19 range from an asymptomatic state to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction [2]. Lu et al. [3] performed a meta-analysis of the clinical presentation of COVID-19 patients and found the main symptoms to be: fever (88.3%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (23.2%), dyspnoea (21.9%), headache or dizziness (12.1%), diarrhea (4.8%) and vomiting/nausea (3.9%). Hyposmia/anosmia and hypogeusia/ageusia were also reported as frequent symptoms [4].

At the time of this research, the primary variant of COVID-19 circulating in Brazil was the Gamma variant. This variant was first identified in Manaus, Amazonas, in late 2020 and became dominant throughout Brazil in early 2021. The Gamma variant is known for its higher transmissibility and potential to evade some aspects of immunity from previous infections [5].

With regards to the duration of COVID-19, the average time reported from the onset of the symptoms to dyspnoea, hospital admission, and ARDS was 5 days (range 1-10 days), 7 days (range 4-8) and 8 days (range 6-12) respectively [6]. The average time from the onset of symptoms until the need for invasive mechanical ventilation or death was 11 or 23 days, respectively [7].

The RT-PCR (reverse-transcriptase polymerase chain reaction) test is considered the gold standard method for the diagnosis of COVID-19, as it can reliably detect the presence of SARS-CoV-2 in a patient sample, preferably obtained by nasopharyngeal swab. PCR is a specific test capable of detecting viral RNA between 2 and 5 days after infection when significant viral replication occurs within the cells of the infected patient. The test is most reliable in samples collected around the 3rd day from the onset of symptoms [8-10].

Treatment for infection caused by SARS-CoV-2 is essentially supportive and symptomatic, allowing mild cases to be treated at home, with adjunctive advice on danger signs, maintaining hydration, nutrition, and fever and cough control [2].

In addition to the impact on physical health, the impact of the pandemic on mental health is being widely reported in the scientific literature. Individuals impacted by COVID-19 are at an increased risk of experiencing a wide range of mental health issues such as depression, anxiety disorders, panic attacks, irrational anger, impulsivity, somatization disorder, sleep disorders,

emotional disturbances, disinterest behavior, decreased concentration, posttraumatic stress symptoms, suicidal behavior; many of which require special mental health care attention [11-13].

Medical efforts to tackle the impact of COVID-19 from diverse areas of knowledge are in high demand, and integrative and complementary medicine is now recommended by some countries [14-16]. Consistent with this, it should be noted that homeopathy has a well-documented history of use in the face of many epidemics [17-19]. Within Brazil, it has been reported that homeopathy has contributed to decreased incidence rates and reduced the impact on the population's health from Dengue fever epidemics [20-22]. In the face of the COVID-19 pandemic, several studies have been published on possible homeopathic treatments for symptomatic cases of COVID-19 in several countries worldwide, showing a positive effect [23-29].

Taking into consideration the severity and challenges of the pandemic as a global public health issue affecting both physical and mental health and the fact that proven and effective treatment protocols have not become fully established, homeopathic treatment could be a potential therapeutic option, especially in mild to moderate cases that can be managed at home.

This study aimed to evaluate the improvement of clinical symptoms and the time to medical discharge in patients with mild to moderate acute SARS-CoV-2 infection treated at home with add-on individualized homeopathic medicinal products (IHMP). We also intended to describe the mental health status at baseline and the most common homeopathic drugs prescribed.

2. Methods

2.1 Trial Design and Setting

The study was a prospective, single-center, double-blind, randomized, placebo-controlled, parallel-group, exploratory clinical trial performed on symptomatic COVID-19 patients with mild to moderate symptoms who were deemed manageable at home and referred to the study by the public health department of a medium-sized municipality in São Paulo state, Brazil. Patients remained at home throughout the study. The research team did not conduct in-person visits with the patients but only communicated with them via cell phone.

2.2 Ethical Approval and Trial Registration

The study was approved by the Research Ethics Committee (CEP - Comitê de Ética em Pesquisa da Faculdade de Medicina de Botucatu) on September 15th 2020, process number 4.383.996, and by the National Research Ethics Committee (CONEP) on November 6th 2020, process 37935120.6.0000.541. The study was retrospectively registered in the Brazilian Registry of Clinical Trials (ReBEC; registration number RBR-4pn5whh) in April 2022 and assigned the Universal Trial Number U111-1276-1615. The study meets the requirements of the Declaration of Helsinki and the recommendations of Resolution 466/12 of the National Health Council of Brazil.

