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Short Communication

Effectiveness of unani regimen in protecting high risk population from COVID -19: A pilot study

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The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally. COVID-19 presents varied clinical features. The present study focuses on number of patients turning COVID-19 positive, change in Immune Status Questionnaire (ISQ) and WHO quality of life- Bref (WHO Qol – BREF) scales after taking intervention. This open labelled, double arm, controlled, interventional, clinical trial was conducted on high-risk individuals i.e., those residing with a COVID-19 positive member in the identified quarantine area. This twin armed study was conducted on asymptomatic individuals exposed to COVID -19. The test group were prescribed Unani poly-herbal decoction together with Unani formulations *Khamira Marwareed* and *Tiryaq e Arba* whereas the control group was not on any intervention. The duration of intervention was 20 days; follow ups were planned on day 10 and day 20. Of the 81 participants enrolled, none of the patients turned COVID-19 positive. However, 13.58% (n=11) developed COVID like symptoms and 70 patients completed the study. The mean age of the participants was 41.42±16.9 years; however, majority of the participants were 18-28 years male with *Damvi* (Sanguine) temperament. The quality of life of the intervention group improved significantly however, the immune status in both the groups increased with P <0.001. The Unani prophylactic regimen provides a 62% (relative risk reduction) protection against COVID -19. This pilot study paves for a study on a larger population. No adverse effects were observed during the study. Absence of biochemical investigations were limitations to the study.

Keywords: COVID -19, Immune status, *Khameera Marwareed*, *Tiryaq Arba*, *Unani Joshanda*.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally. COVID-19 presents varied clinical features. A recent review estimated that at least one-third of the SARS-CoV-2 infections are asymptomatic. The spectrum of the symptomatic disease also ranges from mild to severe[1]. In the absence of any proven treatment for this malady, more and more evidence based studies are warranted on prevention and patient management. The features of SARS–CoV-2 led to the hypothesis that the response to this virus should be systemic to counter its characteristic pathologies. Of late, immune-modulators are being used more frequently to enhance host defence responses[2].

COVID -19 is a *waba* (an infectious disease that affects a large geographical area)[3]. Of the four humors viz *dam* (sanguine), *safra* (chole), *balgham* (phlegm), and *sawda* (melanchole) that constitute the human body, as per the Unani theory; *waba* first strikes the *damvi* (sanguineous) humor, whose nidus is the heart wherein it warms up the blood[4]. Therefore the principle of treatment includes *istifragh* (evacuation), *muqawwiyat e qalb* (cardio tonics), *tiryaq* (antidotes), and *tabreed* (reducing the temperature)[5]. However, *tabreed* is contraindicated in pneumonia, chest disorders or diseases due to coldness.

With the intention to find a prophylaxis for the COVID *waba*, the current study was designed to compare number of individuals turning COVID-19 positive receiving Unani prophylactic intervention with those not receiving Unani prophylactic intervention in selected population at high risk i.e., at least one member from the identified quarantine area was COVID positive at the time of the study. The intervention consisted of *Tiryaq e Arba* (TA), *Khamira Marwareed* (KM), and Unani polyherbal decoction (Unani Joshanda).

TA is classically attributed with antidote, deobsturent, antispasmodic and diuretic properties, and is beneficial in epilepsy, paralysis, and phlegmatic diseases[6]. KM is a general tonic and is classically used in neuro-asthenia, weakness of heart, palpitation, weakness of brain, and polydiypsia[7]. The

Unani Joshanda has evidences proving it as antiviral, immune-modulator, anti-oxidant, and broncho-relaxant[8-12].

Materials and Methods

Study Design

An open label, controlled, randomized, interventional, clinical study was conducted from July to August 2020 in the Janakpuri area of New Delhi (India). The protocol (Fig. 1) was prepared by a multidisciplinary group of scientists of the Central Council for Research in Unani Medicine (CCRUM). Subsequent to ethical approval from Central Ethics Committee (CEC) of CCRUM and registration of the clinical trial with Clinical Trial Registry of India (CTRI) (CTRI/2020/06/26227), individuals were enrolled in the study after obtaining their written and informed consent. The residents of either gender in the age group of 18-65 years having at least one positive member were enrolled in the study. The study was performed in accordance with the Declaration of Helsinki and GCP guidelines issued by the Ministry of AYUSH, Government of India

Participants

Inclusion and Exclusion criteria

Symptomatic or asymptomatic COVID-19 positive patients, pregnant or lactating women, persons exhibiting severe primary respiratory disease or related complications that can be associated with COVID-19, serious critical or mental illness, uncontrolled, unstable co-morbidities, immuno-compromised patients or those on immune-suppressants and steroids, individuals having a past history of allergy to any Unani interventional medicine were excluded.

