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# Therapeutic and palliative role of a Unani herbal decoction in COVID-19 and similar respiratory viral illnesses: Phytochemical & pharmacological perspective

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## ABSTRACT

**Ethnopharmacological relevance:** Outbreaks of respiratory viral infections like Severe Acute Respiratory Syndrome, Middle-East Respiratory Syndrome, and Coronavirus Disease-2019 have been a regular occurrence in the past 100 years. A significant proportion of the morbidity and mortality in influenza is attributed to the co-morbidities and complications induced by the disease, involving the vital organs and physiological functions. In this context, traditional medicines offer effective protective, palliative, and therapeutic benefits, as observed in several studies on various types of influenza, including COVID-19. The Unani herbal decoction comprising of 'Unnāb (*Ziziphus jujuba* Mill. fruit), *Sapistān* (*Cordia dichotoma* G. Forst. fruit), and *Behidāna* (*Cydonia oblonga* Mill. seed) was originally prescribed by Hakim Ajmal Khan (1868–1927 AD) for various respiratory ailments as a bronchodilator, anti-inflammatory, and for clearing the respiratory tract. During COVID-19, the decoction was prescribed by the Ministry of Ayurveda, Yoga, Unani, Siddha, and Homeopathy (AYUSH), Government of India, for mild patients in home isolation, and also as a self-care drink for healthy people. Preliminary studies are of the view that the decoction could reduce COVID-19 incidence and prevent severe disease in the population where it was administered.

**Aims of the study:** We intend to review the pharmacological activity of the Unani decoction ingredients, i.e., *Z. jujuba*, *C. dichotoma*, and *C. oblonga*, in context with respiratory viral infections and their co-morbidities, to develop an understanding of its action mechanism.

**Methodology:** We reviewed Unani classical textbooks for information on the therapeutic activity of the decoction ingredients. Scientific studies published in English from the year 2000 onwards on leading scientific websites (PubMed, MEDLINE, Scopus, and Springer) were searched for information regarding the efficacy of the drugs in influenza and its common complications. Non-English language articles, or those published prior to 2000, and those which included plant parts other than those traditionally included in the decoction were excluded.

**Observations:** A wide range of therapeutic and palliative effects have been observed in the three herbs included in the Unani decoction, including anti-viral, anti-bacterial, immuno-modulatory, anti-inflammatory, hepato-, and nephroprotective, anti-atherosclerotic, anti-tussive, broncho-dilatory, and regulation of gut microbiota. Together, these effects can help to mitigate and prevent most of the complications caused as a result of respiratory viral infections.

**Conclusion:** The combined effects of ingredients in this Unani herbal decoction can potentially help to mitigate most of the pathological changes and complications caused by influenza viruses. With further clinical research, the decoction may be potentially utilized as a prophylactic and therapeutic against viral influenza.

## 1. Introduction

The timeline of viral influenza is an intriguing chronicle covering

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### Abbreviations

|            |   |
|------------|---|
| AYUSH      | Ayurveda, Yoga, Unani, Siddha, and Homeopathy   |
| COPD       | Chronic Obstructive Pulmonary Diseases          |
| CVD        | cardiovascular diseases                         |
| COVID-19   | Coronavirus disease-2019                        |
| DIC        | Disseminated Intravascular Coagulopathy         |
| HAE        | Hydroalcoholic extract                          |
| JFE        | Jujuba fruit extract                            |
| MERS       | Middle East Respiratory Syndrome                |
| MRSA       | Methicillin-Resistant Staphylococcus aureus     |
| RNS        | Reactive Nitrogen Species                       |
| ROS        | Reactive Oxygen Species                         |
| RSV        | Respiratory Syncytial Virus                     |
| RVIs       | respiratory viral infections                    |
| SARS       | severe acute respiratory syndrome               |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus-2 |
| TBHP       | tert-butyl hydroperoxide                        |
| UNA        | Ursonic Acid                                    |

nearly 25 centuries of recorded history, which reveals interesting insights into the versatility, resilience, and devastating nature of a seemingly benign virus. Description of a 'highly contagious respiratory illness' (ca. 410 BC) by Hippocrates (460–377 BC) is generally accepted as the first authentic record of an influenza outbreak in northern Greece. Early influenza epidemics also occurred in 664 AD (Britain), 1173–1174 AD (Europe), 1357 (Italy), and 1414 (France). The term 'influenza' was first used during the 1357 Italian flu epidemic (*Influenza di freddo* meaning 'influence of cold') (Lina, 2008). Later, the influenza virus RNA was isolated from the formalin-fixed lung tissues of 1918 influenza victims and completely sequenced in 2005 (Taubenberger, 2006). In the present century, there have been several outbreaks of influenza, while two deadly pandemics have originated in the past 100 years, i.e., influenza A (H1N1) and SARS-CoV-2 (Hancková and Betáková, 2022).

Several factors have facilitated the omnipresence of influenza across the millennia, with predictions of further outbreaks. Influenza viruses are endemic in several animal species, which support their transmission. In addition, the viruses are highly infectious even before the appearance of symptoms. As is being observed presently with increasing international travel, the infection has usually spread to a few countries even before the initial warning of an outbreak (Fineberg, 2014). Most importantly, the influenza viruses undergo *antigenic shift* (reassortment between several strains of influenza viruses) and *antigenic drift* (gradual mutations which cause changes in surface proteins), over short periods. Hence, the development of effective drugs and vaccines often struggles to keep pace with these *antigenic variations* (Nypaver et al., 2021). For instance, since the first appearance of SARS-CoV-2 in December 2019, it has mutated into several variants, of which five (Alpha [B.1.1.7], Beta [B.1.351], Gamma [P.1], Delta [B.1.617.2], Omicron [B.1.1.529]) have been designated as *variants of concern* as of December 2021. Another eight have been designated as *variants of interest*, i.e. mutations which may cause enhanced transmission, virulence, ability to evade detection, and decreased response to vaccines and drugs (Aleem et al., 2021). A recombinant variant, Delta-Omicron was also reported in the UK on 19<sup>th</sup> January 2022 (WHO, 2022).

What is particularly noticeable is that influenza viruses have persisted through the pre-antibiotic and pre-vaccine era to the present day. Prior to 20th century, there was a dearth of effective anti-microbial measures, so the spread of infectious agents is understandable (Fazil and Nikhat, 2021). Contrastingly, in the case of SARS-CoV-2, the genome sequence was established within a month of its appearance, and many anti-viral measures were put into place (Nikhat and Fazil, 2020). The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2),

responsible for COVID-19, contains four main structural proteins, viz., the Spike (S) protein, Membrane (M) protein, Envelope (E) protein, and Nucleocapsid (N) protein. These proteins are the target of drugs and vaccines; particularly, the spike protein is the target of vaccine development as it is surface-exposed (Ita, 2021). Some of the drugs being used for COVID-19 include Interferons, Anti-virals (Lopinavir, Ritonavir), and repurposed drugs that were originally used for other ailments (Chloroquine, Hydroxychloroquine), steroids (Dexamethasone, Budesonide), and monoclonal antibodies (Bebtelovimab), etc. Currently authorized vaccines for COVID-19 include RNA vaccines (Pfizer–BioNTech, Moderna, CureVaC), DNA vaccines (ZyCoV-D, Covigenix VAX 001, COVI-DeVAX, COVIGEN), Viral vector vaccines (Ad26.COV2.S, Sputnik V, COVIVAC), live attenuated vaccines (COVIVAC, MV-014212), protein subunit vaccines (Recombinant SARSCoV-2 vaccine (Sf9 Cell), NanoCovax, FINLAYFR-1, COVAC-1, COVAC-2), virus-like particles (CoVLP, HBsAg VLP, SARSCoV-2 VLP, ABNCoV2), inactivated virus vaccines (Inactivated SARSCoV-2 vaccine, live recombinant (rNDV) vector vaccine), etc. (Bahrami et al., 2022). However, despite constant efforts, COVID-19 has proven to be more stubborn than anticipated (Fernandes et al., 2022). Although currently on the decline, more than three million new cases and 7600 deaths were reported by WHO between May 30, 2022 to 5<sup>th</sup> June 2022 (WHO, 2022). Hence, it is understandable that influenza outbreak management needs to go beyond anti-viral measures. A holistic approach directed at immune-strengthening and target-organ protection is the need of the hour (Wever and van Bergen, 2014).

During the COVID-19 crisis, traditional medicines were extensively used all over the world as a supportive therapy, for providing symptom relief, and also as exclusive treatment in mild cases. More than 400 RCTs have been published on various traditional medicines in COVID-19 patients, with encouraging outcomes (Jeon et al., 2022). The governments of India, China, and South Korea also published various guidelines regarding the use of indigenous medicines for COVID-19 patients, a practice less witnessed in previous epidemics (Xiong et al., 2021). The Ministry of AYUSH (Ayurveda, Yoga, Unani, Siddha, and Homeopathy), Government of India, recommended the decoction of *Ocimum tenuiflorum* L. leaves, *Cinnamomum verum* J. Presl. bark, *Piper nigrum* L. fruit, *Zingiber officinale* Roscoe. rhizome, and *Vitis vinifera* L. fruit as an immunity booster to prevent severe COVID-19 (Khanal et al., 2022). Targeted scientific studies have provided evidence of definite immunomodulatory and broad-spectrum anti-viral activity in various medicinal plants, including potential benefits in COVID-19 (Khanal et al., 2021; Fazil and Nikhat, 2020).

