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Prophylactic efficacy of Unani herbal and herbo-mineral preparations in population at risk of COVID-19 – A randomised controlled prospective field trial

Abdul Wadud[a], Abdul Nasir Ansari[b], Mohd Nayab*[,b] & Malik Itrat[c]

[a]National Institute of Unani Medicine, Bangalore, India

[b]Department of Ilaj bit Tadbeer, [c]Department of Tahafuzzi wa Samaji Tibb, National Institute of Unani Medicine, Bangalore, India

E-mail: nayabdr@gmail.com

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The present study was aimed to evaluate the efficacy of Unani poly-herbal decoction and *Khamira Marvareed* (herbo-mineral preparation) in COVID-19 susceptible population. This study was conducted as prospective, open label, randomized controlled, prophylactic community-based clinical trial. Overall, 4500 healthy adults from containment zones were allocated randomly into intervention (n=2250) and control groups (n=2250). The intervention group was given a combination of herbal drugs namely *Unnab* (*Ziziphus jujube* Mill.), 5 pieces; *Sapistan* (*Cordia myxa* L.), 9 pieces; *Behidana* (*Cydonia oblonga* Mill.), 3 g in decoction form and *Khameera Marwareed*, 5 g as semisolid preparation, orally once daily in the morning for 20 days. No drug was given in the control group. The subjects were assessed on 0, 20th and 35th day. The prophylactic effect of the Unani intervention was evaluated on the basis of difference of COVID-19 incidence between the groups, COVID-19 like symptoms, scores of immunity status questionnaire and WHOQOL-BREF scale after completion of 35th day of study. The study remained inconclusive to find any difference in COVID-19 incidence, but showed highly significant results ($p<0.001$) in favour of Unani intervention in containing all COVID-19 like symptoms except cough; highly significant results ($p<0.001$) in score of immunity status questionnaire and highly significant results ($p<0.001$) in scores of physical and psychological domains of WHOQOL-BREF scale. The highly significant results in almost all secondary outcomes suggest the efficacy of the Unani interventions in control of COVID-19-like symptoms and may be beneficial in prevention of COVID-19 infection.

Keywords: Behidana, COVID 19, Khameera Marwareed, Sapistan, Unani, Unnab

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The ongoing pandemic of COVID-19 (Coronavirus disease 2019) has challenged the health care systems across the globe. World attention was drawn to the current epidemic in December 2019 in Wuhan, China[1]. In India, first case was reported on 30th January, 2020[2]. The World Health Organization (WHO) declared this disease as pandemic on 11 March 2020[3]. Evidence indicates that the disease is transmitted from human to human through droplets and direct contact[4]. The clinical picture in humans infected with SARS-CoV-2 has ranged from asymptomatic stage to severe signs and symptoms including death. The main symptoms include fever, fatigue, dry cough, myalgia and dyspnea[5,6].

Despite worldwide attempts to contain it, the pandemic persists due to lack of scientifically validated prophylaxis and therapeutic strategy[7]. This turned the world's attention towards strengthening the body's defense force against disease-causing agents[8]. One effective way to control the spread of infection is to strengthen the host defense. A large number of immune individuals in the population can build up herd immunity; which creates an immunological barrier to the spread of disease in the human herd. If herd immunity is sufficiently high, the occurrence of an epidemic is considered highly unlikely[9].

It provides an opportunity to revisit the wisdom of traditional systems of medicine for addressing the challenge of COVID-19 pandemic by modulating immunity among the masses to improve the host defense. Unani medicine pays particular attention to the host and recommends measures for the protection of host. The classical literature of Unani medicine describes epidemic management and various measures to prevent these diseases. There is no direct description of coronavirus disease in Unani system of medicine, but the clinical features of *Nazla-e-Wabaiya* (epidemic common cold) described in Unani texts are

*Corresponding author

strikingly similar to the epidemics such as swine flu, SARS and even COVID-19[10]. The idea of prevention advocated by Unani scholars during an outbreak is primarily based on the use of all those regimes that regulate the humoral imbalance and keep the body in a non-susceptible state. Once the susceptibility for a disease no longer exists, either we do not contract the disease or even if contracted, the episode will be less virulent, as the body is prepared to counter any intrusion of disease-causing agents. Several measures have been recommended in Unani Medicine to strengthen the host defense which includes both pharmacological and non-pharmacological interventions[11-15].