Study procedure

The study was open label, controlled, randomized, interventional, clinical study. The selected individuals were allotted to either Intervention group (IG) or Control group (CG) through convenience sampling (Fig. 2). IG was prescribed 125 mL of Unani herbal decoction consisting of Behidana (seed of *Cydonia oblonga*, Mill.), Unnab (fruit of *Zizyphus jujube*, Mill.) and Sapistan (fruit of *Cordia myxa*, Linn.) in the evening together with Unani formulations *Khamira Marwareed* (KM) and *Tiryaq e Arba* (TA) (Table 1) which were taken in the dosage of 5 g once

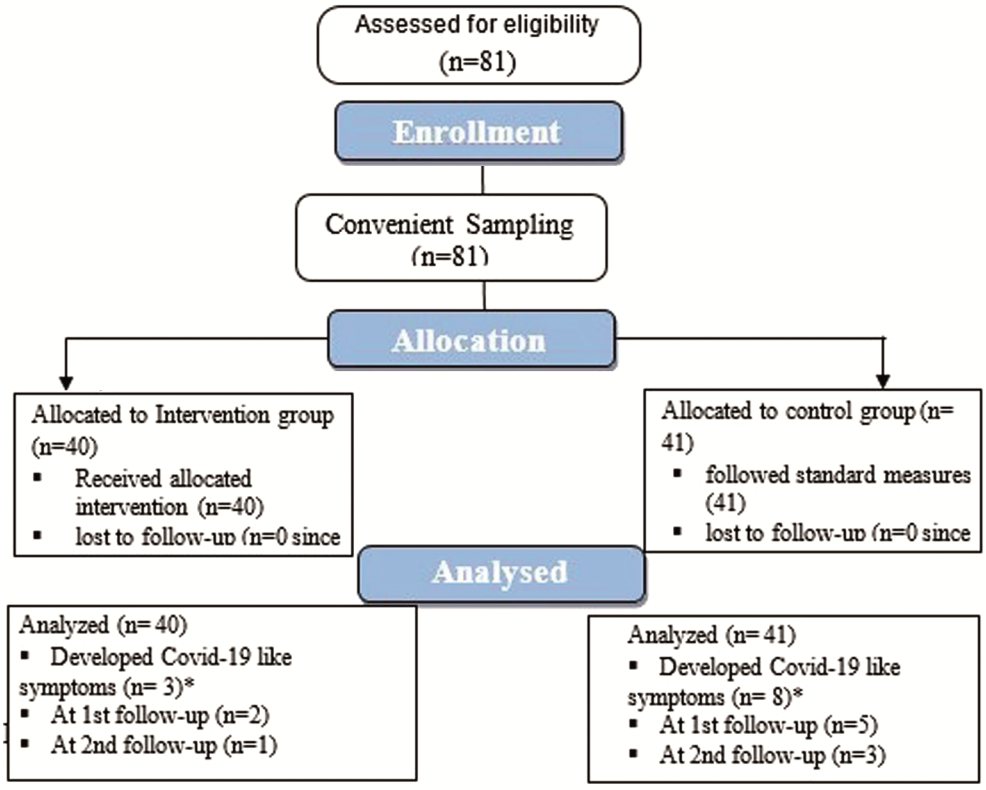

Fig. 1 — Consort flowchart.

daily in the morning whereas CG received no intervention at all. All participants were asked to follow the general measures /guidelines issued by the Ministry of Health and Family Welfare/ Ministry of AYUSH, Govt of India and World Health Organization (WHO)/ State government and local health authorities. Any mandatory general measures recommended by Government Health Authorities were given in both arms of study. The drugs of the same batch were dispensed for the complete treatment period at first visit itself. *Khamira Marwareed* bearing batch no. MKM034-35 and *Tiryaq Arba* bearing batch no. IME0099 were provided by CCRUM. The duration of the protocol therapy was 20 days.

Assessments

Participants were assessed on the basis of Immune Status Questionnaire (ISQ) and WHOQOL-BREF. The data was obtained through door-to-door collection and recorded in a separate case record at day 0 (baseline), day 10 and 20 (at the end of the study). However, on day 10 it was collected telephonically. They were enquired about their Covid status, ISQ and WHOQol-BREF. Any adverse events occurring during the period were to be recorded in the Case record Form.