2.3 Participant Recruitment and Eligibility

The researchers were granted access to a centralized database containing symptomatic, RT-PCR-positive COVID-19 cases identified at the Hospital Service for Epidemiological Surveillance of a regional reference hospital and the municipality's COVID-19 Service. Before recommending home follow-up treatment, the municipal COVID-19 Service team conducted a pre-assessment of the

disease, ruling out severe cases and indicating only mild to moderate cases for such home treatment. Those patients continued to be monitored by the municipal team since, at the time of the pandemic in Brazil, all COVID-19 patients who had their diagnosis confirmed had to receive medical discharge from the COVID-19 Service to be able to return to work or socialize [15, 30].

The classification into mild and moderate cases only includes those cases where, according to the analysis by the municipal health team, they were not considered severe enough to warrant hospitalization, ventilation, or oxygen therapy. Such cases could remain at home without the need for any intervention.

The researchers received the lists of potentially eligible patients daily via cell phone message and performed full eligibility screening according to preestablished criteria supported by the literature [31, 32]. The fact that all patients had initially been tested by the municipality health department with a standardized RT-PCR test also ensured the accuracy of the COVID-19 diagnosis. The start time for treatment was standardized to begin immediately after the positive test confirmation, which typically occurred around the third day after symptom onset, following the recommendation and standardization of the test itself. This ensured that all patients began their treatments at the same stage of the clinical course.

All patients considered for the study were ≥18 years of age and listed in the database with recommendations for home follow-up treatment. Beyond these essential eligibility criteria, patients were also included if they were still presenting physical symptoms related to COVID-19 infection at the time of the first homeopathic appointment (symptomatic patients). That is, patients had to have at least three of the following symptoms related to COVID-19: fever, chills, fatigue, myalgia, arthralgia, anorexia, sore throat, cough, sputum, dyspnoea, chest pain, headache, nasal congestion, conjunctival congestion, coryza, anosmia or hyposmia, dysgeusia, abdominal pain, diarrhea or rash. This data ensured that all patients were symptomatic at the beginning of the follow-up. A signed 'free and informed consent' form (ICF) authorizing their participation in the study was also required.

Additionally, potential patients were excluded if they displayed any of the following co-morbidities: severe heart disease (chronic or congenital), poorly controlled heart insufficiency, poorly controlled chronic obstructive pulmonary disease (COPD) and asthma, cystic fibrosis with recurrent infections, advanced stage of chronic kidney disease or patients on dialysis, immunosuppressed patients, solid organ and bone marrow transplant recipients.

Participants were withdrawn from the study if they no longer wanted to participate or were hospitalized, as they would no longer fit into the category of mild to moderate cases with a recommendation for home follow-up. Moreover, given the possibility of progression to severe COVID-19 symptoms, it was ethically required that the follow-up of that case could be interrupted in the event of any serious adverse event (SAE) regarding the COVID-19 condition or the need for participant hospitalization, consistent with the "Protocol of clinical management of coronavirus (COVID-19) in primary health care" of the Ministry of Health [15].

2.4 Randomization and Blinding

Once the sample size and inclusion/exclusion criteria were defined, and before patient recruitment, a sequence of codes was generated with the 'sample' function of R software version 4.0.2. The random sequence of codes 0 and 1 was generated with equal probability. Code 0 indicated allocation to the placebo control group, and code 1 indicated allocation to the

individualized homeopathic medicinal products (IHMP) intervention group. The homeopathic pharmacist, who was not affiliated with the research, was an administrator for blinding and received the list of previously generated codes (0 and 1) directly from a statistics member of the Universidade Estadual Paulista (UNESP). As the study was double-blind, the pharmacist was the only person aware of the group allocation; researchers and participants were unaware of this information. The code with the sequence was revealed (un-blinded) after the data collection was completed and before the start of the statistical analysis.

2.5 Data Collection at Study Entry

After receiving the list of potentially suitable patients from the municipal health team, the two researchers, specialist homeopathic physicians, called the phone numbers, following the lists received, to explain the project and invite patients to participate in the study. Upon receiving verbal consent to participate over the phone, the patients were assisted through questions in the clinical case report forms (CRFs) for the first appointment. Two medical students from the Universidade Estadual Paulista (UNESP) helped to fill out (manually) patient data on medical records, always under the supervision of the medical researchers.

The researchers developed the clinical CRF records since the study was exploratory, and no validated instruments were available in the literature at that time to assess COVID-19 symptom progression. These records were based on the diagnostic protocols and procedures for treating COVID-19 cases published by the Brazilian Ministry of Health and other supporting publications associated with the official documents [15, 16, 24, 27, 30].