Based on the review of Unani classical literature and contemporary scientific studies, systemic interventions with *Khamira Marwareed* and decoction (*Joshanda*) of *Unnab* (*Ziziphus jujube* Mill.), *Sapistan* (*Cordia myxa* L.) and *Behidana* (*Cydonia oblonga* Mill.) were selected for prophylactic assessment against COVID-19[16].

According to Unani perspective, *Khamira Marwareed* maintains the vitality of organs, protects them from untoward stimuli and strengthens them to cope with the diverse pathological conditions[17]. Immuno-potentiating effect of *Khamira* has been demonstrated by a study conducted on animal models[18]. *Joshanda* is an aqueous extract of herbal drugs containing water soluble principles and inorganic ions used for the treatment of common cold, catarrh, cough and associated fever in Unani medicine[19]. Various studies conducted on *Ziziphus jujube* Mill., *Cydonia oblonga* Mill. and *Cordia myxa* L. have shown to possess antioxidant, immunomodulator, antibacterial and antiviral properties[20-24].

Material and Methods

Study design

This was an open labelled, randomized, controlled, community-based clinical trial conducted in the Padrayanpura containment zone of Bengaluru during months of July and August, 2020.

Informed consent

The trial investigator teams surveyed the containment zone and collected the data from eligible participants on door-to-door basis after taking their written informed consent.

Ethical approval

The study was approved by the Institutional Ethics Committee vide registration number NIUM/IEC/2019-20/001/COVID-19/01 and registered at the clinical trial registry of India vide registration number CTRI/2020/06/025650. The trial was conducted in accordance with the Helsinki declaration, and the Good clinical practice guidelines of Ministry of Health and Family Welfare, Government of India.

Study participants

The target population consisted of low-risk group of COVID-19 patients residing in the identified containment zone between the ages of 18 to 68 years of either gender. Participants below 18 years and above 68 years of age, those with renal, hepatic, respiratory or cardiac comorbidities, mental illness, pregnant and lactating women, laboratory confirmed cases of COVID-19 and unwilling to participate were excluded from the study.

Interventions

Participants were randomized to receive either a test drug or no drug control. Subjects in the test group were given *Khameera Marwareed*, 5 g and decoction consisting of *Unnab* (*Ziziphus jujube* Mill.), 5 pieces; *Sapistan* (*Cordia myxa* L.), 9 pieces and *Behidana* (*Cydonia oblonga* Mill.), 3 g once daily orally in the morning for 20 days. No drug was given in the control group. Mandatory general measures such as social distancing, respiratory hygiene, hand hygiene and use of personal protective equipment recommended by Government Health Authorities were advised to both the groups.

Procurement of test drug

The test drug was purchased from Indian Medicines Pharmaceuticals Corporation Ltd. (IMPCL), a Government of India enterprise with an ISO 9001:2015. The company operates under the license number UK-AY-L-348/2016. The batch number imprinted on the information label of *Khamira Marwareed* was IME-0101 and expiry date as April, 2023. Each 10 g of *Khamira Marwareed* contained *Marwareed* (*Mytilus margaritiferus*), 0.069 g; *Tabasheer (Bambusa bambos bruse*), 0.069 g; *Sandal Safaid* (*Santalum alba*), 0.069 gms; *Ambar Ash-hab* (*Ambra grisea*), 0.027 g; *Qand Safaid* (*Saccharum officinarum*), 4.184 g; *Arq Gulab* (*Rosa damascena*), 2.789 mL and *Arq Gaozaban* (*Borago officinalis)*, 2.789 mL[17]. A pack of *Khamira Marwareed* contained 125 g of drug in it. Crude drugs for the decoction were also procured from IMPCL and supplied to the patients in twenty small sized self-locking covers. The contents of one cover were advised to use as decoction daily.