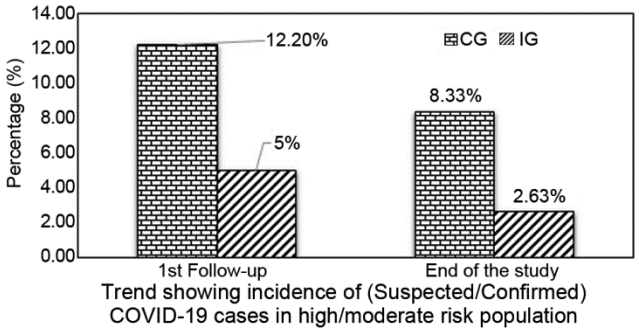

Fig. 2 — No. of participants developing Symptoms of COVID, CG= Control group; IG= Intervention group.

Data analysis

Objective and subjective parameters were analysed to univariate and multivariate analysis using Statistical Package for Social Sciences (SPSS) Ver.25.0. Continuous variable of normal distribution was presented as mean standard deviation (minimum- maximum) and compared by unpaired two-tailed Student's t -test. Continuous variable of skewed distribution was expressed as medians (interquartile ranges) and compared by Mann-Whitney U test. Categorical variables were expressed as number (%) and compared by Chi-square test or Fisher's exact test between both the groups.

Results and Discussion

Participants flow

The study was conducted in a high-risk population wherein at least one family member was COVID positive. A total of 81 participants were enrolled in the study. 11 participants were excluded as they developed symptoms akin to that of COVID-19.

Table 1 — Constituents of *KM* [7] *TA* [6] and Unani Joshanda

Unani name	Botanical Name	English name	Quantity
	Khamira Marwareed (KM)		
Marwareed	Pearls from *Mytilus margaritiferus*	Pearl	25 g
Tabasheer	Root of *Bambusa ardundinacea*, (Retz) Willd.	Common bamboo	25 g
Sandal	Wood of *Santalum album*, L.	Sandal	25 g
Ambar	*Ambragrasea*	Ambar	10 g
Arq e Gulab	*Rosa damascene*, Mill.distillate	Rose	1L
Arq Baidmushk	*Salix capera*, L. distillate	Pussy willow	1L
Qand safed		sugar	1.2 kg
	Tiryaq Arba (TA)		
Juntiyana	Root of *Gentiana lutea*, L.	Yellow gentian	1 part
Zarawand Taweel	Root of *Aristolochia longa*, L.	long aristolochia or sarrasine	1 part
Mur Makki	Resin of *Commiphora myrrha*, (Nees) Engl.	Myrrh	1 part
Habbul Ghar	Fruits of *Laurus nobilis* L.	Bay laurel	1 part
Asal/Qand safed		Honey or Sugar	Q.S.
	Unani Joshanda		
Behidana	Seed of *Cydonia oblonga*, Mill.	Quince fruit	5 g
Unnab	Fruit of *Zizyphus jujube*, Mill.	Common jujube	5 in number
Sapistan	Fruit of *Cordia myxa*, Linn.	Sebsten plum	5 in number

Demographic findings

Mean age of the participants was 41.42±16.9 years. Maximum participants (32.1%) were in the age group of 18-28 years. Mean age of 48 (59.26%) male participants was 42.04±16.80 years whereas mean age of 33 (40.74%) female participants was 40.51±16.73 years. About 18.52% more males enrolled in the study (Table 2).

Young males were more forthcoming to participate in the study. Our findings resonate with study conducted in 2019 wherein; adolescents when faced with adverse situation turn their negative experiences into positive ones, take greater responsibility for themselves and others, contribute to recovery processes, and engage in pro-social behaviours[13].

Mizaj (Temperament) is defined as the unique characteristic of an individual that affects the physical and emotional state of that individual and has a definite impact on the morphological, physiological, and psychological features of that individual[14,15]. People with *Damvi* (sanguineous) temperament have good judgment and have an optimistic outlook[16]. This could be the reason why 49.38% of the individuals enrolled were *damvi* or sanguineous. *Balghami* (phlegmatic) temperament individuals are prone to chest disorders and slow in their disposition[16-17], this could probably be the reason for 29.63% *balghami* individuals participated in the study (Table 2). This is appreciable as there is immense fear and apprehension among the masses regarding stigma associated with COVID-19.

