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Review Article

Plausible role of Arq Ajīb in combating COVID-19: A multi-faceted review

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Abstract

The current pandemic caused by SARS-CoV-2 has led to a massive change in every aspect of our lives. It has grossly affected the healthcare system, business and world trade, disruption of movement and supply of essential goods and has crippled the global economy. Although few vaccines have been approved for the control of disease, targeted therapy options for this virulent disease still remain limited and elusive. Exhaustive search for potent therapeutic candidate is in progress, for which herbal armory are also being explored. Medicinal plants and their products play a vital role in alleviating various diseases and have been reported to exhibit a wide range of biological activities. Plant-based drugs with antiviral, anti-inflammatory and immunomodulatory activities were hypothetically considered as potential drugs to prevent and mitigate the prevailing situation caused by SARS-CoV-2. Arq Ajīb 'a Unani formulation' presents compelling approach in treating numerous diseases. The ingredients of Arq Ajīb and their phytochemicals have been reported for wide-ranging pharmacological activities including antiviral, anti-inflammatory, immunomodulatory, anti-allergic, antitussive and bronchodilatory activities. Scientific data available on the formulation ingredients and their phytochemicals indicates that the formulation may have a significant role in augmenting the immune status of individual, protecting them from infection and providing symptomatic relief to patients affected with COVID-19. Hence, it may be considered as a potential drug for the development of novel therapeutic candidate for SARS-CoV-2 infection. This multi-faceted review highlights the therapeutic significance and pharmacological actions of Arq Ajīb and its ingredients to demonstrate the plausible role of the formulation in combating COVID-19.

Keywords: Arq Ajīb, COVID-19, Pudina, Ajwain, Camphor, Unani formulation

1. Introduction

World is experiencing the most tragic event after 2nd World War as the current pandemic 'COVID-19' still continues to escalate since December 2019 and causing unprecedented morbidity and mortality across the globe. It has led to a substantial loss of human life and presents formidable challenges to public health, economy, social and environmental factors¹. More than 171 million confirmed cases of COVID-19 with more than 3.6 million deaths have been reported globally according to the current statistics². India is experiencing a disastrous second wave and reporting unrestrained growth in the number of COVID19 cases at present. As per the latest updates, there have been more than 28 million confirmed cases with 337989 deaths reported in India³. SARS-CoV-2, the causative organism of COVID-19, belongs to the single-stranded RNA corona virus family 'Coronaviridae' and shares similar morphological characteristics of other viruses in the family such as Severe Acute Respiratory Syndrome corona virus (SARS-CoV) and Middle East Respiratory Syndrome corona virus (MERS-CoV)⁴. Patients infected with SARS-CoV-2 share similar symptoms to those affected with other corona viruses in the family which may include fever, cough, and breathing

difficulties as initial symptoms. Other symptoms may include headache, sore throat, fatigue, muscle pain, diarrhea, dizziness, loss of taste and smell, abdominal pain, anorexia, and vomiting. At the later stage, it may cause severe pneumonia with acute respiratory distress syndrome, multi-organ failure and sudden death^{1,5}.

Viable treatment options for this deadly disease still remain limited and elusive, though few vaccines have been approved and mass vaccination drive has been initiated across the globe for the disease control. Nevertheless, scientists are striving to identify potent targeted therapy options from both the conventional and traditional systems by repurposing of already existing antiviral drugs or discovering novel therapeutics to curb the grave situation caused by SARS-CoV-2^{6,7}. Plants and their products have long been used as medicine and still continue to play a vital role in alleviating a number of diseases. Medicinal plants have attracted renewed attention as they produce a vast array of structurally diverse bioactive compounds exhibiting a wide range of biological activities. These natural products have the potential to be developed as standard targeted therapeutics with least or no adverse effect and many of them have already been developed as current drug

candidate for a number of diseases^{7,8}. Numerous plants and their products being used traditionally in Ayurveda, Unani, Siddha have been reported for their potent antiviral activity against wide-ranging viruses⁹. They may also prove beneficial in containing the ever-spreading current pandemic.

