Original Article

Role of Dantabija, Haridra, and Zingiber (DHZ) combination to restore health and immunity in mild to moderate COVID-19 patients

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Abstract

Background: COVID-19 (SARS-CoV-2) has caused various clinical manifestations ranging from asymptomatic, minor flu-like symptoms to acute respiratory distress syndrome (ARDS), pneumonia, and even death. Early restriction of viruses is of utmost importance in controlling the spread of COVID-19. The present study aimed to evaluate the role of a common herbal extract combination of pomegranate (dantabija), turmeric (haridra), and zinger (DHZ) in mild to moderate covid cases. **Methods:** A hundred covid-positive subjects of mild to moderate severity have been randomized to control and study groups. The study population has been given the fixed-dose combination of DHZ as an adjuvant to standard treatment. Data have been analyzed using standard statistical tools. **Finding:** DHZ as an adjuvant helped in turning 83.33% of patients negative in the home quarantine group whereas 40% of patients in the hospitalized group turned negative with the addition of DHZ in the standard management. The percent negativity was lower in patients who received only standard management. Out of all patients, who did not receive DHZ, only 38% of patients in home quarantine and 32% in hospitalized patients became negative for COVID-19. Patients who received DHZ also showed improvement in blood pressure levels, oxygen levels as well as improvement in all symptoms associated with COVID-19 infections. **Interpretation:** DHZ has shown a promising effect in mild to moderate cases of COVID-19 as an adjuvant to the standard therapy. The study results indicated that the combination probably produces its effect by its immunomodulatory action.

Keywords: COVID-19, Dantabija-Haridra-Zingiber (DHZ), immunity

Introduction

COVID-19 pandemic has been one of the greatest health challenges of the modern era of medical sciences. Even the most advanced Medicare systems across the globe have collapsed to the unprecedented loads of covid patients. Despite well-orchestrated research efforts from the established health authorities, no conclusive management strategies have proved effective in combating covid cases effectively. The scenario has been more challenging for countries like India with compromised health care infrastructure and already overburdened health care infrastructure.

Herbal sources have long been advocated as potential health care resources in various traditional medicine systems including Indian Aayush systems.[1-4] Being commonly used natural products, they are potentially lesser toxic and more acceptable than synthetic drugs[5-7] despite some recent concern over the questionable safety profile of some of the understudied compounds.[8,9] Some studies propose that plant extracts and their mixtures can prevent

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COVID-19. However, limited research has been done so far to identify specific combinations of more than two plant-based extracts which can effectively work toward the goal of controlling this pandemic. Managing COVID-19 at an advanced stage is difficult. Therefore, limiting the disease in the early stages by cutting off the route of transmission could be the best option for controlling the spread.[10]

It has now been discovered that a combination of extracts of Curcuma longa (turmeric or Haridra), Punica granatum (pomegranate), and Zingiber officinalis (ginger), combination (DHZ), displays a strong synergistic activity on disorders of the mouth, throat, and upper respiratory tract. The composition of DHZ has a strong antimicrobial effect, and is particularly useful against infections causing the common cold, cough, and flu.[11] DHZ has also shown promising results in restricting COVID-19 in a small number of asymptomatic COVID-19 positive cases in 3 days by taking 3-4 pastille per day.[12] The mechanism of action of this combination is believed to be due to anti-viral, virucidal, and antibacterial activity, usefully complemented by the anti-inflammatory, antioxidant, and analgesic activities of these ingredients. This combination has also been shown to increase the lysozyme content in saliva by four times thereby enhancing immunity. DHZ has been widely used for the treatment of common cold, cough, flu, and in Bechet's disease for many years. The combination of virucidal and low-dose antivirals, to block the viral spread in saliva, may be a promising solution to control the COVID-19 pandemic. To further evaluate the efficacy of DHZ as virucidal and anti-viral is required in subjects with asymptomatic, mild to moderate cases of COVID-19, we conducted a randomized single-blind clinical trial in AIIMS Patna.

