Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Analytical review of *Tiryāq-i-Wabāī* – A Unani panacea for the control of COVID-19

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ABSTRACT

Introduction: COVID-19 has affected the whole world drastically and led to a substantial loss of human life. Relentless research is underway to identify effective treatment to control the disease. Traditional systems are also being explored to search for a potent drug. Unani formulation '*Tiryāq-i-Wabāī*' has long been used in cholera, plague and other epidemic diseases. This review is aimed at analysing the possible role of *Tiryāq-i-Wabāī* in the prevention and control of COVID-19.

Methodology: Unani classical texts and Pharmacopoeias available in the library of Regional Research Institute of Unani Medicine, Chennai were reviewed to collect information related to epidemics, commonly prescribed drugs during epidemics, and therapeutic uses of *Tiryāq-i-Wabāī* ingredients. ScienceDirect, Springer, PubMed and Google Scholar were searched to collect information regarding current pandemic and pharmacological activities of ingredients and phytoconstituents present in the formulation. The collected data was analyzed and interpreted.

Results: Tiryāq-i-Wabāī was found to be the most recommended prophylactic and curative drug during epidemics. The formulation ingredients, Sibr (*Aloe vera* (L.) Burm.f.), Murr Makki (*Commiphora myrrha* (T.Nees) Engl.) and Zāfrān (*Crocus sativus* L.) are categorized under *Tiryāqi Advia* (literally – antidote drugs) and are considered to be very effective in SARS related conditions. These ingredients have been reported to exhibit immunomodulatory, antioxidant, antiviral, antibacterial, antitussive, smooth muscle relaxant, antipyretic and anti-inflammatory activities corroborating the traditional use of *Tiryāq-i-Wabāī*.

Conclusion: Scientific data imply great potential and utility of the formulation which could be a possible alternative approach for the prevention and control of current and future pandemics.

1. Introduction

The outbreak of coronavirus disease 'COVID-19' has become a matter of great public health concern worldwide and declared as global pandemic by World Heatlth Organization (Gautret et at, 2020). This is the third coronavirus disease to occur in the 21st century, after the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002–03 and Middle-East respiratory syndrome coronavirus (MERS-CoV) in 2012, which caused disastrous outbreak of pneumonia in human beings (Nikhat and Fazil, 2020). The disease was identified first in Wuhan, China and spread to nearly 216 countries in a very short period of time. The rapid increase in cases of Covid-19 caused widespread panic among people across the globe. Despite the fact that the spread and threat of COVID-19 is currently declining, between 5 and 11 September 2022, over 3.1 million new cases and 11,000 fatalities were reported by WHO globally (World Health Organization (WHO), 2022a). As per the current statistics, as at September 16, 2022, more than 608 million confirmed cases of COVID-19 including 6.5 million deaths had been reported globally (World Health Organization (WHO), 2022b).

In India, the first case of Covid-19 reported on 30 January 2020, was a student who traveled from China to India. As of 16 September 2022 there had been 44,522,777 confirmed cases with 528,273 deaths reported in the country (World Health Organization (WHO), 2022c).

There have been many global initiatives to address the situation

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efficiently. However effective and specific therapy options for the pandemic still remain limited (Niknam et al., 2022). Certain drugs have been investigated and recommended for the management of COVID-19, including remdesivir, lopinavir, ritonavir, interferons, steroids, monoclonal antibodies and repurposed drugs such as chloroquine and hydroxychloroquine (Fazil and Nikhat, 2022; Niknam et al., 2022). Chloroquine 'a widely used anti-malarial drug' and hydroxychloroquine were shown to have in vitro antiviral activity. Both drugs share similar chemical characteristics and mechanism of action. Hydroxychloroquine has been reported to curb the SARS-CoV-2 replication. Reports suggest that these drugs may have efficacy in treating patients infected with Covid-19 (Meo et al., 2020). Hydroxychloroquine and azithromycin in combination have demonstrated a synergistic effect in viral load reduction and early recovery (Gautret et al., 2020).

