

Available online on 15.09.2021 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Copyright © 2021 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited



Open Access Full Text Article



Review Article

Unani perspective on COVID-19 and the possible role of *Tiryaaq Wabai* in its management: A Review

Mohd Aleem¹, Md Imran Khan^{2*}, Mohd Danish³, Qamrul Islam Usmani¹, Altaf Ahmad¹

¹ PG Scholar, Department of Ilmul Advia (Pharmacology), National Institute of Unani Medicine, Kottigepallya Magadi Main Road Bengaluru-91, India

² Assistant Prof. Department of Ilmul Advia (Pharmacology), National Institute of Unani Medicine, Kottigepallya Magadi Main Road Bengaluru-91, India

³ PG Scholar Department of Amraz Jild wa Taziniyat (Skin and Cosmetology), National Institute of Unani Medicine, Kottigepallya Magadi Main Road Bengaluru-91, India

Article Info:



Article History:

Received 10 July 2021
Reviewed 13 August 2021
Accepted 20 August 2021
Published 15 Sep 2021

Cite this article as:

Aleem M, Khan MI, Danish M, Usmani QI, Ahmad A, Unani perspective on COVID-19 and the possible role of *Tiryaaq Wabai* in its management: A Review, Journal of Drug Delivery and Therapeutics. 2021; 11(5):158-173

DOI: <http://dx.doi.org/10.22270/jddt.v11i5.5001>

Abstract

Science has uncovered much about SARS-CoV-2 and made extraordinary and unprecedented progress on the development of COVID-19 vaccines, but there is still great uncertainty as the pandemic continues to evolve. We are simply moving to a new phase of the pandemic. *Tiryaaq Wabai*, is on the polyherbal medicine used for centuries by Unani doctors as preventative medicine in epidemics. It consists of three ingredients: *Sibr* (*Aloe barbadensis*), *Zafran* (*Crocus sativus*), and *Mur-Makki* (*Commiphora myrrh*). All the three ingredients of *Tiryaaq Wabai* have various pharmacological activities like immunomodulatory, antitussive, expectorant, and antiviral activity which provide a strong basis for its prophylactic use for covid-19 infection. Further, research on this important prophylactic Unani formulation *Tiryaaq Wabai* in Covid-19 is the need of the hour.

Keywords: Tiryaaq; Epidemic; Covid-19; Unani medicine

*Address for Correspondence:

Md Imran Khan, Assistant Prof., Department of Ilmul Advia (Pharmacology), National Institute of Unani Medicine, Kottigepallya Magadi Main Road Bengaluru-91, India ORCID ID: <https://orcid.org/0000-0002-2166-7520>

Introduction

Traditional medicine is being used widely and rapidly in developing as well as developed countries. Up to 65% of India's population and 80% in Africa depend on traditional medicine to help meet their health care needs ¹. The Unani Medicine, also referred to as Greco-Arabic medicine, Arabic medicine or Unani Tibb, is based on Hippocratic four-humour theory; *Dam* (blood), *Balgham* (phlegm), *Safra* (yellow bile), and *Sauda* (black bile) ^{2,3}, and the four qualities of living human body states such as *hararat* (hot), *barudat* (cold), *ratubat* (moist) and *yabusat* (dry) ¹. Unani medicine uses medicinal products of plant, mineral, and animal origin but mostly plant origin drugs are used for therapeutic and preventive measures ⁴. In many Arab and Eastern Asian countries, Unani is still prevalent. However, in many countries where conventional medicine is readily available, Unani medicine and herbal products are increasingly being used. India has acknowledged and granted its official status as an alternative healthcare system ¹.

In Unani medicine, the disease state is caused by the instability of *Mizaj* (temperament) or *Akhlal* (humour), and health maintenance is carried out by applying the various steps to align six critical health fundamentals in the polar

dimensions. i.e. *Asbab-Sitta-Zarooria*: **1.** *Hawa-e-Muheet* (Air), **2.** *Makool wa Mashrubat* (food and drinks), **3.** *Harkat wa Sakoon-e-Badani* (Rest and physical activity), **4.** *Harkat wa Sukun-e-Nafsaani* (psychological activity and repose), **5.** *Nuam wa yaqza* (Sleep and wakefulness), **6.** *Ishifragh and Ihtabas* (Elimination and retention). The applied aspect of Unani medicine deals with various measures to maintain or restore health ^{1,5,6}.

'*Magneus Felseof*' introduced *Tiryaaq* (*Theriac*) as a semisolid dosage form. *Indrumakhas I* (Andromachus I) has improved *Tiryaaq* by adding flesh of snakes in it ⁷. The term Theriac refers to medicinal substances initially used by the Greeks from the 1st to the 19th century A.D. The name theriac originated from the old Greek word *thēr*, "wild animal." ^{8,9}. By the 8th century, Islamic medicine prescribed *Tiryaaq* for treating complicated diseases which resisted simple drug treatment. *Caliphs* and *Princes* requested the manufacture of *Tiryaaq* mixtures which were thought to have wondrous curative and anti-toxic properties, and whose ingredients may well reach into the hundreds. *Ibn Sina* (Avicenna) explained how *Tiryaaq* was prepared and utilized in the Canon of Medicine. The *Al-Biruni* pharmacopoeia (973-1048) contained a variety of drugs known as *tiryaaq* ¹⁰. The Theriac's prominent role was to neutralize the effects of

toxic substances on the body; it could be used in reaction to an event of poisoning but also on a routine basis to create 'immunity', and it was only a short step from inventing a general solution to declaring a cure-all¹¹. According to *Muhammad bin Zakaria al-Razi* (854–925), Theriac will resist snake venom and all other poisons. *Abū Rayhan Birūni* made numerous references to define the properties and types of theriacs; he explained *tiryāq* as "that which saves" or "that which abstracts body poison"⁸. *Ibn Sina* seems to have believed that the Theriac was effective in countering poison and healing many diseases; the diseases he prescribed included chronic cough, stomachache, asthma, chest pain, fever, colic, seizures, diarrhoea, and urine retention. By the mid-fourteenth century, a Plague outbreak prompted the Paris Faculty of Medicine to recommend that "a little theriac be taken with meals," France became a centre of theriac production and export¹⁰.

Tiryaaq Wabai, also known as *Tiryaaq afa'yi*, is on the polyherbal medicine used for centuries by Unani doctors as preventative medicine in epidemics. *Tiryaaq Wabai* is identified as *Muhafize fasade akhlat* (preventing humoral disorders) and *Muhafize ufoonat* (preventing infection), and therapeutically *Tiryaaq Wabai* is indicated for the prevention of *wabai amraz* (epidemic disorders) during *waba* (epidemic)^{12–15}. The Immunostimulant effect of *Tiryaaq Wabai* has already been done, and the outcome was promising¹⁶. *Tiryaaq Wabai* consists of three ingredients: *Sibr* (*Aloe barbadensis*), *Zafran* (*Crocus sativus*), and *Mur-Makki* (*Commiphora myrrh*)^{14,17–19}. With their anti-viral effectiveness against severe acute respiratory syndrome coronavirus (SARS-CoV), adenovirus and respiratory syncytial virus infections (RSV), influenza A virus, parainfluenza virus, parainfluenza virus type 3, human rhinovirus B, and coxsackievirus, Newcastle disease virus, etc., constituents of *Tiryaaq Wabai* have been supported by evidence.

1. Material and methods

The reviewed literature related to acute respiratory infections, coronaviruses diseases, and all relevant articles written in English till July 10, 2021, were searched through PubMed, Google Scholar, Microsoft Academic, Scopus, the web of science, and web guidelines of world health organization. The Unani literary books to search for a description of "*Waba*" or "*Amraze waba*" or "*Nazle-wabaiya*," which was interrelated with the collection of manifestation related to epidemics of acute respiratory infections. We further emphasized and discovered the concept of "*Waba*" and "*Nazle-wabaiya*" and its aetiopathogenesis in Unani medicine by exploiting specific Unani textbooks, e.g., '*al-Qānūn fī al-Tibb*' (The canon of medicine), '*Akseer e Azam*,' '*Kamil-Us-Sana*,' '*Zakhīra-i Khwārazmshāhi*,' (Treasure dedicated to the king of Khwarazm), and '*Kitab Al-Kulliyat Fi Al-Tibb*.' The literary review of '*Tiryaaq Wabai/ Tiryaaq afa'yi*' was performed using standard Unani pharmacopeial manuscripts such as '*Qarabadeen-e-Jalali*,' '*Bayaz Kabir*,' '*Qarabadeen-e-Najmul Ghani*,' '*Qarabadeen-e-Azam*,' '*Bayaaaz khas*,' '*al-Qarabadeen*,' '*Qarabadeen jaded*.' Above mentioned references and databases were also utilized to search experimental studies on constituents of "*Tiryaaq Wabai*" by searching through their common and botanical name for their anti-viral and immunomodulatory activity. "National Ayush morbidity and standardized terminologies electronic portal" was used to define the correct Unani terminology (<http://namstp.ayush.gov.in/#/Unani>). Scientific names and synonyms were validated through the Plant list (www.theplantlist.org).

2. Background and Current Scenario of Epidemics of Acute Respiratory Viral Infections

One of the earliest winter outbreak reports of respiratory infectious disease can be found in the "Book of Epidemics," an ancient Greek text was written about 400 BC by Hippocrates. Many respiratory viruses have since been established as these epidemics' etiologic agents²⁰. Until the 16th century, all sorts of epidemics were typically reported by laypeople without scientific knowledge and without an understanding of aetiology, pathogenesis, natural history, characteristic pathognomonic signs, or any of the modern ways we now diagnose, recognize, and classify different diseases. Even various conditions, such as measles and smallpox, have long been confused²¹. A massive outbreak of influenza-like disease followed Carolman's (Charlemagne's) army through Europe in 876–877, having first arrived in Italy to spread northward, a geographic trend frequently recorded for other influenza pandemics occurring between 1510 and 1761 and even killing dogs and birds. Another epidemic, "cough that spread like the plague" in 927 A.D, again first reached Italy and spread northward to affect the entire European continent and caused sickness and death in humans, dogs, and birds. Researchers have hypothesized that this was the first known pandemic of influenza, a possibility consistent with its arrival in southern Europe and its rapid spread northward^{21,22}.

Acute respiratory tract infections of viral origin contributed to a severe burden on health care services and society²³. Respiratory tract infections pose a critical health problem, as they are a leading cause of mortality in children globally, especially in developing countries, causing approximately 19% of all deaths among children under five years and 8.2 % of all disability and premature mortality. New respiratory infections have become increasingly significant in modern infectious diseases, since the acute severe respiratory syndrome outbreak in 2003, the influenza A (H1N1) pandemic in 2009, and the influenza A (H7N9) pandemic in 2013²⁴. Acute respiratory viral infections usually start in the upper respiratory tract as the port of entry is the nose, mouth, or eyes, and spread to the lower parts of the airways occurs within two to four days²⁵. The most common infections in the upper tract include rhinitis, laryngotracheobronchitis, sinusitis, pharyngitis, epiglottitis, and laryngitis. Lower-tract conditions are more severe, including tuberculosis, bronchitis, bronchiolitis, and influenza²⁶.