The *Joshānda* (decoction) of *Unnāb* (*Ziziphus jujuba* Mill. fruit), *Sapistān* (*Cordia dichotoma* G. Forst. fruit), and *Behidāna* (*Cydonia oblonga* Mill. seed) was prescribed by Hakim Ajmal Khan (1868–1927 AD) in his treatise *Hāziq* for the management of bronchial asthma, pleurisy, and pneumonia (Khan, 1983). During the COVID-19 pandemic, the Ministry of AYUSH (Ayurveda, Yoga, Unani, Siddha, and Homeopathy), Government of India prescribed this decoction for mild cases of COVID-19. The composition of the decoction (Fig. 1) is as follows: *Unnāb* (5 in No.), *Sapistān* (9 in No.), and *Behidāna* (3 g)-boil in 250 ml of water till it is reduced to half, then the decoction is strained and consumed lukewarm once or twice a day (Ministry of AYUSH, 2021).

In this context, this review aims to explore the multi-dimensional protective and therapeutic actions of this Unani herbal decoction in respiratory viral infections (RVIs), which will help further the understanding of its action mechanism.

## 2. Methodology

We searched the classical textbooks of Unani medicine for information regarding the therapeutic uses of the three ingredients included in the Unani decoction. The books which were available in the authors' respective institutions were reviewed. In addition, we searched leading scientific websites (PubMed, MEDLINE, Scopus, and Springer) for the applications of these drugs in viral influenza and its co-morbidities. The


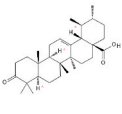
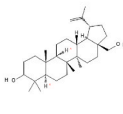
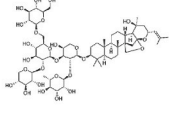
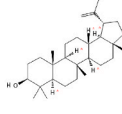

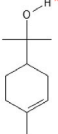
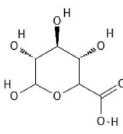
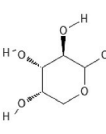
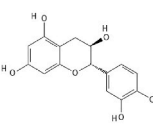

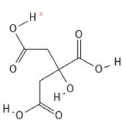
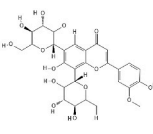
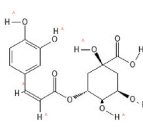
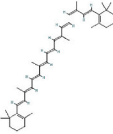
| Drug                   | Figure  | Some important constituents   |   |  |   |
|------------------------|---|---|---|--|---|
| Ziziphus jujuba fruit  |  |  |  |  |  |
|                        |   | Ursonic Acid<br>(C <sub>30</sub> H <sub>46</sub> O <sub>3</sub> )                 | Betulin<br>(C <sub>30</sub> H <sub>50</sub> O <sub>2</sub> )                      | Jujuboside A<br>(C <sub>58</sub> H <sub>94</sub> O <sub>26</sub> )                 | Lupeol<br>(C <sub>30</sub> H <sub>50</sub> O)                                       |
| Cordia dichotoma fruit |  |  |  |  |  |
|                        |   | α-terpineol<br>(C <sub>10</sub> H <sub>18</sub> O)                                | D-Glucuronic Acid<br>(C <sub>6</sub> H <sub>10</sub> O <sub>7</sub> )             | L-arabinose (C <sub>5</sub> H <sub>10</sub> O <sub>5</sub> )                       | (-)-Catechin<br>(C <sub>15</sub> H <sub>14</sub> O <sub>6</sub> )                   |
| Cydonia oblonga seed   |  |  |  |  |  |
|                        |   | Citric Acid<br>(C <sub>6</sub> H <sub>8</sub> O <sub>7</sub> )                    | Stellarin-2<br>(C <sub>28</sub> H <sub>32</sub> O <sub>16</sub> )                 | 5-O-cis-caffeoylquinic acid (C <sub>16</sub> H <sub>18</sub> O <sub>9</sub> )      | 9-cis-β-carotene<br>(C <sub>40</sub> H <sub>56</sub> )                              |

Fig. 1. Unani decoction ingredients and structures of their important constituents.

search was restricted to articles published from the year 2000 onwards; with the keyword 'Ziziphus jujuba' OR 'Jujuba fruit', 'Cordia dichotoma', and 'Cydonia oblonga' OR 'Quince fruit' in combination with 'COVID-19', 'influenza epidemics' OR 'respiratory viral infections, alongwith 'complications', 'anti-viral', 'health-protective', 'immuno-modulatory', etc. and more as per need. Throughout the manuscript, we focused on researches which included that part of the plant which is prescribed in the Unani decoction (i.e., fruits of *Z. jujuba* and *C. dichotoma*, and seeds of *C. oblonga*). Non-English language articles, or those published before 2000, and those which included plant parts other than those traditionally included in the decoction were excluded. The Unani medicine terms was translated to their English equivalent using the "Standard Unani Medical Terminology" textbook published by Central Council for Research in Unani Medicine in collaboration with World Health Organization (CCRUM, 2012). All botanical names were verified from [www.theplantlist.org](http://www.theplantlist.org).

### 3. Brief overview of the constituents of Unani herbal decoction

#### 3.1. Unnāb (Ziziphus jujuba Mill., Rhamnaceae)

'Unnāb, also known as ber, Jujuba, and Chinese date, is the fruit of *Z. jujuba* Mill., a plant reportedly domesticated in South Asia since 9000 BC (Villanueva and Villanueva, 2017). In Unani medicine, whole Jujuba fruits are used as medicine. According to Ibn Hubal Baghdādī (1122–1213 AD), the ripe fruits of Jujuba are mildly nutritive, health-protective, laxative, and particularly helpful in expelling morbid humors of the respiratory tract through the intestines. While dried jujuba is more beneficial for the respiratory tract, particularly the lungs (Baitar, 1999). It is useful in hoarseness of voice and relieves burning micturition (Baghdadi, 2005). It is hailed as a blood purifier by Ibn Sīnā (Avicenna, 980–1035 AD), and relieves the 'abnormal hot temperament' of blood (Sina, 1992). According to Ibn al-Baytār (1197–1248 AD), 'unnāb provides relief in throat irritation, bronchial asthma, and flatulence. It may be used as infusion or decoction, both are equally effective (Baitar, 1999). In Traditional Chinese Medicine, it is believed that

Jujuba can increase life expectancy by nourishing the blood, improving digestion, and regulating sleep quality (Chen and Tsim, 2020). In Morocco, a decoction of *Z. jujuba* leaves is used by traditional healers as an anti-diabetic medication (Mrabti et al., 2021).

*Z. jujuba* fruits are rich in polysaccharides (55–85%), which mainly consist of five monosaccharides, i.e., glucose, galactose, rhamnose, arabinose, and xylose. Many important bioactivities of *Z. jujuba* fruits like immune-modulatory, hepatoprotective, hypoglycemic, anti-oxidant, and gastro-protective activities are attributed to their saccharide content (Ji et al., 2017). Besides, the fruits also contain moisture (25–30%), fibre (2.4–8.4%), phyto-proteins (2.9–6.6%), saturated and un-saturated lipids, of which nearly one-third are in the form of mono-meric fatty acids (Villanueva and Villanueva, 2017). Jujuba fruits are also rich in iron and vitamin C (average 0.48 and 0.69 mg/100 g respectively) (Chen and Tsim, 2020). Also, other essential vitamins (α-tocopherol), minerals (calcium, phosphorous, selenium) are present in a significant proportion. Jujuba fruits also contain flavonoids (kaempferol, quercetin), anthocyanins (cyanidin-3-glucoside), triterpenic acids, nucleosides, phenolic acids, tannins, stilbenes, saponins (32 mg/100 g), and alkaloids (8 mg/100 g) (Villanueva and Villanueva, 2017). Jujubosides (saponins) isolated from *Z. jujuba* fruits, have cardioprotective (jujuboside B), neuroprotective (jujuboside A), and anti-inflammatory activity. The fruits also contain a significant proportion of cAMP as compared to other fruits, which contributes to the anti-melancholic activity (Chen et al., 2017; Chen and Tsim, 2020). Hence, the fruits have a high nutritional as well as therapeutic value.

#### 3.2. Sapistān (Cordia dichotoma G. Forst., Syn. Cordia myxa L., Boraginaceae)

Sapistān, famously known as Sebitān (Arabic and Persian), Sebestan plum, Lehsora and Indian Cherry, is the fruit of *C. dichotoma*, a small-to-medium-sized deciduous tree, commonly found in tropical and sub-tropical regions of North and Central India, southern China, peninsular part of Malaysia, Myanmar, and tropical regions of Australia and Polynesia (Jamkhanda et al., 2013). In Unani textbooks, it is mentioned



that *sapistān* relieves the irritation of the chest and throat, and expels morbid humors from respiratory organs through purgation. It also quenches thirst and relieves constipation (Baghdadi, 2005; Sina, 1992). According to Ibn al-Baytār, *sapistān* is particularly beneficial for cough associated with hot and dry temperament. It is also effective in relieving fevers caused by sanguine, bilious, or saline phlegmatic humours. Its respiratory and intestinal effects are attributed to the sticky, gum-like substance which is secreted from the fruits (Baitar, 1999). In *Charaka Samhita*, one of the authentic textbooks of Ayurveda, *C. dichotoma* is listed as an anti-toxin (Biswas, 2018). In India, *C. dichotoma* fruits have been traditionally used as an anti-arthritis (Sadia et al., 2018).

*C. dichotoma* fruit pulp contains fats (37 g/100 g), proteins (35 g/100 g), carbohydrates (18 g/100 g), and minerals (Calcium, Phosphorous, Zinc, Iron, Manganese, Chromium, etc). In addition, several bioactive phytochemicals like flavonoids, saponins, D-glucose, L-arabinose, arabinoglucan, coumarins, terpenes, and sterols have also been isolated from the fruits (Jamkhande et al., 2013). The gum exudate from fruits is a polyuronide consisting of arabinose, galactose, glucuronic acid (10:7:2 mol), and traces of rhamnose (Pawar et al., 2018). The sugars are mainly represented by glucuronic acid (34.08%), sucrose (25.61%), glucose (11.82%), fructose (8.95%), and starch (4.82%). In addition, volatile compounds like  $\alpha$ -terpineol,  $\alpha$ - and  $\beta$ -phellandrene, linalool, carvacrol, sabinene, and linalyl butyrate have also been isolated from the fruits. Also, phenols (gallic acid), flavonoids (quercetin), uronic acids, tannins (catechin), and pyrrolizidine alkaloids are present in a significant proportion (Ibrahim et al., 2019).