At present, a number of vaccines are available for the control of COVID-19. Mass vaccination drive has been implemented across the globe. However, the search for potent and specific treatments is still imperative, particularly in nations with low vaccination rates and where mutations can potentially threaten vaccine evasion. Further, the effectiveness of COVID-19 vaccine is limited in some individuals such as the immunocompromised, patients with malignancies and those receiving chemotherapies (Niknam et al., 2022).

The scientific community across the globe is actively engaged in exploring novel therapeutics to address the current need. In a similar vein, prophylactic and curative aspects of traditional medicines are also being explored for the treatment of the disease. Significant antiviral activities against a wide range of viruses have been reported for many traditional remedies used for millennia in Ayurveda, Unani, Siddha and other traditional systems of medicine (Mukherjee, 2019). A recent study on a siddha formulation demonstrated a high binding affinity and interactions with spike protein of SARS-CoV-2 (Kiran et al., 2020). These studies support the hypothesis that traditional remedies may have a direct effect against SARS-CoV-2. Epidemics and infectious diseases had been discussed meticulously in classical literature of Unani medicine, one of the most recognized traditional systems of medicine in India, with evidence of a wide range of prophylactic and therapeutic potential. (Nikhat and Fazil, 2020). *Tiryāq-i-Wabāī* is one such well documented formulations in Unani classical literature for its wide use as a prophylactic during epidemics. The very nomenclature of the drug connotes "an antidote during epidemics". The ingredients of this pharmacopoeial formulation have been reported for a wide range of pharmacological activities including antiviral, antimicrobial, antioxidant and immunomodulatory activities. The formulation may prove beneficial in augmenting immune resilience and may be used for prophylactic and therapeutic purposes in the current situation as well as in future pandemics. This review will highlight the potential of *Tiryāq-i-Wabāī* in epidemics and its possible role in combating COVID-19.

2. Methodology

The authors reviewed Unani classical texts and Unani Pharmacopoeias available in the library of Regional Research Institute of Unani Medicine, Chennai and collected information related to epidemic diseases, commonly prescribed drugs for prophylactic and therapeutic purposes during epidemics, and ingredients of *Tiryāq-i-Wabāī*. Major text books and Pharmacopoeias reviewed include *Kitāb al-Mansūrī* by Muḥammad ibn Zakariyā Rāzī (865–925 CE), *Minhāj al-Ilāj* by Al-Qamarī (10th CE), *Al-Qānūn fi'l Ṭibb* by Ibn Sīnā (980–1035 CE), *Kitāb al-Mukhtārāt fi'l Ṭibb* by Ibn Hubal (1121–1213 CE), *Kitāb al-Kulliyāt* by Ibn Rushd (1126–1198 CE), *Kitāb al-Jāmi' li Mufradāt al-Advia wa'l 'Aghziya* by Ibn Baitār (1197–1248 CE), *Al-Asbāb wa'l 'Alāmāt* by Najīb al-Din Samarqandī (13th CE), *Zakhīrā Khawārizm Shahī* by Ismā'īl Jurjānī (11th CE), *Iksīr-i A'zam* by A'zam Khan (1813–1902 CE), *Qarābādīn-i Najm al-Ghanī* and *Khazāin al-Advia* by Najm al-Ghanī (1859–1932 CE). Other books and journals were also reviewed for further information. Major scientific databases including ScienceDirect, Springer, PubMed and Google Scholar were searched to collect information regarding current pandemic and pharmacological activities of formulation ingredients. The search terms used included COVID-19, SARS-CoV-2, etiology, symptoms, traditional medicine for COVID-19, bioactive compounds, antiviral, immunomodulatory, antitussive, antipyretic, anti-inflammatory activities along with drug name such as saffron, *Aloe vera*, Myrrh. Selected reviews and original articles were reviewed and interpreted accordingly.

