

Intervention of Unani Medicine in the Prevention and Management of COVID-19: An Overview

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Abstract

Background & Objective: An acute respiratory disease caused by a novel coronavirus (SARS-Cov-2), the coronavirus disease 2019 (COVID-19) originated in Wuhan, China and spread throughout the world. On 30th January 2020, World Health Organization (WHO) officially declared the COVID-19 pandemic as a public health emergency of international concern. Meanwhile, several independent research groups have identified that SARS-CoV-2 belongs to β -coronavirus, with a highly identical genome to bat coronavirus, pointing to bat as a natural host. This novel coronavirus uses the same receptor, angiotensin-converting enzyme-2 (ACE 2) as that for SARS-CoV, and mainly spreads through the respiratory tract. The clinical symptoms of COVID-19 include fever, cough, fatigue and a small population that appeared gastrointestinal infection symptoms. The elderly and people with underlying disease are more susceptible to infection and more prone to a serious outcome. The development of vaccines for SARS-CoV-2 is ongoing and various clinical trials are currently underway around the world, however, an effective vaccine may take years to develop and to manufacture on a global scale. At present no pharmacological treatment has been shown to be reliable, safe and effective for treating COVID-19. Hence it is the need of the hour to provide safe and effective treatment to combat this global pandemic and for this purpose Unani system of Medicine can play an important role. These medicines are in use since antiquity, easily available and have lesser known side-effects. In Unani Medicine, there is a large number of single drugs and compound formulations which are clinically as well as experimentally proved to be effective in the prevention and management of epidemics. The present review has been embarked on to explore the Unani perspective into the scientific insight on epidemic diseases with a focus to unearth the prevention and treatment of the COVID-19 pandemic.

Material and Methods

A manual survey of classical Unani literature was conducted to collect the information on epidemics, its prevention and management. In addition, articles were retrieved using PubMed, Science Direct and Research Gate with the search name Unani Medicine, COVID-19, Waba (Epidemic), Antiviral, Anti-inflammatory, Immunomodulators and Prophylaxis. The search was carried out to identify experimental and clinical studies on drugs mentioned in the literature in context with the pandemic of COVID-19.

Conclusion

The aforesaid Unani literature and contemporary materials surveyed have yielded substantial key information in the prevention and management of COVID-19. However, their efficacy and safety still need scientific validation through rigorous randomized controlled trials.

Keywords: Unani Medicine, Epidemic, COVID-19, Immunomodulators, Antiviral, Prophylaxis.

Introduction

In the winter of 2019, another SARI outbreak occurred in Wuhan, China, which very quickly spread around the world. The culprit was identified as another novel coronavirus, which the WHO named as SARS-CoV-2 due to similarities to SARS-CoV, and the disease was called coronavirus disease 2019 (COVID-19). SARS-CoV-2 first emerged in Wuhan, Hubei Province, China in December 2019, after a cluster of pneumonia cases with unknown causes was reported. The COVID-19 outbreak in Wuhan quickly spread around the world within a very short period. There are 5.5 million confirmed cases of COVID-19 and 347,587 COVID-19 related deaths worldwide up to 27 May 2020, giving a crude case-fatality rate of approximately 7%. SARS-CoV-2 is a newly emergent coronavirus closely related to SARS and MERS¹. As of 26 July 2020, there were 467,882 active cases, 885,576 cured 1 migrated and 32,063 death in India. This was the highest ever recovery registers in a single day with over 36,000 patients' discharges with a new high recovery rate of 64%. As per the report, on 2 August 2020, there were 567,730 active cases, 1145629 cured 1 migrated, and 37,364 Deaths in India. India's Case Fatality Rate (CFR) is its lowest at 2.15% since 1st lockdown. As of 8th August 2020, a total of 2152,020 cases and 43,453 deaths have been reported in the country. Total number of 7,19,36 tests have been done in India till 8th August 2020. The data have opted from the dashboard of the Government of India (GOI) which daily updates the number of confirmed, recovered, and death cases in the country². The