### 3.3. *Behidāna* (*Cydonia oblonga* Mill., *Rosaceae*)

*Behidāna* is the seed of Quince (referred to as *Safarjal* or *Behi* in Unani texts), a plant popular for its nutraceutical, industrial, ornamental, and medicinal properties (Zhang et al., 2021). The fruits are pomes, 10–12 cm in diameter, and contain numerous seeds (Silva et al., 2004). In Unani medicine, *Behidāna* and its mucilage are acknowledged as effective soothing agents in the irritation of the trachea and throat. According to Avicenna, *Behidāna* is mildly astringent and is beneficial in hemoptysis, asthma, and orthopnea (Sina, 1992). It also has a mild laxative effect on the intestines (Baghdadi, 2005). In Traditional Uighur Medicine, Quince is believed to both prevent and treat cardiovascular diseases (Zhou et al., 2014). In Iranian Traditional Medicine, Quince seed mucilage is used orally and intra-urethrally in the treatment of dysuria (Jaladat et al., 2015).

On phytochemical analysis, Quince seeds demonstrate a rich antioxidant profile, distinct from that of the fruit (Silva et al., 2004). Caffeoylquinic acids represent 50% of the phenolic composition of the seed extract, of which 20% is 5-O-caffeoylquinic acid. The seed extract also distinctively contains a lesser proportion of organic acids as compared to the peel and pulp of the fruit. While the fruit pulp and peel are rich in malic acid, citric acid, and ascorbic acid. Flavone C-glycosides (particularly stellarin-2) are present only in seed extract, and not in other parts of the fruit. Concerning the comparative antioxidant activity among pulp, peel, and seed extract of quince, the phenolic extract of seeds demonstrated the strongest activity ( $IC_{50} = 0.1$  mg/ml). Interestingly, when methanolic extracts were compared, the peel extract demonstrated the highest antioxidant activity ( $IC_{50} = 0.6$  mg/ml), followed by those of pulp and seed ( $IC_{50} = 1.7$  mg/ml and 2.0 mg/ml respectively). The antioxidant behaviour was possibly different due to different phenolic composition (Silva et al., 2004). The seed oil is also particularly rich in tocopherols and carotenoids.  $\alpha$ -tocopherol represents 88–94% of the total tocopherol composition of Quince seed oil. Some of the carotenoids present in the oil are all-*trans*-neoxanthin, 9-*cis*-neoxanthin, all-*trans*-violaxanthin, all-*trans*- $\beta$ -carotene, and 9-*cis*- $\beta$ -carotene, etc. (Fromm et al., 2012). Quince seeds are also rich in tannins, owing to which they also have an anti-diarrheal activity (Zhang et al., 2021).

## 4. Pharmacological activity of phytoconstituents

The ingredients of the Unani herbal decoction, i.e., *Z. jujuba*, *C. dichotoma*, and *C. oblonga*, are well-known herbal drugs, widely used in various traditional medicines. In this context, we provide an overview of the potential beneficial effects of the decoction ingredients which are relevant to the management of COVID-19 and other RVIs. The observations are summarized in Table-1 and Table-2.

### 4.1. Anti-viral activity against SARS-CoV-2 and other influenza viruses

SARS-CoV-2 has structural resemblance to bat coronavirus (CoV RaTG13), SARS-CoV (Nikhat and Fazil, 2020), and also shares many characteristics with other respiratory viruses such as RSV and influenza viruses (H1N1, H1N2, H2N2, H5N1) (Wever and van Bergen, 2014). The transmission, host receptors, pathogenesis, and clinical picture also show a high degree of similarity among the viruses. Many medicinal plants have demonstrated definite anti-viral activity against multiple respiratory viruses (Singh et al., 2021). Hence, we were interested in exploring the anti-viral activities of the Unani decoction ingredients, against SARI (severe acute respiratory infection) viruses in general and SARS-CoV-2 in particular.

#### 4.1.1. *Z. jujuba*

Uronic acid (UNA), a pentacyclic triterpenoid isolated from ripe fruits of *Z. jujuba*, has demonstrated a suppressant activity against SARS-CoV-2, by inhibiting its replication. It binds to endoribonuclease Nsp15, an essential structure in the virus lifecycle (Son and Lee, 2020a,b). In an *in vitro* study, a Jujuba fruit-containing preparation inhibited the attachment and replication of human coxsackievirus B4 and prevented airway and renal injuries (Yen et al., 2014). Hong et al. (2015) demonstrated the anti-viral activity of Betulinic acid extracted from *Z. jujuba* roots. Betulinic acid inhibited the proliferation of influenza A/PR/8 virus *in vitro* (98% at 50  $\mu$ M), without any significant toxicity. *In vivo*, it decreased inflammatory cytokines, particularly IFN- $\gamma$ , and reduced pulmonary inflammation (Hong et al., 2015). Since Betulinic acid is also present in JFE (Goswami et al., 2019), similar results may be obtained by the use of *Z. jujuba* fruit.

#### 4.1.2. *C. oblonga*

In an interesting *in vitro* study, phenolic compounds from *C. oblonga* fruit ethanolic extract exerted anti-viral activity against influenza virus (A/PR/8/34 strain) in a concentration of 0.5 mg/mL ( $p < 0.001$ ), by

**Table-1**

Summary of the pharmacological activities of Unani decoction ingredients reported in scientific studies.

|  | Z. jujuba | C. oblonga | C. myxa |
|--|-----------|------------|---------|
| Anti-SARS-CoV-2                                  | ✓         | –          | –       |
| Anti-viral                                       | ✓         | ✓          | –       |
| Anti-bacterial                                   | ✓         | ✓          | ✓       |
| Anti-hyperglycemic                               | ✓         | –          | –       |
| Anti-inflammatory, anti-allergic, anti-asthmatic | ✓         | ✓          | ✓       |
| Anti-oxidant                                     | ✓         | ✓          | ✓       |
| Immune-modulatory                                | ✓         | –          | ✓       |
| Anti-atherosclerosis/anti-thrombotic             | ✓         | –          | ✓       |
| Cardioprotective                                 | ✓         | –          | ✓       |
| Neuroprotective                                  | ✓         | ✓          | ✓       |
| Regulation of gut microbiota                     | ✓         | –          | –       |
| Anti-depressant                                  | –         | –          | ✓       |
| Anti-proliferative                               | –         | ✓          | ✓       |
| Haemopoietic                                     | ✓         | –          | –       |
| Hepatoprotective                                 | ✓         | –          | ✓       |
| Anti-protozoal                                   | –         | –          | ✓       |
| Nephroprotective                                 | –         | ✓          | –       |
| Anti-diarrheal                                   | –         | ✓          | –       |
| Gastro-protective                                | ✓         | –          | –       |