3. Results and discussion

3.1. Coronavirus disease 2019 (COVID-19)

The current pandemic of novel Coronavirus disease-2019 (COVID-19) has grossly affected the livelihood of the world population with dwindling GDP of several nations. It is a highly contagious and transmittable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Shereen et al., 2020). SARS-CoV-2 belongs to the genus β-coronaviruses and shares similar characteristics of other coronaviruses with spike protein (Phan, 2020a; Shereen et al., 2020). It uses ACE2 (angiotensin-converting enzyme 2) cell receptor and mechanism for entry into host cells as previously reported by Shereen et al. (2020). The primary target of antibodies and vaccines is spike glycoprotein which is a mixture of bat SARS-CoV and unknown beta-CoV (Shereen et al., 2020; Walls et al., 2020). Mutation in spike protein of SARS-CoV-2 has been reported which may enhance its binding affinity to ACE2 and hence its infectivity (Wan et al., 2020). Human to human transmission of virus can occur through different modes; speech and respiratory droplet or fomites is considered to be the direct and most significant mode as 50–80% of virus transmission is reported from asymptomatic carriers (Anfinrud et al., 2020). Various reports have confirmed the presence of virus in sputum, saliva, bronchoalveolar secretions, and nasopharyngeal swab of infected individuals (Phan, 2020b). The virus can also be transmitted through tears and other body fluids. Oro-fecal route is also possible as viral RNA has been detected in feces (Ling et al., 2020).

In most cases, average incubation period for Covid-19 is 5–6 days and in few cases, up to 24 days has also been reported (Jean et al., 2020). The novel coronavirus disease affects both male and female with a slight predominance in male (Guo et al., 2020). The disease is characterized by fever, dry cough and malaise in most of the cases (83–98%), however, few cases present other symptoms like shortness of breath, diarrhea, abdominal pain, headache and vomiting (Del Rio and Malani, 2020). Most of the patients present flu-like mild symptoms and recover within few days; however some cases may develop hypoxemia leading to cardiac arrest. Elderly and people with comorbid conditions such as cardiovascular disease, hypertension, diabetes, and chronic obstructive pulmonary disease, are more vulnerable to the infection, and are likely to develop complications such as acute respiratory distress syndrome, arrhythmia, shock, acute renal failure, acute cardiac injury and other conditions leading to death (Guo et al., 2020).

3.2. Ta'diya and Wabāī (infection and epidemic) and its management in Unani medicine

Unani scholars postulated the basic form of germ theory a millennium ago before the transitional period began in the late 1850 s. Various Unani scholars have narrated the contagion theory and given detailed description of *Ta'diya* (infection) and *Wabāī* (epidemic) in their texts. They named the causative factors of epidemic and putrefaction as *Ajsām Arḍiyya Khabītha* (close resemblance to microorganism) which may pollute water and air. These factors after invasion in the body cause *Ta'diya* (infection) in immunocompromised individuals and can migrate from diseased to healthy individuals (Baghdādī, 2005; Rushd, 1987; Sīnā, 2010). Unani scholars have advocated several measures to adopt for preventing the spread of epidemic and pandemic diseases including quarantine, oxygenation and purification of air, and improving host

immunity (Jurjānī, 2010; Rāzī, 1991; Samarqandī, 2007). A number of single and compound drugs have been prescribed by Unani scholars for the prevention, control and symptomatic treatment of infectious diseases and epidemics (Nikhat and Fazil, 2020). *Tiryāq-i-Wabāī* is one such time tested Unani formulation used during epidemics, which may have great potential in the current pandemic.