For thousands of years, the seasonal cycle of respiratory viral diseases has been commonly known as regular epidemics of common cold and influenza disease that strike the human population in temperate regions. Besides, epidemics from viruses such as SARS-CoV and the newly emerging SARS-CoV-2 arise in the winter months²⁰. SARS-CoV, Middle East respiratory coronavirus syndrome (MERS-CoV), influenza, adenovirus, human bocavirus, human metapneumovirus, parainfluenza virus, rhinovirus, RSV, and other common respiratory pathogens have been identified as a cause of pneumonia²⁷. Additionally, these viruses can cause co-infections in community-acquired bacterial pneumonia^{28,29}.

2.1. Covid-19

A cluster of patients was admitted to hospitals with an initial diagnosis of an uncertain aetiology of pneumonia in late December 2019. These patients were epidemiologically linked to a wholesale market of seafood and wet animals in Wuhan, Hubei Province, China³⁰. The pathogen was

confirmed to be a distinct clade from the β -coronaviruses related to the MERS and SARS ^{27,31}. On February 11, 2020, the World Health Organization (WHO) declared a new name for the 2019-nCoV epidemic: Corona Virus Disease 2019 (COVID-19). Concerning the virus itself, the International Committee on Virus Taxonomy has designated 2019-nCoV as a SARS-CoV-2 ²⁸. The WHO declared the outbreak of SARS-CoV-2 on January 30, 2020, to be a public health emergency of international concern. SARS-CoV-2 has a more robust transmission capacity than the SARS-CoV, which caused a SARS outbreak in 2003 ³². Coronaviruses are enveloped, positive single-stranded, large RNA viruses infecting humans, and a wide variety of animals ³³. It is pleomorphic or spherical particles, 150 to 160 nm in size, unsegmented, nucleoprotein, capsid, matrix, and S-protein. Essential viral proteins are nucleocapsid protein (N), membrane glycoprotein (M), and spike glycoprotein (S). COVID-19 differs from other coronaviruses by encoding a different glycoprotein having properties of acetyl esterase and hemagglutination (HE)³⁴. In 1966, Tyrell and Bynoe first identified coronaviruses, which cultivated the viruses in patients with common colds. They were called coronaviruses (Latin: corona \rightarrow crown), based on their morphology as spherical virions with a central shell and surface projections resembling a solar corona. There are four subfamilies, including alpha-, beta-, gamma- and delta coronaviruses. Although alpha and beta-coronaviruses come from mammals, particularly bats, gamma and delta viruses come from pigs and birds ³³

Coronavirus is one of the major pathogens affecting the human respiratory system ³⁰. Respiratory droplets mainly transmit SARS-CoV-2 from person to person, customarily released when an infected person coughs or sneezes. Since droplets typically fall within a few meters, the transmission risk will decrease if people stay at least 1 m apart. Transmission is assumed not to occur through the inhalation of aerosols typically, but there are regards that the virus may be aerosolized during certain events or procedures (e.g., singing, intubation, or the use of nebulizers) and that it may

persist in aerosols for more than 3 hours ³⁵. COVID-19 can also be present in the stool and urine of patients with diarrheal symptoms besides with aerosol and large respiratory droplets ³⁴. Transmission may occur from symptomatic or asymptomatic patients, where the rates of secondary infection vary between 0.5% and 5%. SARS-CoV-2 has been shown to remain stable in aerosolized form for up to 3 hours, in cardboard for 24 hours, and plastic or stainless steel for three days ³⁶.

Following an incubation period of 1 to 12.5 days (average estimates vary from 5 to 6 days), COVID-19 symptoms appears, but they can last for as many as 14 days. The time from the onset of symptoms of COVID-19 to death ranged from 6 to 41 days, with an average of 14 days. This time depends on the patient's age and immune system status. It was lower in patients > 70 years of age relative to those less than 70 years of age ³⁰. Early reports suggest fever (88%) and dry cough (67.7%) are the most common symptoms, which are associated with many other viral syndromes (Figure 1). Noticeably, rhinorrhoea (4.8%) and gastrointestinal symptoms (diarrhoea 4% to 14%, nausea or emesis 5%) appear to be uncommon in COVID-19 ³⁶.

Infection with SARS-CoV-2 can activate innate and adaptive immune responses. Nevertheless, uncontrolled innate inflammatory responses and impaired adaptive immune responses can damage the tissue, both locally and systemically. Lymphopenia is a typical occurrence in patients with severe COVID-19, with significantly reduced numbers of CD4⁺ T cells, CD8⁺ T cells, B cells, natural killer (NK) cells, and a decreased percentage of monocytes, eosinophils, and basophils. The increase in neutrophils' count and neutrophils' ratio to lymphocytes typically suggest higher severity of the disease and poor clinical outcome. Additionally, exhaustion markers, such as NKG2A, on cytotoxic lymphocytes, including N.K cells and CD8⁺ T cells, are upregulated in patients with COVID-19 ³⁷. The identification of SARS-CoV-2-specific IgM and IgG in patients, combined with RT-PCR-based tests, provided the basis for disease diagnosis ^{35,37}.

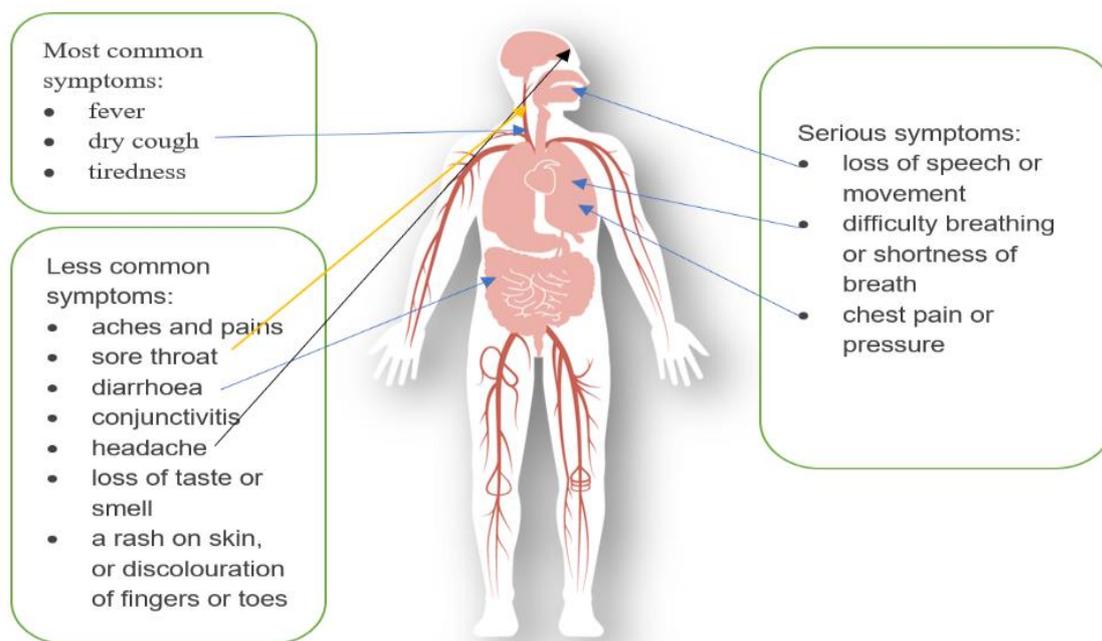


Figure 1: Symptoms of COVID-19

Source: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses#:~:text=symptoms>

To date, no anti-viral drugs with specific effects have been identified, and the primary therapeutic strategy focused on symptomatic support. Upon hospitalization, partial patients demonstrated low treatment effectiveness and experienced severe pneumonia, pulmonary oedema, acute respiratory distress syndrome (ARDS), or multiple organ failure. Information about the clinical features of refractory COVID-19 has been scarce³¹.

3. Background of Epidemics in Unani Medicine

The epidemic of infectious diseases has been recognized throughout history. Classical literature in ancient Greece and Egypt revealed the prevalence of certain conditions such as meningitis, tuberculosis, Hansen's disease, and smallpox in those times. The Greeks were also aware of pulmonary tuberculosis, which seems to have raged in the Hippocrates period.

The germ hypothesis was formulated in the middle of the 16th century A.D. It gained much popularity based on scientific findings between the 17th and the late 19th century A.D. The germ hypothesis also complemented the ancient explanation of infectious diseases such as Galen's miasma theory³⁸. There is no explicit reference in Unani medicine to the definition of microbes as disease-causing agents. Nevertheless, it is well known that certain *ajsam-i-khabitha* (harmful substances) can move from the diseased to healthy people and cause disease. Epidemics, referred to as *waba* in Unani medicine, are thought to occur if *ajsam-i-khabitha* is detected in the air and water³⁹. Unani scholars suggest that the spread of epidemics take place through infected air, water, and soil. The air may be impaired due to trouble in the natural equilibrium of the earth or could be due to global warming. Unani scholars proclaimed that certain parts of the earth have changes in intensity/wavelength of rays, which have a harmful effect on that area's air. The old air near the soil normally gets purified with healthy rays turn out to be infected due to bad changes in the rays. These contaminated vapours can trigger the growth and mutation of the infectious agent. Unani scholars have reported that inadequate management of waste, water collection, and poor community hygiene encourages the production and spread of epidemics. It may be a possible explanation for the rise of epidemics/pandemics in this period⁴. *Ibn Sina* and *Zakariya Razi* (865–925 CE) state in *Al-qanoon* (Canon of Medicine), *Kitab al-Mansoori* (Caliph Mansoor Book), respectively, the majority of epidemics spread during the autumn season, mainly if the previous summer season was humid and the weather is still windy^{39,40}. According to *Ibn Abbas Majusi* (d. 994 A.D.): "Whenever imbalance occurs in the material of the air and decomposition are produced in together the material (*Maddah*) and quality, producing plenty of bad symptoms (*a'rad-rdiyah*) and diseases in human beings." At another place, he says: "Epidemic (*Waba*) only spreads where the natural air quality changes"⁴¹. Such variations in the air are either in composition or characteristics. The change in composition occurs when one of its components is unusual or uncommon and this causes epidemics due to the air putrefaction similar to that which occurs in a pond or stagnant water. Every single component of the air does not rot but varies in quality; it may transform into another component as water becomes vapour. The high moisture environment is conducive to epidemics and putrefaction. For fact, stagnant waters are also becoming mouldy³⁹. This alteration causes hot and harmful fevers (*hummiyat-harrah raddiyah*), plagues, and other diseases in humans, as well as severe and dangerous animal diseases⁴¹. *Ibn Sina* (980–

1035 CE) said that epidemics spread from one person to another, and from one city to another 'like a message'³⁹. *Zakariya Razi* (865–925 CE) emphasized this fact and said that 'there will always be something common in epidemic patients, whether a place, food, drink or travel history'⁴². Arab scholar *Ibn Khatib* (1313–1374 CE) pointed out during the plague pandemic in the 14th century that 'any people who come into touch with a victim of the plague will die.' In the same way, the disease is transmitted via clothing, utensils and jewellery, thus stressing transmission through fomites⁴³.