The case report forms (CRF) contained identification (name, age, civil state, profession, weight, height, relevant familiar details), pre-existent medical history data (reflecting the specified exclusion criteria), and clinical symptoms. The forms also included fields for reporting conventional medications that the patients were already using, the homeopathic symptoms used for repertorisation [33], the most well-indicated homeopathic medicine, and the prescription.

The Brazilian Ministry of Health protocols contained 24 symptoms peculiar to COVID-19 [15, 30]. In our study, we used this list of symptoms in the CRF and asked patients to assign an intensity score from 0 to 3 for each, with 0 being no symptoms, 1 a mild symptom, 2 a moderate symptom, and 3 a severe symptom. The sum of all scores for the COVID-19 symptoms reported by the patients was calculated, giving a possible score from 0 to 72 points. A score of ≤2 points from at least two different symptoms was considered to be of little clinical significance, essentially the same as no symptoms. The COVID-19 score was calculated at each follow-up appointment until discharge.

At the time of the first telephone appointment, the validated Hospital Anxiety and Depression Scale (HADS scale) was also applied by the researchers to allow for a baseline assessment of the prevalence of mental health issues in our patient group. The HADS scale [34] contains 14 multiple-choice questions. It consists of two sub-scales, one for anxiety and one for depression, with seven items each and a score between 0 and 3 for each question. The overall score ranges from 0 to 21 on each sub-scale. The questions about anxiety are odd numbers from 1 to 13, and the questions about depression are even numbers from 2 to 14. In the sum of each sub-scale, scores from 0 to 7 show a reduced probability of the patient having depressive or anxious symptoms; for scores of 8 to 11 points, mental suffering is doubtful; and for scores from 12 to 21 points, the patient probably has anxiety or depression. The HADS tool was primarily developed to detect milder degrees of affective

disorders in non-psychiatric settings, making it relevant to our study; it is also short, quick to apply, and refers to how the patient has felt during the last week [35, 36].

2.6 Intervention - Individualized Homeopathic Medicine Selection

Before the start of the study, the team of researchers studied several possible homeopathic medications that could be used in cases of COVID-19. Still, it was agreed that each case's individuality would be considered rather than selecting a single medicine for all cases. Case management was standardized, in which each researcher would follow the same case from the beginning until discharge, and all homeopathically relevant symptoms for each case would be recorded manually, based on Kent's concepts of repertorial totality [37]. That is, physical, general, and local symptoms were selected according to their importance from a homeopathic perspective, leading to the characteristic totality - or the Maximum Value Minimum Symptom (MVMS) [38] - representative of that patient, facilitating the selection of the best-indicated IHMP. This concept (MVMS) in homeopathy refers to identifying the smallest number of symptoms most characteristic and unique to the patient's condition. These key symptoms, which are highly individualized, guide the selection of the most appropriate homeopathic remedy. All homeopathic medication choices were verified and confirmed by cross-checking with Homeopathic Materia Medica [39].

The data collected for mental symptoms were not included in the repertorisation, which was mainly based on the acute symptomatic presentation of COVID-19, as contained in the CRFs, and any additional information (e.g., generals and modalities) gathered during case taking. Therefore, although individual mental symptoms are a fundamental part of homeopathic anamnesis, they were not explicitly included in the collected data. This decision was made because we aimed to base our symptom collection on those listed in the literature and clinical management manuals for COVID-19, which did not include mental symptoms.

2.7 Intervention - Individualized Homeopathic Medicine Preparation

After the initial appointment, the add-on IHMP prescriptions were sent to the study pharmacist, who prepared the appropriate treatment according to the randomization code (as detailed above). The medications were prepared in a hydro-alcoholic solution, manipulated individually (not on an industrial scale) on the Hahnemannian centesimal scale (1:100), containing 0.2 ml of active ingredient at the required potency (the IHMP) for 19.8 ml of the inert vehicle (4 ml of grain alcohol and 15.8 ml of deionized water); the placebo contained 4 ml of grain alcohol and 16 ml of deionized water; thus ensuring that both IHMP and placebo were identical in taste, smell and appearance.

All medicines and placebo were packaged in standard 20 ml amber glass bottles, labeled with the patient's name, prescribed medication, its potency, and directions for use. The bottles were numbered in the order of patients' entry into the study for later identification between the case and control groups. The doses were to be administered orally by the patient, dispensing 3 drops on the tongue every 2 hours, according to recommendations described in the literature and consistent with Brazilian homeopathic posology [40-42].