3.3. Tiryāq-i-Wabāī: overview

Tiryāq-i-Wabāī is a well-documented formulation in Unani medicine for its wide use for prophylaxis during epidemics of cholera, plague and other epidemic diseases. It is comprised of 3 ingredients, viz Sibr/*Aloe vera* (*Aloe vera* (L.) Burm.f.), Murr Makki/myrrh (*Commiphora myrrha* (T. Nees) Engl.) and Zāfrān/saffron (*Crocus sativus* L.). During literature survey, authors have found three different names i.e. *Tiryāq-i-Afāī, Tiryāq-i-Af'ā* and *Tiryāq-i-Wabāī* containing same ingredient, however the formulation is not mentioned in few classical Unani literatures by its name; rather its composition is mentioned and claimed to be very effective as prophylaxis during epidemics (Baghdādī, 2007; Rushd, 1987; Sīnā, 2010). In some books, the composition is mentioned separately, while formulation name is separately mentioned with reference to Jālīnūs statement, which creates confusion as to whether these formulations are same or are different. Rāzī (Rhazes, 865–925 CE) recounts from an old physician that *'whoever has used a mixture of two part of Sibr, one part Zāfrān and one part Murr Makki, remained protected during epidemics'*. Further he reported from Jālīnūs (Galen, 131–199 CE), that *Tiryāq-i-Af'ā* is very effective during epidemics (Rāzī, 1991). Abū al-Manṣūr ibn Nūḥ al-Qamarī (10th CE) followed the same pattern in his treatise '*Minhāj al-Ilāj*' and discussed the composition separately; later he narrated from Jālīnūs that *Tiryāq-i-Afāī* has a miraculous effect during epidemics (Qamarī, 2008).

Unani pharmacopoeias suggest that all these are same formulations, as it is mentioned in different pharmacopoeia with different names but with same composition. The formulation is claimed to have antivenom property and has been a very effective remedy during epidemics. The formulation was used by Galen and Avicenna in healthy persons as well as in patients during epidemics. It is indicated that the use of *Tiryāq-i-Wabāī* twice or thrice a week in a dose of 2 – 2.25 g, with *Arq Gulāb* 60 ml or *Arq Bādiyān* 120 ml, may protect the individual from infection during epidemics (Anonymous, 2006; Ghanī, 2019; Hafīz, 2005; Kabīruddīn, 1935).

According to Unani system of medicine all the three ingredients of the formulation, *Aloe vera*, myrrh and saffron, fall under the category of *Tiryāqi Advia* (literally – antidote drugs) and are considered to be very effective in SARS-like conditions especially in respiratory distress (Baghdādī, 2007; Kabīruddīn, 2007; Khan, 2011). These drugs have been reported to possess a wide range of pharmacological activities. *Aloe vera* has been reported to have anti-inflammatory, hepatoprotective, antiviral, antimicrobial, anticancer, immunomodulatory and antioxidant activities (Kumar et al., 2019). Saffron has been reported to have anti-HSV, anti-HIV (Soleymani et al., 2018), immunomodulatory, anti-oxidant, anticancer, chemopreventive, antigenotoxic, anti-inflammatory, antihypertensive, and antihyperlipidemic activities (Kianbakht and Ghazavi, 2011). Myrrh, on the other hand, has been reported to have antioxidant, anti-inflammatory, antimicrobial and antiviral activities (Fahad and Shameem, 2018; Ghadir and Ahmed, 2014; Mohammad et al., 2014). The formulation (*Tiryāq-i-Wabāī*) has been reported to possess immune-stimulation activity in immunocompromised elderly persons (Nigar and Itrat, 2013).

3.4. Potential of Tiryāq-i-Wabāī ingredients: scientific appraisal

3.4.1. Sibr / Aloe vera (Aloe vera (L.) Burm.f.)

The medicinal use of *Aloe vera* can be traced back thousands of years in the history, and has been used for various diseases in Unani system of medicine including digestive, respiratory, nervous system and skin disorders. The drug is known to possess anti-inflammatory, antiseptic, detergent and cleansing, purgative, deobstruent, and anthelmintic properties. It prevents sepsis and body decay, hence it was applied on dead bodies in the past; evacuates morbid matter from the body and cleans mainly head, chest, stomach and joints; and resolves obstructions in liver mesentery and other organs. It is claimed to be very effective in liver disorders, splenomegaly, bronchial asthma and other respiratory distress conditions; useful in non-healing ulcers and prevents spread of septic wounds (Baitār, 1999; Ghanī, 2011). It has been reported that the use of *Aloe vera* in any form; oral intake, fumigation, and spraying has promising effects during epidemics. Gargle of *Aloe vera* in combination with myrrh is claimed to be very effective in shortness of breath (Khan, 2011).