The basics of the Unani System of Medicine (USM) being humoral physiology, the temperament of human beings as a whole, individuals, *humours*, diseases, foods, drinks, seasons, etc. form the qualitative aspect of this system. Any disruption in the equilibrium of *humours* causes disease. According to the doctrine of Unani Medicine, there are three causes; bodily predisposition, environmental factors, and a mediating cause. The environmental causes are one of the most typical causes of an epidemic or pandemic⁴⁴.

Rabban Tabri said that people with excess waste in their bodies are usually affected by the epidemic fever *Humma wabaiya/nazle-e-wabaiya*⁵. According to Avicenna (980–1037 AD), *Humma-e-Wabai* is a severe fatal fever caused by contaminated air, spreading rapidly between larger populations³⁹. *Humma-e-Wabaiya* is the form of catastrophic fever triggered by unavoidable changes in climate (qualitatively or quantitatively). As a consequence, Air is impure and eventually induces an irregular *Rooh* temperament, which results in morbidity and death. As fresh and pure air is essential for health, any contamination in the air may disturb the person's health, and it depends on the intensity of contamination. Those people are mainly susceptible to a weak immune system, i.e., older and children³⁹. Renowned Unani Scholars like *Hippocrates* (370–460 BC), *Galen* (130–200 AD), *Rhazes* (865–925 AD), *Avicenna* (980–1037 AD) described that there are four etiological factors responsible for *Amraz-e-Wabai* (epidemic disease), i.e., change in the quality of air, water, earth and celestial bodies⁴⁵.

The following are the two fundamental theories of USM related to the causation of diseases, depending on the mode of origin.

1. Diseases are caused by the imbalance of the humour born inside the body.
2. Diseases are caused by the invasion of foreign bodies, which attack the humour. For instance, a vital organ like the heart may be invaded, affecting its normal functions and stimulating activities, which, as a result, may be disturbed.

The infectious and epidemic diseases belong to the second category. The main things affected by the "*Tadia*" or *adva* (infection) and *Waba* (epidemic) are:

1. The humour
2. The heart and other vital organs like the stomach, liver, etc.
3. *Hararat-e-Gharizia* or Vital heat

The clinical manifestation of "*nazle-e-wabaiya*" in the Unani literature simulates clinical presentation of ARIs that propagate in epidemic form as an influenza virus, RSV, type 1, and 2 parainfluenzas, MERS CoV, SARS CoV, SARS-CoV, etc. Unani scholars could not detect and discern these infectious agents because of unadvanced diagnostic methods in the ancient period, but had been aware of their existence and

named 'wabai bukharat' ⁴. The Persian scholar *Najeebuddin Samarqandi* (d. 1222 CE) states about *Nazla-e-Wabaiya* that it is associated with fever, sneezing, sore throat, nasal inflammation, and malaise. Weakness, in particular, develops at an early stage of the disease. He also says that a *nazla-e-wabaiya* patient may also have cough, diarrhoea, and delirium ⁴³. The Unani scholars also stated that the infection could complicate and progress to pneumonia (*za'tul riya*) and pleurisy (*za'tul janab*) in the elderly, infants, and low immune patients. Some literary findings suggest that Unani scholar was well aware of the ARI epidemic. Hence, their clinical indices and management recommendations may be used as a method for addressing increasingly growing current-era respiratory epidemics ⁴.

4. "Tiryaaq Wabai" as Prophylactic in Unani Medicine Against Epidemics

The name of the polyherbal wording justifies its effect, e.g., 'Tiryaaq' refers to 'antidote' and 'Waba' to 'epidemic.' The medicine was used as a prophylactic antidote against epidemics and as an antidote to poisoning.

Unani supports disease prevention by prescription of certain medicines and regimes to improve immunity and overall body health. An epidemic history has taught ancient Unani practitioners to encourage preventative measures during epidemics, such as cleanliness and hygiene, the isolation of sick patients, care of patients with infectious material, and usage of prophylactic medicine, and general tonics before and during infective seasons. *Tiryaaq* was explicitly planned to accomplish similar goals by Unani scholars ⁴.

Prevention of *wabai amraz* with *Tiryaaq* Advia is recommended in the Unani system of medicine since ancient

times. As a prophylactic drug, *Tiryaaq* is generally recommended for toxicity prevention (sepsis). *Tiryaaqiyat* is the formulation that reinforces the *Rooh* so that *Rooh* can neutralize the body's toxicity. *Tiryaaqiyat* enhances the *rooh*, activates *hararte-gharizia*, and allows *Tabiyat* to avoid morbid substances ¹⁷. *Avicenna* mentioned that those who use *Tiryaaq* in good health would not be affected by infection because it helps reinforce the *rooh* and maintain health ³⁹. *Ismail Jurjani* states that *Tiryaaq* is used to protect the heart during epidemics, maintain the faculties, and avoid sepsis. *Jalinoos* said that people who used *Tiryaaq Wabai* as prophylaxis had not been affected by infectious diseases ¹⁶.

Tiryaaqat is characterized in various diseases by a prophylactic function and effectiveness. Some important *Tiryaaqat* is mentioned in Table 1. *Tiryaaq Wabai* identified as *Muhafize fasade akhlat* (preventing humoral disorders) and *Muhafize ufoonat* (preventing infection) and therapeutically *Tiryaaq Wabai* are indicated for the prevention of *wabai amraz* (epidemic disorders) during *waba* (epidemic). *Tiryaaq Wabai* is based on three ingredients (Table 2), namely *Sibr* (*Aloe barbadensis*), *Zafran* (*Crocus sativus*), and *Mur-Makki* (*Commiphora myrrh*). *Sibr* is described to be *Muhafize fasade akhlat* (preventing humoral disorders), *Daf-e-Ufoonat* (antiseptic), *Muharrik-e-Kabid* (a liver stimulant). *Zafran* is defined to be *Muharrik-e-Hararate Ghareezia* (stimulate innate immunity), *muhafize fasade akhlat* (preventing humoral disorders), *daf-e-Ufoonat* (antiseptic), *muhafize tabiyat* (immunomodulator), *muqawwie jigar* (liver tonic), *mufarrahe quwa* (exhilarant). *Mur-Makki* is described to be *muharrik* (a stimulant) and *daf-e-taffun* (antiseptic) ^{13-15,17-19,46}.

Table 1: Some important Tiryaaq mentioned in different Qarabadeen (Unani Pharmacopoeia)

S.N.	Tiryaaq name	Dose	Action/Uses	Ref.
1.	<i>Tiryaaq wabai/Tiryaaq afa'yi</i>	2 gm with Arq badyaan	Beneficial in <i>Haija</i> (cholera), <i>Chechak</i> (smallpox), and <i>Taoon</i> (Plague) and Removes animal poison. According to <i>Jalinoos</i> , if any person takes it in an epidemic of <i>Taoon</i> , then he is not suffering from this disease.	13-15,17-19,46
2.	<i>Tiryaaq nazla</i>	14 g	Relieves in colds, prevent cough, beneficial in eye pain and <i>Atishk</i> (syphilis)	13-15,17-19,47,48
3.	<i>Tiryaaq al-asnaan</i>	1 or 2 drops	To prevent toothache due to cold	14,15,17-19,46,47,49
4.	<i>Tiryaaq al-dharab/zarab</i>	3-5 gm	Beneficial in <i>Zarab</i> (dysentery), <i>Zo'f-i-mi'da</i> (weakness of stomach), <i>Zo'f-i-am'a</i> (weakness of intestine), <i>Qabz</i> (constipation) <i>Dard-i-shikam</i> (stomach pain), to strengthen the <i>Aza-e-raesa</i> (vital organs), <i>Mujarrab</i> (tested) in <i>Ishaal-i-mida</i> (stomach purgation)	15,17-19,47
5.	<i>Tiryaaq Farooq</i>	4 g in snake bite, 2 g in scorpion bite	<i>Mufattitey Suddae Kabid</i> (Liver deobstruent), anti-inflammatory, Beneficial in <i>Istisqa'</i> (Ascites), <i>Yarqaan-i-suddi</i> (Obstructive Jaundice), <i>Dard-i-gurda</i> (pain in the kidney), and <i>Qoolinj</i> (Colic). To prevent <i>Haija</i> (cholera) and the antidote for the snake, scorpion, and other poisonous animal bites.	13,15,39,47,48,50
6.	<i>Tiryaaq arba</i>	4.5 g with Luke warm water	The antidote for the scorpion and other poisonous animal bites. Beneficial in <i>Qoolinj</i> (Colic), liver, and spleen diseases.	13-15,17-19,39,46,47,49-52
7.	<i>Tiryaaq Kabir</i>	4.5 g	Use as an antidote for all kinds of poisonous animal bites.	15,47
8.	<i>Tiryaaq tyn makhtoom</i>	3.5g	Antidote for poison	15,47
9.	<i>Tiryaaq al-tyn</i>	3.5g before or after a meal	Antidote for poison	19,50

10.	<i>Tiryaaq tyn-Romi</i>	3.5g	The antidote for all kinds of poisons and any poisonous animal bites	50
11.	<i>Tiryaaq thamania/samania</i>	3.5g with Luke warm water	The antidote for the scorpion and other poisonous animal bites. Beneficial in liver and spleen diseases.	14,15,18,19, 46-50
12.	<i>Tiryaaq baligun nafa</i>	14g	The antidote for the snake bite	18,19,47
13.	<i>Tiryaaq ashkari</i>	7g	The antidote for the scorpion bite, instant relief in wound pain	47,50
14.	<i>Tiryaaq sartan</i>	4.5g	The antidote for the mad dog bite	15,18,19,47, 50
15.	<i>Tiryaaq al-dhahab/zahab</i>	3.5 g	Beneficial in Melancholia, epilepsy, <i>juzam</i> (leprosy), <i>Istisqa'</i> (Ascites), <i>yarqaan</i> (Jaundice), <i>bawasir</i> (Hemorrhoids). Protect from epidemic diseases when used with Roghan banafsha	15,17,19
16.	<i>Tiryaaq habbe utraj</i>	Local application	Use as an antidote for all kinds of poisonous animal bites.	15
17.	<i>Tiryaaq afyoon</i>	9g	The antidotes for opium (<i>Afyoon</i>) cannabis (<i>Bhang</i>) and belladonna (<i>Yabroojus sanam</i>) poisoning	15,19,50
18.	<i>Tiryaaq sagheer</i>	4.5g	The antidote for all kinds of poisonous animal bites. According to <i>Sheikh al-raees</i> , in animal bites, it is more beneficial than <i>Tiryaaq arba</i> .	15,18,19,49
19.	<i>Tiryaaq aqrab</i>	7g with Luke warm water	The antidote for the scorpion bite, beneficial in <i>Qoolinj</i> and intestinal pain	15,19
20.	<i>Tiryaaq rateela</i>	3.5g	The antidote for all kinds of poisonous animal bites.	15,18
21.	<i>Tiryaaq thabit bin qurrah</i>	7g	The antidote for the scorpion bite	50
22.	<i>Tiryaaq Muhammad zakarya</i>	7g	The antidote for all kinds of poisons and any poisonous animal bites	50
23.	<i>Tiryaaq yohina saryaani</i>	4.5g	The antidote for the scorpion bite	50
24.	<i>Tiryaaq musannif kunnash buqrati</i>	3.5 to 4.5g	The antidote for all kinds of poisons and any poisonous animal bites	50
25.	<i>Tiryaaq shekh bu ali sina</i>	4.5g	the antidote for all kinds of poisons, <i>Muqawwi-i-qalb</i> (heart tonic), <i>muqawwi-i-bah</i>	18,19,50
26.	<i>Tiryaaq mathana</i>	5 gm	Beneficial in diseases of kidney, bladder and uterus	19,48,49
27.	<i>Tiryaaq 'adhra/azra</i>	4.5g	Beneficial in sar'a (epilepsy), <i>Khafqaan</i> (Palpitation) and diseases of liver and spleen	13
28.	<i>Tiryaaq al-raham</i>	2g with majoon supari pak	beneficial in leucorrhoea (<i>Sailanur reham</i>)	13,14
29.	<i>Tiryaaq al-markah</i>	6g with Luke warm water	The antidote for the scorpion bite, beneficial in <i>quling</i> , intestinal and visceral pain	49
30.	<i>Tiryaaq akbar</i>	3 gm	Beneficial in epidemic diseases, vertigo, epilepsy, hematemesis, stomach pain, liver pain, jaundice, urinary inconsistency, arthritis, amenorrhoea, palsy. The antidote for any poisonous animal bites and also the antidote for all kinds of poisons	52
31.	<i>Tiryaaq athanasiya</i>	1g with Luke warm water	Beneficial in cough, hematemesis, the pain of liver, stomach, spleen.	52
32.	<i>Tiryaaq dara'ul suhtah</i>	½ to 4½ g	The antidote for all kinds of poisons and any poisonous animal bites	18
33.	<i>Tiryaaq al-tihal</i>	1g	Beneficial in diseases of the spleen	18,19
34.	<i>Tiryaaq 'aam al-nafa</i>	1g	The antidote for all kinds of poisons and any poisonous animal bites	18
35.	<i>Tiryaaq didan</i>	1gm	Used to get rid of roundworms in humans	18,19
36.	<i>Tiryaaq al-kabid</i>	1gm	Beneficial in diseases of the liver	18,19