Sampling and sample size

Convenient sampling was adopted in view of feasibility for the study. The total sample size of the study was taken as 4000 subjects plus 20% dropout, thus, adding to a total of 4800 participants, divided equally in test and control groups. However, only 4500 participants could be enrolled randomly with 2250 participants in each group. Finally, 2240 participants in the intervention and 2073 participants in control group completed the study (Fig. 1).

Randomization and masking

Participants were allocated to test or control group by a simple random method using a pre-generated randomization sequence. The allocation sequence was generated by the principal investigator while patient enrollment was assigned by the field investigators. No blinding was done in the study.

Follow-up and assessment

The overall duration of the protocol was 35 days (20 days treatment period and 15 days post-treatment follow-up). The patients were assessed clinically at day 0 (baseline), day 10 (telephonic follow-up), day 20 (physical follow-up) and at day 35 (post-treatment telephonic follow-up). The subjective and objective clinical observations were recorded in the case record form (CRF).

Outcomes measures

The primary outcome was the observable difference in incidence of COVID-19 cases in control and intervention groups. Secondary outcomes were based on improvement in immunity status questionnaire (ISQ)[25] and WHO-Quality of Life (WHOQOL-BREF) scales[26,27].

Study procedure

The COVID-19 case positivity was determined by enquiring the participants about the development of suspected symptoms of COVID-19, consequently, RT-PCR done for COVID-19 and the report thereof. Phone numbers were exchanged between the study participants and the field investigators to provide participants with the proper guidance, to conduct timely telephonic follow-up and to receive any voluntary information about COVID-19-like symptoms and report of COVID-19 testing. Any participant who developed COVID-19 symptoms along with positive RT-PCR report during the course of study was notified to the concerned district authorities for shifting to a COVID-19 treatment facility. Such patients were withdrawn from the study and their count maintained for comparison between test and control group after the study period.

Statistical analysis

Trial results were analyzed using the per-protocol approach. Descriptive and inferential statistical analyses were carried out after the completion of the study. Categorical data was represented by number and percentage while quantitative data by mean and SD. Independent proportion test and Mann-Whitney U Test were applied for the analysis of categorical data while two tailed, paired and unpaired Student t test were used for intragroup and intergroup analysis