Patients received their medication bottles at home, supplied by trained couriers, who delivered them along with duplicate copies of the ICF. After signing the ICF, patients retained one copy, along with their medicines and written instructions on how to use them. They also received previous instructions during the telephone conversation. As required by the study protocol and the CEP

approval, the ICF contained the CEP's and the researcher´s telephone contact details and was stored according to data confidentiality laws [43, 44].

2.8 Intervention - Follow-up

Patients received follow-up phone calls approximately every 48 hours, depending on each patient's needs, until discharged. The precise timing of each follow-up could vary, particularly if the patient phoned the researchers or needed additional homeopathic support. During each follow-up call, patients reported their clinical and COVID-19 specific symptoms, all changes (improvement or worsening) and the timing of the call were rigorously recorded by the researchers on the case forms. The follow-up case forms contained fields to document the patient's improvement status, new symptoms, possible use of other non-homeopathic medications, adverse symptoms, new repertorization, and prescriptions, as needed.

During the treatment period, the researching physician could modify the prescribed homeopathic medicine as many times as necessary, following the assumption that the homeopathic medicine must continue to cover the symptomatic totality of the individual´s clinical picture [45-47].

Patients were discharged from treatment either by the municipality health team or by the homeopathic physician in charge of their case when they no longer had typical symptoms of the acute COVID-19 condition (i.e., a total COVID-19 symptom score of ≤2). The research team then filled out the medical discharge form for this study, which contained all clinical data, individualized scores, and prescriptions.

All data were collected between February and July 2021.

2.9 Outcomes

The primary outcomes were changes in COVID-19 symptom scores during the treatment period and the time to discharge. When the study was conducted, no validated instrument was available to measure COVID-19 symptom severity quantitatively. The COVID-19 symptom scores documented in the CRF were used as an indicator of clinical improvement. Still, it was impossible to suggest *a priori* a minimal clinically significant difference (MCID). Time from recruitment (first baseline appointment) to medical discharge was used to assess 'time to recovery quantitatively'.

We also aimed to assess the mental health impact of COVID-19 at baseline and verify and describe which homeopathic medications were most commonly employed in cases of acute COVID-19.

2.10 Adverse Events

When prescribed by trained professionals, the literature shows that high dilutions of homeopathic medicines are likely to be safe, with a shallow risk of causing SAEs [48-50].

However, according to the protocol recommendations for clinical trials and as an essential part of the approval of this study by the research ethics committees, both locally (CEP) and nationally (CONEP), it was established that in the event of significant worsening of a patient's clinical condition and if it is confirmed as a Serious Adverse Event (SAE) [51, 52], it would be reported to specialist doctors from the municipal healthcare system of Municipality (Covid Service).

2.11 Sample Size

Given that no validated instruments were available in the literature to evaluate COVID-19 symptoms quantitatively and that the MCID was unknown for our novel scoring system, it was impossible to perform a robust sample size calculation on our primary outcome of interest. Instead, we used the validated HADS score to calculate the required sample size.

As described in the validation of the HADS scale [34], assuming simple random sampling type I and II errors equal to 0.05 and 0.20, respectively, an allocation ratio of 1:1, the absence of confounders, a mean HADS-A score of 6.6 ± 3.7 and the mean score of HADS-D of 5.3 ± 3.3 it would require at least 54 patients per group to detect a 2-point difference between the control and homeopathy groups.

2.12 Changes to Protocol

There were no significant deviations from the study protocol regarding eligibility criteria, outcomes, or analyses. Therefore, a per-protocol (PP) analysis was chosen, as participants adhered strictly to the unaltered protocol throughout the study, minimizing the risk of overestimating effects.

However, introducing a project to vaccinate the whole population (mass vaccination) in the city where this study was being carried out in June 2021 stopped the trial prematurely when we reached the eighty-second patient. So, the recruitment was interrupted at the 82th unvaccinated individual to prevent any alteration of our intended sample population.

2.13 Statistical Analysis

A descriptive analysis was carried out, calculating mean and standard deviation for quantitative variables and frequencies and percentages for categorical variables per treatment group at baseline.

Initial comparisons of means between groups were made using the student t-test, where the variable distribution was normal or symmetric. A generalized linear model with gamma distribution was fitted in the case of asymmetry. For discrete variables, comparisons were made by fitting a model in Poisson distribution.