Arq Ajīb, is an Unani formulation comprising of three herbal drugs i.e. *Jauhar-e-Pudina* (plant extract of *Mentha arvensis*), *Jauhar-e-Ajwain* (seed extract of *Trachyspermum ammi*) and Kafoor (Camphor). The formulation is claimed to possess antispasmodic, analgesic, digestive, anti-flatulent, anti-catarrh properties and has been used extensively both internally as well as externally to treat a number of afflictions¹⁰⁻¹². However, the formulation has hardly been evaluated scientifically for its beneficial effects, except one study which reports potent antidiarrhoeal activity of the formulation in rats¹³. The ingredients of the formulation have been reported to exhibit a wide range of biological activities including antiviral, antimicrobial, insecticidal, antioxidant, analgesic, anti-inflammatory & anti-allergic, broncho-dilating, antitussive, anticancer and radioprotective activities. Reports available on ingredients of the formulation support the hypothesis that Arq Ajīb may prove beneficial in alleviating the prevailing situation caused by SARS-CoV-2. This review highlights the therapeutic significance and pharmacological actions of Arq Ajīb and its ingredients to demonstrate the plausible role of Arq Ajīb in combating COVID-19.

2. Description of Arq Ajīb and its therapeutic applications

Arq Ajīb is a viscous liquid preparation, light pale in color, highly pungent in taste with camphor like smell. It is obtained by mixing *Kafoor*, *Jauhar-e-Pudina* and *Jauhar-e-Ajwain* in air tight glass container at room temperature and allowing it to liquefy. The liquid is then filtered to get the transparent homogenous liquid and stored in moisture free glass containers¹⁰.

2.1 Formulation composition

Jauhar-e-Ajwain (seed extract of *Trachyspermum ammi*) = 1 part (6 gram)

Jauhar -e-Pudina (plant extract of *Mentha arvensis*) = 2 parts (12 gram)

Kafoor (Camphor – *Cinnamomum camphora*) = 2 parts (12 gram)^{11,12,14}.

2.2 Istemal (Therapeutic uses)

The formulation has been in use in Unani medicine to treat various afflictions, justifying its nomenclature as ArqAjīb (Liniment of wonder). It has been used to treat *Hayda* (Cholera), *Ishāl* (Diarrhoea), *Sū' al-Haḍm* (Dyspepsia), *Sill* (Pthisis), *Waja' al-Mi'da* (Gastralgia), *Waja'al- Am'a'* (intestinal colic), *Waja' al-Fu'ād* (GERD), *Waja' al-Qalb* (Cardiac Pain), *Waja' al-kabid* (Hepatic Pain), *Pechish* (Dysentery), *Qūlanj* (Colicky pain), *Tā'ūn* (Plague), *Matli* (Nausea), *Qay'* (Vomiting), *Ṣudā'* (Headache), *Waja' al-'Aqib* (achillodynia), *Dard-e-Abrū* (pain in eyebrows), *Waja' al-Asnān* (Toothache), *Nafkh al-Mi'da* (Flatulence), *Waja' al-Udhun* (Otagia). It is also useful in snake, scorpion and other poisonous insects' sting¹⁰⁻¹⁴.

2.3 Miqdar -e- Khurak (Dosage)

Orally- 2-5 drops with water; external application Q.S.^{11,12,14}.

3. Potential of Arq Ajīb ingredients

3.1 Pudina (*Mentha arvensis*)

3.1.1 Overview:

Pudina (*Mentha arvensis* Linn) belongs to the family Lamiaceae is a common edible and aromatic perennial herb cultivated throughout India and widely used in pharmaceutical, cosmetic and flavoring industries. It is a well known kitchen herb and has been utilized medicinally since ages in Unani medicine as an analgesic, stomachic, carminative, anthelmintic, anti-inflammatory, diuretic, diaphoretic, antidote. Mostly, leaves and stem of *Pudina* are used for medicinal purpose. It is administered to treat diarrhea, dysentery, gastric problem, liver and spleen diseases, asthma, jaundice, rheumatic pains, arthritis. It has also been used to treat patients with hypertension and ischemic heart disease. The oil contents of *Pudina* leaves yields 40-50% menthol, which exhibits antiseptic, carminative, refrigerant, stimulant and diuretic properties. Menthol is widely utilized in pharmaceutical, perfumery and food industries and has also been used against various skin infections^{15,16}.