Aims

To evaluate the safety and efficacy of a combination containing Dantabija (Punica granatum or pomegranate) 20 mg, Haridra (Curcuma longa or turmeric) 50 mg, and Zingiber officinalis (ginger) 5 mg (DHZ), in controlling COVID-19 disease.

Objectives

- Evaluation of reduction of signs/symptoms of COVID-19 disease with the use of DHZ pastille.
- Evaluation of reduction in duration of COVID-19 disease with the use of DHZ combination pastille.
- Evaluation of DHZ pastille in enhancing the immunity of COVID-19-infected patients.
- Evaluation of DHZ pastille in treating asymptomatic and mild cases of COVID-19-infected patients.

Material and Methods

This study was conducted at AIIMS Patna after approval by the Institutional Ethical Committee (ECR/1387/Inst/BR/2020).

Methodology

A total of 100 patients with COVID-19 disease, who met the inclusion criteria and gave informed consent, were included in this study. Patients who fell under one or more exclusion criteria were excluded from the study.

Inclusion criteria

- COVID-19 RT-PCR test/COVID-19 antigen test/ COVID-19 TRUNAT test positive
- All males and females between 15 and 70 years
- Showing symptoms of dry cough/fever/malaise/rhinorrhea/ recent-onset loss of taste and smell/gastrointestinal upset
- Patients who can take medicines orally
- Oxygen requirement of less than 5 L/min.

Exclusion criteria

- Oxygen requirement of more than 5 L/min
- Patients who are on ventilator support
- Patients who are on dialysis
- Patient with a known history of chronic liver disease
- Patients taking any other ayurvedic supplement.

Randomization

This trial was registered on the clinical trial registry- India with registration number CTRI/2020/11/029038. These 100 patients were divided into two main categories. Each category was further divided into two groups based on the treatment given for COVID-19 [Table 1]. An alphanumeric coded set of Intervention arm (DHZ)/Control arm containers was used. Participants were automatically randomized in each category to two groups in the ratio of 1:1.

Category one

In this, 50 COVID-19-positive patients who were admitted in various COVID wards of AIIMS Patna were included. Patients were COVID -19 RT-PCR positive with no signs of severe disease, that is, RR 15–30/min and spO2 92 to 97%. These patients were further subdivided into groups as:

Group A: - Admitted standard treatment only

Group B: - Admitted standard treatment along with intervention (DHZ)

Table 1: Demographic profile of subjects recruited in the study

	Age	Height	Weight
Group A (Admitted Standard treatment only) *n*=25	49.5±14.41	165±8.26	64.32±6.05
Group B (Admitted Standard treatment along with intervention) *n*=25	55.5±15.46	164.6±9.91	63.76±6.97
Group C Home quarantined on Standard treatment. *n*=18	37.17±10.12	165.5±12.36	65.56±9.15
Group D Home quarantined and on Standard Treatment along with intervention. *n*=18	32.56±7.59	173.56±14.98	71.12±9.11

Category two

In this, 50 COVID-19-positive patients who visited the flu clinic of AIIMS Patna and who were advised home quarantine were enrolled. These patients were of mild category, that is, having fever, cough with RR <15/min, and spO2 92 to 98%. These patients were further subdivided into groups as:

Group C: - Home quarantined on standard treatment.
Group D: - Home quarantined on standard treatment along with intervention (DHZ).

On the day of enrollment, all patients who were admitted to the hospital were assigned to either group A (standard treatment) or group B (standard treatment along with intervention, DHZ) by randomization. Similarly, all patients who were advised home quarantine were also assigned to group C (standard treatment) or group D (standard treatment along with intervention, DHZ) by randomization.