An adjustment in a generalized linear model with a gamma distribution followed by Walds´ multiple comparison test for the continuous variable was applied. The Poisson distribution was used in the case of discrete variables for the same design and the same multiple comparison test. Normality or symmetry was tested using the Shapiro-Wilk test.

Associations between categorized variables and groups were made by using the chi-square trend test at each moment. All analyses were performed in SAS (Statistical Analysis System) for Windows v.9.4, and significance was set at 5%.

Regarding the mental symptoms observed on the first appointment, the proportions between groups, setting the categories A (Anxiety) and D (Depression) for HADS, were compared using a chi-square proportions test.

3. Results

3.1 Participant Flow

Eighty-two patients with mild to moderate symptoms of acute COVID-19, manageable from home, were enrolled in the study. Three patients refused to receive the medication and sign the ICF, so they were excluded from the study as they did not meet the eligibility criteria. Thus, 79 eligible patients were randomized: 42 in the intervention group (IHMP) and 37 in the control group (placebo). During the study period, 11 patients were withdrawn: 8 lost to follow-up (5 IHMP; 3 placeboes), and 3 were hospitalized (1 IHMP; 2 placeboes), leaving 68 patients for analysis (36 IHMP; 32 placeboes) as shown in the flowchart (Figure 1).

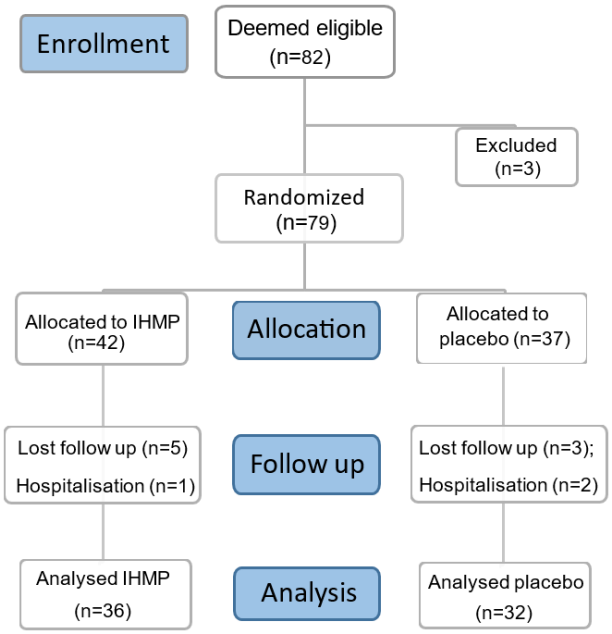

Figure 1 Flowchart for Patient Enrollment, Allocation, Follow-up, and Analysis. Developed by author, 2021.

3.2 Baseline Data

No statistically significant differences between the two treatment groups were observed at baseline regarding bio-demographic characteristics (sex, age, weight, height) (Table 1). These characteristics were selected to control the variables that could negatively impact the evolution of COVID-19, such as advanced age and obesity/overweight, as pointed out in the literature [53, 54]. Thus, we used as a starting point the analysis of a population with the same characteristics of sex, age, and body mass index (BMI), which would point to the same risks of the COVID-19 prognosis [55-57].

Table 1 Distribution of sex, age, weight, and height between IHMP and placebo groups at baseline.

	Placebo (n = 32)		**IHMP (n = 36)**		**p-value**
	Mean	Std Dev	Mean	Std Dev	

Age (years)	37.09	9.29	40.22	11.25	0.21
Weight (kg)	82.86	21.26	79.47	18.35	0.48
Height (cm)	166.91	9.95	166.92	11.24	0.99
Sex	**N**	**%**	**N**	**%**	**p-value**
Female	21	65.6	22	61.1	0.70
Male	11	34.4	14	38.9	

At the time of the first consultation, 31 patients (45.58%) were using some allopathic medication, with some of them using more than one type (combination) at the same time. In contrast, no significant differences were observed between the two groups (Table 2).

Table 2 Distribution of allopathic medications being used in the first consultation.

	IHMP		**Placebo**		**Total**
	N	%	N	%	p-value
Paracetamol	9	45	11	55	0.7081
Dypirone	6	54.55	5	45.45	0.9892
NSAID	6	60	4	40	0.8743
Antiallergics	4	50	4	50	0.9881
Antibiotics	4	57.1	3	42.9	0.9669
Antiemetics	2	66.6	1	33.4	0.9669

Regarding the collection of mental health data at baseline by applying the HADS scale, we were able to observe (Table 3):

Table 3 Categorical distribution of anxiety and depression at first appointment, HADS scale, 2021.