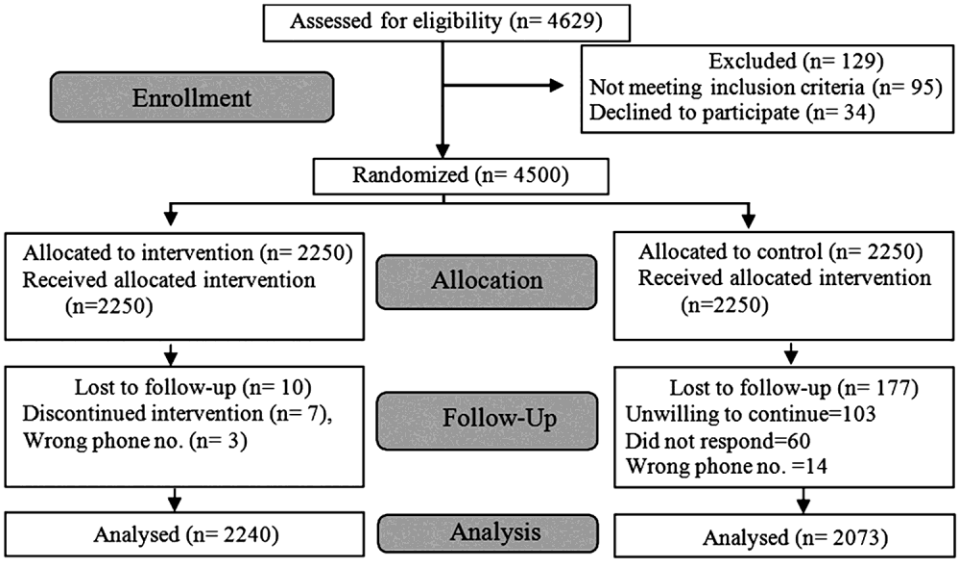

Fig. 1 — Consort Flow Diagram

of quantitative data. Level of significance was set at p<0.05. The Statistical software namely SPSS 22.0 and R environment ver.3.2.2 were used for data analysis**.**

Results

Among all participants enrolled, 58.62% were male in intervention and 53.16% in control group with a significant difference of p<0.001. The mean age of the participants in intervention group was 39.77 years while it was 39.5 years in control group. Further, 3.34% participants had the history of an exposure to COVID-19 patients in intervention group and 3.04% in control group. Other baseline variables were also not significantly different as depicted in Table 1.

Table 2 shows the efficacy of Unani intervention on immunity status of the participants. Mean rank of ISQ was 2155.2 at 0 day in intervention group which increased to 2286.9 at 20th day and 2296.5 at 35th day. In control group, the mean rank was 2159.0 at 0 day, 2016.6 at 20th day, and 2003.1 at 35th day. The difference in mean ranks of ISQ was significant between test and control groups at 20th day (p<0.001) and 35th day (p<0.001).

As reflected in Table 3, all participant enrolled in the study had no COVID-19 like symptom at 0 day. At 20th day, 4.46%, 8.57%, 3.66%, 7.81% and 1.29% participants reported of fever, cough, sore throat, runny nose and fatigue/malaise, respectively, in intervention group; while, 6.99%, 8.92%, 5.89%, 9.94% and 5.74% participants complained of fever, cough, sore throat, runny nose, and fatigue/malaise, respectively, in control group. On statistical comparison between the groups, significant difference was found in score of fever (p<0.001), a sore throat (p<0.001), runny nose (p=0.014) and fatigue/malaise (p<0.001), while no significant difference was observed in cough (p=0.6818). At 35th day in intervention group, 3.84%, 7.28%, 2.9%, 5.4% and 1.92% participants reported of fever, cough, sore throat, runny nose, and fatigue/malaise, respectively, while in control group, 6.95%, 8.35%, 5.89%, 9.12% and 5.26% participants complained of fever, cough, sore throat, runny nose, and fatigue/malaise, respectively. On statistical comparison between the groups, significant difference was found in score of fever (p<0.001), sore throat (p<0.001), runny nose (p<0.001) and fatigue/malaise (p<0.001), while no significant difference was observed in cough (p=0.190).

Table 4 shows an analysis of efficacy of Unani intervention on WHO Quality of Life (WHOQOL-BREF) scale. At 0 day, the mean±SD was 60.35±16.08, 55.95±15.60, 51.72±16.45 and 49.00±14.41 for physical

Table 1 — Demography of participants

Parameter	Intervention (n=2240)	Control (n=2073)	p value
Age	(39.77±12.1)	(39.5±12.21)	0.55
Male (no.)	1313(58.62%)	1103(53.16%)	<0.001
Any exposure to COVID patient	75(3.34%)	63(3.04%)	0.56
History of any social gathering	25 (1.11%)	15(0.72%)	0.17
Smoker	17 (0.76%)	14(0.68%)	0.74
Alcoholic	5 (0.22%)	3 (0.14%)	0.54

Table 2 — Effect of Unani intervention on Immunity Status Questionnaire (ISQ)

Study groups	0 day			20th day			35th day		
	Mean rank	Mean ranks difference	p value	Mean ranks	Mean ranks difference	p value	Mean ranks	Mean ranks difference	p value
Intervention	2155.2	-3.8	0.12	2286.9	270.3	<0.001	2296.5	293.4	<0.001
Control	2159.0			2016.6			2003.1		