Pharmacological activities of herbs are attributed to the presence of biologically active compounds in the plant. *Aloe vera* contains several bioactive compounds including vitamins, minerals, enzymes, polysaccharides, anthraquinones or phenolics, lignin, saponins, sterols, amino acids and salicylic acids among others. It exhibits a wide range of pharmacological activities such as anti-inflammatory, antiviral, antimicrobial, antiseptic, immune-stimulating and wound healing activities (Kumar et al., 2019; Surjushe et al., 2008). Studies suggest that *Aloe vera* exerts antiviral activity via a number of mechanisms on different viruses. Saoo et al. (1996) reported the interference of DNA synthesis as the major mechanism involved in the inhibitory effect of *Aloe vera* extract against human cytomegalovirus (HCMV). A recent study demonstrated antiviral activity of emodin 'anthraquinone compound' against influenza A virus (IAV), and suggested that emodin could inhibit viral replication and influenza viral pneumonia via activation of nuclear factor E2-related factor 2 (Nrf2) signaling and by inhibiting IAV-induced activation of Toll-like receptor 4 (TLR4), Mitogen-Activated Protein Kinase (MAPK) and Nuclear Factor Kappa B (NF-kB) Pathways (Dai et al., 2017). Antiviral activity of *Aloe vera* extract has also been reported against herpes simplex type 2 virus (HSV-2) via inhibiting virus replication in both pre and post attachment stages of virus to host cell (Zandi et al., 2007). It is reported that Aloe polysaccharide exerted significant antiviral activity against H1N1 subtype influenza virus in vivo and in vitro via direct interaction with PR8 (H1N1) influenza virus particles to prevent its adsorption and replication (Sun et al., 2018). *Aloe vera* may exert antiviral activity in two ways; directly and indirectly. Directly, through biologically active compounds such as emodin having direct effect on virus, and indirectly, through stimulating immune system of the host. Aloe polysaccharide is known to have immune stimulating effect besides its other activities, and has a complex mechanism of antiviral activity. It can directly interfere with virus and limit its infectivity and it can improve host immunity as well, which in turn can promote the differentiation of immature dendritic cells (Sun et al., 2018; Surjushe et al., 2008). Six antiseptic compounds 'namely lupeol, urea nitrogen, cinnamonic acid, salicylic acid, phenol and sulphur' have been identified in *Aloe vera* and reported to have significant inhibitory effect on bacteria, fungi and viruses (Kar and Bera, 2018).

3.4.2. Zāfrān / Saffron (Crocus sativus L.)

Saffron is one among the acclaimed herbs extensively used as spice and medicine to promote human health since ages (Leone et al., 2018). It is known to possess a wide range of therapeutic actions such as exhilarant, deobstruent, antispasmodic, anti-inflammatory, expectorant, antitussive, anticatarrhal, aphrodisiac, diaphoretic, stomachic and stimulant. It has been used widely as tonic for vital organs including brain, heart, lung, liver and kidney (Hosseini et al., 2018; Khazdair et al., 2015). In traditional medicines, saffron is used in treating numerous diseases such as fever, cold, asthma, chest pain, small pox, scarlet fever, atherosclerosis, coronary artery diseases, hypertension, diabetes, stomach disorders, dysuria, dysmenorrhea, renal colic, cancer, insomnia and other neurodegenerative disorders (Baitār, 2000; Bukhari et al., 2018; Ghanī, 2011;). The vitality of saffron in treating respiratory diseases is well acknowledged by many Unani scholars. It is reported that saffron is

very effective in all kinds of altered respiratory functions (Khan, 2011). Ibn Baitār (1197–1248 CE) reported that saffron has antiseptic property and prevents *Khilṭ* (humour) from sepsis. Further he stated that '*saffron invigorates the pneuma and respiratory organs and facilitates respiration*' (Baitār, 2000). Avicenna has also stated that saffron especially its oil facilitates respiration and strengthens the respiratory organs (Hosseinzadeh and Nassiri-Asl, 2013).