pathophysiology of COVID-19 has yet to be confirmed, but it is likely to involve inflammatory processes that can trigger a massive cytokine storm. The cytokine profile of critically ill patients revealed increased levels of interleukin (IL)-2, IL-7, IL-10, granulocyte-colony stimulating factor, interferon- γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- α , and tumour necrosis factor- α ³. Histopathological examination of the lungs of patients with COVID-19 revealed immunopathological changes including diffuse alveolar damage, desquamation of pneumocytes, pulmonary oedema, hyaline membrane formation, and interstitial mononuclear inflammatory infiltrates⁴. According to the limited number of reports of biopsy/autopsy results of patients with COVID-19, the pathological features resemble those seen in SARS and MERS virus infections^{4,5,6}. The virus is commonly spread when people come in close contact with each other. It is spread via small droplets produced by coughing, sneezing, and talking. As per WHO the droplets can stay on the ground for more than 24 hrs. One can get infected by touching a contaminated area and then touching their nose, eyes, and mouth. It is also possible for the virus to spread before showing any symptoms. The symptoms usually show up between 14-28 days. It is most contagious during the first three days after the onset of symptoms, although the spread is possible before symptoms⁷. Based on the current epidemiological investigations, the incubation period is 1-14 days, mostly 3-7 days and COVID-19 is contagious during the latency period. The viral research institution in china has conducted a preliminary identification of the SARS CoV-2 through the classical Koch's postulates and observing its morphology through electron microscopy. So far, the golden diagnosis method of COVID-19 is nucleic acid detection in the nasal and throat swab sampling or another respiratory tract sampling by real time PCR and further confirmed by next generation sequencing⁸. COVID-19 is characterized by symptoms such a fever, sore throat, lesions in lungs and difficulty in breathing. People have also experienced dry cough, lymphopenia, fatigue, anorexia, arrhythmia and shock. The severity of the symptoms depends on the overall health of a person, extent of spread, and virulence of the strain⁹. Most adults or children with SARS-CoV-2 infection presented with mild flu like symptoms and a few patients are in critical condition and rapidly develop acute respiratory distress syndrome, respiratory failure, multiple organ failure and death.⁸

In this regard, Unani system of Medicine can play an important role in protecting public health by providing preventive, supportive and rehabilitative care to the patients. In Unani Medicine, there is no disease mentioned in the name of COVID-19 although many Unani scholars have mentioned the disease of *Nazla-e-Wabaiya* with their symptoms closely resembles that of COVID-19^{10,11}. As per Unani classical wisdom, improving immunity with immune boosters is one of the key approaches for the prevention of disease and maintenance of health. Therefore, a strategy to enhance immunity and providing symptomatic relief in upper respiratory tract infection is advocated in the management of COVID-19¹².

There are large number of single drugs and compound formulations in Unani Medicine which exhibits many pharmacological properties base on its phytochemical constituents which can be further utilized alone or in combination to combat this global pandemic. Scientific studies and clinical researches reveal the presence of a large number of pharmacologically substances which may provide new insight into the management of COVID-19. Hence in this review, the authors have attempted to highlight the knowledge and practice of Unani medicine with a possible approach in the prevention and management of COVID-19 in the present scenario.

Material and Methods

A manual survey of classical Unani literature was conducted to collect the information on epidemics, its prevention and management. In addition, articles were retrieved using PubMed, Science Direct and Research Gate with the search name Unani Medicine, COVID-19, Waba (Epidemic), Antiviral, Anti-inflammatory, Immunomodulators and Prophylaxis. The search was carried out to identify experimental and clinical studies on drugs mentioned in the literature in context with the pandemic of COVID-19. The discussion is based on, but not limited to search results.

Waba (Epidemic) in Unani Medicine

Epidemic referred to as *Waba* in Unani medicine, are thought to occur if such *ajsam-i-khabitha* (contagions) find a place in air and water. According to Ibn-e-Sina (980-1035 AD), air and water are contaminated only after admixture of *ajsam-i-khabitha*. He also stated that epidemics spread from one person to another and from one city to another like a message¹³⁻¹⁴. He also stated one of the bilious forms of infectious fever and advised to restrict fruit juices for at least one week and encouraged to use barley water¹⁵. Zakariya Razi (865-925AD) mentioned in his classical text *Kitab fi al-jadari wa-al-hasbah* (book on small pox and measles) the mode of spread of the two diseases and their differential diagnosis. In another famous book *Kitab-al-Mansoori*, he further states that epidemic spread in the autumn season, especially if the preceding summer season was humid and the wind is still. He stressed the fact that there will always be something common in the patients of epidemics, whether a place, food, drink, or travel history^{14,16}. The 13th century Persian scholar Najeebuddin Samarqandi mentioned about the type of *Nazla-e-Wabaiya* in his treatise *Al Asbab-wa-Alamat* that these type of patients shows the symptoms of fever, sneezing, sore throat, nasal irritation and malaise. He further states that the patient of *Nazla-e-Wabaiya* may also suffer from cough, diarrhoea and delirium. Pleurisy and pneumonia, if present worsens the prognosis¹⁰.

Thus, despite the lack of technological advancement at that time, it is evident that Unani scholars are quite aware of the concept of the epidemic, its transmission from infected to a healthy person, and the symptoms mentioned under the disease of *Nazla-e-Wabaiya* which closely resembles with the symptoms of COVID-19.

Management

As of date, there is no specific treatment available against COVID-19, hence the emphasis is being laid on preventive and symptomatic treatment. In the literature of Unani medicine, the symptoms of COVID-19 closely resemble with *Nazla-e-Wabaiya*. The important ways that are employed for the treatment in Unani medicine for epidemic diseases are:

- I. Preventive Measures
- II. Sanitization
- III. Dieto-therapy
- IV. Pharmacotherapy

I. Preventive Measures

Unani system stresses the importance of prevention of disease more than its treatment. The Unani system is holistic which considers the whole personality of an individual rather than a reductionistic approach¹⁷. Zakariya Razi (865-925 AD) in his classical text advised not to visit a place where an epidemic is spreading. If an epidemic is present then a person is advised to live-in a well-ventilated room. Care must be taken while interacting with an infectious person, air current must not flow from the patients to healthy persons¹⁵.