	HADS-A					HADS-D				
	placebo		IHMP			Placebo		IHMP		
	N	%	N	%	p-value	N	%	N	%	p-value
No cases	19 (0-7)	59.4	13	36.1	0.03	18	56.3	16	44.4	0.46
Doubtful cases	5 (8-11)	15.6	12	33.3	0.16	6	18.8	8	22.2	0.95
Severe cases	8 (12-21)	25	11	30.6	0.81	8	25.0	12	33.3	0.62

When analyzing the data collected through the HADS scale in the first consultation, we were able to observe a significant difference (p = 0.03) between the IHMP and placebo groups in the reduced probability category (0-7) on the anxiety subscale (HADS-A). This statistical difference validates that the sample size collected during the research was sufficient. Therefore, based on this data, we can infer that the analyzed sample size proved adequate for our objective. The other comparisons between categories on the HADS-A did not show significant differences, with a p-value of 0.16 among unlikely cases and 0.81 among cases with anxiety.

Between the IHMP and placebo groups, regarding depressive symptoms, no significant association was equally evident between the groups, with p-values of 0.46 in the group without depression, 0.95 among the unlikely, and 0.62 among cases with depression.

3.3 COVID-19 Symptom Scores

No significant difference was seen in the total score of COVID-19 symptoms between the two groups at baseline: the IHMP group had a mean score of 16.5 (+/- 6.6) and the placebo group had a mean score of 17.31 (+/- 6.04) ($p > 0.05$).

Duration of treatment and the mean time to recover varied considerably across all patients (range 24 h -504 h). However, the mean time from the first appointment to medical discharge in the IHMP group was significantly lower than the placebo group (IHMP mean 74.5 hours; +/- SD 57.47, 95% CI: 55.73-93.27) versus placebo mean (137.42 hours; +/- SD 87.85, 95% CI: 106.98-167.86) ($p < 0.05$).

Upon confirming the presence of these two instances of medical discharge, we proceeded to verify the case report form (CRF) scoring about patients at these specific temporal nodes. Utilizing this dataset, we juxtaposed the scores from the two distinct time points, subsequently checking the differences between the two groups (IHMP and placebo).

It was verified that around the 74.5 (th) hour of treatment, there was a change in the total score for the two groups, with a total score of 11.72 (+/- 5.5) for the control group and 7.31 (+/- 5.19) for the intervention group, showing a difference between them (p-value < 0.05). In a third moment, around the 137.42 (nd) hour after the start of treatment, this score varied between 5.09 (+/- 4.78) in the control group and 2.83 (+/- 2.79) in the treated group (p-value < 0.05). Therefore, it is evident that at baseline (first appointment), there was no difference between the groups considering the symptom score. Still, at time points 1 and 2 (74.5 h/137.42 h), the groups differed, showing a p-value < 0.05 (Table 4).

Table 4 Analysis of mean total COVID-19 scores between groups at different treatment moments, 2021.

	Placebo			**IHMP**			
	N	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**	***p-value**
Baseline	**32**	17.31^{aA}	6.04	**36**	16.5^{aA}	6.6	0.718
74.5 h	**32**	11.72^{aB}	5.5	**36**	7.31^{bB}	5.19	0.001
137.42 h	**32**	5.09^{aC}	4.78	**36**	2.83^{bC}	2.79	0.001

*p-values referring to the treatment versus moment interaction test; Poisson adjustment followed by the multiple Wald comparison test for a repeated measures model for treatments and moment; means followed by the same lowercase letter (fixing moments and testing treatment) do not differ at the 5% level. Means followed by the same uppercase letter (fixing treatments and testing moments) do not differ at the 5% level.

These data show a shorter time to medical discharge in the IHMP-treated group compared to the placebo group. The data also highlight that patients treated with IHMP exhibited clinical improvement, with symptom intensity decreasing in a shorter time than the placebo group.

3.4 Homeopathic Medicines

The most frequently prescribed homeopathic medicine was *Arsenicum album* (47%; 32/68 patients: 19 IHMP group and 13 placebo group); after which, 31% received *Bryonia alba* (21 patients:

9 IHMP group and 12 placebo group); 12% received *Antimonium tartaricum* (8 patients: 6 IHMP group and 2 placebo group); 6% received *Phosphorus* (4 patients: 1 IHMP group and 3 placebo group); 1% received *Camphora* (1 patient, IHMP group); 1% received *China officinalis* (1 patient, placebo group) and 1% received *Nux vomica* (1 patient, placebo group). Considering the distribution of prescribed homeopathic medicines between the IHMP and placebo groups, the order of the primary prescribed medicine did not change, with the *Arsenicum album* remaining the most prescribed in both groups. We also observed no change in the prescription of homeopathic medication during the treatment in any of the cases monitored.