Table 3 — Efficacy of Unani Intervention on COVID-19-like symptoms

S. No.	Symptoms	0 day		p value	20th day		p value	35th day		p value
		Intervention	Control		Intervention	Control		Intervention	Control	
1	Fever	0	0	-	100 (4.46%)	145 (6.99%)	<0.001	86(3.84%)	144 (6.95%)	<0.001
2	Cough	0	0	-	192 (8.57%)	185 (8.92%)	0.6818	163 (7.28%)	173 (8.35%)	0.190
3	Sore throat	0	0	-	82 (3.66%)	122 (5.89%)	<0.001	65 (2.9%)	122 (5.89%)	<0.001
4	Runny nose	0	0	-	175 (7.81%)	206 (9.94%)	0.014	121 (5.4%)	189 (9.12%)	<0.001
5	Fatigue/ malaise	0	0	-	29 (1.29%)	129 (5.74%)	<0.001	43 (1.92%)	109 (5.26%)	<0.001

(Test applied= Independent proportion test)

health, psychological, social relationship and environment, respectively, in intervention group, while it was 60.55±15.34, 56.98±16.35, 50.60±15.19 and 47.88±14.41 for physical health, psychological, social relationship and environment, respectively, in control group. On statistical comparison between the groups on 0 day, no significant difference was found in any subgroup of WHOQOL-BREF Scale.

At 20th day, the mean±SD was 62.54±14.60, 60.50±16.04, 49.92±14.73 and 48.41±13.93 for physical health, psychological, social relationship and environment, respectively, in intervention group, while it was 61.00±15.93, 57.80±16.27, 50.33±14.95 and 48.89±14.269 for physical health, psychological, social relationship and environment, respectively, in control group. On statistical comparison between the groups, significant difference was found in score of physical health (p=0.025) and psychological (p<0.001) while no significant difference was observed in social relationship (p=0.536) and environment subgroups (p=0.75).

At 35th day, the mean±SD was 63.40±15.07, 61.51±15.36, 51.24±15.31 and 50.17±14.90 for physical health, psychological, social relationship and environment, respectively, in intervention group while it was 60.03±16.01, 56.81±16.23, 50.30±14.95 and 49.79±14.80 for physical health, psychological, social relationship and environment, respectively, in control group. On statistical comparison between the groups, significant difference was found in score of physical health (p<0.001) and psychological (p<0.001) while no significant difference was observed in social relationship (p=0.18) and environment subgroups (p=0.57).

Table 5 shows the efficacy of Unani intervention on WHOQOL-BREF Scale within the groups. In intervention group, the mean±SD was 60.35 ±16.08, 55.95 ±15.60, 51.72 ±16.45 and 49.00±14.41 at 0 day, while it was 62.54±14.60, 60.50±16.04, 49.92±14.73 and 48.41±13.938 at 20th day for physical health, psychological, social relationship and environment, respectively. On statistical comparison between 0 day and 20th day within the intervention group, significant difference was found in score of physical health (p=0.002) and psychological (p<0.0001), social relationship (p=0.01) while no significant difference was observed in environment subgroup (p=0.35). At 35th day in intervention group, the mean±SD was

Table 4 — Analysis of WHO-Quality of Life (WHOQOL-BREF) between the groups

S. No.	Parameters	0 day		p value	20th day		p value	35th day		p value
		Mean±SD			Mean±SD			Mean±SD		
		Intervention	Control		Intervention	Control		Intervention	Control	
1	Physical health	60.35 ±16.08	60.55 ±15.34	0.77	62,54 ±14.60	61.00±15.93	0.025	63.40± 15.07	60.03± 16.01	<0.001
2	Psychological	55.95 ±15.60	56.98 ±16.35	0.16	60.50 ±16.04	57.80±16.27	<0.001	61.51± 15.36	56.81± 16.23	<0.001
3	Social relationships	51.72 ±16.45	50.60 ±15.19	0.10	49.92 ±14.73	50.33±14.95	0.536	51.24± 15.31	50.30± 14.95	0.18
4	Environment	49.00 ±14.41	47.88±14.41	0.07	48.41 ±13.938	48.89±14.269	0.75	50.17 ± 14.90	49.79± 14.80	0.57