Unani physicians have given importance to the prevention of disease, and the promotion of health is better than cure that can be achieved by maintaining proper equilibrium in *Asbab-e-Sitta-Zarooria* (six essential factors of life) and they can play an important role in the maintenance of human health. It has a theory on the six essential prerequisites for the prevention of disease and it places great emphasis on the maintenance of a proper ecological balance and on keeping water, food and air free from all pollution and pathogens. The six essential factors are illustrated as, *Hawa-e-Muheet* (air), *Makoolat wa Mashrubat* (foods and drinks), *Harkat wa Sukoon Badani* (physical activity and rest), *Harkat wa Sukoon-e-Nafsani* (psychological activity and repose), *Nuam wa Yaqza* (sleep and wakefulness), *Is'tifragh wa Ihtebas* (elimination and retention). When all six factors are in equilibrium health is preserved, otherwise it requires modification^{17,18}.

Riyazat (Exercises) can also be adapted as a preventive measure in the current pandemic as it enhances the overall health and well-being. It is a voluntary movement that helps in the diversion of morbid humour and thus helps in disease prevention. It improves the metabolism of the body, removes toxic matter, tone up individuals and maintains the flexibility of the body. Various Unani physicians like Avicenna, Ismail Jurjani, Zakariya Razi, Rabban Tabri, and Buqrat have described employment of exercise for various parts of the body like exercise for eyes, ears, chest and respiratory organs, digestive system, various muscular exercises were also explained by them¹⁹.

II. Sanitization

In addition to the above measures, proper sanitization of the surroundings is necessary which includes the fumigation of medicinal herbs and spraying of medicinal herbs solution in the residential places. *Arq-e-gulab* (*Rosa damascena*) is advised to use on the body and curtains. If the air smells foul then fumigation with *Sandal* (*Santalum album L.*) and Camphor is also advisable¹⁴. A large number of drugs such as *Sandrus* (*Trachylobium hornemannianum*), *Kafoor* (*Cinnamomum camphora*), *Qust* (*Sausurea lappa*), *Kundur* (*Bowsellia serrata*), *Ood* (*Aquilaria agallocha*), *Mushk* (Musk), *Murr* (*Commiphora myrrh*), *Loban* (*Styrax benzoin*), *Sa'ad kufi* (*Cyperus rotundus*), *Izkhar* (*Cymbopogon jwarancusa*), *Abhal* (*Juniperus communis*), *Waj* (*Acorus calamus*), *Tagar* (*Valeriana wallichii*), *Aas* (*Myrtus communis*), and *Safarjal* (*Cydonia oblonga*) have been mentioned by Unani scholars for the purification of air. Sprinkling the mixture of *Sirka* (vinegar) and *Hilteet* (*Ferula asafoetida*) or vinegar and water in residential places has also been recommended during epidemics²⁰.

Unani Immunomodulatory Herbs

Unani system of Medicine believes that Medicatrix Naturae (*Tabiat* or *Quwwat-e-Mudabbira-e-Badan*) is the supreme power that controls all physiological functions of the body, provides resistance against diseases and helps in healing naturally. Toning up the organs and the immune system is the unique approach of Unani medicine known for its beneficial effects^{12,21}.

Immunity can be defined as the ability of the body to neutralize and eliminate the pathogenic micro-organisms and their toxic products, thus protecting the individual. Intervention by the physician is required to help *Tabiat* so that it can accelerate the process of elimination of the disease from the body. Herbal drugs are known to possess immunomodulatory properties and generally act by stimulating both specific and non-specific immunity²².

So, the effective way to control the spread of infection is to strengthen the host defence by the rational use of Unani immunomodulator drugs during the epidemic and pandemics. Some important Unani herbs are listed below.

Neem (*Azadirachta indica*)

Aqueous extract of neem flower possesses potent immune-stimulant activity when they are given at doses of 200 to 400mg/kg, p.o to albino mice by stimulating both specific and nonspecific immune response and thus it can be used as a complementary therapeutic agent²³.

Asgand (*Withania somnifera*)

A significant increase of antibody titer to B. Pertussis was noticed when a standardized aqueous extract of Asgand was evaluated in laboratory animals immunized with DPT vaccine²². Administration of an extract from the powdered root of the plant with Somnifera was found to stimulate immunological activity in Bab/mice. Treatment with five doses of *Withania* root extract (20mg/dose/animal; i.p) was found to enhance the total WBC count (17125 cells/mm) on 10th day²⁴.