3.1.2 Mizaj (Temperament): Hār Yabis (Hot & Dry)^{17,18}

3.1.3 Afaal (Action):

Muḥammir (Rubefacient), *Musakkin-i-Alam* (Analgesic), *Mu'arriq* (Diaphoretic), *Muqawwi-i-Mi'da* (Stomachic), *Qātil-i-Dīdān* (Anthelmintic), *Mujaffif* (Dessicative), *Musakkhkhin* (Calorific), *Munḍij* (Concoctive), *Mulaṭṭif* (Demulcent), *Mudirr-i-Hayḍ* (Emmenagogue), *Muḥallil* (Resolvent), *Kāsir-i-Riyāh* (Carminative), *Mudirr-i-Bawl* (Diuretic), *Tiryāq* (Antidote), *Qābiḍ* (Astringent)¹⁷⁻¹⁹.

3.1.4 Istemal (Therapeutic uses):

Waja' al-Mi'da (Gastralgia), *Ihtibās al-Tamth* (Amenorrhoea), *Ḍiq al-Nafas* (Bronchial Asthma), *Qay'* (Vomiting), *Ḍuf al-Mi'da* (Gastric Debility), *Ḍuf al-Ishthā'* (Anorexia), *Nafkh al-Mi'da* (Flatulence), *Gazīdgī-i-'Aqrab* (Scorpion Sting), *Hayḍa* (Cholera), *Dīdān al-Am'ā'* (Intestinal worms), *Waja' al-Udhun* (Otagia), *Ṣudā'* (Headache), *Nafth al-Dam* (Haemoptysis), *Khafaqān* (Palpitation), *Githyān* (Nausea), *Dā' al-Fīl* (Filariasis), *Dawālī* (varicose veins), *Niqras* (Gout), *Waja' al-Asnān* (Toothache)¹⁷⁻¹⁹.

3.1.5 Miqdar-e-Khurak (Dose): 7 grams¹⁷.

3.1.6 Chemical constituents:

Organic constituents of *Mentha arvensis* (MA) include glycosides, phenolics, tannins, steroids, terpenes and terpenoids, proteins, reducing sugars and resins. The leaves yield about 0.2 - 0.8% essential oil of which menthol is the major component (30-55%). Other constituents include limonene (1.0-5.0%), cineole (3.5-14.0%), menthone (14.0-32.0%), menthofuran (1.0-9.0%), isomenthone (1.5-10.0%), menthyl acetate (2.8-10.0%), isopulegol (max. 0.2%), menthol (30.0-55.0%), pulegone (max. 4.0%) and carvone (max. 1.0%). Inorganic chemical constituents include antimony, calcium, iron, magnesium, potassium and sodium. It also contains flavonoids such as quercetin, menthoside, and isorhoifolin, vitamin K, thymol and eugenol^{15,16}.

3.1.7 Pharmacological activities:

MA has been reported for a wide range of biological activities including antiviral and cytotoxic²⁰, antimicrobial²¹⁻²⁴, antioxidant, analgesic²¹, anti-inflammatory & anti-allergic²⁵, anticancer^{26,27}, radioprotective^{28,29}, anticataleptic, antidepressant, antifertility activities^{15,16}.

3.1.7.1 Antiviral & cytotoxic activity:

A study investigated antiviral activity of 61 medicinal plants including *Mentha arvensis* (MA) against herpes simplex type 1 (HSV-1) and vesicular stomatitis (VSV). Cytotoxic activity was assayed using HeLa cell line. MA exhibited potent cytotoxic activity and very strong antiviral activity against HSV-1 but weak activity against VSV²⁰. Cytotoxic potential of ethanolic extract of MA was investigated using Brine shrimp lethality assay. The extract exhibited lethality against the brine shrimp nauplii with the LC₅₀ values of 40 µg/ml, and also 90% mortality (LC₉₀) value was found to be 160 µg/ml²¹.

3.1.7.2 Antimicrobial activity:

Various reports suggest potent antimicrobial activity of MA. The essential oil of MA has been reported to inhibit the proliferation of *Helicobacter pylori*, *Salmonella enteritidis*, *Escherichia coli* O157:H7, methicillin-resistant *Staphylococcus aureus*, and methicillin sensitive *S. aureus* in liquid culture in a dose dependent manner. It exhibited bactericidal activity in phosphate-buffered saline against both antibiotic-resistant and antibiotic-sensitive strains²². The essential oil of MA exhibited promising antibacterial activity against zoonotic enteropathogens including *Salmonella* spp., *E. coli* O157, *Campylobacter jejuni*, and *Clostridium perfringens*²³. Ethanolic extract of MA produced prominent antimicrobial activity against *Salmonella typhi*, *Salmonella paratyphi*, *Shigella boydii*, *Streptococcus pyogenes* and *Staphylococcus aureus*²¹. MA extract has been reported to exhibit potent antimicrobial activity and potentiating effect on antibiotics such as gentamicin, kanamycin and neomycin²⁴.