3.5 Harms

Three patients were hospitalized during the study due to worsening COVID-19 symptoms. These patients sought medical assistance independently for increased respiratory discomfort and decreased oxygen saturation levels: they were placed on oxygen therapy, and all were discharged from the hospital. None presented serious sequelae or died. The worsening of symptoms was typical of the natural progression of COVID-19 and occurred between the first and second study consultations (within 48 h). The deterioration of the clinical condition of these cases was confirmed by the municipal medical teams of the hospitals consulted to be attributed to the natural progression of COVID-19 and not to the treatment proposed by the research.

No serious complications or death occurred during the study, and no severe adverse effects (SAE) were reported.

4. Discussion

The findings of this study suggest that the effect of homeopathic treatment differed from the placebo group in terms of the outcome time (medical discharge) and the score points at different observation points. Such data indicate that patients treated with IHMP experienced a reduction in symptom intensity in a shorter period than the placebo group, which could result in a quicker return to their routine.

During the data analysis, it was observed that the duration of treatment, from the first appointment to the medical discharge appointment, varied greatly among patients (24h - 504h). However, during analyses, two-time points emerged: patients in each group (IHMP and placebo) were, on average, discharged from treatment (74.5 hours and 137.42 hours, respectively). This made it possible to quantify each group's perceived gradation in the overall clinical record score. The observation revealed a statistically significant difference in the total score between the two groups within 74.5 hours and after 137.42 hours, with the intervention group consistently showing better outcomes than the control group (p-value < 0.05).

The difference between the groups indicates that patients treated with homeopathic medicine (IHMP) experienced a milder progression of symptoms, with more pronounced symptom resolution. This highlights a statistically significant disparity in the effects of COVID-19 symptoms between add-on IHMP-treated patients and those receiving placebo (p-value < 0.05). Consequently, the time away from regular activities for COVID-19-infected individuals could be reduced in the IHMP-treated group (74.5 hours) compared to the placebo-treated group (137.4 hours).

Data analysis revealed a faster decline in symptoms in the homeopathy group and demonstrated that IHMP-treated symptomatic patients experienced a quicker resolution of COVID-19, allowing for a speedier return to routine activities, as evidenced by other publications in the field [28, 29].

Furthermore, the IHMP group exhibited lower symptom intensity at different time points, potentially contributing to a return to routine activities with a sense of well-being 62.9 hours faster than the control group. This represents returning to normal life more than 2 days faster than the control group.

The initial chosen sample showed homogeneous characteristics between the two groups. Bio-demographic characteristics such as sex and age and anatomical-physiological characteristics such as weight and height, which could bias the case severity and evolution characteristics [53-57], were homogeneous in both groups (Table 1).

We were also able to observe during the first consultation that patients who were already using some allopathic medication were evenly distributed, with no difference between the IHMP and the placebo groups, which again brings us a uniformity of the sample (Table 2).

Health professionals in the municipality were responsible for deciding on home follow-up, eliminating bias from researchers' initial involvement. All patients underwent initial testing by the municipality health department with a standardized RT-PCR test, ensuring correct diagnosis. Treatment initiation was standardized to begin around three days after symptom onset following positive test confirmation [58, 59]. The initial symptom scores in clinical records showed homogeneity, indicating mild to moderate COVID-19 infection in both groups [60-62].

Initially, the study aimed to assess the impact on patients' mental health using the Hospital Anxiety and Depression Scale (HADS) during the first appointment. The sample size, which was intended to be larger than what was collected, was statistically calculated based on this scale due to the lack of validated questionnaires or scales at the time of the epidemic in Brazil. Despite the study's early termination due to a mass vaccination campaign altering the sample's homogeneity, the data revealed a statistically significant difference ($p = 0.03$) between IHMP and placebo groups in the absence of anxiety symptoms category, demonstrating the study's objective was achieved with the available sample size.

We observed that concerning the mental distress of patients in the first consultation, 30.6% of patients exhibited anxiety (score 12-21), and 33.3% showed depression (score 12-21), according to the HADS scale.