4.1. Method of preparation of *Tiryaaq wabai*

Take all the ingredients of pharmacopeial quality. Clean the drugs *Zafran*, *Sibr* and *Mur-Makki*, by removing foreign matter. Dry the drugs in the shade, powder the drugs *Sibr* and *Mur-Makki* separately in a pulveriser and pass through a sieve of mesh number 80. *Zafran*, are ground in a dry mortar (Kharal), with Arq Ghulab (Rosewater) 10 tola (120 ml). Mix the powder of *Sibr Zard* and *Mur-Makki* to the *Zafran* paste and make the pill manually to get the tablets of 500 mg. Then

tablets are wrapped with Warq-e-Nuqra (silver foils) ^{14,15,17,46}.

4.2. Dose: 1-2 tablets of 500 mg thrice weekly Orally ^{14,46}.

4.3. Actions: *Muhafize fasade akhlat (preventing humoral disorders) and Muhafize ufoonat (preventing infection)*, Antidote, Chemoprophylactic during the epidemic ^{14,46}.

4.4. Therapeutic uses: Infectious disease, plague, chickenpox, cholera, any epidemic outbreak ^{14,46}

Table 2: Component of “Tiryaaq Wabai.”

Constituent (Unani Name)/ Botanical Name	Part Used	Temperament	Actions	Ratio of drug	Ref.
<i>Sibr (Aloe barbadensis)</i>	Fresh and dried juice of leaves pulp	Hot and dry 2 ⁰	<i>Tiryaaq, Mushil, Mudir haiz, Mohallil-e-waram, muharrik kabid</i>	2	14,18,46, 53
<i>Mur-Makki (Commiphora myrrh)</i>	resin	Hot 3 ⁰ and dry 2 ⁰	<i>Tiryaaq, Muharrik, Dafe taffun, Munaffis Balgham, Mudir haiz</i>	1	14,18,46, 53
<i>Zafran (Crocus sativus)</i>	Dried stigma and styles	Hot 2 ⁰ and dry 1 ⁰	<i>Tiryaaq, Mudir bowl, Muqawwi jigar, Muqawwi asab, Mudir haiz, Muqawwi bah</i>	1	14,18,46, 53

5. Scientific studies

The use of immunomodulators has the potential to stimulate innate and acquired defence processes such as cytokines, which enables the body to aid itself. Many disorders such as viral infections, different cancers and autoimmune diseases can be managed with immunostimulant drugs. A study evaluated the immunostimulant effect of *Tiryaaq Wabai* in immunocompromised elderly patients to validate the Unani claims. The test group was treated with *Tiryaaq Wabai* 500mg thrice a week in capsule form, while the control group was

given roasted wheat flour, a placebo in the dose of 500mg thrice a week for 45 days. Significant improvement was observed in TLC, ALC, Lymphocyte % and CD4 count and CD8 counts in the test group in comparison to the control group. An increase in CD4 and CD8 counts indicate a significant positive effect on the proliferation and differentiation of lymphocytes. The result suggests the immunostimulant activity of test drug *Tiryaaq Wabai* and recommends its use in conditions where immunostimulant is required ¹⁶.

Table 3: Scientific studies and chemical constituents of different Components of “Tiryaaq Wabai.”

Drugs	Chemical constituents	Activities
<i>Sibr (Aloe barbadensis)</i>	Acemannan, Alanine, arginine, aspartic acid, cysteine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, threonine, serine, tyrosine, valine, Aloe-emodin, aloetic acid, anthranol, aloin A& B, anthracene, anthranon, barbaloin, chrysophanic acid, emodin, ethereal oil, ester of cinnemomic acid, isobarbaloin, resistanol, Auxins, gibberllins, Arachidonic acid, γ -linolenic acid, triglycerides, triterpenoid, potassium sorbate, salicylic acid, uric acid, Acetic acid, citric acid, formic acid, fumaric acid, lactic acid, malic acid, pyruvate, succinic acid and tartaric acid, Minerals such as calcium, chlorine, chromium, copper, iron, magnesium, manganese, phosphorous, potassium, sodium and zinc ⁵⁴⁻⁵⁸ .	Anti-viral, Immunomodulatory, Anticancer activity, Antioxidant effects, Antidiabetic effects, Anti-inflammatory, Wound healing, Anti-ulcer effects, Antihyperlipidemic activity ⁵⁹⁻⁶⁷
<i>Mur-Makki (Commiphora myrrh)</i>	alpha-elemene, cuminic aldehyde, eugenol, metacresol, pinene, limonene, diterpenes, and sesquiterpenes, delta elemene, beta-bourbonene, beta-elemene, beta-caryophyllene, gama-elemene, alpha-humulene, dehydroaromadendrane, 9-epi-caryophyllene, gama-murolene, allo aromadendrene, curzerene, gama-cadinene, delta-cadinene, beta-sesquiphellandrene, selina-3,7(11)-diene, elemol, caryophyllene alcohol, caryophyllene oxide, cis-beta-elemenone Katayoun, furanogermacra-1E,10(15)-dien-6-one, 2-methoxyfuranogermacra-1(10),4-diene, T-cadinol, 3 α hydroxy-T-cadinol, epicurzerenone ⁶⁸⁻⁷⁰ .	Anti-viral, Immunomodulatory, Analgesic, Anticancerous, Antioxidant activity, Anti-microbial activity, Anti-fungal activity, Anti-inflammatory, Antihyperlipidemic, Hepatoprotective effect ⁷⁰⁻⁷⁹
<i>Zafran (Crocus sativus)</i>	Crocin, picrocrocin, safranal, carotenoids including zeaxanthin, lycopene, and various α - and β -carotenes, carotenes, crocetin, picrocrocin, zeaxanthin ⁸⁰⁻⁸³ .	Anti-viral, Immunomodulatory, Antinociceptive, antihypertensive, Anticonvulsant, Antitussive, Antigenotoxic, cytotoxic, Anxiolytic, anti-inflammatory, Anti-Alzheimer effect ⁸⁴⁻⁹³

5.1. Anti-viral activities and their Mechanism of different Components of "Tiryag Wabai."

5.1.1. Sibr (*Aloe barbadensis*)

The research examines Aloe Vera's anti-viral activity and conducts molecular docking with COVID-19 main protease (3CLpro/M^{pro}) to classify possible COVID-19 protein inhibitors as well as the ADME analysis. The binding affinity of ligands indicates that the most potent ligands to be used as potential COVID-19 M^{pro} inhibitors are three ligands (6, 1 and 8) obtained from the range of 10 Aloe Vera compounds. In conclusion, Lipinski's rule of five based on ADME analysis approves ligand 6 to be the best drug candidate ⁹⁴. In another study, two anthraquinones, aloesaponarin-I (1) and aloesaponarin-II (2) were isolated from *A. vera* roots, and seven derivatives were obtained from these isolated compounds. These compounds were tested by the cytopathic effect reduction assay (CPE) against two strains of influenza virus AH1N1. The anti-viral activity was determined by the ability of compounds to prevent virus replication on Madin Darby Canine Kidney cells (MDCK). Results showed both compounds were most effective if applied at concentrations of 50 µM and 100 µM 6–10 h post-infection and inhibited significantly viral titres (> 70 %) ⁹⁵. Another study investigates the anti-norovirus activity of the natural extracts of *Aloe vera*. Murine norovirus 1 (MNV-1), was pre-incubated with aloe extracts and then plaque assays were performed in RAW 264.7 cells. Pre-treatment of Aloe extract effectively suppressed the infectivity of MNV-1 with an estimated half-maximal inhibitory concentration (IC₅₀) of 0.778 mg/mL. ⁹⁶. Other studies have shown an unusual behaviour of Bioaron C® (a drug containing *Aloe arborecens* aqueous extract) against representatives of Orthomyxoviridae-influenza A and influenza B viruses. Following the addition of Bioaron C® to infected cell cultures, replication of both the analysed influenza A strains-H1N1 and H3N2, and influenza B strains-Yamagata and Beijing-was significantly reduced. Bioaron C® also blocked the replication of human rhinovirus and coxsackievirus, all picornaviridae families and non-enveloped RNA viruses ⁹⁷.

Another study showed that Aloin has a potent anti-influenza compound that inhibited viral neuraminidase activity, even of the oseltamivir-resistant influenza virus. By blocking this virus mechanism, aloin enhances immunity to the infection with an improved hemagglutinin-specific T cell response. Furthermore, adjuvant aloin therapy improves the disease and enhances survival in the sense of impaired gain with delayed oseltamivir medication ⁹⁸. Another study showed that Aloe-emodin inhibits the replication of Japanese encephalitis virus (JEV) and enterovirus 71 (EV71) through interferon (IFN) signalling responses ⁹⁹. Another study showed that Galectin-3 blocked replication of the influenza A virus. A proteomic study of MDCK cells revealed up-regulation of galectin-3 as one anti-influenza A virus action by aloe-emodin ⁵⁹

5.1.2. Zafran (*Crocus sativus*)

Soleymani et al⁸⁴ explore the anti-viral function of saffron extract and its main ingredients. The result suggested that aqueous saffron extract was not active in some doses (i.e. a mild activity) against HIV-1 and HSV-1 virions, but that crocin and picrocrocin suggested important anti-HSV-1 and anti-HIV-1 activities.