Table 2 — Demographic distribution of the participant

	Group		Total (%)
	Intervention (%)	Control (%)	
Age (Mean±SD)	39.35±13.23	43.44±19.79	41.42±16.9
Temperament			
Damvi	22(55%)	18(43.9%)	40(49.38%)
Saudavi	0(0%)	5(12.2%)	5(6.17%)
Safravi	7(17.5%)	5(12.2%)	12(14.81%)
Balghami	11(27.5%)	13(31.71%)	24(29.63%)
Gender			
Male	24(60%)	24(58.54%)	48(59.26%) (42.04±16.80)
Female	16(40%)	17(41.46%)	33(40.74%) (40.51±16.73)

Efficacy

Number of patients turning COVID positive

None of the participant in either group was found COVID-19 positive at the end of study period. The participant from control group, 5 (12.20%) at first follow up and 3 (8.33%) by the end of the study developed COVID-19 like symptoms while in the Intervention group, 2 (5.0%) at first follow up and 1 (2.63%) by end of the study developed COVID-19 like symptoms respectively (Table 3, Fig. 3). The study was based on the hypothesis that Unani regimen could potentially be used as a safe prophylactic intervention along with standard precautionary measures, to prevent symptomatic infection in population having high risk of exposure to COVID-19. This can be because the regimen demonstrated its immune-modulating, anti-viral, and anti-oxidant effect within 2 weeks through its phyto-constituents[10-15,18-24]. Hence by the 15th day, most of the participants had experienced an improvement in their immune status and QoL.

Quality of life as measured with WHO QoL BREF

The mean changes in all the domains at baseline and end of the trial are statistically significant. The mean difference in physical health domain is 3.20 in IG and 0.12 in CG respectively while in psychological domain the mean difference is 2.02 in IG and -0.59 in CG respectively it is 0.21 in IG and 0.08 in CG

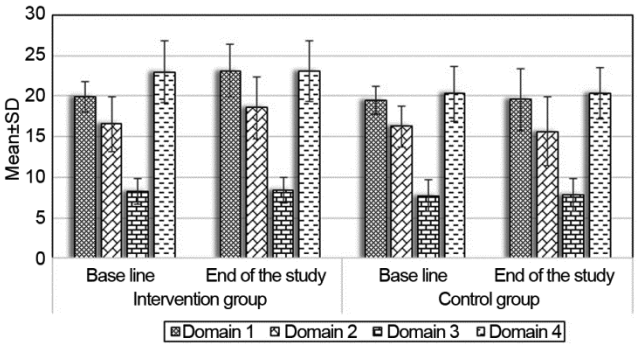

Fig. 3 — WHO-QOL-BREF Questionnaire wise distribution of participant.

Table 3 — No. of Participants developing Symptoms of COVID

	1st follow-up (%)	End of the study (%)	Cumulative total
No. of COVID-19 Suspected in Control group (Fever/Cough/Sore Throat/ Runny Nose) cases in Control Group	5(12.20%)	3(8.33%)	8(19.51%)
No. of COVID-19 Suspected (Fever/Cough/Sore Throat/ Runny Nose) cases in Intervention Group	2(5.0%)	1(2.63%)	3(7.5%)

respectively in social relation domain and 0.13 in IG and 0.06 in CG respectively in environmental factors domain (Table 4, Fig. 3). The improvement could be because KM is classically known for its immune-modulation properties[25] whereas TA is classically known as a brain and heart tonic[26]. The social relation domain and environmental factors are beyond the purview of therapeutics however, a statistically significant result was observed in them because a healthy body with a peaceful mind perceives thing in a positive manner.

The immune-modulating effect of the regimen was initiated within 14 days. KM increases bone marrow and spleen cells within 10-14 days[25]. The regimen demonstrated anti-viral effect within 2-10 days and so purged any viral nidus[18-19,27].

Immunity status as assessed with ISQ

There has been a highly significant improvement in the sudden high fever of the intervention group with a mean difference of 1.13 (P <0.001) over baseline and also significant results were obtained in the control group as well with the mean difference over baseline as 0.56. Although the mean difference between the two groups is approx. twice (Table 5, Fig. 4), but the fact that the population is acquiring immunity cannot be understated. There has been highly significant (P <0.001) improvement in the immune associated symptoms like diarrhoea, common cold and cough in both the groups. This improvement can be attributed to the phyto-constituents in the regimen which are anti-inflammatory and antioxidant too[20-22].

There has been significant improvement in the skin problems with P =0.05 in intervention group. This could be due to the fact that *Zizyphus jujube* is blood cleanser[24] and that most of the constituents are antioxidants. This is in contrast to a non-significant (P=0.34) decrease in skin problems in control group.