Table 5 — Analysis of WHO-Quality of Life (WHOQOL-BREF) within the groups

S. No.	Parameters	Mean±SD		P value	Mean±SD		P value
		0 day	20th day		0 day	35th day	
		Intervention Group					
1	Physical health	60.35 ±16.08	62.54 ±14.60	0.002	60.35 ±16.08	63.40±15.07	0.0001
2	Psychological	55.95 ±15.60	60.50 ±16.04	0.0001	55.95 ±15.60	61.51±15.36	0.0001
3	Social relationships	51.72 ±16.45	49.92 ±14.73	0.01	51.72 ±16.45	51.24±15.31	0.49
4	Environment	49.00 ±14.41	48.41 ±13.938	0.35	49.00 ±14.41	50.17 ±14.90	0.07
		Control Group					
1	Physical health	60.35 ±16.08	61.00±15.93	0.36	60.35 ±16.08	60.03±16.01	0.65
2	Psychological	56.98 ±16.35	57.80±16.27	0.26	56.98 ±16.35	56.81±16.23	0.81
3	Social relationships	50.60 ±15.19	50.33±14.95	0.68	50.60 ±15.19	50.30±14.95	0.65
4	Environment	47.88±14.41	48.89±14.269	0.11	47.88±14.41	49.79±14.80	0.003

63.40±15.07, 61.51±15.36, 51.24±15.31 and 50.17±14.90 for physical health, psychological, social relationship and environment, respectively. On statistical comparison between 0 day and 35th day values within the intervention group, significant difference was found in score of physical health ($p<0.0001$) and psychological ($p<0.0001$), while no significant difference was observed in social relationship ($p=0.49$) and environment subgroup ($p=0.07$).

The mean±SD in control group was 60.55±15.34, 56.98±16.35, 50.60±15.19 and 47.88±14.41 at 0 day, while it was 61.00±15.93, 57.80±16.27, 50.33±14.95 and 48.89±14.26 at 20th day for physical health, psychological, social relationship and environment, respectively. On statistical comparison between 0 day and 20th day values within the control group, no significant difference was found in score of physical health ($p=0.36$), psychological ($p=0.26$), social relationship ($p=0.68$) and environment subgroup ($p=0.11$). The mean±SD was 60.03±16.01, 56.81±16.23, 50.30±14.95 and 49.79±14.80 at 35th day in control group for physical health, psychological, social relationship and environment, respectively. On statistical comparison between 0 day and 35th day scores within the control group, no significant difference was found in score of physical health ($p=0.65$) psychological ($p=0.81$), social relationship ($p=0.65$) but a significant score was observed in environment subgroup ($p=0.003$).

Discussion

The World Health Organization (WHO) has declared the ongoing COVID-19 pandemic to be a global health emergency[28]. No specific and effective antiviral drug has been discovered against COVID-19 yet. With this reason, traditional systems of medicine were being explored for the preventive as well as curative aspects. History is replete with onslaught of many disastrous epidemics and pandemics during human civilization and their description has fairly been accommodated in Unani medicine. Though, there is no direct description of coronavirus disease in Unani system of medicine, but the clinical presentation of *Nazla-e-Wabaiya* described in Unani texts is strikingly similar to the COVID-19[10]. According to the concept of Unani medicine, *tabiyat* (medicatrix naturae) is the sole planner for the physiological functions in the body and alone fights against the diseases. The drugs are given to help and boost the *tabiyat* to tide over the invasion of the disease. Immunity is one of the several important functions served by the *tabiyat* and at times requires its invigoration in the face of a fierce infections as occurs during an epidemic[29]. Various single drugs and compound formulations are used as *muqawwiyat* (tonics) in *Nazla-e-Wabaiya*. According to Unani perspective, *muqawwiyat* strengthen and maintain the vitality of organs in order to protect them from adverse stimuli and noxious pathological conditions. Therefore, the decoction of *Behidana* (*Cydonia oblonga* Mill.), *Unnab* (*Ziziphus jujube* Mill.), and *Sapistan* (*Cordia myxa* L.) in combination with *Khamira Marwareed* was evaluated for their prophylactic effect among the individuals at risk of contracting COVID-19 infection.