Mechanism: Crocin prevented the HSV replication of virions in Vero cells before and after entry. Crocin carotenoid inhibited the penetration of HSV in the target cells as well as disrupted virus replication after cell entry. Picrocrocin also prevents the entry and replication of viruses.

5.1.3. Mur-Makki (*Commiphora myrrh*)

Alamri et al⁷¹ examined the effect of Myrrh extract on Vero cells infected with Herpes Virus Type-1. The findings showed that Vero cells were toxic to high concentrations (10% and 5%) while lower concentrations (2%,1%, 0,5%) protected Vero cells against the cytopathic effect of HSV-1.

Mechanism: Treated Vero cells will result in a decrease in IL-1B levels, which in turn will reduce cytokine production due to HSV-1, including IL6 and IL8.

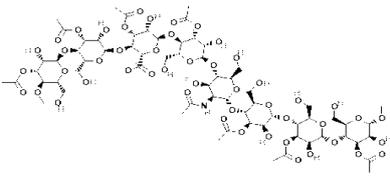
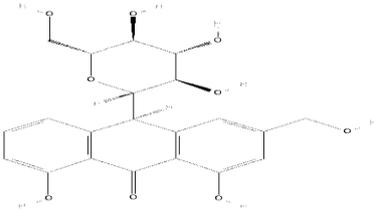
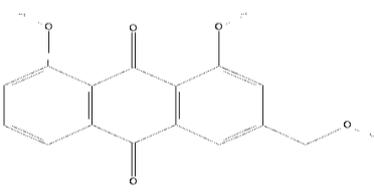
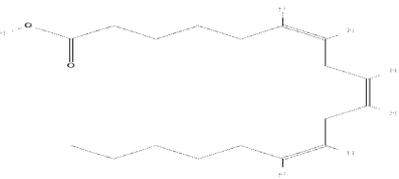
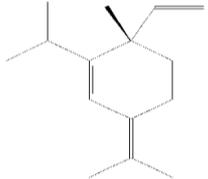
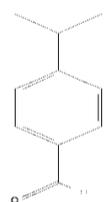
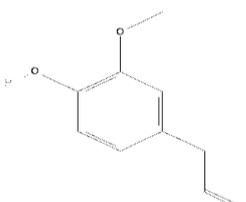
Table 4: Immunomodulatory activities and their Mechanism of different Components of "Tiryag Wabai."

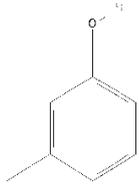
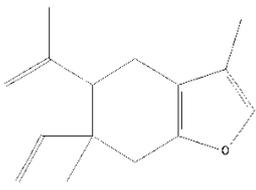
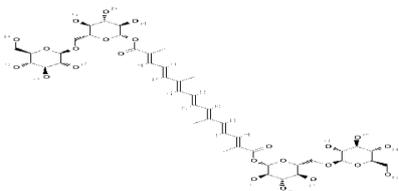
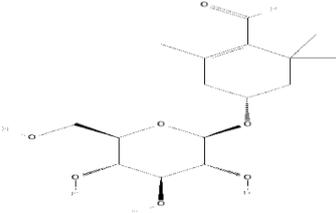
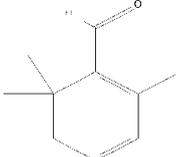
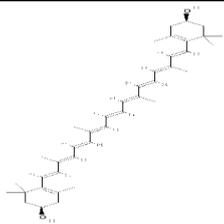
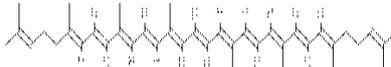
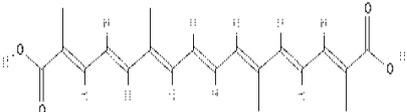
Drug	Immunomodulatory activity	Mechanism	Ref.
<i>Sibr (Aloe barbadensis)</i>	Ahluwalia et al ¹⁰⁰ research indicate that AVH200® (<i>A. barbadensis</i> Mill. dried frozen inner leaf gel extract) has an in vitro suppressive effect on human blood T cells.	Reduced expression of CD25 among CD3 ⁺ T cells and suppression of T cell proliferation, and also reduced the expression of CD28 on CD3 ⁺ T cells, ↓ secretion of IL-2, IFN-γ and IL-17A in PBMC cultures	¹⁰⁰
	Dziewulska et al research assess the effect of herbal extracts on selected mechanisms of immunity in clinically stable pigeons and pigeons inoculated with type 1 pigeon paramyxovirus (PPMV-1). The test indicates that aloe vera extract has immunomodulatory properties and can be used effectively for viral disease prevention, immune enhancement and as an alternative treatment for viral diseases.	Aloe vera activated both cell and humoral immunity, as shown by the higher expression of genes encoding CD4 and CD8 surface receptors	¹⁰¹
	One research found that dietary supplementation with Aloe vera prevented immunosuppression caused by transportation stress, injection and bacterial infection; treatment also increased Serum lysozyme concentrations (SLC) tested in pacu (<i>Piaractus mesopotamicus</i>) after heat-killed infection with <i>Aeromonas hydrophila</i> .	Prohibited falls of both respiratory leukocyte burst and haemolytic activity of complement system caused by transport. Significantly ↑ leukocyte respiratory burst, serum lysozyme concentrations and activity of complement system 24 h after bacterial infection	¹⁰²
	Madan et al found Aloe Vera extract (300	It stimulates the proliferation of stem cells → ↑ to	¹⁰³

	mg/kg, i.p) have immunostimulatory action	total white blood cells. It also ↑ plaque-forming cells in the spleen and circulating antibody titre → ↑ humoral immune response	
	On mice confronted with <i>S. typhimurium</i> DT104, an in vivo anti-microbial activity and immunomodulation effects of aloe peel extracts were tested. The faecal shedding of <i>S. typhimurium</i> DT104 ↓ significantly and the intestinal Salmonella specific IgA and IgG titers ↑ significantly in mice fed with aloe peel extracts	Promote the production of Th2 cytokines, i.e. IL-4 and IL-10	104
	Mesbah et al concluded that the feeding of shirbot (<i>Barbus grypus</i>) by <i>Aloe vera</i> (specifically 0.2%) extract boosted immunological parameters better than <i>Echinacea</i> .	↑ respiratory burst activity (an important indicator of nonspecific defence in fish, which is a measure of the increased oxidation level in phagocytes stimulated by foreign agents), ↑ serum bactericidal activity, ↓ Total protein and globulin, ↑ Lysozyme activity	105
	Aloe Vera treatment significantly ↓ the clinical signs of experimental autoimmune encephalomyelitis (an animal model of multiple sclerosis) and delayed onset of disease	significant ↓ TNF-4	106
	The immunomodulatory activity of PAG in immunosuppressed and <i>Candida albicans</i> infected mice has been investigated. The findings show clearly that Aloe Vera gel has immunomodulatory activity.	Acemannan (major polysaccharide) → activates macrophages → enhanced phagocytic and candidacidal activities	107
	Another study showed that aloe vera improved the capacity of broiler chickens with humorous responses to viral infection.	↑ antibody production against the NDV → increase humoral response	108
	Another study found that rainbow trout (<i>Oncorhynchus mykiss</i>) fortified with aloe vera powder had improved immunity parameters, leading to significantly lower mortalities in the challenge with <i>S. parasitica</i> compared to the control.	↑ lysozyme activity, ↑ respiratory burst activity, Significant ↑ in an expression of TNF-α gene	109
	Farahnejad et al investigated the effect of <i>Aloe vera</i> extract and its fractions on infected macrophages with <i>C. albicans</i> . The extract as well as fractions of <i>Aloe</i> significantly ↑ cell viability of macrophages in utmost doses	Acemannan, a beta-(1,4)-acetylated mannan → ↑ macrophage activity	110
<i>Zafran</i> (<i>Crocus sativus</i>)	Khajuria et al evaluate immunomodulatory activity of <i>Crocus sativus</i> and its active constituent crocin in Male Sprague Dawley rats. <i>Crocus sativus</i> and crocin were orally administered in doses of 50 mg/kg and 9.69 mg/kg, respectively. The result revealed that <i>Crocus sativus</i> and crocin prompt both cellular and humoral immune responses.	Cellular immunity: 1. ↑ in adhesion of neutrophils, 2. attenuation of cyclophosphamide-induced neutropenia, 3. ↑ in the phagocytic index in carbon clearance assay Humoral immunity: 1. ↑ in serum immunoglobulin levels 2. ↑ thymus gland weight and hemagglutination titre value	111
	Kadri et al evaluate the immunomodulatory effects <i>C. sativus</i> (petals) and <i>B. officinalis</i> (whole plant) aqueous extracts in albino mice by administering the immune-suppressive drug cyclosporine (10 mg/kg). The metaphase index of bone marrow and spleen cells was	↑ Arthus reaction and Delayed-type hypersensitivity reactions. Both reactions are important in evaluating humoral and cellular immune responses, respectively. A.R. is a hypersensitivity type III reaction, which depends on the production of specific antibodies against an	112

	significantly ($P \leq 0.05$) ↓ in mice treated with cyclosporine as compared with mice treated with the extracts of <i>C. sativus</i> . These findings suggest that <i>C. sativus</i> extract exerted some positive effects on the metaphase index of bone marrow or spleen cells, and accordingly an enhancement of immune functions.	antigen in a second challenge; therefore, the produced antibodies are of the class IgG. Delayed-type hypersensitivity (DTH) reaction is mediated by macrophages and specific T-helper lymphocytes that are called TDTH cells and occurs locally after 24-48 hours of a second challenge with the same antigen.	
	Boskabady et al investigated the <i>Crocus sativus</i> extract on human lymphocytes' cytokines and T helper 2/T helper one balance. Various concentrations of the extract substantially inhibited lymphocyte cell viability in peripheral blood mononuclear cells stimulated with phytohemagglutinin. They were even inhibiting IFN- γ secretion in stimulated cells and IL-10 secretion both in stimulated and non-stimulated cells at high concentrations of extract (500 $\mu\text{g} / \text{ml}$). The findings indicate that saffron could have therapeutic effects on inflammatory conditions linked to increased development of Th2 cytokines such as asthma.	↑ the ratio of IFN-c to IL-4, which indicates a ↑ Th1/Th2 balance	113
	Significant macrophage activation observed with the release of nitric oxide was encouraged by non-cytotoxic defence from a saffron corm. After proteoglycan therapy, fast activation of protein kinase C and NF-kappa B was achieved, which may clarify nitric oxide synthase induction. The rapid apoptosis of macrophages was promoted in proteoglycan concentrations ranges from 10 to 1,000 ng/ml, possibly due to their activation. This molecule did not prevent in vitro migration or invasion of human tumour cells. The results supported a plausible immune-modulating activity for <i>Crocus proteoglycan</i> .	Specific stimulation of PKC activity, probably triggered by the ↑ calcium levels caused by treatment with this glycoconjugate. The compound alters plasma membrane permeability on HeLa cells, causing calcium influx → ↑ intracellular calcium levels and activation of PKC induce NF-kB DNA-binding (a process necessary to activate iNOS transcription and NO production in macrophages)	114
	Another study indicated that <i>C. sativus</i> hydro-ethanolic extract reduced histamine level in asthmatic guinea-pigs	prevent ↑ serum histamine level, ↓ eosinophil counts in lung lavage	115
<i>Mur-Makki (Commiphora myrrh)</i>	A study investigates the effects of myrrh supplementation on WBC numbers in the blood before and during an injury. The result showed treatment with myrrh induced an initial ↑ in WBC levels that persisted through the post-injury healing period.	induce maturation/differentiation/ activation of both myeloid and lymphoid cell types during the effector phase of wound healing immune response	72
	Another research found that myrrh suspension facilitates the healing and reconstruction of damaged tissue when used for a relatively short period (less than 2 weeks) and when suspended in low concentration.	-----	116
	Another research showed that <i>Commiphora</i> has a strong antioxidant and can defend against lead-induced hepatic oxidative damage and immunotoxicity by reducing lipid peroxidation and enhancing the mechanisms of antioxidant and immune defence.	Lead-acetate induced-hypoproteinaemia and hypoalbuminemia, and ↑ aminotransferases activity. It ↓ the values of lymphocyte transformation test, phagocytic activity, phagocytic index and antibody titer against sheep sRBCs. Pre-treatment with <i>Commiphora</i> extract reduced these adverse effects in a dose-dependent protection	117
	Abdel-Aziz et al study indicate that myrrh can improve the cellular immunity of schistosomiasis infected mice. This study showed that serum antischistosomal antibodies of mice infected with <i>Schistosoma mansoni</i> were ↓ significantly ($p < 0.0001$) after three weeks of the treatment with myrrh compared with the infected non-treated group.	Significantly ↓ mean serum level of IL-2, non significantly ↓ level of gamma interferon (IFN- γ)	118