Day 1 of study: -

1. Demographic details of all subjects in all groups were recorded.
2. Detailed clinical history was taken and baseline pulse rate, blood pressure, and oxygen saturation with a pulse oximeter were recorded.
3. Taking all the aseptic precautions blood samples were taken from a peripheral vein and total leukocyte count, differential leukocyte count, platelet count, and CRP and Ferritin levels were determined.

Day 2 to the 10th day of study: - Interventions as listed below were done.

Group A received only standard treatment as prescribed at AIIMS Patna.

1. Antipyretic (paracetamol) for fever and pain if a complaint of fever.
2. Adequate nutrition and appropriate rehydration.
3. Supplements like zinc and vitamin C
4. Tab azithromycin 500 mg OD, if there were symptoms of upper respiratory tract infection.

Group B received the above-mentioned standard treatment plus pastilles containing extract of Dantabija (Punica granatum or pomegranate) 20 mg + Haridra (Curcuma longa or turmeric) 50 mg + Zingiber officinalis (ginger) 5 mg (DHZ) in a dose of three pastilles/day for 10 days.

Group C received a tablet of paracetamol 500 mg if the patient presented with fever and supplements like zinc and vitamin C.

Group D received tablet paracetamol 500 mg if the patient presented with fever and supplements like zinc and vitamin C along with a pastille of DHZ in a dose of three pastilles per day for 10 days.

All the patients enrolled in both the groups were observed for:

a. Patients were followed up daily for temperature, vitals, and oxygen saturation (SpO2).
b. Daily monitoring for increased work of breathing (use of accessory muscles), hemodynamic instability, and increase in oxygen requirement.
c. COVID-19 RT-PCR test from nasopharyngeal swab sample. All the above-mentioned blood tests were repeated on the 5th day and day 10th day of the intervention.
d. If any patient developed severe symptoms for which they require intubation or more than 5 L of oxygen then those were dropped out from the study.

Blood Parameters

Taking all the aseptic precautions blood samples were taken from a peripheral vein and total leukocyte count, differential leukocyte count, platelet count, and CRP and Ferritin levels were determined before and on day 5 and 10th day after intervention.

Adverse experiences

Possible adverse events due to the supplementation were monitored in a daily diary from day 1 of intervention to 7 days after the end of the period of administration of the supplement. All clinical adverse experiences if reported were classified in terms of intensity: mild, moderate, or severe, also considering duration, seriousness, outcome, and relationship to the study product.

Results

A total of 100 patients, who tested positive for COVID-19, were enrolled in the study. Out of these 100 positive patients, only 86 could complete the study, and 14 home quarantine patients dropped out in between the study when called on the 5th day for repeat sampling. Out of 14 subjects, 9 told that now they felt better and refused to continue in the study and 5 subjects were relocated and were not able to continue the study. Demographic details of the patients are given in Table 1 and basic clinical parameters are given in Table 2. Out of 86 patients, 67 (77%) patients presented with no symptoms or mild symptoms like mild fever, lightheadedness, lethargy, etc., whereas, other 20 (23%) presented with moderate signs and symptoms like high-grade fever, perspiration, malaise, headache, body ache, palpitations, difficulty in breathing, low spO2, etc.

Out of 86 patients, 50 were admitted to the hospital and 36 patients were home quarantined. All these patients were evaluated for hematologic parameters before and after the study. All symptoms reported by patients at the time of admission were recorded and observed for the entire duration of treatment in both categories. These patients were closely monitored for their blood pressure and level of oxygen saturation throughout the trial.