**Table-2**  
Multidimensional action of Unani decoction ingredients in respiratory viral infections.

| Activity   | Type of study                      | Mode of administration   | Dosage/concentration   | Mechanism/Evidence  | Phyto-constituent responsible for the activity                   | Reference              |
|--|------------------------------------|--|--|---|--|------------------------|
| <i>Z. jujuba</i> fruit<br>Anti-SARS-CoV-2        | Molecular dynamics analysis        | <i>In silico</i> docking by SwissDock server   | Appropriateness of docked pose with UNA = -7.10 deltaG Kcal/mol  | Binds with SARS-CoV-2 Nsp-15, an endoribonuclease, and inhibits viral replication   | Ursonic Acid   | Kumar et al. (2021)    |
| Anti-viral                                       | <i>In vitro</i>                    | Betulinic acid added to influenza A/PR/8 virus-infected A549 human lung adenocarcinoma epithelial cell line  | 0.4, 2, 10, and 50 µg/ml concentration of Betulinic Acid   | Inhibition of influenza A/PR/8 virus (98% at 50 µM)   | Betulinic acid   | Hong et al. (2015)     |
| Anti-bacterial                                   | <i>In vitro</i>                    | Plant extract added to bacterial inoculum  | Zone of Inhibition = 14–20 mm, Minimum Inhibitory Concentration: 7.81–31.25 µg/mL  | Inhibition of MDR <i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> (MIC-6.25 µg/ml)   | Flavonoids (methanolic extract)                                  | Mehreen et al. (2016)  |
| Anti-hyperglycemic                               | <i>In vitro</i>                    | Glucose uptake in rat L6 myotubes was observed   | L6 myotubes treated with insulin (0.1 µM) and triterpenoids (50 µM) for 4 h  | Inhibition of α-glucosidase, increased expression of glucose transporter type-IV protein, hence increased glucose uptake              | Triterpenoids (Betulonic, ursonic, oleanic, and betulinic acids) | Kawabata et al. (2017) |
| Anti-inflammatory, anti-allergic                 | <i>In vitro</i>                    | Production of Nitric Oxide in lipopolysaccharide-induced RAW264.7 murine macrophage cells was observed   | IC50 = 4.94 µM   | Inhibition of Nitric Oxide production   | Ursonic Acid   | Zhang et al. (2017)    |
| Anti-allergic, anti-anaphylactic, anti-asthmatic | Animal study                       | Oral, in Swiss albino mice models of asthma and allergy  | 250, 500 and 1000 mg/kg  | Inhibition of acetylcholine and histamine-induced tracheal contraction  | Betulin, betulinic acid, lupeol, oleanolic acid                  | Naik et al. (2013)     |
| Anti-oxidant                                     | Molecular dynamics analysis        | A549 human Non-small-cell lung cancer cells and HaCaT human keratinocytes treated with UNA for 24 h  | 40% inhibition at 10 µM  | Decrease in intra-cellular reactive oxygen species  | Ursonic Acid   | Son and Lee (2020)     |
| Immune-modulatory                                | <i>In vitro</i>                    | Jurkat T-cells treated with deproteinated polysaccharides  | 125–2500 µg/ml for 48 h  | Inhibition of IL-2 production, possibly mediated via interrupting activation of mitogen-activated protein kinase                      | Deproteinated polysaccharides                                    | Hsu et al. (2014)      |
|  | <i>In vivo</i>                     | Oral, Kunming male mice  | 50 mg/kg, 100 mg/kg and 200 mg/kg  | Increase in thymus and spleen index, proliferation of immune cells, antibody production, increased phagocytic activity of macrophages | Polysaccharides (HP1, HP2)                                       | Zou et al. (2018)      |
|  | <i>In vitro</i>                    | Mice spleen cells cultured with polysaccharides  | 2.5, 10, 30, and 100 µg/ml   | Mitogenic effect on lymphocytes, anti-complementary, proliferation of peritoneal macrophages and splenocytes                          | Water-soluble crude polysaccharides                              | Zhao et al. (2008)     |
| Anti-atherosclerosis/anti-thrombotic             | <i>In vitro</i> and <i>in vivo</i> | <i>In vitro</i> - Platelet rich plasma treated with ethanolic extract of <i>Z. jujuba</i><br><i>In vivo</i> - Observation of mice tail bleeding time | <i>In vitro</i> - 30, 100, and 300 µg/ml<br><i>In vivo</i> - Ethanol extract of <i>Z. jujuba</i> (30, 100, 300 mg/kg), or jujuboside B (10, 30, 100 mg/kg) | Inhibition of TXB <sub>2</sub> formation, decreased platelet aggregation  | Jujuboside B   | Seo et al. (2013)      |
| Cardioprotective                                 | Animal study                       | Male Wistar Rats, treated with oral Isoprenaline with or without aerobic exercise  | 400 mg/kg Jujuba extract   | Decreased lipocalcin-2  | Flavonoids, jujubosides, terpenes                                | Hosseini et al. (2019) |
| Neuroprotective                                  | Animal study                       | Cultured hippocampal cells of rats treated with Jujuboside A   | 50 µl/ml   | Anti-melancholic, modulation of GABA receptors  | Jujuboside A   | (Wang et al., 2015)    |
|  | Animal study                       | Oral administration of <i>Z. jujuba</i> aqueous extract in amnesic rats  | 166 mg/kg  | Anti-amnesic (modulation of cholinergic and inflammatory pathway)   | Polyphenols  | Kandeda et al. (2021)  |
| Regulation of intestinal flora                   | Animal study                       | Oral, in male C57BL/6 mice treated with azoxymethane and dextran sodium sulfate to trigger colorectal cancer   | 1000 mg/kg   | Immune-enhancing, anti-cancer through enrichment of gut microbiota  | Polysaccharides  | Ji et al. (2020)       |
| <i>C. oblonga</i> seeds<br>Anti-viral            | <i>In vitro</i>                    | Phenolic compounds (acetone extract) from quince added to solution of influenza virus  | 50 µL of influenza virus solution to 50 µL of undiluted fruit extract  | Inhibition of haemagglutination by influenza virus (A/PR/8/34 strain in chicken erythrocyte suspension)                               | Phenolic compounds   | Hamazu et al. (2005)   |

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Table-2 (continued)

| Activity                         | Type of study                      | Mode of administration  | Dosage/concentration   | Mechanism/Evidence  | Phyto-constituent responsible for the activity   | Reference                 |
|----------------------------------|------------------------------------|---|--|---|--|---------------------------|
| Anti-inflammatory, anti-allergic | <i>In vitro</i> and <i>in vivo</i> | <i>In vitro</i> -Hot water extract of quince added to RBL-2H3 cells<br><i>In vivo</i> - Hot water extract of quince given orally to atopic mice model   | <i>In vitro</i> - 50, 100, 200 µg/ml of hot water extract of quince for 24 h<br><i>In vivo</i> - diet containing 2.5% and 5% of quince extract                   | Inhibition of degranulation of mast cells, suppression of conversion of IgM to IgE in B-cells   | Low-molecular weight polyphenols (caffeoylquinic acids, quercetin glycosides, and kaempferol glycosides) | Shinomiya et al. (2009)   |
| Anti-bacterial                   | <i>In vitro</i>                    | Ethanol extract of <i>C. oblonga</i> added to bacterial strains   | Sensitivity: <i>S. epidermidis</i> sensitive at 500 mg/ml; <i>K. pneumonia</i> sensitive at 250 mg/ml; <i>S. aureus</i> sensitive at 125, 250, 500 mg/ml         | Inhibition of gram-positive bacteria ( <i>S. aureus</i> , <i>S. epidermidis</i> )   | Ethanol extract (phenolic compounds, tannins)  | Al-Khazraji (2013)        |
|                                  | <i>In vitro</i> and <i>in vivo</i> | <i>In vitro</i> - fruit extract (ethanolic and acetonetic extract of seed) added to bacterial strains <i>E. coli</i> , <i>K. pneumoniae</i> , <i>E. aerogenes</i><br><i>In vivo</i> - Intra-peritoneal injection in albino mice | <i>In vitro</i> -1.5 × 10 <sup>8</sup> CFU/ml suspension of bacteria loaded with 80 ml of extracts at 37°C for 24 h<br><i>In vivo</i> -500 µl of fruit extract   | Anti-bacterial activity against <i>E. coli</i> , <i>K. pneumonia</i> , and <i>E. aerogenes</i>  | Ethanol extract  | Alizadeh et al. (2013)    |
|                                  | <i>In vitro</i>                    | <i>E. coli</i> varying incubated with varying concentrations of aqueous extract   | 1, 5, 10, 20, 30, 40, 50, 60, 65, 70, 75, and 80 mg/mL   | Reduction of bacterial ( <i>E. coli</i> ) adhesion, disappearance of biofilm  | Aqueous extract (fruit)  | Hendrich et al. (2020)    |
| Anti-oxidant                     | <i>In vitro</i>                    | Pre-treatment of tert-butyl hydroperoxide (TBHP) damage by aqueous extract of the <i>Z. jujuba</i> fruit  | Pre-treatment of human fibroblast cells with varying concentrations (1, 2, 4, 8 mg/mL) of <i>Z. jujuba</i> for 24 h; followed by exposure to 75 µM TBHP for 24 h | Cytoprotective against TBHP-induced damage, anti-oxidant  | Aqueous extract  | Arab et al. (2019)        |
|                                  | <i>In vitro</i> and <i>in vivo</i> | <i>In vitro</i> -Human lymphocytes incubated with jujuba fruit ethanolic extract or Betulinic acid<br><i>In vivo</i> - Pre-treatment of male Swiss albino mice with Betulinic Acid, oral  | <i>In vitro</i> -Jujuba extract (250, 500, 1000 µg/ml) and Betulinic Acid (10, 20, 40 µg/ml)<br><i>In vivo</i> -2.5, 5.0 and 10 mg/kg body weight for 6 days     | Anti-genotoxic, anti-oxidant, hepatoprotective against methyl methane sulphonate and hydrogen peroxide-induced damage                             | Phenolics, betulinic acid  | Goswami et al. (2019)     |
|                                  | <i>In vitro</i>                    | Observation of the scavenging effect of Quince jam and methanolic extract on 1,1'- diphenyl-2-picrylhydrazyl (DPPH)   | IC <sub>50</sub> - 0.6, 1.7, 2.0 mg/mL for peel, pulp, seed extract respectively   | Antiradical activity  | Citric acid, ascorbic acid, caffeoylquinic acid  | Silva et al. (2004)       |
| Neuro-protective                 | Animal study                       | Methyl isobutyl ketone-induced rat model of depression treated with aqueous and ethanolic extract of <i>C. oblonga</i> , oral   | 200 mg/kg  | Antioxidant: modulation of superoxide dismutase, glutathione peroxidase, catalase, total cholesterol, and thiobarbituric acid reacting substances | Flavonoids and vitamins  | (Din Ganaie et al., 2020) |
| <b><i>C. dichotoma</i> fruit</b> |                                    |   |  |   |  |                           |
| Anti-microbial                   | <i>In vitro</i>                    | Aqueous and methanolic extract of <i>C. latifolia</i> added to <i>P. aeruginosa</i> , <i>E. coli</i> suspensions  | Zone of Inhibition = 16–20 mm, Minimum Inhibitory Concentration: 12.62–62.5 µg/mL  | Inhibition of MDR <i>E. coli</i> , <i>P. aeruginosa</i> (MIC-12.5 µg/ml)  | Alkaloids  | Mehreen et al. (2016)     |
| Anti-inflammatory                | Animal study                       | Fruit pulp fed (by gastric intubation) to animal models of colitis (Male Wistar rats)   | 12 g/kg in the morning for 4 days  | Restoration of anti-oxidant enzymes, trace elements   | Fruit extract  | Al-Awadi et al. (2001)    |
|                                  | Animal study                       | Hydroalcoholic extract of <i>C. myxa</i> fruit given to rat models of pain  | 100 mg/kg and 200 mg/kg oral; 100 mg/kg intra-peritoneal   | Analgesic and anti-inflammatory, mechanism not elucidated   | Polyphenols, alkaloids, and flavonoids   | Ranjbar et al. (2013)     |
| Anti-bacterial                   | <i>In vitro</i>                    | Alkaloids from <i>C. latifolia</i> added to methicillin-resistant staphylococcus aureus suspension  | Minimum Inhibitory Concentration - 12.5 µg/mL  | Inhibition of MRSA  | Alkaloids  | Mehreen et al. (2016)     |
|                                  | Animal study                       | Oral administration (force-feeding) of plant extract to infected mice   | 200 mg/ml per kg body weight once daily for 7 days   | Reduction of gross lung lesions caused by MRSA  | Methanolic extract   | Arshad et al. (2017)      |
|                                  | <i>In vitro</i>                    | Bacteria from blood and oral swab culture added to plant extracts   | Minimum Inhibitory Concentration - 250 µg/mL   | Anti- <i>Staph. aureus</i> in neutropenic oral cancer isolates  | Acetone extract  | (Panghal et al., 2011)    |
| Anti-atherosclerotic             | <i>In vitro</i> and <i>in vivo</i> | <i>In vitro</i> - IC <sub>50</sub> observed by inhibition of free radicals<br><i>In vivo</i> - Oral in hyperlipidemic rats  | <i>In vitro</i> - 1 000, 500, 250 and 100 µg/mL<br><i>In vivo</i> -0.5 and 1.0 g/kg body weight/day for four weeks   | Decreased hepatic lipids, TC, LDL, TG, increased HDL, increased fecal fat excretion, antioxidant  | Aqueous extract (flavonoids, polyphenols, mucilage, alkaloids)   | El-Newary et al. (2018)   |
| Cardioprotective                 | <i>In vitro</i> and <i>in vivo</i> | <i>In vitro</i> - Methanol extract added to DPPH solution   | <i>In vitro</i> -50, 100, or 200 µg/ml of extract added to 3 ml of   |   | Flavonoids, saponins, tannins  | Ashour et al. (2012)      |