Table 5: Classification and structure of critical chemical constituents of the component of *Tiryag Wabai*

Drug name	Classification	Chemicals	Structures	PubChem CID
<i>Sibr (Aloe barbadensis)</i>	polysaccharide	Acemannan		72041
	anthraquinone glycoside	Aloin		14989
	anthraquinone glycosides	Aloe-emodin		10207
	omega-6 fatty acid	γ -linolenic acid		5280933
<i>Mur-Makki (Commiphora myrrh)</i>	sesquiterpenoids	alpha-elemene		80048
	natural organic compound	Cumic aldehyde		326
	phenylpropanoids	eugenol		3314

	organic compound	metacresol		342
	aromatic monoterpenoids	curzerene		572766
Zafran (<i>Crocus sativus</i>)	diterpenoids	Crocin		5281233
	monoterpene glycoside	picrocrocin		130796
	organic compound (degradation product of the carotenoid zeaxanthin)	safranal		61041
	carotenoid alcohols	zeaxanthin		5280899
	acyclic carotene	lycopene		446925
	carotenoids	crocetin		5281232

6. Conclusion and discussion

It is a likely possibility that epidemics will continue to occur, and with the emergence of new organisms may be more aggressive than ever. Hence, the need arises to develop new effective methods of infection control that are accessible to the maximum population. Prevention of *wabai amraz* with *Tiryaqi Advia* is recommended in the Unani system of medicine since ancient times. As a prophylactic drug, *Tiryaq* is generally recommended for toxicity prevention (sepsis). *Tiryaqiyat* is the formulation that reinforces the *Rooh* so that *Rooh* can neutralize the body's toxicity. *Tiryaqiyat* enhances the *rooh*, activates *hararte-gharizia*, and allows *Tabiyat* to avoid morbid substances. All the three ingredients of *Tiryaq Wabai* have various pharmacological activities like an immunomodulatory, antitussive, expectorant, antiviral activity which provide a strong basis for its prophylactic use for covid-19 infection. Further, research on this important prophylactic Unani formulation *tiryaq e wabai* in Covid-19 is the need of the hour. Greater impetus on research in the Unani system of medicine will not only boost trade and practice of herbal products but will also help in spreading the traditional Indian knowledge to other parts of the world.

Conflicts of Interest: None

References

- Husain A, Sofi GD, Tajuddin, Dang R, Kumar N. Unani System of Medicine- Introduction and Challenges. *Med J Islam World Acad Sci* 2010; 18:27-30.
- Ahmad S, Unani SA, Introduction M, Status P, Internet T, Medicine A. Unani Medicine: Introduction and Present Status in India. *Internet J Altern Med* 2012; 6:4-7.
- Aleem M, Imran Khan M, Islam Usmani Q, Ahmad A. Review on Darunaj-aqrabi (*Doronicum hookeri* C.B. Clarke): an Unexplored Medicinal Plant of Unani System of Medicine. *J AYUSH Ayurveda, Yoga, Unani, Siddha Homeopath* 2020; 9:41-52. <https://doi.org/10.37591/joayush.v9i2.2108>
- Ansari S, Ahmad I, Ali M, Maaz M. " Tiryaq Arba " (a Polyherbal Unani Formulation) as Prophylactic Medicine Against Epidemics of Acute Respiratory Viral Infections. 2020; 1-10. <https://doi.org/10.5812/mejrh.102965>
- Moazzam SW, Manzoor F. Prevention and Treatment Approach in Unani Medicine Against Covid-19- a Review. 2020; 7:625-628.
- Aleem M, Anis M. Therapeutic potential of Habb-ul-Aas (*Myrtus communis* Linn.) with Unani Perspective and Modern Pharmacology: A review. *J Pharmacogn Phytochem* 2021; 10:910-923. <https://doi.org/10.22271/phyto.2021.v10.i1m.13452>
- Ansari AP, Ahmed NZ, Dar PA. Empirical evidence of animals used in biomedical research in unani medicine : An appraisal. 2018; 2:11-13.
- Taghizadieh A, Mohammadinasab R, Ghazi-Sharbfaj J, Michaleas SN, Vrachatis D, Karamanou M. Theriac in the Persian traditional medicine. *Erciyes Med J* 2020; 42:235-238.
- Aleem M, Khan I, Danish M, Ahmad A. History and traditional uses of Tiryaq (Theriac): An important formulation in Unani medicine. *J Phytopharm* 2020; 9:429-432. <https://doi.org/10.31254/phyto.2020.9608>
- Nappi C. Bolatu's pharmacy theriac in early Modern China. *Early Sci Med* 2009; 14:737-764. <https://doi.org/10.1163/138374209X12542104914000>
- Kahl O. Two antidotes from the 'empiricals' of Ibn at-Tilmid combining macron below. *J Semit Stud* 2010; 55:479-496. <https://doi.org/10.1093/jss/fgq009>
- Hafeez A. Qarabadeen e Jadeed. Central Council for Research in Unani Medicine: New Delhi (India), 2005.
- Jalaluddin H. Qarabadeen-e-Jalali. CCRUM: New Delhi (India), 2006.
- Kabiruddin M. Bayaz-e-Kabeer. Idara Kitabu-us-Shifa: New Delhi (India), 2010.
- Ghani HN. Qarabadeen-e-Najmul Ghani. CCRUM: New Delhi (India), 2010. <https://doi.org/10.1355/SEAA10P>
- Nigar Z, Itrat M. Evaluation of a Unani polyherbal formulation (*Tiryaqe wabai*) as an immunostimulator in elderly persons. *Anc Sci Life* 2013; 33:117. <https://doi.org/10.4103/0257-7941.139054>
- Khan A. Qarabadeen E Azam (Urdu translation). Central Council for Research in Unani Medicine, Ministry of Health and Family Welfare, Govt. of India: New Delhi (India), 1996.
- Khan MS. Bayaz E Khas (Urdu Translation). Ejaz publishing house: New Delhi (India), 2006.
- Kabiruddin M. Al-Qarabadeen. Central Council for Research in Unani Medicine, Ministry of Health and Family Welfare, Govt. of India: New Delhi (India), 2006.
- Moriyama M, Hugentobler WJ, Iwasaki A. Annual review of virology seasonality of respiratory viral infections. *Annu Rev Virol* 2020; 7:1-19. <https://doi.org/10.1146/annurev-virology-012420-022445>
- Morens DM, Taubenberger JK. Historical thoughts on influenza viral ecosystems, or behold a pale horse, dead dogs, failing fowl, and sick swine. *Influenza Other Respi Viruses* 2010; 4:327-337. <https://doi.org/10.1111/j.1750-2659.2010.00148.x>
- Morens DM, Folkers GK, Fauci AS. Emerging infections: a perpetual challenge. *Lancet Infect Dis* 2008; 8:710-719. [https://doi.org/10.1016/S1473-3099\(08\)70256-1](https://doi.org/10.1016/S1473-3099(08)70256-1)
- Lenoir-Wijnkoop I, Merenstein D, Korchagina D, Broholm C, Sanders ME, Tancredi D. Probiotics reduce health care cost and societal impact of flu-like respiratory tract infections in the USA: An economic modeling study. *Front Pharmacol* 2019; 10:1-9. <https://doi.org/10.3389/fphar.2019.00980>
- Liu J, Wang M, Zhao Z, Lin X, Zhang P, Yue Q et al. Viral and bacterial coinfection among hospitalized children with respiratory tract infections. *Am J Infect Control* 2020; 000:1-6.
- Doorn HR van, Yu H. Viral Respiratory Infections. In: Hunter's Tropical Medicine and Emerging Infectious Diseases. Elsevier, 2020 doi:<https://doi.org/10.1016/B978-0-323-55512-8.00033-8>
- Naz R, Gul A, Javed U, Urooj A, Amin S, Fatima Z. Etiology of acute viral respiratory infections common in Pakistan: A review. *Rev Med Virol* 2019; 29:1-6. <https://doi.org/10.1002/rmv.2024>
- Islam A, Ahmed A, Naqvi IH, Parveen S. Emergence of deadly severe acute respiratory syndrome coronavirus-2 during 2019-2020. *VirusDisease* 2020; 31:128-136. <https://doi.org/10.1007/s13337-020-00575-1>
- Lai C, Shih T, Ko W, Tang H, Hsueh P, Shih T et al. Journal Pre-proof. 2020; 2.
- Drosten C, Günther S, Preiser W, Van der Werf S, Brodt HR, Becker S et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003; 348:1967-1976. <https://doi.org/10.1056/NEJMoa030747>
- Rothan HA, Byrareddy SN. 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 . 2020.
- Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis* 2020. doi:10.1093/cid/ciaa270. <https://doi.org/10.1093/cid/ciaa270>
- Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat. Rev. Cardiol.* 2020.