Out of 50 patients who were admitted to the hospital, 25 received only standard treatment, and the other 25 patients

Table 2: Baseline clinical parameters of all the subjects

	Admitted Standard treatment only. (Group A) *n*=25	Admitted Patients Standard treatment along with intervention. (Group B) *n*=25	Home quarantined on Standard treatment. (Group C) *n*=18	Home quarantined and on Standard Treatment along with intervention. (Group D) *n*=18
Temperature	99.80±0.89	99.32±1.43	99.31±0.99	98.84±0.60
Pulse Rate	96.92±13.17	94.48±14.02	96.33±8.46	93.33±7.19
SPO_2	93.8±1.47	94.88±1.64	93.72±1.13	96.22±1.00
Systolic Blood Pressure	144.88±11.67	128.08±11.58	132.5±11.83	123.78±9.67
Diastolic Blood Pressure	89.2±6.08	74.0±8.73	86.67±3.94	85.22±5.36
Cough episodes/ day	11.24±4.56	10.08±5.25	4.22±2.02	4.28±2.30

received standard treatment along with intervention, DHZ, a slow dissolving pastille. Similarly, in the home quarantine group, out of 36 patients, 18 patients received only standard treatment whereas the other 18 patients received standard treatment along with the intervention, DHZ pastilles.

It was observed that in the home quarantine category, out of 18 patients who were on standard treatment plus intervention (DHZ), 15 patients (83.33%) became COVID-19 RT-PCR negative by the 10th day. Whereas, on the other hand, out of 18 patients, who do not receive the intervention (DHZ), only 7 patients (38.88%) turned out to be COVID-19 RT-PCR negative by the 10th day. Similarly, out of 25 hospitalized patients, who received additional treatment of DHZ, 10 patients (40%) turned COVID-19 RT-PCR negative by the 10th day, whereas, on the other hand, among 25 hospitalized patients who received only standard treatment, only 8 patients (32%) turned COVID-19 RT-PCR negative by 10th day.

All these patients were also observed for the number of cough and cold episodes per day as one of the important signs of improvement from COVID -19 infection. It was observed that those patients who received intervention along with standard management have a significant reduction in the number of cold and cough episodes [Figure 1] as compared to the control group who did not have DHZ.

The home quarantine group responded well to the intervention (DHZ) and showed a significant reduction in clinical symptoms associated with COVID-19. Out of 18 patients who were home quarantined and took intervention along with standard treatment, by the 10th day, 12 (66.6%) patients had no cough, 11 out of 18 (61.1%) had no sore throat, and 17 out of 18 (94.4%) had no myalgia as compared to control group, where only 33% were relieved from cough and sore throat and 83.3% patient had no myalgia. Similar results were observed in a hospitalized group, where patients who received the intervention (DHZ) with standard management had more improvement from symptoms and signs of the infection as compared to the control group [Tables 3 and 4].

All those who took DHZ in both hospitalized and home quarantine groups showed improvement in WBC count as compared to the control group. It was interesting to note that the intervention group showed a reduction in WBC count by

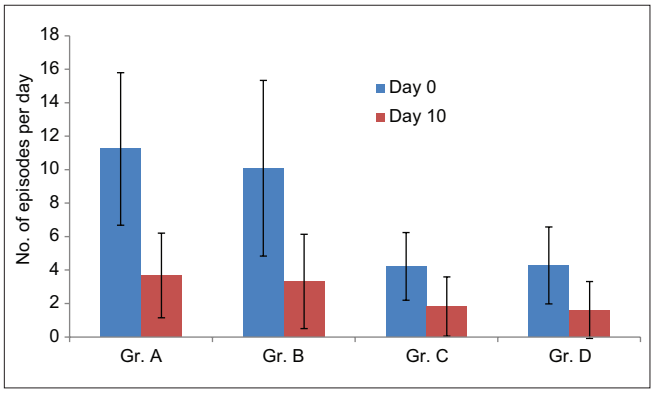

Figure 1: Number of cough episodes at day 0 (baseline) and day 10 of treatment in all patients recruited under the study

2% in admitted group and 7% reduction in the home quarantine group [Figure 2]. The reduction in WBC count signifies the reduction in inflammation thereby showing improvement in infection. On contrary, in the control group, even after the 10th day of treatment, there was 11% increase in WBC in admitted patients and a 6% increase in home quarantine patients. This increase is reflecting that the immune system is still struggling to control the inflammation and the symptoms. Moreover, CRP levels in the intervention group either admitted or in home quarantine were reduced as compared to control groups but to conclude that the reduction in CRP levels has been influenced by the presence of DHZ, a greater number of studies in large patient populations need to be elucidated [Table 5].