Current scientific studies, on saffron and its major bioactive compounds such as crocin, crocetin and safranal, indeed substantiate the claims made by Unani sholars about therapeutic benefits of saffron. Several in vitro and in vivo studies have shown that saffron has numerous biological activities, including smooth muscle relaxant, antitussive, anti-allergic, antibacterial, anti-inflammatory and anti-nociceptive, immunomodulatory, antioxidant, antispasmodic, anticancer, anti-genotoxic, antihypertensive, antidiabetic, neuroprotective, cardioprotective, hepatoprotective, nephroprotective, anti-Alzheimer's, anticonvulsant and antidepressant (Bukhari et al., 2018; Hosseini et al., 2018; Hosseinzadeh and Nassiri-Asl, 2013; Khazdair et al., 2015). Despite the wide use and exhaustive scientific work done on saffron, it is hardly reported for its antiviral activity. To our knowledge, only one study has reported antiviral effect of saffron and its constituents. Soleymani et al. (2018) demonstrated significant anti-HSV and anti-HIV activity of the bioactive components of saffron 'crocin and picrocrocin'. Both the components inhibited virus replication and suppressed their penetration in the target cells (Soleymani et al., 2018). Recent computational studies suggest great potential of saffron bioactive molecules, crocin and crocetin, for inhibiting SARS-CoV-2 spike glycoprotein and main protease and limiting the virulence of the disease (Ahmed et al., 2021; Kordzadeh et al., 2020).

Various in vitro and in vivo studies suggest the potential of saffron in respiratory diseases. Studies have demonstrated the relaxant effect of saffron and its compounds on various smooth muscles including vascular, tracheal, gastrointestinal and urogenital smooth muscles (Mokhtari-Zaer et al., 2015). It is established fact that the ratio of type 1 T helper (Th1) and (Th2) cells play major role in the occurrence of asthma and airway inflammation. Th1 cells produce cytokines such as interleukin (IL)− 2, interferon gamma (IFN-γ) and tumor necrosis factor (TNF)-α, whereas T2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13. Various studies have reported suppressant effect of saffron and its constituents 'crocin and safranal' on airway inflammation and asthma and demonstrated a stimulatory effect on Th1 cells and suppressive effect on Th2 cells (Zeinali et al., 2019). A number of recent studies suggest saffron as promising immunomodulatory agent to treat various immune disorders. It is reported that saffron and its constituents 'crocin, crocetin and safranal' modulate inflammatory mediators, humoral immunity, and cell-mediated immunity responses. Saffron inhibits serum levels nuclear transcription factor κB (NF-κB) p65 unit, TNF-α, IFN-γ and IL-1β, IL-6, IL-12, IL-17A; it suppresses key pro-inflammatory enzymes such as myeloperoxidase (MPO), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), phospholipase A2; and modulates MAPK and NF-κB pathways. It controls the expression of genes encoding of pro-inflammatory cytokines, inducible enzymes and adhesion molecules etc which play vital roles in controlling inflammatory processes (Boskabady and Farkhondeh, 2016; Zeinali et al., 2019). There is a close interaction between inflammatory response, oxidative stress and immune system. Deregulation of normal immune response may activate the inflammatory pathways resulting in inflammation which plays a vital role in pathogenesis of several diseases including allergy, asthma, cardiovascular and other diseases. It could be inferred that immunomodulatory and anti-inflammatory effects of saffron may reverse the destructive processes and prevent human beings from various diseases (Boskabady and Farkhondeh, 2016).