- doi:10.1038/s41569-020-0360-5.
<https://doi.org/10.1038/s41569-020-0360-5>
- 33 Velavan TP, Meyer CG. The COVID-19 epidemic. *Trop Med Int Heal* 2020; 25:278-280. <https://doi.org/10.1111/tmi.13383>
- 34 Kannan S, Shaik Syed Ali Pakeer P, Sheeza Ali A, Hemalatha K. Reply Letter - COVID-19 (Novel Coronavirus 2019) - Recent trends. *Eur Rev Med Pharmacol Sci* 2020; 24:6482-6483.
- 35 Gandhi RT, Lynch JB, del Rio C. Mild or Moderate Covid-19. *N Engl J Med* 2020; : 1-9. <https://doi.org/10.1056/NEJMcp2009249>
- 36 Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A et al. COVID-19 and Cardiovascular Disease. *Circulation* 2020; 2019:1648-1655. <https://doi.org/10.1161/CIRCULATIONAHA.120.046941>
- 37 Cao X. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol* 2020; 20:269-270. <https://doi.org/10.1038/s41577-020-0308-3>
- 38 Parvez A, Ahmed Z, Anwar N, Ahmed K. Razi 's unique approach to Amraz-e-Wabaiya (Infectious Diseases): An overview. 2016; 4:176-178.
- 39 Sina I. Al-Qanun fit-Tibb. Vol. I-V (Urdu translation by Ghulam husain Kantoori). Idara Kitabu-us-Shifa: New Delhi (India), 2007.
- 40 Shaksaz FA. Overview of Covid-19; its prevention and management in the light of Unani medicine. *J Emerg Technol Innov Res* 2020; 7:553-561.
- 41 Ansari RUI, Alam M, Khan LA, Ansari AA. Asbab-e-Sitta Zarooriya (Six Essential Factors) for Prevention of Lifestyle Diseases. *Hippocrat J Unani Med* 2010; 5:9-15.
- 42 Razi Z. *Kitab al Hawi*. CCRUM: New Delhi (India), 2004.
- 43 Nikhat S, Fazil M. Overview of Covid-19; its prevention and management in the light of Unani medicine. *Sci Total Environ* 2020; 728. doi:10.1016/j.scitotenv. 2020.138859. <https://doi.org/10.1016/j.scitotenv.2020.138859>
- 44 Rushd I. *Kitab Al-Kulliyat* (Urdu). Maktaba Daniyal: Lahore, 1987.
- 45 Majoosi A bin A. *Kamil-us-sana* (Urdu translation by Hkm. Ghulam Hussain Kantoori). Idara Kitabu-us-Shifa: New Delhi (India), 2010.
- 46 Abdul Hafiz H. *Qarabadeen Jadeed*. Central Council for Research in Unani Medicine, Ministry of Health and Family Welfare, Govt. of India: New Delhi (India), 2005.
- 47 Arzani A. *Qarabadeen-e-Qadri* (Urdu translation by CCRUM). Central Council for Research in Unani Medicine, Ministry of Health and Family Welfare, Govt. of India: New Delhi (India), 2009.
- 48 Anonymous. *Qarabadeen Majeedi*. 9th ed. (Waqf Hamdard) All India Unani Tibbi Confrence: New Delhi (India), 1986.
- 49 Ali E. *Qarabadeen-e-Ehsani*. Central Council for Research in Unani Medicine, Ministry of Health and Family Welfare, Govt. of India: Dehli-6, 2006.
- 50 Sherazi MMBK. *Qarabadeen-e-masoomi*. National mission for manuscripts: New Delhi (India), 2017.
- 51 Bin ali bin Umar M. *Qarabadin-i Maristani*. Al-Qazi printers: New Delhi (India), 2006.
- 52 Tabri A. *Firdous Al-Hikmat* (Urdu translation by Hakeem Muhammad Shah). 2nd ed. Idara Kitabus Shifa: New Delhi (India), 2017.
- 53 Ghani M. *Khazainul Advia* (Urdu). Idara Kitabu al Shifa: New Delhi (India), 2011.
- 54 Bozzi A, Perrin C, Austin S, Arce Vera F. Quality and authenticity of commercial aloe vera gel powders. *Food Chem* 2007; 103:22-30. <https://doi.org/10.1016/j.foodchem.2006.05.061>
- 55 N NR. The effect of aloe vera plant (aloe barbadensis) extracts on sickle cell blood (hbss). *African J Food Sci Technol* 2010; 1:58-063.
- 56 Kiliç N. The effect of Aloe vera gel on experimentally induced peritoneal adhesions in rats. *Rev Med Vet (Toulouse)* 2005; 156:409-413.
- 57 Hamman JH. Composition and applications of Aloe vera leaf gel. *Molecules* 2008; 13:1599-1616. <https://doi.org/10.3390/molecules13081599>
- 58 Femenia A, Sánchez ES, Simal S, Rosselló C. Compositional features of polysaccharides from Aloe vera (Aloe barbadensis Miller) plant tissues. *Carbohydr Polym* 1999; 39:109-117. [https://doi.org/10.1016/S0144-8617\(98\)00163-5](https://doi.org/10.1016/S0144-8617(98)00163-5)
- 59 Li S, Yang T, Lai C, Huang S, Liao J, Wan L et al. Antiviral activity of aloe-emodin against in fluenza A virus. 2014; 1-9.
- 60 Yagi A. Putative Prophylaxes of Aloe vera Latex and Inner Gel as Immunomodulator. *J Gastroenterol Hepatol Res* 2015; 4:1585-1598. <https://doi.org/10.17554/j.issn.2224-3992.2015.04.506>
- 61 Peret T, Ph D, Emery S, Tong S, Ph D, Urbani C et al. *new england journal*. 2003; 1953-1966.
- 62 Tian B, Hua Y. Concentration-dependence of prooxidant and antioxidant effects of aloin and aloe-emodin on DNA. *Food Chem* 2005; 91: 413-418. <https://doi.org/10.1016/j.foodchem.2004.06.018>
- 63 Kim K, Kim H, Kwon J, Lee S, Kong H, Im SA et al. Hypoglycemic and hypolipidemic effects of processed Aloe vera gel in a mouse model of non-insulin-dependent diabetes mellitus. *Phytomedicine* 2009; 16:856-863. <https://doi.org/10.1016/j.phymed.2009.02.014>
- 64 Park MY, Kwon HJ, Sung MK. Evaluation of aloin and aloe-emodin as anti-inflammatory agents in aloe by using murine macrophages. *Biosci Biotechnol Biochem* 2009; 73:828-832. <https://doi.org/10.1271/bbb.80714>
- 65 Choi SW, Son BW, Son YS, Park YI, Lee SK, Chung MH. The wound-healing effect of a glycoprotein fraction isolated from aloe vera. *Br J Dermatol* 2001; 145:535-545. <https://doi.org/10.1046/j.1365-2133.2001.04410.x>
- 66 Saito H, Imanishi K, Okabe S. Effects of aloe extracts, aloctin A, on gastric secretion and on experimental gastric lesions in rats. *Yakugaku Zasshi* 1989; 109:335-339. https://doi.org/10.1248/yakushi1947.109.5_335
- 67 Dhingra D, Lamba D, Kumar R, Nath P, Gauttam S. Antihyperlipidemic Activity of Aloe succotrina in Rats: Possibly Mediated by Inhibition of HMG-CoA Reductase. *ISRN Pharmacol* 2014; 9. <https://doi.org/10.1155/2014/243575>
- 68 Morteza-Semnani K, Saeedi M. Constituents of the essential oil of commiphora myrrha (Nees) Engl. var. molmol. *J Essent Oil Res* 2003; 15:50-51. <https://doi.org/10.1080/10412905.2003.9712264>
- 69 Zhu N, Sheng S, Sang S, Rosen RT, Ho CT. Isolation and characterization of several aromatic sesquiterpenes from Commiphora myrrha. *Flavour Fragr J* 2003; 18:282-285. <https://doi.org/10.1002/ffj.1193>
- 70 Mohamed AA, Ali SI, EL-Baz FK, Hegazy AK, Kord MA. Chemical composition of essential oil and in vitro antioxidant and antimicrobial activities of crude extracts of Commiphora myrrha resin. *Ind Crops Prod* 2014; 57:10-16. <https://doi.org/10.1016/j.indcrop.2014.03.017>
- 71 Alamri BM. Effects of Myrrh on HSV-1 Using Plaque Assay. 2017.
- 72 Haffor ASA. Effect of myrrh (Commiphora molmol) on leukocyte levels before and during healing from gastric ulcer or skin injury. *J Immunotoxicol* 2010; 7:68-75. <https://doi.org/10.3109/15476910903409835>
- 73 Su S, Wang T, Duan JA, Zhou W, Hua YQ, Tang YP et al. Anti-inflammatory and analgesic activity of different extracts of Commiphora myrrha. *J Ethnopharmacol* 2011; 134:251-258. <https://doi.org/10.1016/j.jep.2010.12.003>
- 74 Gao W, Su X, Dong X, Chen Y, Zhou C, Xin P et al. Cycloartan-24-ene-1 α ,2 α ,3 β -triol, a cycloartane-type triterpenoid from the resinous exudates of Commiphora myrrha, induces apoptosis in