Discussion

We all are aware that most cases of COVID-19 develop mild (80%) symptoms, whereas 20% of cases may develop severe disease.[13] Asymptomatic infections are left unnoticed and have the same rate of infectivity as symptomatic infections. It makes them highly contagious. Treating asymptomatic infections is required for early prevention and helps in controlling the spread of COVID-19 worldwide.[14]

The mechanism of action of DHZ can be explained in the following way. The presence of viruses in the salivary glands may be responsible for the wider spread of the virus to a large number of individuals through respiratory droplets. The role of oral mucosa in COVID-19 infection and salivary glands in the epidemic process of asymptomatic infections is

Table 3: Comparisons of patient features in home quarantine patients at the start of study

Patient features	Total (*n*=36)	Home quarantined on Standard treatment. (Group C) *n*=18	Home quarantined and on Standard Treatment along with intervention. (Group D) *n*=18	*P*
Gender				
Female	13 (36.1%)	5 (27.8%)	8 (44.4%)	
Male	23 (63.9%)	13 (72.2%)	10 (56.6%)	
Age (years)†				
General	34.81±9.12	37.16±10.12	32.56±7.59	0.132§
	34.5 (22-57)	40 (22-57)	30 (24-48)	
Female	45.86±5.90	46.6±6.47	44±5.66	0.65§
	44 (40-57)	44 (40-57)	44 (40-48)	
Male	32.21±7.68	32.6±7.59	31.13±6.59	0.426§
	30 (22-45)	30 (22-45)	30 (30-42)	
Symptoms				
Fever	8 (22.22%)	5 (27.77%)	3 (16.66%)	
Cough	36 (100%)	18 (100%)	18 (100%)	
Sore throat	21 (58.33%)	12 (66.67)	9 (50%)	
Myalgia	36 (100%)	18 (100%)	18 (100%)	
Rhinorrhea	4 (11%)	3 (16.67)	1 (5.56%)	

†Mean±standard deviation/median (interquartile range: Q1-Q3). §Independent samples *t*-test.

Table 4: Comparisons of patient features in hospital-admitted patients

Patient features	Total (*n*=50)	Admitted Standard treatment only. (Group A) *n*=25	Admitted Patients Standard treatment along with intervention. (Group B) *n*=25	*P*
Gender				
Female	20 (40%)	10 (50%)	10 (50%)	
Male	30 (60%)	15 (50%)	15 (50%)	
Age (years)†				
General	52.36±15.06	49.6±14.41	55.2±15.46	0.191§
	52.5 (21-81)	52 (21-78)	54 (31-81)	
Female	52.15±12.07	50.4±10.51	53.9±13.80	0.531§
	50 (35-72)	50 (35-63)	54 (35-72)	
Male	52.5±16.96	49±16.86	56±16.89	0.265§
	52.5 (21-81)	52 (21-78)	54 (31-81)	
Symptoms				
Fever	29 (58%)	20 (80%)	9 (36%)	
Cough	50 (100%)	25 (100%)	25 (100%)	
Sore throat	19 (52.77%)	7 (38.8%)	12 (66.6%)	
Myalgia	30 (60 %)	14 (56 %)	16 (64%)	
Rhinorrhea	6 (12%)	3 (12%)	3 (12%)	

†Mean±standard deviation/median (interquartile range: Q1-Q3). §Independent sample t-test.