3.4.3. *Murr makki / Myrrh (Commiphora myrrha (T.Nees) Engl.)*

Murr makki, commonly known as myrrh is an aromatic resin produced by *C. myrrha* tree. It has been used as medicine for millennia in different cultures such as Egyptian, Greece, Roman and Chinese to treat various diseases (Ghadir and Ahmed, 2014; Shen et al., 2012). Myrrh has been used in Unani system and other traditional systems of medicine to treat a number of diseases including fever, common cold, chronic cough, diphtheria, tonsillitis, pharyngitis, bronchitis, flu, catarrh, asthma, arthritis, tumors and cancer, gastrointestinal and urogenital disorders, infectious diseases including leprosy and syphilis, septic wounds and other skin disorders etc (Alhussaini et al., 2015; Baitār, 2003; Ghani, 2011). It is considered to be very beneficial during epidemics due to its antiseptic property. Ancient Unani physicians used to apply it on dead bodies to prevent sepsis. It has also been utilized as antidote for insect and snake bite (Baitār, 2003; Ghani, 2011). Myrrh alone and in combination with other suitable drugs is considered to be very effective for asthma and respiratory distress syndrome in different forms i.e. oral, fumigation and local application on chest. It evacuates thick phlegm and pus from the lung and facilitates respiration (Khan, 2011).

Myrrh contains several secondary metabolites including phenolic acids, flavonoids, tannins, glycosides, alkaloids, terpenoids, steroids, lignans and quinines (Al-Samarrai et al., 2017). Monoterpenoids, sesquiterpenoids, diterpenoids and triterpenoids are the major chemical compounds possessing a number of biological activities (Ge and Zhang, 2019; Ghadir and Ahmed, 2014). Myrrh has been reported to exhibit antitumor, anticancer (Shoemaker et al., 2005), anti-inflammatory, analgesic, antipyretic (Su et al., 2011; Tariq et al., 1986), antioxidant (Al-Samarrai et al., 2017; Racine and Auffray, 2005), antimicrobial, antifungal, antiviral (Ghadir and Ahmed, 2014; Khalil et al., 2020), antiparasitic (Shen et al., 2012), anti-diarrhoeal and anti-gastric ulcer activities (Kamil and Abdalla, 2019). Myrrh has also been reported to attenuate oxidative stress and inflammatory processes by down-regulating the expression of NO, prostaglandin E_2 (PGE_2), IL-1β, TNF-α, ROS, COX and modulating MAPK and NF-κB pathways (Batiha et al., 2023). Despite extensive use of myrrh in various respiratory ailments, it is hardly investigated scientifically to validate its traditional use. However, a case report suggests its potential in relieving dry cough, progressive respiratory distress and pneumonia in children (Michie and Cooper, 1991). It is suggested that the drug may attenuate respiratory problems by conquering inflammatory processes and also through its immunomodulatory, analgesic and cytotoxic activities (Batiha et al., 2023).

Immunomodulatory effect of myrrh has been demonstrated by various studies. It induced significant improvement in cellular immune response via stimulation of lymphocyte transformation, phagocytic activity; it improved levels of IL-4 in a patient suffering from fascioliasis. It exhibited protective effect against lead-acetate (PbAc)-induced hepatic oxidative damage and immunotoxicity by reducing lipid peroxidation and enhancing the antioxidant and immune defense mechanism (Ashry et al., 2010). Though some articles reviewed and claimed antiviral activity of myrrh essential oil against influenza virus type A (H1N1) and herpes simplex virus type 1 (HSV-1), this survey could not find any such study upon exhaustive online literature review. To our knowledge, only one study has been carried out to investigate antiviral effect of myrrh essential oil which showed moderate antiviral activity against Newcastle virus (NDV) on chicken embryo (Ghadir and Ahmed, 2014).