- human prostatic cancer PC-3 cells. *Oncol Rep* 2015; 33:1107-1114. <https://doi.org/10.3892/or.2015.3725>
- 75 Lee K, Lee JH, Kim S II, Cho MH, Lee J. Anti-biofilm, anti-hemolysis, and anti-virulence activities of black pepper, cananga, myrrh oils, and nerolidol against *Staphylococcus aureus*. *Appl Microbiol Biotechnol* 2014; 98:9447-9457. <https://doi.org/10.1007/s00253-014-5903-4>
- 76 Irfan UM, Ali S, Alotaibi G. AN IN-VITRO STUDY TO TEST ANTIMICROBIAL EFFECTS OF COMMIPHORA MYRRHA IN COMPARISON TO BIOCIDES. *Eur J Pharm Med Res* 2017; 4:449-453.
- 77 Su S, Hua Y, Wang Y, Gu W, Zhou W, Duan JA et al. Evaluation of the anti-inflammatory and analgesic properties of individual and combined extracts from *Commiphora myrrha*, and *Boswellia carterii*. *J Ethnopharmacol* 2012; 139:649-656. <https://doi.org/10.1016/j.jep.2011.12.013>
- 78 Shalaby M, Hammouda A. Analgesic, Anti-inflammatory and Antihyperlipidemic Activities of *Commiphora molmol* Extract (*Myrrh*). *J Intercult Ethnopharmacol* 2014; 3:56. <https://doi.org/10.5455/jice.20140130015014>
- 79 Ahmad A, Raish M, Ganaie MA, Ahmad SR, Mohsin K, Al-Jenoobi FI et al. Hepatoprotective effect of *Commiphora myrrha* against d-GalN/LPS-induced hepatic injury in a rat model through attenuation of pro inflammatory cytokines and related genes. *Pharm Biol* 2015; 53:1759-1767. <https://doi.org/10.3109/13880209.2015.1005754>
- 80 Evans WC. *Trease and Evans Pharmacognosy*. 16th ed. Saunders elsevier: New York, 2009.
- 81 Wallis T. *Text book of Pharmacognosy*. CBS Publication: New Delhi (India), 2005.
- 82 Liakopoulou-Kyriakides M, Kyriakidis DA. *Crocus sativus*-biological active constituents. *Stud Nat Prod Chem* 2002; 26:293-312. [https://doi.org/10.1016/S1572-5995\(02\)80009-6](https://doi.org/10.1016/S1572-5995(02)80009-6)
- 83 Amin B, Malekzadeh M, Heidari MR, Hosseinzadeh H. Effect of *Crocus sativus* extracts and its active constituent safranal on the harmaline-induced tremor in mice. *Iran J Basic Med Sci* 2015; 18:449-458.
- 84 Soleymani S, Zabihollahi R, Shahbazi S, Bolhassani A. Antiviral Effects of Saffron and its Major Ingredients. *Curr Drug Deliv* 2018; 15:698-704. <https://doi.org/10.2174/1567201814666171129210654>
- 85 Bakshi HA, Faruck HL, Yadav SA, Tambuwala MM. The Remarkable Pharmacological Efficacy of Saffron Spice via Antioxidant, Immunomodulatory, and Antitumor Activities. In: *Saffron*. Elsevier, 2020, pp 245-262. <https://doi.org/10.1016/B978-0-12-818462-2.00019-X>
- 86 Amin B, Hosseinzadeh H. Analgesic and Anti-Inflammatory Effects of *Crocus sativus* L. (Saffron). In: *Bioactive Nutraceuticals and Dietary Supplements in Neurological and Brain Disease: Prevention and Therapy*. Elsevier Inc., 2015, pp 319-324. <https://doi.org/10.1016/B978-0-12-411462-3.00033-3>
- 87 Imenshahidi M, Razavi BM, Faal A, Gholampoor A, Mousavi SM, Hosseinzadeh H. The effect of chronic administration of saffron (*Crocus sativus*) stigma aqueous extract on systolic blood pressure in rats. *Jundishapur J Nat Pharm Prod* 2013; 8:175-179. <https://doi.org/10.17795/jjnpp-12475>
- 88 Hosseinzadeh H, Talebzadeh F. Anticonvulsant evaluation of safranal and crocin from *Crocus sativus* in mice. *Fitoterapia* 2005. doi:10.1016/j.fitote.2005.07.008. <https://doi.org/10.1016/j.fitote.2005.07.008>
- 89 Hosseinzadeh H, Ghenaati J. Evaluation of the antitussive effect of stigma and petals of saffron (*Crocus sativus*) and its components, safranal and crocin in guinea pigs. *Fitoterapia* 2006; 77:446-448. <https://doi.org/10.1016/j.fitote.2006.04.012>
- 90 Abdullaev FI, Riverón-Negrete L, Caballero-Ortega H, Manuel Hernández J, Pérez-López I, Pereda-Miranda R et al. Use of in vitro assays to assess the potential antigenotoxic and cytotoxic effects of saffron (*Crocus sativus* L.). In: *Toxicology in Vitro*. Elsevier Ltd, 2003, pp 731-736. [https://doi.org/10.1016/S0887-2333\(03\)00098-5](https://doi.org/10.1016/S0887-2333(03)00098-5)
- 91 Hosseinzadeh H, Noraei NB. Anxiolytic and hypnotic effect of *Crocus sativus* aqueous extract and its constituents, crocin and safranal, in mice. *Phyther Res* 2009; 23:768-774. <https://doi.org/10.1002/ptr.2597>
- 92 Mahmoudzadeh L, Najafi H, Ashtiyani SC, Yarijani ZM. Anti-inflammatory and protective effects of saffron extract in ischaemia/reperfusion-induced acute kidney injury. *Nephrology* 2017; 22:748-754. <https://doi.org/10.1111/nep.12849>
- 93 Nassiri-Asl M, Hosseinzadeh H. Neuropharmacology Effects of Saffron (*Crocus sativus*) and Its Active Constituents. In: *Bioactive Nutraceuticals and Dietary Supplements in Neurological and Brain Disease: Prevention and Therapy*. Elsevier Inc., 2015, pp 29-39. <https://doi.org/10.1016/B978-0-12-411462-3.00003-5>
- 94 Mpiana PT, Ngbolua K te N, Tshibangu DST, Kilembe JT, Gbolo BZ, Mwanangombo DT et al. Identification of potential inhibitors of SARS-CoV-2 main protease from *Aloe vera* compounds: A molecular docking study. *Chem Phys Lett* 2020; 754. doi:10.1016/j.cplett.2020.137751. <https://doi.org/10.1016/j.cplett.2020.137751>
- 95 Borges-argáez R, Chan-balan R, Cetina-montejo L. 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. 2020.
- 96 Ng YC, Kim YW, Ryu S, Lee A, Lee JS, Song MJ. Suppression of norovirus by natural phytochemicals from *Aloe vera* and *Eriobotryae Folium*. *Food Control* 2017; 73:1362-1370. <https://doi.org/10.1016/j.foodcont.2016.10.051>
- 97 Glatthaar-Saalmüller B, Fal AM, Schönknecht K, Conrad F, Sievers H, Saalmüller A. Antiviral activity of an aqueous extract derived from *Aloe arborescens* Mill. against a broad panel of viruses causing infections of the upper respiratory tract. *Phytomedicine* 2015; 22:911-920. <https://doi.org/10.1016/j.phymed.2015.06.006>
- 98 Huang CT, Hung CY, Hseih YC, Chang CS, Velu AB, He YC et al. Effect of aloin on viral neuraminidase and hemagglutinin-specific T cell immunity in acute influenza. *Phytomedicine* 2019; 64. doi:10.1016/j.phymed.2019.152904. <https://doi.org/10.1016/j.phymed.2019.152904>
- 99 Lin CW, Wu CF, Hsiao NW, Chang CY, Li SW, Wan L et al. Aloe-emodin is an interferon-inducing agent with antiviral activity against Japanese encephalitis virus and enterovirus 71. *Int J Antimicrob Agents* 2008; 32:355-359. <https://doi.org/10.1016/j.ijantimicag.2008.04.018>
- 100 Ahluwalia B, Magnusson MK, Isaksson S, Larsson F, Öhman L. Effects of *Aloe barbadensis* Mill. extract (AVH200®) on human blood T cell activity in vitro. *J Ethnopharmacol* 2016; 179:301-309. <https://doi.org/10.1016/j.jep.2016.01.003>
- 101 Dziejulska D, Stenzel T, Śmiałek M, Tykałowski B, Koncicki A. The impact of *Aloe vera* and licorice extracts on selected mechanisms of humoral and cell-mediated immunity in pigeons experimentally infected with PPMV-1. *BMC Vet Res* 2018; 14:1-11. <https://doi.org/10.1186/s12917-018-1467-3>
- 102 Zanzuzo FS, Sabioni RE, Montoya LNF, Favero G, Urbinati EC. *Aloe vera* enhances the innate immune response of pacu (*Piaractus mesopotamicus*) after transport stress and combined heat killed *Aeromonas hydrophila* infection. *Fish Shellfish Immunol* 2017; 65:198-205. <https://doi.org/10.1016/j.fsi.2017.04.013>
- 103 Inamdar N, Rao H, Singh R, Madan J, Sharma A. Immunomodulatory properties of *aloe vera* gel in mice. *Int J Green Pharm* 2008. doi:10.4103/0973-8258.42732. <https://doi.org/10.4103/0973-8258.42732>
- 104 Kwon KH, Hong MK, Hwang SY, Moon BY, Shin S, Baek JH et al. Antimicrobial and immunomodulatory effects of *Aloe vera* peel extract. *J Med Plant Res* 2011; 5:5384-5392.

- 105 Mesbah M, Mohammadian T, Alishahi m, Jangaran nejad A. Effects of dietary Aloe vera and Echinacea on some nonspecific immunity in shirbot (*Barbus grypus*). *Iran J Aquat Anim Heal* 2016; 2:24-36. <https://doi.org/10.18869/acadpub.ijaah.2.1.24>
- 106 A G, G M, B A, A M. Immunomodulating activity of Aloe Vera in animal model of multiple sclerosis . *Arak Med Univ J* 2009; 12:109-115.
- 107 Im SA, Lee YR, Lee YH, Lee MK, Park YI, Lee S et al. In vivo evidence of the immunomodulatory activity of orally administered Aloe vera gel. *Arch Pharm Res* 2010; 33:451-456. <https://doi.org/10.1007/s12272-010-0315-1>
- 108 Ojjezeh TI, Eghafona N. Humoral responses of broiler chickens challenged with NDV following supplemental treatment with extracts of Aloe vera, *Alma millsoni*, *Ganoderma lucidum* and *Archachatina marginata*. *Cent Eur J Immunol* 2015; 40:300-306. <https://doi.org/10.5114/ceji.2015.54590>
- 109 Mehrabi Z, Firouzbakhsh F, Rahimi-Mianji G, Paknejad H. Immunostimulatory effect of Aloe vera (*Aloe barbadensis*) on non-specific immune response, immune gene expression, and experimental challenge with *Saprolegnia parasitica* in rainbow trout (*Oncorhynchus mykiss*). *Aquaculture* 2019; 503:330-338. <https://doi.org/10.1016/j.aquaculture.2019.01.025>
- 110 Farahnejad Z, Ghazanfari T, Yaraee R. Immunomodulatory effects of Aloe vera and its fractions on response of macrophages against *Candida albicans*. *Immunopharmacol Immunotoxicol* 2011; 33:676-681. <https://doi.org/10.3109/08923973.2011.560158>
- 111 Khajuria DK, Asad M, Asdaq SMB, Kumar P. The potency of *Crocus sativus* (Saffron) and its constituent crocin as an immunomodulator in animals. *Lat Am J Pharm* 2010; 29:713-718.
- 112 Hussein Z, Kadri M. Immunomodulatory effects of *Crocus sativus* L. (petals) and *Borago officinalis* L. (whole plant) aqueous extracts in albino mice. 2014; 25:7-16.
- 113 Boskabady MH, Seyedhosseini Tamijani SM, Rafatpanah H, Rezaee A, Alavinejad A. The effect of crocus sativus extract on human lymphocytes' cytokines and T helper 2/T helper 1 balance. *J Med Food* 2011; 14:1538-1545. <https://doi.org/10.1089/jmf.2011.1697>
- 114 Escribano J, Díaz-Guerra MJM, Riese HH, Ontañón J, García-Olmo D, García-Olmo DC et al. In vitro activation of macrophages by a novel proteoglycan isolated from corms of *Crocus sativus* L. *Cancer Lett* 1999; 144:107-114. [https://doi.org/10.1016/S0304-3835\(99\)00211-6](https://doi.org/10.1016/S0304-3835(99)00211-6)
- 115 Boskabady MH, Tabatabaee A, Byrami G. The effect of the extract of *Crocus sativus* and its constituent safranal, on lung pathology and lung inflammation of ovalbumin sensitized guinea-pigs. *Phytomedicine* 2012; 19:904-911. <https://doi.org/10.1016/j.phymed.2012.05.006>
- 116 Al-Mobeeriek A. Effects of myrrh on intra-oral mucosal wounds compared with tetracycline- and chlorhexidinebased mouthwashes. *Clin Cosmet Investig Dent* 2011; 3:53-58. <https://doi.org/10.2147/CCIDE.S24064>
- 117 Ashry KM, El-Sayed YS, Khamiss RM, El-Ashmawy IM. Oxidative stress and immunotoxic effects of lead and their amelioration with myrrh (*Commiphora molmol*) emulsion. *Food Chem Toxicol* 2010; 48:236-241. <https://doi.org/10.1016/j.fct.2009.10.006>
- 118 Abdel-Aziz MM, Abbas AT, Elbakry KA, Toson EA, El-Sherbiny M. Immune Response on Mice Infected with *Schistosoma mansoni* and Treated with Myrrh. *J Med Sci* 2006; 6:858-861. <https://doi.org/10.3923/jms.2006.858.861>