The findings of other studies are not directly comparable with this study, since, to the best of our knowledge, this is the first clinical study that assessed the prophylactic efficacy of Unani test formulation. Therefore, we have equated our study findings with previous animal studies conducted on the ingredients of the formulation.

The primary objective of the study was to compare the incidence of COVID-19 between the intervention and the control groups. However, the study remained inconclusive to find the direct answer for the primary objective due to unavoidable limitation in the design of the study. The confirmatory diagnostic test (RT-PCR) was not involved as an essential criterion for the enrollment of the study participants due to its high cost, scarcity of available facilities and general apprehension in the public to undergo any testing for the fear of being confined to the isolation centre and their close contacts in a quarantine centre for two to three weeks, if found positive for the COVID-19 infection during its surge. The investigators, however, encouraged the enrolled participants to undergo COVID-19 testing, a service usually rendered by the fever clinics established in the containment zones, in case the participants developed COVID-19-like symptoms. The investigators had to rely on the reporting of the participants for any development of symptoms or RT-PCR done in the wake of the developing symptoms. No participant admitted convincingly of any testing done for COVID-19 confirmation but reported about developing symptoms. Therefore, the incidence of COVID-19 could not be compared between the groups.

There was, however, significant difference in secondary outcomes. The developing symptoms in the participants were taken as surrogate marker for the positivity of COVID-19 infection in this scenario. The highly significant difference in proportion of COVID-19-like symptoms barring cough in favour of Unani intervention is a convincing indication of the efficacy of Unani formulation in prevention of COVID-19-like symptoms (Table 3). The development of COVID-19-like symptoms in lesser number of participants in intervention group may be due to the immunomodulator activities of the ingredient used in decoction and *Khamira Marvareed*.

The immunomodulator actions of the drugs may further be corroborated by significantly higher score in intervention group in comparison to the control group in immunity status questionnaire (Table 2).

Various studies conducted on *Cydonia oblonga* Mill., *Ziziphus jujube* Mill. and *Cordia myxa L.* in animal models revealed that these drugs possess antioxidant, immunomodulator, antibacterial and antiviral properties. Zhuo-ping *et al*. (2016) reported the immunomodulatory effects of *Ziziphus jujube* Mill. on innate and adaptive immunity in healthy ICR mice, as well as potential antioxidant activity for prevention of oxidative stress, which was suggested to partly contribute to the immune enhancement[30]. Chi *et al*. (2015) reported that *jujube* polysaccharide conjugates (JPC) treatment enhanced T-lymphocyte proliferation and NK cells activity in CFS rat models[19]. Antioxidant activity of *Cordia myxa* L. is reported by Afzal *et al*.[31]. Ali *et al.* (2015) investigated the immunomodulatory activity of aqueous extract of *Cordia myxa* L. in rat model and found that aqueous extract stimulates cell-mediated immune responses in mice[22].