Muscle and joint pain increased in both the groups. The raise was not very significant (P=0.11) in intervention group however; it was significant in

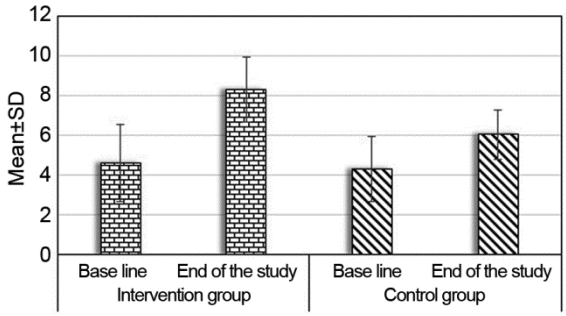

Fig. 4 — ISQ -wise distribution of participant.

Table 4 — WHO-QOL-BREF Questionnaire wise distribution of participant

Domain	Intervention Group		Control Group		Intervention Group			Control Group		
	Mean ± SD		Mean ± SD		Mean changes					
	Base Line	End of the study	Base Line	End of the study	Base Line vs End of the study		p-value	Base Line vs End of the study		p-value
Domain1 (physical)	19.93±1.91	23.13±3.28	19.46±1.75	19.59±3.83	3.20	↑	<0.001	0.12	↑	0.84
Domain2 (Psychological)	16.53±3.34	18.55±3.76	16.24±2.57	15.66±4.29	2.02	↑	0.002	-0.59	↑	0.43
Domain3 (Environmental)	8.21±1.58	8.42±1.63	7.75±1.90	7.83±1.96	0.211	↑	0.07	0.08	↑	0.18
Domain4 (Social)	22.95±3.81	23.08±3.72	20.28±3.41	20.33±3.23	0.13	↑	0.46	0.06	↓	0.76

Table 5 — ISQ -wise distribution of participant

ISQ Scores	Intervention Group		Control Group		Intervention Group			Control Group		
	Follow-up Period		Follow-up Period		Mean Changes					
	Base Line	End of the study	Base Line	End of the study	Base Line vs End of the study		p-value	Base Line vs End of the study		p-value
Sudden high fever	1.18±0.69	0.05±0.32	0.97± 0.37	0.42±0.50	-1.13	↓	<0.001	-0.56	↓	<0.001
Diarrhoea	0.74±0.64	0.08±0.27	1.19±0.88	0.39±0.59	-0.66	↓	<0.001	-0.81	↓	<0.001
Headache	1.63±0.97	1.42±1.00	1.81±0.85	1.80±0.82	-0.21	↓	0.17	-0.01	↓	0.97
Skin problems (e. g. acne& eczema)	1.00±1.04	0.87±0.99	1.53±1.29	1.36±1.31	-0.13	↓	0.05	-0.17	↓	0.34
Muscle and joint pain	1.47±1.28	1.71±1.18	1.33±1.28	1.94±1.54	0.24	↑	0.11	0.61	↑	0.03
Common Cold	1.84±0.85	0.05±0.23	1.39±0.76	0.92±0.60	-1.79	↓	<0.001	-0.47	↓	0.004
Coughing	1.29±0.73	0.13±0.52	1.31±0.78	0.31±0.46	-1.16	↓	<0.001	-1.00	↓	<0.001
ISQ Scores Final Score	4.61±1.91	8.29±1.62	4.33±1.63	6.03±1.25	3.68	↑	<0.001	1.69	↑	<0.001

control group (P <0.03). This raise in test group can be attributed to the fact that some of the drugs were cold in their temperament which could have accentuated the joint pain in *Balghami* individuals.

Conclusion

Of the 81 participants enrolled, none of the participants were tested COVID positive however, 11 (13.58%) participants developed COVID like symptoms and 70 (86.42%) non COVID-19 patients completed the study. The mean age of the participants was 41.42±16.9 however, 18-28 years male with *damvi* (sanguine) temperament participated zealously in the study despite the palpable fear of COVID-19 among the masses. The study provides evidences of enhanced immunity as both the groups registered a highly significant (P <0.001) improvement in their immunity status. Relative risk reduction for the test group was 62% after taking Unani prophylactic regimen. The Unani regimen worked at different areas because of the array of phyto-constituents present in each formulation. Since the phyto-constituents brought about the anti-viral, immune-modulator, anxiolytic, anti-inflammatory and anti-oxidant within 2 weeks hence the intervention group did give an advantage over the control group. No adverse events were reported during the study. The study being a pilot study may open avenues for studies on a larger sample size and for a possible study on hospitalized cases.

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Conflict of interest

The authors declare no conflict of interest

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