Kalongi (*Nigella sativa*)

It is reported that there is an increase in the phagocytic activity by immune cells and an increase in the activity of immune potential when ethanol extract of Kalongi seeds 1.5g/kg, b.w was orally administered in dexamethasone induced immune suppressed male rabbits for 42 days. The immunomodulatory actions may be due to its main constituents thymoquinone, nigellone and d-limonene through their antioxidant and anti-inflammatory activities²².

Haldi (*Curcuma longa*)

Administration of Haldi aqueous extract in carbon tetra chloride intoxicated mice renders the macrophages to acquire abnormal surface morphology so that they can function normally. The mechanism involving this protection by the Haldi extract is probably due to the production of monocyte colony stimulating factor or granulocyte-monocyte stimulating factor. Curcumin is the main active constituent of Haldi²⁵.

Gilo (*Tinospora cordifolia*)

Tinospora cordifolia extract was tested for acute toxicity at the given dose (150mg/Kg body weight) by lactate dehydrogenase (LDH) assay. The number of morphologically altered macrophages was increased in mice exposed to carbon tetrachloride. At the end of study, it was observed that the polar fractions of *Tinospora cordifolia* stem parts contain major bioactive compounds, which directly act on peritoneal macrophages and have been found to boost the non-specific host defences of the immune system²⁶.

Besides these single drugs, there are some Unani compound formulations, used for toning up the organs and can act as an immunomodulator such as Habb-e-Asgand, Habb-e-Jawahar, Habb-e-Papita, Tiryaq-e-Wabayi, Khamira Marwareed, Khamira Gaozaban Sada, Dawaul Kurkum Kabeer, Dawaul Misk Motadil Sada, Jawarish Shahi, Jawarish Amla and Arq-e-Gaozaban^{27,28,29}.

Compound immunomodulatory formulations**Tiryaq-e-Wabayi**

Prevention of *Wabai Amraz* with *Tiryaqi adviya* (Antidote drugs) is recommended since ancient times. Ibn-e-Sina (980-1035 AD) described that the person who uses Tiryaq-e-Wabayi in healthy conditions will not be affected by infectious disease because it helps in strengthening *Rooh* (pneuma) and maintaining health. *Rooh* stimulates *Harart-e-Ghariziya* (innate heat) thus helps to protect *Tabiat* from harmful effects of morbid materials³⁰.

Tiryaq-e-Wabayi is well documented and well known pharmacopeial drug in Unani system of medicine used as prophylaxis during the epidemic of cholera and other epidemic diseases^{29,31}. Dosage is 1-2 pills morning and evening with 60ml Arq-e-Gulab or with 120 ml Arq-e-Badiyaan two times in a week²⁹.

Table No. 1: Constituents of Tiryaq-e-Wabayi

S.No.	Name of drug	Part used	Action	Chemical constituents
1.	Sibr (<i>Aloe barbadensis</i>)	Pulp	Immunomodulation antiviral, anticancer, hepatoprotective and antioxidant	Anthraquinones, tricyclic aromatic quinines, polysaccharides, vitamins, minerals and enzymes, sterols ³² .
2.	Mur makki (<i>Commiphora myrrh</i>)	Resin from the stem	Antidote, cytotoxic, anti- inflammatory, analgesic, antioxidant, antiviral and expectorant	Volatile oil (cuminic aldehyde), resins, gums, flavonoids, alkaloids, glycosides, saponins, terpenoids ^{33,34} .
3.	Zafran (<i>Crocus sativus</i>)	Dried stigmas and top of styles	Immunostimulatory, antioxidant, antimicrobial, anti- inflammatory and anxiolytic.	Crocin, crocetin, safranal and picrocrocin, anthocyanin, α and β carotene ³⁵ .

A study was conducted to evaluate the immunostimulating effect of Tiryaq-e-Wabayi in elderly persons at the dose of 500mg three times a week for 45 days. The response was measured by the assessment of total leucocyte count (TLC) every 15th day up to 45 days and lymphocyte percentage, absolute lymphocyte count (ALC), CD4 count, CD8 count, pre and post-treatment. This study suggests that Tiryaq-e-Wabayi has immunostimulating capabilities and provides direct evidence for its immunostimulant effects in humans. Thus, this compound formulation can be used in the condition where immunostimulant is required like immunodeficiency diseases, allergic manifestations and combined therapy with antibiotics³¹. According to the Unani perspective this formulation provides strength and vitality to the organs and it can be used as a prophylaxis in SARS-CoV-2.

Khamira Marwareed

Khamira Marwareed is an Unani preparation that has been used as a rejuvenator and vitalizer for centuries. It is generally prescribed as a tonic for the heart, brain and useful in palpitation and general weakness. It usually acts as a recuperating agent to overcome fatigue and weakness in chicken pox and typhoid³⁶. It is a compound Unani formulation containing four constituents of plant origin, two constituents of animal origin and prepared according to NFUM³⁷.