In view of the above summarized information about all the three ingredients of *Tiryāq-i-Wabāī*, it may be reasonable to state that the traditional use of these drugs has been substantiated by scientific evidence. It is worth mentioning here that Unani formulations contain multiple herbs and a single herbal drug contains several bioactive compounds with a wide range of pharmacological activities. The complex mixture of these compounds may act synergistically on multiple targets. Hence, it may be assumed that the combined effect of all the three ingredients of *Tiryāq-i-Wabāī* may exhibit an enhanced antioxidant, immunomodulatory, antiviral and other beneficial effects and, therefore, effective in the treatment of COVID-19.

With the ever increasing use of herbal medicine, safety has become a

major concern for both health authorities and the public across the globe. There are very limited data available on the potential adverse effects of herbal medicines. Though herbal medicines are considered to be least toxic compared with synthetic drugs, their misuse and self-medication are issues of great concern (Zhang et al., 2015). Thus, herbal medicines should be used with caution and only on the advice of a registered practitioner. Self-medication and over-the-counter use should always be discouraged.

It is an established fact that the immune system plays a vital role in fighting against infection and protecting the body from infectious diseases. Maintenance of immune fitness is the prime concern in preventive healthcare (Nigar and Itrat, 2013). This has become even more important given the periodic outbreak of infectious diseases. Strengthening and building a more resilient immune system is considered to be a sustainable way to survive in the current pandemic (Aman and Masood, 2020). *Tiryāq-i-Wabāī* is one among the widely used formulations during epidemics as prophylaxis and generally not recommended for respiratory diseases. However, its ingredients are highly recommended by Unani scholars in treating SARS-like conditions including respiratory distress. The formulation has been reported to possess significant immune-stimulation activity in immunocompromised elderly persons with no potential adverse effects at a dose of 500 mg thrice a week for 45 days (Nigar and Itrat, 2013). There have been no major side effects reported to date despite wide use of the formulation as a prophylaxis in epidemic diseases. However, establishing the safety profile of the formulation is vital for its wide and global acceptability, and for providing equally safe and effective remedy to human beings.

Tiryāq-i-Wabāī may exert its protective effect against COVID-19 via a number of possible mechanisms. It may exert its effect by modulating inflammatory mediators, humoral immunity and cell mediated immunity responses. It may directly interfere with the virus and limit its infectivity as the ingredients of the formulation have shown their inhibitory effects against various viruses via interference of DNA synthesis, inhibition of virus adsorption and replication and suppression of its penetration in the target cells. Recently, a preliminary molecular docking study has been carried out to generate in-silico evidence and evaluate the potency of *Tiryāq-i-Wabāī* against SARS-CoV-2 Spike Glycoprotein and Main Protease. The study result was encouraging as the phytoconstituents present in the formulation exhibited good binding capacity, suggesting its potential in inhibiting the SARS-CoV-2 spike glycoprotein and main protease (Ahmed et al., 2021). The formulation may reduce cough frequency and facilitate respiration by relaxing airway smooth muscles, suppressing airway inflammation and reversing lung pathological changes. Hence, the formulation may be used as a prophylactic during the current and future pandemics to improve the host immunity. It may also be used as an adjuvant therapy for symptomatic relief in infected individuals.

4. Conclusion

The novel coronavirus disease has severely affected livelihoods, and led to a substantial loss of human life with catastrophic social and economic consequences. Although the disease is currently on decline with the roll out of vaccines, there is still a need to identify effective remedies with the capability of targeting virulence, augmenting immune resilience and protecting target-organs. Traditional medical systems are being explored to search for equally effective remedies along with conventional treatment. Unani system of medicine may play a vital role in protecting and reducing disease burden and improving overall well-being. It would be fair to state that the combination of all the three ingredients of Unani pharmacopeial formulation '*Tiryāq-i-Wabāī*' (*Aloe vera*, saffron, and myrrh) with their bioactive compounds, may help in strengthening the immune system and protect individuals from infections during current and future pandemics. But these claims have to be validated through vigorous evidence-based research to establish the real effect of the formulation.

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Conflict of interest

None of the authors has any conflict of interest.

Availability of Data

The authors have not used any personal data that require to be available for the readers.

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