The homeopathic model emphasizes the importance of individualized medicine based on the symptomatic totality of the clinical condition, which is crucial for effective treatment [37, 45, 63]. Some studies compare a predetermined homeopathic medicine based on the symptomatic totality of a specific epidemic, known as a genus epidemic [19, 47], and use it for all acute cases of that pathology [64, 65]. However, in mild to moderate COVID-19 cases, a wide range of symptoms can appear, and each patient may manifest specific individual symptoms [47, 66]. Therefore, it is crucial to ascertain the symptoms and administer a homeopathic medicine tailored specifically (IHMP) to each patient's condition, as pointed out by the theoretical principles of homeopathy. This approach is supported by previous studies in the field [67, 68].

Therefore, it is essential to individualize the selection of homeopathic medicine for each patient's specific condition, covering the symptomatic totality and adhering to the theoretical foundations of homeopathy. This will allow for a model that aligns with the theoretical assumptions of homeopathy and current research models [69-71].

In this study, the homeopathic medicines that were more frequently used in treating the acute condition of the patients were *Arsenicum album, Bryonia alba, Antimonium tartaricum*, and *Phosphorus*, in that order. Some studies in the field indicated *Arsenicum album* as a possible treatment and prevention for COVID-19 cases [72, 73]. The frequencies and distribution of these medicines were similar in both the intervention and control groups. However, the selection of these drugs differed from those reported in some publications worldwide [23, 26, 74-76], forming a characteristic symptomatic group specific to the moment and place studied [77]. This suggests that, as Samuel Hahnemann [47] described, the genus epidemics and the homeopathic medicine that best covers the symptoms (IHMP) in an epidemic may vary depending on population characteristics, geographic and climatic conditions, as well as the individual expression of acute epidemic diseases and the characteristics of Sars-Cov-2 virus variants [22, 65, 77].

This study thus suggests that the model where individualized homeopathic medicinal products (IHMP) are compared to a placebo proves more suitable in clinical trials than when a single medication is compared [23]. Therefore, we understand that the IHMP versus placebo model can yield more noticeable results in clinical trials, contributing to the possibility of conducting more effective research in homeopathy [78].

It is worth noting that although three hospitalizations were observed, none of them can be directly attributed to the treatment proposed by the research. Instead, they were likely a result of the natural clinical course of the disease. It is also important to mention that none of these cases progressed severely, as they only required oxygen therapy and clinical support measures.

This study faced several limitations, including a small sample size, limited involvement of homeopathic researchers, possible overestimation of the results, spontaneous recovery, the effect of confounding factors, and a lack of funding. Furthermore, the mass vaccination campaign that was concurrently being carried out in the municipality reduced the researchers' availability for data collection. Another challenge was the absence of validated instruments in the homeopathic research area for COVID-19, leading the researchers to develop clinical records specifically for this study.

We also want to point out that the lack of blinding of the involved pharmacist could introduce biases in the collected data, serving as a limiting factor. The data collection process was also challenging, as maintaining regular telephone follow-ups with the patients proved difficult.

The choice of the HADS scale as a tool for assessing mental distress (anxiety and depression) in patients did not yield the expected results because the test could only be administered during the first consultation, as the recommended time for reapplying the scale is after a 7-day interval, which proved unfeasible given the shorter medical discharge time [79].

Despite these limitations, the study provides valuable insights into the potential benefits of individualized homeopathic treatment for patients with mild to moderate COVID-19. The results suggest that this treatment may lead to a quicker resolution of symptoms, with no observed adverse effects linked to the use of homeopathic medicines. The findings indicate that individualized homeopathic medicine could serve as a valuable complementary option for symptom management at home alongside conventional medication.

However, further studies with more participants are needed to understand better the effects of homeopathic treatment in acute or epidemic conditions.

5. Conclusion

The study suggests that individualized homeopathic medicinal products (IHMP) had a significantly different effect than placebo in treating COVID-19 cases at home, with faster symptom resolution. These findings highlight the potential of IHMP as a possible therapeutic approach for home-based COVID-19 treatment and demonstrate its significance in expanding available treatment options.

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Author Contributions

Renata Lemonica was responsible for the conceptualization, methodology, validation, formal analysis, investigation, data curation, writing of the original draft, review and editing, and project administration. Isabela Almeida Cunha and Jéssica Layane Costa Melo contributed to data curation. Sandra Regina Caram provided resources, handled project administration, and assisted with data curation. José Eduardo Fuser Bittar was involved in investigation and data curation. Karina Pavão Patrício planned and supervised all the work, and contributed to writing, review and editing of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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