Ingredients	Quantity
Marwareed (<i>Mytilus margaritifera</i>)	25 g
Tabasheer (<i>Bambusa arundinacea</i>)	25 g
Sandal Safaid (<i>Santalum album</i>)	25 g
Ambar (<i>Ambra grasea</i>)	10 g
Arq-e-Gulab (<i>Rosa damascena</i>)	1 Lt
Arq-e-Baidmushk (<i>Salix caprea</i>)	1 Lt
Qand Safaid	1.2 kg

A study was conducted to evaluate the immunopotentiating effect of Khamira Marwareed in an animal model. The administration of Khamira Marwareed resulted in elevated levels of IgG2a and IgG2b. Administration of Khamira Marwareed for 10 or 15 days elicited an increase in a delayed type hypersensitivity response suggesting an immunostimulatory effect for Khamira Marwareed through a mechanism leading to a TH1-dominant immune state³⁶. The normal dosage of Khamira Marwareed is 3-5 gm, empty stomach in the morning²⁸.

As we are aware of the fact that COVID-19 is affecting elderly persons with comorbid conditions and the persons in which immunity is greatly affected, so these single and compound formulations may provide some promising results to cope with the pandemic of COVID-19 by enhancing the basic level of an immune response against the virus with its prophylactic properties based on the active constituents present in these drugs.

III. Dieto-therapy

The physical and mental health of a human being is largely dependent on good nutrition. Unani medicine lays great stress on treating certain ailments by the administration of a specific diet or by regulating the quantity and quality of food. In the current pandemic of COVID-19, patients are advised to take diet according to their temperament. The diet should be nutritive, easily digestible and frequent meals in small quantity is advised. Coldwater should be avoided to drink. It is also advised to avoid sweets, fruits and meat. Citrus and sour fruits such as grapes, apples and lemon are supposed to be beneficial in an epidemic^{12,14,16}. In addition to nutritive properties there are several food items and dry fruits discussed below that possess certain research proven pharmacological properties which can be beneficial in the prevention and management of COVID-19.

1. Anjeer (*Ficus carica*)

It is known to be the first plant cultivated and the oldest fruit tree by a human. Commonly fruit (fresh & dried) bark, leaves, roots, and latex are used. It is *Mughazzi* (nutritive), *Mohallil* (anti-inflammatory), *Mulayyin* (laxative) and it is a drug of choice for chicken pox and measles. It is used in chronic dry cough, throat dryness, chest pain, breathlessness, constipation and colitis. Normally 2-3 fruits per day can be used³⁸.

1.1 Antioxidant activity

One study stated that the hydroalcoholic extract was found to scavenge the superoxide generated by photo-reduction of riboflavin in a concentration dependent manner. The presence of flavonoids which are reported to be found in a drug is responsible for its antioxidant property³⁹. Another study stated that flavonoids, carotenoids and triterpenes have antioxidant activity by scavenging reactive oxygen species which prevent potential damage to cellular components such as DNA, proteins and lipids⁴⁰.

1.2 Antibacterial activity

Antibacterial activity was also reported using the well diffusion method by measuring the zone of inhibition by an antimicrobial susceptibility test. Three gram positive bacteria (*Staphylococcus epidermidis*, *Bacillus subtilis*, *Staphylococcus aureus*), and a gram negative bacterium *Proteus mirabilis* were used to evaluate the antibacterial activity of dried fig extract. The dried extract of fig was found to have higher antibacterial activity against *Proteus mirabilis*⁴¹.

1.3 Antiviral activity

Houda Lazreg Aref et al. proved in his study that hexanic extract and hexane-ethyl acetate extract, both possessed antiviral activity against HSV-1, ECV11 and ADV. Extract of *Ficus carica* are capable of deteriorating the integrity of the virus and to prevent it from carrying out its infection. This activity could be due to the presence of ferulic acid as the main phenolic compound⁴².

It is a good source of vitamins, minerals (calcium, sodium and potassium), essential amino acids, dietary fibres and the best nutrient score among the dried fruits. *Ficus carica* is a rich source of naturally occurring antioxidants like phenolic compounds, flavonoids, phytosterols, sterols, anthocyanins and volatile compounds. Phenolic compounds and flavonoids play a vital role in preventing the health disorder which is related to oxidative stress including cardiovascular diseases, neurodegenerative diseases and cancer³⁸.

2. Khajoor (*Phoenix dactylifera*)

This plant is widely used by the Unani Medical practitioners for nutritive purposes and to cure various diseases. Its fruit is known as date which is the edible part of the plant. It is safe to suggest that their consumption should be recommended daily for better health and vigor. This plant has great medicinal value as it has been reported to have versatile phytochemicals including phenolics, sterols, carotenoids, anthocyanins, procyanidins, flavonoids, different minerals and vitamins. The fruit are rich in carbohydrates, vitamins and proteins. It has different pharmacological actions like antibacterial, anti-inflammatory, antidiabetic, antiasthmatic, nephroprotective and hepatoprotective activities⁴³.