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Table-2 (continued)

| Activity  | Type of study   | Mode of administration  | Dosage/concentration  | Mechanism/Evidence   | Phyto-constituent responsible for the activity | Reference               |
|---|-----------------|---|---|--|--|-------------------------|
| Anti-depressant, neuro-protective               | <i>In vitro</i> | <i>In vivo</i> - Methanolic extract of <i>C. myxa</i> fruit orally<br>Antioxidant potential determined by Ferric Reducing Antioxidant Power | 0.004% DPPH solution<br><i>In vivo</i> -100 mg/kg body weight<br>IC <sub>50</sub> of FRAP = 90.93 µmol/g for <i>C. myxa</i> fruit extract | Preventive against Doxorubicin-induced cardiotoxicity<br>Anti-anxiety, non-sedative anxiolytic | Flavonoids                                     | El-Massry et al. (2021) |
| Anti-oxidant, cytotoxic on lung carcinoma cells | <i>In vitro</i> | Cytotoxicity determined on human hepatocellular carcinoma cells;  | IC <sub>50</sub> = 70 µg/mL for <i>C. myxa</i> fruit extract  | Inhibition of DPPH radical scavenging, scavenging of FRAP radical                              | Phenolics and flavonoids                       | El-Massry et al. (2021) |

preventing haemagglutination. It was also speculated that highly polymerized procyanidins, though not absorbed from the gut, may play a role in inactivating the influenza virus in the throat (Hamauzu et al., 2005). Yaermaimaiti et al. (2021) carried out a bioassay-guided fractionation of *C. dichotoma* fruit extract. They identified seven phytoconstituents with moderate anti-viral activity against influenza virus A/Hanfeng/359/95 (H3N2), including rosmarinic acid, balanophonin, evofolin B, and coniferyl aldehyde, etc. (Yaermaimaiti et al., 2021). We could not find any study on the anti-SARS-CoV-2 activity of *C. oblonga*.

#### 4.2. Antipyretic and analgesic activity

Fever, febrile feeling, and associated symptoms like myalgia, arthralgia, and headache occupy a significant proportion of the morbidity spectrum in nearly all types of influenza, irrespective of gender, age, etc. (Zayet et al., 2020). This necessitates the use of NSAIDs, analgesics, and antipyretics in almost all influenza patients. Although the drugs help in relieving symptoms, they lead to adverse effects like gastric ulceration, hepatotoxicity, etc. (Rainsford, 2006). On an extensive review, we did not find any studies reporting the antipyretic activity of any of the components of the Unani decoction under study. However, there is positive evidence that the drugs can ameliorate some of the adverse effects caused by the antipyretics.

##### 4.2.1. *Z. jujuba*

In an animal study, Jing et al. (2015) demonstrated that aqueous and ethanolic extracts of Jujube fruits increased the plasma concentration of acetaminophen (53.2% and 64.9% increase in AUC<sub>0-120</sub> respectively), and also increased its clearance from hepatic microsomes. This implies that JFE can enhance the efficacy of acetaminophen, and also prevent its adverse effects (Jing et al., 2015). In another study, pre-treatment with flavonoids from Jujube fruits protected against acetaminophen-induced hepatic injury due to anti-oxidant activity, and also dampened the acetaminophen-induced expression of inflammatory mediators in the liver (Huang et al., 2017). Polysaccharides from Jujube fruits reversed the hepatic toxicity via antioxidant effect and augmentation of nuclear factor erythroid 2-related factor 2 (Nrf2) in experimental mice (Yue et al., 2014).

##### 4.2.2. *C. myxa*

Ranjbar et al. (2013) studied the anti-inflammatory effects of *C. myxa* fruit hydro-alcoholic extract (HAE) in experimental animals. The extract demonstrated significant anti-inflammatory and analgesic activity comparable to indomethacin and tramadol (Ranjbar et al., 2013).

##### 4.2.3. *C. oblonga*

In a recent animal study, aqueous and ethanol extracts of whole Quince fruits demonstrated protective activity against Indomethacin-induced gastric ulcers by decreasing gastric pH, antioxidant, and anti-inflammatory activity (Parvan et al., 2017). It has been previously

elucidated that quince seed mucilage contains long-chain mucopolysaccharides which help in retaining water and keep the wound moist. Besides, it also contains several phenolic compounds which also act as antioxidants and assist healing by increasing collagen and fibroblast synthesis (Tamri et al., 2014; Fazil and Nikhat, 2022). Hence, quince seeds in the Unani decoction can protect the gastric mucosa against the adverse effects of NSAIDs and antipyretics.

#### 4.3. Immunomodulatory, anti-inflammatory, anti-allergic

All seven coronaviruses discovered so far are known to cause systemic inflammation leading to multi-organ pathology like pneumonia, hepatitis, nephritis, encephalitis, etc. (Tahaghoghi-Hajghorbani et al., 2020). Clinical experience and researches on COVID-19 are of the view that such inflammatory responses contributed to a significant degree of morbidity and mortality. Infection with SARS-CoV-2 stimulates Toll-like receptors and NOD-like receptors which triggers a cascade of intracellular signaling mechanisms, resulting in the release of enormous amounts of cytokines and chemokines. These substances are necessary for the development of innate immunity, but due to continued stimulation, lead to the much-dreaded 'cytokine storm' resulting in complications such as ARDS and vital-organ failure (Golpour et al., 2021). Such abnormal and uncontrolled immune response has been recognized as a leading contributor to COVID-19, SARS-CoV, and MERS-CoV deaths. At a COVID-dedicated hospital in Wuhan, it was observed that most patients who succumbed to COVID-19 had increased levels of immunoglobulins A, G, and E at admission (Zhao et al., 2020). In another study, increased serum IgE was suggested as an early screening marker for COVID-19 (X. Liu et al., 2020a). Hence, it is imperative to search for therapeutic agents which may control the dysregulated immune and inflammatory response during the early stages of COVID-19 and similar diseases.

##### 4.3.1. *Z. jujuba*

The components of Unani decoction have demonstrated effective immune-regulatory activity. The immunomodulatory and anti-inflammatory activity of *Z. jujuba* fruit polysaccharides were demonstrated *in vitro* by Hsu et al. (2014). Statistically significant suppression of IL-2 production was caused by deproteinated polysaccharides composed of mono-saccharides xylose, rhamnose, glucose, galactose, arabinose, and mannose in a dose-dependent manner (Hsu et al., 2014). In another study, *Z. jujuba* fruit acidic polysaccharides increased spleen and thymus index, phagocytic activity of macrophages, proliferation of immune cells, and antibody production in experimental rats. The polysaccharides were named HP1 and HP2, and were composed of arabinose, mannose, rhamnose, glucose, and uronic acid (Zou et al., 2018). In an animal study, crude water-soluble polysaccharides from *Z. jujuba* fruit increased the proliferation of peritoneal macrophages and splenocytes; and demonstrated potential anti-complementary activity (Li et al., 2011). In an interesting study, Naik et al. (2013) demonstrated the anti-allergic and anti-anaphylactic effects of *Z. jujuba* fruit ethanolic



extract *in vitro* and *ex vivo*. The extract prevented milk-induced eosinophilia and degranulation of mast cells, possibly mediated by flavonoids. Pre-treatment with the extract inhibited the anaphylactic reactions (cutaneous and respiratory manifestations) to egg albumin in a dose-dependent manner (Naik et al., 2013).

#### 4.3.2. *C. dichotoma*

*C. myxa* is a well-known smooth muscle relaxant, anti-allergic, immuno-modulatory, and anti-influenza drug (Khanna et al., 2021). Ma et al. (2021) isolated seven phenolpropane compounds from *C. dichotoma* fruits having an anti-complementary activity (Ma et al., 2021). In a recent *in vivo* study, *C. myxa* fruit cured experimentally-induced colitis by restoring the activity of antioxidant enzymes (glutathione peroxidase and superoxide dismutase) and also elevated the levels of trace elements (selenium, zinc, copper, and manganese) hitherto reduced due to colitis (Al-Awadi et al., 2001). In an interesting study, Azhaoet. al. demonstrated that *C. myxa* aqueous extract increased the mitotic index of spleen and marrow cells in mice injected with hydatid cyst fluid antigen. This improvement in cell-mediated immunity was attributed to polyphenols and saponins (Ali et al., 2015).