documented.[12] ACE2, an important receptor for COVID-19, is very common in salivary gland epithelial cells; these cells have a high expression (higher than in lungs) of ACE2 and can be easily infected. This suggests that salivary glands are a potential target for COVID-19 and act as an incubator. DHZ is to be chewed which increases its concentration in oral mucosa and may prevent infection by neutralizing the virus in the saliva itself. SARS-CoV RNA is detected in saliva (the first incubator) before lung lesions.[15]

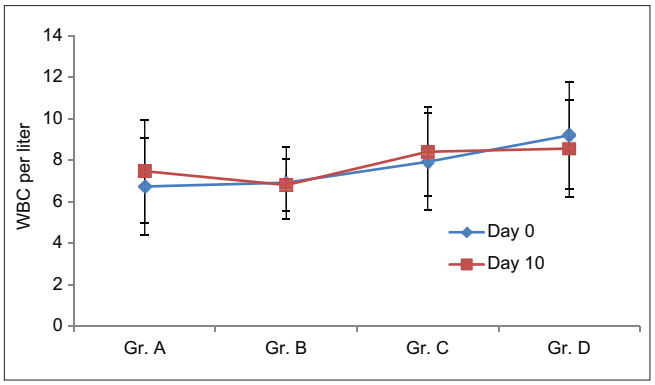

Figure 2: WBC count (per L) at day 0 (baseline) and day 10 of treatment in all patients recruited under the study

A study, on the effect of Punica granatum (pomegranate or Dantabija) on influenza A virus, has shown that polyphenols (especially ellagic acid, caffeic acid, luteolin, and punicalagin) and punicalagin, present in pomegranate act as virucidal against the virus, suppress the replication of the virus in host cells, and also inhibit agglutination in chicken red blood cells caused by the virus. Punica granatum has been shown to have inhibitory effects on ACE and thus can be used as a potential anti-COVID-19 drug candidate. It has been studied that the polyphenolic fraction of Punica granatum may be associated with NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) inhibition, with useful effects on inflammation and immune response to infection. NF-κB plays a key role in regulating the immune response to infection.[16]

Zingiber officinalis (ginger) along with its phytochemicals has shown to have anti-viral, anti-fibrotic, antioxidant, anti-inflammatory, and hepatoprotective properties. It inhibits prostaglandin and leukotriene biosynthesis, cyclooxygenase, and lipoxygenase activities, and inhibits the synthesis of pro-inflammatory cytokines such as IL-1, TNF-α, and IL-8 without any significant effect on IL-6 levels.[17]

Curcuma longa (turmeric or haridra) has anti-emetic, anti-nociceptive, anti-fatigue, and bronchodilator effects which help in controlling the spread of upper respiratory infection. A study using the in silico approach involving docking and stimulation shows the dual binding affinity of polyphenolic compounds, in which both the viral S protein and ACE2 receptor bind to curcumin. This binding of curcumin to the receptor-binding domain (RBD) site of viral S protein and also to the viral attachment sites of ACE2 receptor, demonstrated that curcumin can act as a potential inhibitory agent preventing the entry of SARS-CoV2 viral protein inside the cells. The curcumin present in Curcuma longa has the property to prevent SARS-CoV replication and inhibits 3Cl protease.[18,19]

DHZ has shown promising results in controlling upper respiratory tract infection, common cold, flu, mouth ulcers, and even Bechet's disease.[20] DHZ has also shown the ability to kill bacteria by 94% within 1 week due to the synergistic

Table 5: Comparisons of hematologic parameters in home quarantine patients

Hematologic parameters	Home quarantined on Standard treatment. (Group C) *n*=18			Home quarantined and on Standard Treatment along with intervention. (Group D) *n*=18		
	Day 0	Day 5	Day 10	Day 0	Day 5	Day 10
CRP	21.25±31.33	16.39±22.59	8.93±7.83	24.90±32.68	19.13±26.84	11.08±11.30
Ferritin	111.27±82.33	97.05±70.78	88.90±62.02	117.27±85.34	99.58±72.04	81.16±63.73
Hemoglobin	13.36±1.91	13.47±1.85	13.48±1.79	13.93±1.29	13.96±1.10	14.131.08
Leukocytes	7.93±2.34	8.07±2.28	8.42±2.15	9.21±2.58	8.76±2.11	8.57±2.34