Salimimoghadam *et al*. (2019) compared the pharmacological efficacy of *Cordia myxa* hydro-alcoholic extract (Bulk Extract [BE]) and nanoparticles of hydro-alcoholic extract (NPE) including antitussive, anti-inflammatory and analgesic activity. Both extracts were found to have better therapeutic activities than dextromethorphan. NPE exerted better anti-inflammatory and analgesic activity compared to BE[32]. Hamauzu *et al*. (2005) reported that the antioxidant functions of Chinese quince (*Cydonia oblonga* Miller) and quince phenolic extracts were superior to that of chlorogenic acid standard or ascorbic acid evaluated in both the linoleic acid peroxidation system and the DPPH radical scavenging system[33]. A study, conducted by Shinomiya *et al*. (2009), reported the inhibitory effect of crude hot-water extract (HW) of quince (*Cydonia oblonga* Miller) fruit on type I allergy by suppressing IgE production and IgE-mediated degranulation[23]. *Kamira marwareed* is known as one of the best general tonics to strengthen the *tabiyat*, which as a sole planner of human physiology, improves the host defense and antagonizes the virulence of infectious agents, thereby lowering the risk to acquire an infection during an epidemic.

Analysis of WHO Quality of Life (WHOQOL-BREF scale) depicts a significant difference with favourable higher score in physical health and psychological domains in intervention group in comparison to the control group. However, no significant difference was observed in social relationship and environment domains of the scale between both the groups. The impact of the *Unani* drugs on the physical and psychological health may be explained due to the impact of *Unani* drugs as general well-being enhancers[34,35]. The involvement of significantly smaller number of participants in COVID-19-like symptoms and improvement in immunity status questionnaire due to attrition of recurring ailments in intervention group might have contributed to the significantly improved score in physical and psychological health. No difference in social relationship and environment domains may be due to negligible consequential effect of drugs on these two domains.

With regard to within-group analyses of WHOQOL-BREF scale in intervention and control groups, a consistently significant improvement in score of physical and psychological health on 20^{th} and 35^{th} days with respect to the baseline values in intervention group is convincing evidence of association between the effect of test drugs and the quality of life[34, 35]. No or inconsistent significance of *Unani* drugs in social relationship and environment domains in intervention group exhibits no association between them. There was no or inconsistently significant difference in all domains of WHOQOL-BREF scale in control group.

Implications of findings

Although the immune-stimulation activities of test drugs were not assessed by any objective parameters,

the overall effect of the test drug was found encouraging in improving the immune status as assessed by immune status questionnaire (ISQ). The findings outlined above indicate immune-stimulating activity of test drugs and suggest their use in conditions where immune stimulation is required. Such plant-based immune stimulants may have application in improving the host defense with the broad goal of disease prevention.

Limitations of study and further research

This study has suffered a number of limitations, notably the lack of diagnostic tests to assess the COVID-19 status of the participants before and after trial, therefore, masking the true and reliable picture of COVID incidence in both the groups. The convenience sampling method used in this study may restrict the generalizability of the results. Hence, randomized double-blind, controlled clinical trials may be needed to better assess the effect of test formulation on COVID incidence. The immunity status may further be objectively analyzed with inclusion of CD4 count, CD4/CD8 ratio and natural killer cells in healthy and immunocompromised individuals.

Conclusion

The preliminary findings as regard to significantly lower numbers of incidence in COVID-19-like symptoms in intervention group corroborated by significant improvement in immunity status and quality of life suggest the efficacy of Unani intervention as a prophylactic regimen in COVID-19. The positive findings in this study with respect to COVID-19-like symptoms, immunity status questionnaire and WHOQOL-BREF scale are attributed to the immunomodulator, antioxidant, antibacterial, and antiviral activities of *Unani* decoction and *Khamira Marwareed*. However, the limitations in study may be compensated by framing more robust design and compulsory testing of COVID-19 in future studies.

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Conflict of Interest

All the authors declare no conflict of interest.

Authors' Contributions

Conceptualization & Designing of the study: A W & A N A; Original draft, Reviewing and Editing: M N & M I; Formal Analysis, Methodology & Interpretation of data A N A & M N; Final Approval of the Manuscript: A W, A N A, M N & M I.

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