#### 4.3.3. *C. oblonga*

In an interesting study, oral administration of hot-water extract of whole Quince fruits (seeds, pulp, and peel) decreased the serum concentration of IgE and consequently inhibited degranulation of mast cells in animal models of atopic dermatitis. The results were attributed to low-molecular-weight polyphenols and quercetin glycosides (Shinomiya et al., 2009). In another study, a similar extract of whole quince fruit significantly suppressed the expression of inflammatory cytokines, including interleukins and tumor necrosis factor- $\alpha$ , and cyclooxygenase-2 in an *in vitro* study. The results were also attributed to the polyphenols (Kawahara and Iizuka, 2011). In an *in vitro* study on the anti-allergic effects of lemon and quince aqueous extract, it was observed that each component exerted inhibitory activity on different cytokines and chemokines, which results in effective control of the allergic reaction. Interestingly, neochlorogenic acid from *C. oblonga*, although held responsible for the activity, did not exert any such effect when isolated. This advocates for the use of natural drugs as a whole (Huber et al., 2012). Since quince seeds contain a significant proportion of phenolic compounds, specifically caffeoylquinic acids (Silva et al., 2004), it seems likely that quince seeds used in the Unani decoction may also produce similar effects on the respiratory tract.

#### 4.4. Broncho-dilatory, anti-tussive, and soothing effects on respiratory tract

Regardless of the causative agent, nearly all types of viral influenza characteristically share respiratory symptoms like cough (mostly dry), sore throat, nasal obstruction, and discharge (Krammer et al., 2018). Sensory alterations like disturbed taste and smell have been particularly observed with SARS-CoV-2 infection (Flerlage et al., 2021). Infection with most influenza viruses like SARS, SARS-CoV, MERS, and Ebola virus is also known to trigger asthma and COPD attacks in otherwise controlled patients (Macias et al., 2021). In nearly all types of influenza, supportive treatment like maintenance of airway and general health go a long way in preventing complications and promoting recovery (Tyrrell et al., 2021).

##### 4.4.1. *Z. jujuba*

In this context, the present Unani decoction offers several benefits. The drugs included in the decoction are traditionally known to relieve the respiratory symptoms, resulting in a feeling of well-being and relief, which assists in early recovery. In Unani medicine, *Z. jujuba* fruits have been prescribed for various kinds of cough, bronchial irritation, asthma, etc. (Baitar, 1999; Sina, 1992). Similarly, in traditional Persian

medicine, Jujube fruit is prescribed for inflammation of the lungs and difficulty in breathing (Bahramsoltani and Rahimi, 2020). In traditional Chinese medicine, it is believed that Jujube fruits moisten the lungs and alleviate cough (Liu et al., 2021). In a double-blind RCT, a *Z. jujuba* fruit-containing herbal mixture relieved the symptoms of asthma and cold in children aged 7–12 years (Javid et al., 2019). Mucilage from *C. dichotoma* raw fruits is an expectorant and effective in treating lung diseases (Choudhary and Pawar, 2014).

##### 4.4.2. *C. oblonga*

*C. oblonga* has been prescribed in traditional Persian medicine for orthopnea, hemoptysis, asthma (Karegar-Borzi et al., 2016), and acute respiratory infections due to its antitussive, anti-hoarseness, and lung-protective effects; and high nutritive value (Moslemifard et al., 2020). On being soaked in water, the seeds release a mucous which has a demulcent effect (Tamri et al., 2014). Janbaz et al. (2013) demonstrated the bronchodilator activity of Quince seed extract on isolated rabbit trachea. It was observed that the extract relieved tracheal spasm induced by potassium and carbachol ( $EC_{50} = 0.41$  mg/mL and 0.94 mg/mL respectively), through a possible  $Ca^{++}$  antagonist mechanism. The effects were comparable to verapamil (Janbaz et al., 2013). Although clinical studies on the palliative effects of the three drugs are lacking, there is convincing evidence from traditional literature and pre-clinical studies regarding their beneficial effects which warrants further research.

#### 4.5. Anti-bacterial activity

Viral infections of the respiratory tract often pre-dispose to bacterial and fungal co-infections (Hughes et al., 2020), often with an ominous prognosis. In a recent cohort of COVID-19 and influenza patients, it was observed that secondary bacterial infections were associated with higher mortality, 2.7-fold for COVID-19 and 3.09-fold for influenza (Shafraan et al., 2021). Co-infection with other viruses, bacteria, fungi, and archaea has also been reported in patients of COVID-19, mostly with adverse outcomes (Hoque et al., 2021). Similar co-infections and superadded infections were also observed during the previous outbreaks of Spanish flu (1918), influenza A (2009–12), SARS-CoV (2002–03), and MERS (2012) pandemics (Hoque et al., 2021). Several factors predispose to the higher susceptibility of superadded infections in patients with viral respiratory diseases. Viruses may cause both structural and functional disruption of the airways, e.g. ciliary damage, disruption of defense mechanisms (phagocytes, host defense peptides, dendritic cells, T-cells, etc.), increased availability of receptors, and a generalized immunosuppressed state (Bakaletz, 2017). Hence, it is imperative to prevent the occurrence of secondary infections for a better prognosis of influenza.

##### 4.5.1. *Z. jujuba*

The components of the three-herb Unani decoction have demonstrated specific anti-microbial activity against common respiratory pathogens. In a recent *in vitro* study, the aqueous and methanolic extracts of *Z. jujuba* fruit demonstrated anti-bacterial activity against multi-drug resistant strains of *P. aeruginosa*, *S. aureus*, and *E. coli*, identified to be caused by phenolic compounds and flavonoids (Mehreen et al., 2016). *In vivo*, the methanolic extract decreased heart and lung lesions in animal models of sore-throat infected with MRSA (Arshad et al., 2017).

##### 4.5.2. *C. dichotoma*

Acetone extract of *C. dichotoma* demonstrated anti-microbial activity against *Staphylococcus aureus* in clinical isolates from oral cancer patients, most (87.5%) of whom were neutropenic (Panghal et al., 2011). *In vitro*, the alkaloid fractions of *C. latifolia* fruit demonstrated *in vitro* inhibitory activity against MRSA, with implications that it may be potentially useful in treating infective sore-throat. On hemolysis assay, it

was declared safe for human use (Mehreen et al., 2016). In animal models of sore throat caused by MRSA, the methanolic extract of *C. latifolia* reduced gross pulmonary lesions, a sign of bacterial virulence (Arshad et al., 2017).

#### 4.5.3. *C. oblonga*

*C. oblonga* fruit has been prescribed in Persian medicine for acute respiratory infections as a medicinal nutrient (Moslemifard et al., 2020; Nikhat and Fazil, 2022). Since the seeds of Quince are included in this Unani decoction, we are interested in exploring their antimicrobial activities. In an important *in vitro* study, the ethanolic extract of quince seeds demonstrated a concentration-dependent inhibitory activity against gram-positive bacteria (*S. aureus*, *S. epidermidis*), attributed to phenolic compounds, tannins, and glycosides (Khazraji, 2013). Hendrich et al. (2020) evaluated the *in vitro* antibacterial effect of quince fruit extracts (methanolic and aqueous) on *E. coli*. Both extracts were effective in reducing bacterial adhesion to epithelial cells. The aqueous extract caused complete disappearance of the biofilm, while the methanolic extract exerted only a weak effect. The aqueous extract was rich in flavanols, flavonols (quercetin 3-O-galactoside, quercetin 3-O-rutinoside), and phenolic compounds (chlorogenic acid, phenolic acid) (Hendrich et al., 2020). Since the aqueous extract closely resembles the traditional method of use in Unani medicine, it is postulated that it may provide similar benefits in the decoction.

#### 4.6. Anti-oxidant activity

Influenza viruses have the propensity to modulate intracellular redox status in order to facilitate replication, immunosuppression, and pathogenesis. Compromised antioxidant defense system, increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) is characteristically associated with influenza virus infection. The resulting high levels of ROS and RNS activate several pathways which lead to cell death (Sgarbanti et al., 2014). In addition, the oxidative stress induced by the viral infection may also abet the onset and progress of natural aging changes, neurodegenerative disorders, diabetes, etc. (Nencioni et al., 2007; Fazil et al., 2021). In various studies, it is observed that the judicious use of anti-oxidants helps in decreasing viral load and also counteracts the tissue damage (Sgarbanti et al., 2014). Due to its therapeutic importance in influenza, we were interested in studying the possible antioxidant activity of the Unani decoction ingredients.

##### 4.6.1. *Z. jujuba*

In a recent study by Arab et al., pre-treatment with aqueous extract of Jujuba fruits protected human fibroblast cells against TBHP-induced damage in a dose-dependent manner. The cytoprotective activity was demonstrated by scavenging of TBHP-induced peroxyl radicals and increased anti-oxidant activity. Hence, Jujuba fruit extract (JFE) can be potentially used as a protective against oxidative-stress-induced diseases (Arab et al., 2019). In another study, Jujuba fruit ethanol extract exhibited anti-genotoxic activity *in vitro* and *in vivo*. The results were attributed to polyphenols and betulinic acid, a pentacyclic triterpene. The protective effects of betulinic acid against oxidative damage caused by dexamethasone have also been demonstrated in experimental animals. Clinically, the results implicate that JFE may be used as a hepato-protective, anti-oxidant, and immunomodulatory (Goswami et al., 2019).

##### 4.6.2. *C. myxa*

*C. myxa* fruit is rich in phenolics and flavonoids such as gallic acid, gentisic acid, caffeic acid, syringic acid, quercetin, kaempferol, and chrysin, etc which are potent antioxidants. *In vitro*, El-Massry et al. (2021) demonstrated the dose-dependent anti-oxidant and cytotoxic activity of *C. myxa* fruit extract by the FRAP method, which was directly proportional to the level of flavonoids and phenolics (El-Massry et al., 2021).