†Mean±standard deviation

effect of the composition. A study conducted to evaluate the effect of DHZ on the common cold has shown that it reduces the severity, duration, and frequency of cold, cough, and flu.[11] The virucidal and anti-viral action of this combination has also been evaluated against COVID-19 in a small study group of asymptomatic positive cases, where it shows that 91% of early-stage carrier turns negative in 3 days of taking 3-4 lozenges/pastille.[12] Though the study was conducted on small sample size, the results were encouraging and need to be evaluated in a large study group.

The present study shows that the addition of DHZ to standard management acts as a booster in controlling the spread of the virus, and therefore, a greater number of COVID-19-positive patients who took DHZ along with standard treatment turn negative as compared to those who did not take DHZ and were only on standard management. This shows that anti-viral, virucidal, and antibacterial properties present in DHZ may have resulted in controlling the virus spread in a very effective way in mild cases of COVID-19. Although, a greater number of cases in moderate disease do not turn negative with DHZ however, the disease progression was slowed down and the patient's condition did not deteriorate further in the DHZ group, apparently indicative of a positive influence on the immune system thereby suggesting that DHZ helps the patients in recovering from the covid infection in a much easier way.

It is observed in the study that episodes of cough were the least in patients who were in home quarantine and were receiving the intervention. This indicates that the pastille form of DHZ has added advantage over standard treatment in mild cases which helps in limiting the spread of infection inside the body in the early stage. The major symptoms associated with COVID-19 infection like cough, sore throat, and myalgia were relieved in patients who received intervention along with standard treatment, supporting previous studies of DHZ as antimicrobial, anti-inflammatory, and analgesic. However, all symptoms of COVID-19 were not eased in the case of moderate disease. This may be due to increased viral load in moderate cases, which may take time to clear from the body with a natural product but the overall recovery was seen better with the addition of DHZ along with the standard treatment group.

The hematologic parameters strongly support the observation that DHZ helps in recovering both mild and moderated cases by boosting the immune system which will help in limiting the spread of the virus. Moreover, DHZ has shown to increase the lysozyme content in saliva by four times, thereby, increasing the immunity and helping in controlling the COVID-19 infection.[21]

Conclusion

Various natural products have been studied for their potential use in SARS-CoV-2 without any conclusive evidence. A combination of Dantabija 20 mg, Haridra 50 mg, and Zingiber officinale 5 mg (DHZ) in pastille form as used in the present study has shown significant beneficial effects based upon various parameters. By its apparent immunomodulatory action, DHZ can potentially modify the course of the disease. Therefore, it can be concluded that the DHZ when combined with standard treatment, produces a synergistic effect and early positive outcome in controlling the spread of COVID-19. However, more studies in large COVID-19-positive groups are required to further evaluate the specific anti-viral, virucidal action of DHZ. A further clinical trial with a bigger database for evaluation of target-level interaction of the proposed combination is pertinent.

Limitation of study

It was a single-center study. The sample size was only 100. A multicentric clinical trial with a large sample size can be done.

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Statement of ethics

The study complies with the "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants 2018" of the Indian Council of Medical research. This study also complies with the guidelines for human studies following this 'World Medical Association Declaration of Helsinki.' This research was conducted with the Institutional Ethical Committee approval vide letter no. AIIMS/Pat/IEC/2020/609. Written consent was taken from each participant before including them in the study as per above-mentioned national guidelines.

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Conflicts of interest

The authors have no conflicts of interest to declare pertaining to the study. The funding agency did not have any direct or indirect influence on any aspect of the study process. The pre-formulated combination of the molecules used in the study have been provided by the agency free of cost.

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