2.1 Antioxidant activity

Saleh Mobarak Al-Turki analyzed antioxidant properties of date palm cultivars from the United States and Saudi Arabia for their total phenolic content and antioxidant activity for two years. The amount of phenolic compound and antioxidant activity in all date fruit and pit cultivars tested in this study. Results showed that the total polyphenolic content of fruit ranged from 507.03 to 225.02 mg gallic acid equivalent and antioxidant activity ranged from 1400.00 to 228.06⁴⁴.

2.2 Anti-inflammatory activity

Oral administration of the methanolic and aqueous extracts of the edible portion of *Phoenix dactylifera* fruits suppressed the swelling in the foot significantly by 67.8 and 61.3% respectively, while the methanolic extracts of date seeds showed a significant reduction by 35.5% in adjuvant arthritis in rats by mechanistically reducing ESR and plasma fibrinogen and normalizing the plasma level of antioxidants. Administration of the extracts also produced a significant increase in body weight gain and food efficiency ratio⁴⁵.

2.3 Immunostimulatory activity

Immune activation is an effective as well as a protective approach against infectious diseases. It enhances the overall immunity of the host, and present a non-specific immune response against the microbial pathogens. They also work to heighten humoral and cellular mediated immune responses, by either enhancing cytokine secretion, or by directly stimulating B or T-lymphocytes. Ingestion of phytochemicals to support the immune system or to combat infections has been a long standing traditional practice. Feeding of ethanol extract of dry dates to parturated mice enhanced both cell mediated and humoral immunity ⁴⁶.

3. Badam shireen (*Prunus dulcis*)

In Unani literature, it is mainly described as *Muqawwi-e-Dimagh* (brain tonic), *Murattib-e-Dimagh* (brain demulcent), *Mulayyin* (laxative), *Muqawwi-e-Bah* (aphrodisiac) and *Mughazzi* (nutritious) etc. Its nutritional values are very high, most of the essential nutrients are present in sufficient amounts which are necessary for the body development and immunity boosting against the diseases and so it is one of the best immune-boosters which is needed by a person to remain healthy. In epidemic and pandemic, people need such types of nutritional immuno-enhancers which strengthen their body to fight against the diseases. Its nutritional value is very high and is full of all the essential ingredients of a healthy diet. Almond contains carbohydrates, fat, proteins. It also contains many important and essential minerals and vitamins like calcium, phosphorous, iron, potassium, magnesium, manganese, zinc, copper, sulphur, chlorine, iodine, thiamine, riboflavin, nicotinic acid and folic acid. The active constituents of almonds are globulins such as amandine and albumin; amino acids such as arginine, histidine, lysine, phenylalanine, leucine, valine, tryptophan, methionine and cysteine ^{47,48}.

3.1 Immunostimulant properties

A recent study conducted by Adriana Arena, et al. has suggested that almonds, specifically the skin of almonds, may support immune system function, in this study they have evaluated that with almonds, high levels of cytokine production were observed i.e., interferon- α (INF- α), interleukins (IL-12), INF-gamma and tumour necrosis factor (TNF- α). Their data suggested that almonds improved the immune surveillance of the peripheral blood mono nuclear cells towards viral infections. Almonds also were found to induce a significant decrease in the Herpes simplex virus (HSV-2) replication. Thus, the study indicates that (natural) almond skins may stimulate the immune response and thus contribute to an antiviral immune defence ⁴⁹.

3.2 Antioxidant activity

A study conducted by Ali Jahanban Isfahan, and others demonstrate that the methanolic extracts of almonds possessed antioxidant and antiradical activities and that their phenolic extract may help prevent or slow the processes of various oxidative stress related diseases. The results showed that the antioxidant and the anti-radical activities of the almond hull (green outmost layer of almond) were higher than those of its shell ⁵⁰.

4. Asal (Honey)

Asal (Honey) can be considered as a serine potential natural antioxidant medicine and natural food supplement. It has been established as a potential therapeutic antioxidant agent for various biodiverse ailments. Data report that it exhibits strong wound healing, antibacterial, anti-inflammatory, antifungal, antiviral, and antidiabetic effects. It also retains immunomodulatory, estrogenic regulatory, antimutagenic, anticancer, and numerous other vigor effects. Data also show that honey, as conventional therapy, might be a novel antioxidant to abate many of the diseases directly or indirectly associated with oxidative stress ⁵¹.

4.1 Antibacterial activity

Different clinical trials and in vitro studies have reported broad spectrum antimicrobial properties of honey ⁵². It was reported that honey constrains the growth of pathogenic strains such as *Streptococcus pyogenes*, *Streptococcus typhi*, *Staphylococcus aureus*, coagulase negative *Streptococcus* and *E. coli*, and species ⁵³.

4.3 Antiviral activity

The viral activity is usually elicited by native or universal stimuli which lead to infections and lesions. Data of in vitro studies has shown antiviral activity of honey against different types of viruses such as Rubella, herpes simplex, and varicella zoster viruses ⁵⁴.