##### 4.6.3. *C. oblonga*

*C. oblonga* seeds and fruits contain significant amounts of tocopherols ( $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -) and carotenoids. Tocopherols and carotenoids are among the best-known anti-oxidants and free-radical scavengers. Tocopherols are lipophilic and exert significant protection against degenerative diseases, atherosclerosis, cardiovascular diseases, etc., as demonstrated in various studies (Fromm et al., 2012). Quince seeds contain a significant amount of citric (36%), ascorbic (31%), malic and quinic acids (33% combined) which exert antioxidant and free-radical scavenging activity (Silva et al., 2004).

#### 4.7. Cardioprotective activity

Acute respiratory infections are known to precipitate cardiovascular diseases (CVDs), leading to protracted morbidity and higher mortality. Seasonal influenza, MERS, SARS, RSV, and acute bacterial infections can induce vascular inflammation, myocarditis, acute coronary syndrome, and thromboembolism. A pre-existing CVD is also associated with increased complications, often leading to a fatal outcome (Madjid et al., 2020). Recently, Shao et al. proposed that endothelial cells (ECs) function as first-line immune cells, and also have trained immunity functions. Since human cardiac ECs express all four coronavirus receptors, they are affected directly by the viral infection. The resulting EC death triggers thromboembolism through vascular inflammation, DIC, and thrombosis (Shao et al., 2021). Clinically, this implies that antithrombotic measures should be integral to the management of COVID-19 and similar infections, from the early stage of the disease.

##### 4.7.1. *Z. jujuba*

In a recent study, ethanolic extract of Jujuba seeds exerted anti-platelet activity in animal models of acute pulmonary thromboembolism. The extract caused a statistically significant dose-dependent inhibition of collagen-, arachidonic acid-, thrombin-, and ADP-induced thromboxane B<sub>2</sub> (TXB<sub>2</sub>) formation. The results were mainly attributed to Jujuboside B. In addition, pre-treatment with the extract or Jujuboside B alone had a protective effect on platelets and tissues against acute thromboembolism (Seo et al., 2013). In an interesting study, JFE extract decreased the level of lipocalcin-2 in MI rats over 6 weeks, thus having a protective effect on heart tissue (Hosseini et al., 2019).

##### 4.7.2. *C. dichotoma*

Various extracts of *C. dichotoma* fruit have also demonstrated cardioprotective, anti-hypertensive, and anti-atherosclerotic activity in different studies. In a recent study, the anti-hyperlipidemic effect of *C. dichotoma* aqueous extract was studied *in vitro* and *in vivo*. *In vivo*, the extract exhibited significant reducing power and free radical scavenging activity. In rats fed on a high-fat diet, the extract caused a significant reduction in liver cholesterol, TC, TG LDL-C, and VLDL-C; and elevation of HDL-C. The effects were attributed to flavonoids (hypolipidemic) polyphenols (inhibition of pancreatic lipase), mucilage (decreased fat absorption), and alkaloids (El-Newary et al., 2018). In another study, methanolic extract of *C. myxa* fruits normalized blood pressure and oxidative stress in animal models of hypertension (Orekhov, 2016). In an animal study, methanolic extract of *C. myxa* fruits demonstrated a cardioprotective activity against Doxorubicin. The effects were attributed to the antioxidant activity of flavonoids, tannins, and saponins present in the extract (Shah et al., 2019).

##### 4.7.3. *C. oblonga*

In a recent study, aqueous extract of whole quince fruits protected heart against doxorubicin-toxicity by suppressing the generation of mitochondrial ROS, lipid peroxidation, and elevation of mitochondrial glutathione. The results were attributed to the organic acids, polyphenols, and amino acids, which are present in pulp (Gholami et al., 2017) as well as seeds (Silva et al., 2004). High levels of mitochondrial ROS are a known risk factor for cardiovascular diseases, including

atherosclerosis. Hence, the presence of quince seeds in this Unani decoction may be protective against COVID-induced atherosclerosis (Mirmohammadlu et al., 2015).

#### 4.8. Neuro-protective activity

A wide spectrum of neurological complications is frequently associated with both seasonal and pandemic influenza (Ekstrand, 2012). Jang et al. (2009) observed that the people born between 1988 and 1924, i.e., those who were likely exposed to the 1918 influenza pandemic, had a two to three-fold higher risk of developing Parkinsonism as compared to others (Jang et al., 2009). In a systematic review of 67 studies, polyneuropathy, encephalitis, stroke, and demyelinating disease were identified as the commonest complications of SARS, MERS, and COVID-19 patients (Montalvan et al., 2020). In COVID-19, anosmia and ageusia were observed in more than 85% of patients (Aghagoli et al., 2021). Besides direct tissue invasion by influenza viruses, hypercytokinemia leading to disruption of the blood-brain barrier is speculated to be the most likely mechanism behind neuronal death resulting in cerebral dysfunction (Tsai and Baker, 2013). Hence, neuroprotective measures must be given due importance in the management of RVIs.

##### 4.8.1. *Z. jujuba*

Jujube fruits have been described as a brain-nourishing and calming food in traditional Chinese medicine. Recent studies have identified many bioactive ingredients in jujube fruits that have neuroprotective effects. For instance, kaempferol 3-O-rutinoside has a neuroprotective effect on focal cerebral ischemia, and also reduced oxidative stress and memory dysfunction in animal models of dementia caused by infarction. In separate studies, cAMP present in aqueous extract of jujube fruit exerted effects on neuronal differentiation on cultured PC12 cells, and also exhibited anti-melancholic activity in animal models of depression. It was also demonstrated that JFE could increase the cAMP in plasma and hippocampus in experimental mice (Chen et al., 2017). In an interesting study, Chen et al. (2015) observed that aqueous extract from mature jujube fruits was more effective in stimulating neurofilament expression than that of immature fruits. In corroboration of the observed effect, it was found that seven nucleotides including cGMP and cAMP were present in a higher concentration in mature fruits (Chen et al., 2015). In an interesting animal study, aqueous extract of Jujuba fruit alleviated the amnesia induced by D-galactose injection, with implications for the treatment of Alzheimer's disease. The effects were caused by the reduction of pro-inflammatory cytokines and increased bioavailability of acetylcholine, possibly caused by the polyphenol content (Kandeda et al., 2021).

##### 4.8.2. *C. myxa*

*C. myxa* fruit pulp contains significant amounts of flavonoids (up to  $37.2 \pm 0.43$  µg/g total flavonoids), as observed in various extracts. The flavonoid content is higher in ripe fruits as compared to green ones. Hence, the ripe fruits exert important antioxidant activity. In addition, flavones (chrysin and apigenin) found in *C. myxa* are known to possess anxiolytic activity on benzodiazepine receptors without causing sedation (El-Massry et al., 2021).

##### 4.8.3. *C. oblonga*

In a recent study, aqueous and ethanolic extract of *C. oblonga* whole fruit demonstrated anti-depressant activity in experimental animals through modulation of nor-adrenergic and serotonergic pathways. The results were attributed to flavonoids (quercetin, myricetin, kaempferol), and Vitamins A, C, and E (Ganaie et al., 2020).

#### 4.9. Gut-microbiota regulation

In recent years, it has been elucidated that the gastrointestinal tract (GIT) is the largest organ of the immunological system, and a key player

in host defense against various infections (Yeoh et al., 2021). The gut microbiome also helps to control RVIs by various mechanisms. Desaminotyrosine, produced by *Clostridium orbiscindens* (an obligate clostridial anaerobe) from the digestion of plant flavonoids augments the synthesis of type-I interferons in the lungs. A similar role is played by the short-chain fatty acids produced by the fermentation of dietary fiber by commensal bacteria (Sencio et al., 2021). Besides, the gut microbiota also plays a role in the formation of CD4<sup>+</sup> T-cells, secretion of IgA, IL-12, IL-22, and some antiviral cytokines. It has been demonstrated that RVIs are associated with an increase in Enterobacteriaceae and decrease in Lactobacilli and Lactococci (Baradaran Ghavami et al., 2021). Among several factors, the dysbiosis may be caused by antibiotic therapy (Sencio et al., 2021), or may be induced by the infection itself (Groves et al., 2020) leading to weakened adaptive and immune responses. Interestingly, GI symptoms were observed in a significant number of COVID-19 patients, while SARS-CoV-2 RNA was isolated in stool samples from 46.7% of asymptomatic cases. Also, an imbalance of intestinal flora was observed in COVID-19 patients which persisted for 12 days after nasopharyngeal clearance of the virus (Baradaran Ghavami et al., 2021). In a systematic review of 58 animal and clinical studies, Shi et al. (2021) concluded that pre-treatment with probiotics has protective effects against influenza viruses, with therapeutic implications (Shi et al., 2021). Therefore, regulation of intestinal flora is imperative in the management of influenza.

##### 4.9.1. *Z. jujuba*

In a recent study, extract of jujube seeds improved insomnia in experimental animals by correcting metabolic abnormalities and composition of intestinal flora (Hua et al., 2021). In another study, polysaccharides from jujube seeds regulated the composition of intestinal flora in animal models of colitis (Y. Liu et al., 2020b). Wang et al. (2020) demonstrated that water-soluble polysaccharides from jujube exert immune-enhancing activity by enriching gut microbiota (Wang et al., 2020). In two separate studies, polysaccharides from jujube fruit exhibited anti-cancer (Ji et al., 2020) and immune-enhancing activity (Han et al., 2020) by enrichment of gut flora.