4.3 Anti-Inflammatory activity

Recent evidence of in vivo studies has shown the anti-inflammatory mechanisms of honey. These studies showed that honey decreases edema and plasma levels of proinflammatory cytokines such as IL-6, TNF- α , PGE2, NO, iNOS, and COX-2. It was also demonstrated that honey attenuates NF- κ B translocation to the nucleus and suppresses I κ B α (inhibitor of kappa B) degradation. It has been reported that phenolic acids and flavonoids such as chrysin, quercetin, and galangin can suppress the activity of proinflammatory enzymes, for example, cyclooxygenase-2 (COX-2), prostaglandins, and inducible nitric oxide synthase (iNOS) ⁵⁵.

4.4 Immunomodulatory activity

Honey was found to provoke stimulation to the immune system of the body to combat infections in rats. It stimulates T-lymphocytes, B-lymphocytes, and neutrophils in cell culture. B-lymphocytes ultimately stimulate the production of antibodies in primary and secondary immune responses against thymus-dependent and thymus-independent antigens. It stimulates monocytes to release cytokines such as TNF- α , IL-1, and IL-6, activating numerous aspects of an immune response ⁵⁶.

These food supplements and dry fruits not only provide energy and essential nutrients to the body but the research based phytochemical analysis shows that the active constituents present in these food supplements also possess pharmacological properties against some bacteria and viruses and have immunostimulatory effects suggesting its use in COVID-19. They can be given to the healthy persons during an epidemic or the persons infected by the SARS-CoV-2 as prophylaxis or to cure the disease.

IV. Pharmacotherapy

Unani physicians have prescribed several single drugs as well as compound formulations for the prevention and treatment of infectious disease in general which are discussed in Table No.2 and Table No.3.

Table No. 2: List of Single Drugs

S. No.	Name of the Drug	Scientific Name	Parts Used	Pharmacological Actions	Chemical Constituents
1.	<i>Aslussoos</i>	<i>Glycyrrhiza glabra</i>	Root	Antitussive, expectorant, antioxidant, anti-inflammatory, antibacterial, antiviral, immunostimulatory and hepatoprotective.	Glycyrrhizin (glycyrrhizic acid; glycyrrhizinate), flavonoids, isoflavones glabridin and hispaglabridins A, B, geraniol, pentanol, propnoic acid, benzoic acid, 6-acetyl-, 5-hydroxy-4-methylcoumarin and asparagine ⁵⁷ .
2.	<i>Banafsha</i>	<i>Viola odorata</i>	Leaves, flowers and stems	Antibacterial, analgesic, antipyretic, antioxidant, anti-inflammatory, anticancer, diuretic, hepatoprotective and diuretic. It is useful in asthma, tonsillitis, peritonsillar abscess, chronic rhinosinusitis, insomnia and depression.	Salicylic acid, violin, volatile oil rutin, glycoside of methylsalicylate, essential oil, alkaloids, vitamin C, flavonoids, potassium, magnesium, sodium and iron ⁵⁸ .
3.	<i>Behidana</i>	<i>Cydonia oblonga</i>	Seeds, fruit and leaves	Immunological and antiallergic effects, antioxidant, antimicrobial, anti-inflammatory and antidiabetic	Phenolics, pectins, volatile oil, essential oil contains aromatic aldehyde, fatty acids, oxygenated monoterpene. Fruit contains proteins, carbohydrates, lipids, minerals such as Na, K, Ca, Mg, Fe, Cu, Zn and Mn ⁵⁹ .
4.	<i>Darchini</i>	<i>Cinnamomum zeylanicum</i>	Bark	Analgesic, antipyretic, antimicrobial, anti-inflammatory, antioxidant, antiviral, expectorant, sedative and hepatoprotective. Useful in asthma, bronchitis, cough, cold, flu and sinusitis.	Cinnamic acid, cinnamaldehyde, eugenol and essential oils ⁶⁰ .
5.	<i>Gaozaban</i>	<i>Borage officinalis</i>	Flowers and leaves	Antioxidant and anti-inflammatory. Useful in cough, bronchitis, respiratory infections and cardiovascular disorders.	Mucilage, tannins, saponins, essential oil, alkaloid, vitamin C, Ca, K. It has tannins resins, beta carotene, niacin, riboflavin, thiamine, silicic acid and choline arabinose ¹⁵ .
6.	<i>Gilo</i>	<i>Tinospora cordifolia</i>	Stem/whole plant	Analgesic, antipyretic, anti-asthmatic, immunomodulatory, anti-inflammatory, antioxidant, antibacterial, anticancer and useful in allergic rhinitis.	Alkaloids, glycosides, steroids, sesquiterpenoids, aliphatic compounds, essential oils, mixture of fatty acids and polysaccharides. The alkaloids include berberine, bitter gilonin and non-glycoside gilonin gilosterol ⁶¹ .