#### 4.10. Other activities

In addition to the above activities, the components of the three-herb Unani decoction also exert other important therapeutic effects which may positively affect the disease outcome in influenza patients and improve general health. For instance, flavonoids from Jujube fruit stimulate erythropoietin expression in a dose-dependent manner (Chen and Tsim, 2020). In addition, anti-obesity, gastro-intestinal protective, and hepatoprotective activities have also been identified in Jujube (Gao and WuSenWang, 2013). In an *in vitro* study, *C. myxa* mucilage exerted anti-protozoal activity against *L. infantum* and *L. major*, attributed to its phenolic and flavonoid compounds (Saki et al., 2015). In an animal study, aqueous extract of *C. oblonga* fruit demonstrated hypolipidemic, nephroprotective, and hepatoprotective effects in streptozotocin-induced diabetic rats (Mirmohammadlu et al., 2015). *C. oblonga* fruit extract also exhibited anti-proliferative activity against human colon and kidney cancer cells *in vitro* in a concentration-dependent manner (Carvalho et al., 2010). An anti-diarrheal activity has also been identified in Quince seeds, attributed to tannins, triterpenes, and sterols (Ashraf et al., 2016).

## 5. Discussion

As observed in this review, the three-herb Unani decoction (composed of *Z. jujuba*, *C. oblonga*, and *C. myxa*) reviewed in this article can play a potentially important prophylactic and therapeutic role in many of the co-morbidities associated with influenza (Table 1 and 2).

*Prophylactic effects of Unani decoction in influenza:* From the prophylactic aspect, the Unani decoction can be potentially beneficial in



preventing many types of RVIs, including COVID-19. The Betulinic acid present in *Z. jujuba* and phenolic compounds of *C. oblonga* have anti-viral activities against many influenza viruses, as discussed above, while UNA present in *Z. jujuba* also has anti-SARS-CoV-2 activity (Hamauzu et al., 2005; Son and Lee, 2020a,b), hence they can prevent many types of influenza. Besides, the flavonoids of *Z. jujuba* (Mehreen et al., 2016), phenolic compounds and tannins of *C. oblonga* (Al-Khazraji, 2013), and alkaloids from *C. myxa* (Mehreen et al., 2016) have a proven anti-bacterial activity, by which they can prevent and treat many secondary bacterial infections. Bacterial infections are known to worsen the disease outcome in influenza, hence, as per guidelines, empirical antibiotic therapy is recommended for all influenza patients suffering from acute respiratory distress syndrome (ARDS). In this context, the Unani decoction offers additional benefits by having an anti-microbial activity. Also, the decoction ingredients offer immune-modulatory, anti-depressant, neuroprotective, anti-inflammatory, and anti-allergic activities (Kawahara and Iizuka, 2011; Naik et al., 2013). This can help to protect vital organs, maintain the integrity of respiratory organs, and can potentially suppress the disease severity. In addition, anti-oxidant, hepatoprotective, cardioprotective, anti-hyperglycemic, anti-thrombotic, and anti-proliferative activities have been observed in the decoction ingredients, due to which it can prevent a significant proportion of the morbidity spectrum of viral influenza (El-Massry et al., 2021; Goswami et al., 2019). From the preventive aspect, this is important because good general health leads to early recovery and lesser complications in case of influenza infection (Akhtar et al., 2021). Evidence to this observation was made in a recent RCT on 4313 healthy subjects in which the prophylactic effect of this Unani decoction was evaluated against COVID-19. It was found that the treated patients had a lesser positivity rate than the control group (Nayab et al., 2022). In addition, *Z. jujuba* fruit polysaccharides also help in regulating the imbalance of gut flora which is now recognized as an important mediator in the immune response and also plays a significant role in the disease outcome (Ji et al., 2020).

**Therapeutic and palliative effects of Unani decoction in influenza:** From the therapeutic, palliative, and rehabilitative viewpoint, the phytoconstituents in the Unani decoction can be potentially beneficial in alleviating many of the pathological processes of influenza, and also provide palliative benefits which inculcate a sense of well-being, thus improving the disease outcome. UNA, Betulin, betulinic acid, lupeol, and oleanolic acid present in *Z. jujuba* have anti-inflammatory, anti-allergic, bronchodilatory, and anti-tussive effects (Zhang et al., 2017; Naik et al., 2013). Similar effects are seen with polyphenols (caffeoylquinic acids, quercetin glycosides, and kaempferol glycosides) present in *C. oblonga* (Shinomiya et al., 2009) and flavonoids present in *C. myxa* (Ranjbar et al., 2013). Quince mucilage is also recognized in traditional Unani medicine as a soothing agent for throat and trachea due to its adherent nature (Baghdadi, 2005). Together, these effects can help in relieving the symptoms of cough, and bronchospasm which are observed in nearly all types of influenza. The clinical relief leads to a feeling of well-being and early recovery (Rainsford, 2006). The Unani decoction ingredients can also regulate the cytokine reactions, e.g., *Z. jujuba* polysaccharides suppress IL-2 production (Hsu et al., 2014), while *C. myxa* provides anti-inflammatory effect by restoring the activity of anti-oxidant enzymes and trace elements (Kawahara and Iizuka, 2011). Owing to the multi-dimensional activity, it can be postulated that this particular Unani decoction may be effective against various disease agents and their respective pathologies. Also, the anti-oxidant activity of the three drugs provides cyto-protective effects (Arab et al., 2019; El-Massry et al., 2021), which may help in minimizing the complications. Although an anti-pyretic activity has not been reported for any of the three drugs, *Z. jujuba* can mitigate the adverse effects caused by common anti-pyretics, particularly hepatic damage (Jing et al., 2015). In addition, anti-hyperlipidemic activity of *C. dichotoma* (El-Newary et al., 2018), anti-atherosclerotic activity of *Z. jujuba* (Seo et al., 2013), and cardioprotective activity of *C. oblonga* (Silva et al., 2004) can prevent

influenza-induced thromboembolism.

Historically, it is observed that all types of influenza, including COVID-19, have many non-respiratory afflictions, and often cause significant morbidity and mortality. For instance, encephalopathy, encephalitis, and myelitis have been observed in about 8.5–10% of Influenza A and B patients long after recovery (Radzišauskienė et al., 2021). In addition, exacerbation of existing lung diseases, renal failure, systemic complications like cardiovascular, endocrine, musculo-skeletal, and cerebro-vascular complications have been recorded for influenza A in the post-pandemic period (Reed et al., 2014). In COVID-19 patients, radiological and functional abnormalities have been observed in approximately 71% and 25% patients respectively 3 months after initial infection. These include pulmonary fibrosis, alveolar damage, abnormal echocardiography, myocardial hypertrophy and necrosis, thrombotic events, headache, myalgia, depression, insomnia, skin rashes, worsening of diabetes, diabetic ketoacidosis, acute renal injury, hepatic steatosis, arthralgia, and male infertility (Desai et al., 2022). Hence, it is apparent that influenza management needs to take into account the extra-pulmonary and long-term effects of the disease. In this context, the Unani decoction discussed in this paper offers a practical solution to overcome the disease burden and reduce adverse outcomes.

## 6. Conclusion and future directions

In the words of Hakim Abdul Hameed (1908–1999), founder Jamia Hamdard, New Delhi:

*“At a point of time, there were deliberations on whether medicine should be considered a science or an art. The proponents of both sides provided their justifications, while medicine remained a timid spectator to the contention. For its basic nature, it wasn't willing to be confined to either of the categories, as it knew that it deals with the human being, who is, in essence, a coalescence of body and soul. Hence, medicine ought to be an integration of both art and science.”*

-Preface to *Tajurbāt-i-Ṭabīb* (Said, 1973).

It was December 2019 when modern medical history was forever divided into two phases: the pre-COVID-19 phase and the post-COVID-19 phase. By bringing the world to a physical standstill, the COVID-19 pandemic has given many a moment to reckon, to ponder upon the very nature of holistic health, and to deliberate if ‘going back’ may be the best way to the future. It is becoming increasingly evident that effective preventive strategies for epidemics should include immuno-modulation, vital-organ protection, and symptom relief, in addition to anti-infective measures. It is in this context that the role of ‘art of medicine’ comes to the fore. As per Hippocratic concept, the goal of medicine is ‘to remove the distress completely’, which includes ‘complete physical, mental and social well-being’ as advocated by WHO (Francis, 2020). Such a holistic approach is best-possible with the use of natural drugs, owing to the presence of several beneficial phyto-chemicals, which exert multifarious actions (Panyod et al., 2020).

Influenza outbreaks are here to stay, as opined in several studies. During the COVID-19 crisis, various traditional medicines have been utilized across the world, which may have contributed to reduction of disease burden. The three-herb Unani decoction reviewed in this study has also shown promising results as prophylactic against COVID-19 in a recent clinical study, and further clinical researches are underway (Ahmad et al., 2021). Due to the multi-dimensional action, it is envisioned that the decoction may be potentially beneficial in influenza caused by various disease agents. By virtue of the multi-dimensional actions contributed by numerous bioactive ingredients, the Unani decoction can potentially help in preventing and treating the non-respiratory complications of influenza in addition to its respiratory complications. Hence, it is a one-of-a-kind medicine which offers preventive, therapeutic, palliative, and possibly restorative effects in RVIs. Most importantly, the decoction consists of easily available herbal drugs, and can be prepared in domestic and low-resource settings. This

article generates credible evidence regarding its efficacy against viral influenza and its complications. Hence, it may be subjected to large-scale clinical trials across various age-groups for the benefit of all mankind. It is also observed in the review that the decoction ingredients also contain a significant number of bioactive compounds which are insoluble or partially soluble in water, hence different extraction methods may be employed in the future to reap maximum benefits out of the formulation.

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## CRediT authorship contribution statement

**Mohammad Fazil:** Conceptualization, Editing, Development of search strategy, Literature search. **Sadia Nikhat:** Formal analysis, Writing – review & editing, Literature review, Analysis, Writing, and Editing. Both authors read and approved the final manuscript.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

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