7.	<i>Karanjwa</i>	<i>Caesalpinia bonducella</i>	Seeds	Anti-inflammatory, antimicrobial, antipyretic, immunomodulator antitumor, antiviral, antimalarial and antioxidant	Alkaloids, flavonoids, glycosides, saponins, tannins and triterpenoids ^{12,62} .
8.	<i>Berg-e-Reehan</i>	<i>Ocimum sanctum</i>	Leaves	Anticancer, antipyretic, analgesic, cardioprotective, antiviral, antibacterial, immunomodulator, antistress, anticoagulant and expectorant. Useful in asthma, bronchitis, cold and flu.	Volatile oil (71% eugenol & 20% methyl eugenol), phenolic compounds such as cirsilineol, circimaritin and rosameric acid. Flavanoids (orientin & vicenin), sesquiterpenes and monoterpenes ⁶³ .
9.	<i>Sapistan</i>	<i>Cordia myxa</i>	Fruits and leaves	Analgesic, anti-inflammatory, antimicrobial, immunomodulators, antioxidant and broncho-relaxant effect.	Glycosides, flavonoids, sterols, saponins, terpenoids, alkaloids, phenolic acids, coumarins, tannins, resins, gums and mucilage ⁶⁴ .
10.	<i>Khaksi</i>	<i>Sisymbrium irio</i>	Seeds	Antimicrobial, anti-inflammatory, antipyretic, analgesic, bronchoprotective and expectorant.	Glycosides, alkaloids, flavonoids, phenolics, amino acids, stigmasterol's, sitosterols and glucosinolates ⁶⁵ .
11.	<i>Unnab</i>	<i>Zizyphus jujube</i>	Fruit	Antioxidant, anti-inflammatory, antimicrobial, anticancer, nutritive, blood purifier, cough suppressant and anti-asthmatic.	Vitamin C, phenolics, flavonoids, triterpenic acids, polysaccharides, alkaloids and glycosides ⁶⁶ .
12.	<i>Zanjabeel</i>	<i>Zingiber officinale</i>	Rhizome	Antimicrobial, anti-inflammatory, analgesic, anxiolytic, digestive, expectorant and hepatic cholesterol lowering activity. Useful in flatulence, asthma, bronchitis, cold and flu, dry cough, hoarseness of voice and headache.	Protein, fat, fibre, carbohydrates, Ca, P, Fe, traces of iodine and fluorine, vitamin C, fructose, sucrose and raffinose in trace ⁶⁷ .

Table No. 3: Compound Unani Formulations^{12,28,29}

S.No.	Symptoms	Unani Formulation	Dose
1.	Fever	Habb-e-Bukhar	2 tablets twice a day
2.	Dry Cough	Khameera Banafsha Laoq Sapistan Sharbat Sadar	10 gm twice a day 10 gm twice a day 20 ml twice a day
3.	Sore Throat	Sharbat Toot Siyah	20 ml twice a day
4.	Difficulty in Breathing	Laoq Katan Sharbat Zoofa Murakkab	10 gm twice a day 20 ml twice a day

General Measures ¹²

- Isolation of vulnerable peoples like elderly, pregnant women and people having comorbid conditions such as hypertension and diabetes.
- Maintain social distancing
- Frequent washing of hands with soap and water
- Use face mask
- Avoid touching eyes, nose and mouth
- Maintain good bowel habits

- Perform moderate exercises

Conclusion

Over the past few months, with the sudden outbreak of COVID-19, there was an urge to discover the root cause of corona virus infection and this has become a major global concern. Till date, there is no specific vaccine or treatment available against COVID-19 although several clinical trials are being in progress on vaccines and drugs. The development of vaccine might take a year as there is always a change in the sequence. Most of the treatment focus on using drugs such as lopinavir, ritonavir, HCV and steroids in case of severe illness. Thus, due to the absence of any decisive treatment available, stress is being laid on the traditional system of medicine to fight against the disease.

The purpose of this review is to appraise the readers about the concept of epidemics along with the prevention and management of COVID-19 in context with Unani system of Medicine. Unani is a comprehensive medical system that provides preventive, curative and rehabilitative healthcare. Medicinal plants constitute effective source of natural products, consumed as phytomedicines and the products obtained from medicinal plants have been playing significant role in drug discovery efforts for the treatment of various diseases. Unani herbs possess several biochemical compounds such as alkaloids, phenol, flavonoids, saponins which exhibit various pharmacological activities ranging from antioxidant, antibacterial anti-inflammatory, antiviral to immunostimulatory actions. They can be helpful to boost immunity as well as the pharmacological properties may provide some cure in the symptoms of COVID-19. Dietary supplements are also an important factor in the management of certain diseases in Unani medicine and it can also help to boost immunity to the healthy as well as diseased persons during epidemics and pandemics.

The review has its limitations as it does not include any direct evidence on the efficacy of these drugs in the treatment of the coronavirus disease. Though many medicinal plants and compounds formulations have been identified, a lot of research has to be carried out for the development of drug specific to SARS-CoV-2.

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