3.1.7.3 Antioxidant activity:

A number of studies have demonstrated significant protective effects of MA extracts and its active components. Ethanolic extract of MA exhibited significant free radical scavenging activity *in vitro* comparable to standard drug ascorbic acid²¹. Methanolic extract showed more powerful radical scavenging activity compared to aqueous extract¹⁵. Cineole, an important phytoconstituent of MA, mitigated the ethanol-induced gastric mucosal damage in rats which is attributed to its antioxidant, lipooxygenase inhibitory activity and capacity to restore the non-protein sulfhydryl to the normal level. Cineol, eugenol, thymol, terpenes, flavonoids like quercetin are reported to be good antioxidant and inhibit lipid peroxidation¹⁶.

3.1.7.4 Anti-inflammatory & anti-allergic activity:

A study evaluated anti-inflammatory and anti-allergic potential of ethanolic and aqueous extracts of MA by using histamine- induced paw edema mice and histamine release inhibition test respectively. Results for anti-allergic activity revealed that ethanolic extracts of leaf and root possessed marked inhibitory activity expressed as percentage inhibition, that is, 57% and 53%, respectively. Anti-inflammatory potential exhibited by ethanolic extracts of plant parts was leaf = 68.30 > root = 48.80 > stem = 10.70% and compared with percentage inhibitory potential of standard drug, diclofenac sodium which caused 77.87% edema inhibition²⁵.

3.1.7.5 Anticancer activity:

A study demonstrated that ethanolic extract of MA significantly suppressed the growth and induced apoptosis in Hep G2 cell lines by MTT assay²⁶. Another report suggests potent anticancer activity of methanolic and aqueous extracts against eight human cancer cell lines -A-549, COLO-

205, HCT-116, MCF-7, NCI-H322, PC-3, THP-1 and U-87MG, from different origins which include breast, colon, glioblastoma, lung, leukemia and prostate. Methanolic extracts of *Mentha* Spp. displayed anti-proliferative effect against four human cancer cell lines, namely COLO-205, MCF-7, NCI-H322 and THP-1; however, aqueous extracts were found to be active against HCT-116 and PC-3²⁷.

3.2 Ajwain (*Trachyspermum ammi*)

3.2.1 Overview:

Ajwain (*Trachyspermum ammi* Linn) belonging to the family Apiaceae, is a popular spice and highly valued medicinal herb. It is extensively used in Unani System of medicine for various diseases such as amenorrhoea, leucorrhoea, pruritus vulvae, renal stone, dyspepsia, obesity, diarrhea, epilepsy, intestinal worms and asthma in different forms. The roots act as diuretic and the seeds as excellent aphrodisiac, carminative, laxative, stomachic and anthelmintic. The fruit possesses stimulant, antispasmodic and carminative properties. It is an important remedy for diarrhea, flatulence, and atonic dyspepsia. It also cures piles, abdominal pain, abdominal tumors, and respiratory problems. Essential oil of seeds contains about 50% thymol which acts as a strong anti-spasmodic, germicide and fungicide^{30,31}.

3.2.2 Mizaj (Temperament): Haar Yabis (Hot & Dry 3)¹⁷⁻¹⁹.

3.2.3 Afaal (Action):

Musakkin (Anodyne), *Mufattiḥ Sudad* (Deobstruent), *Jāli* (Detergent), *Mushtahī* (Appetizer), *Qātil wa Mukhrij-i-Didān-i-Am'ā'* (Anthelmintic & Vermifuge), *Dāfi'-i-Tashannuj* (Antispasmodic), *Dāfi'-i-Ta'affun* (Antiseptic), *Musakkhkhin* (Calorific), *Mujaffif* (Desiccant), *Muḥallil* (Resolvent), *Mudirr-i-Bawl* (Diuretic), *Tiryāq-i-Samūm* (Antidote), *Kāsir-i-Riyāḥ* (Carminative), *Mudirr-i-Ḥayḍ* (Emmenagogue)¹⁷⁻¹⁹.

3.2.4 Istemal (Therapeutic uses):

Ṣalāba al-Kabid (Cirrhosis of Liver), *Ṣalāba al-Tiḥāl* (Chronic Splenitis), *Shahīqa* (Whooping Cough), *Daḡḡt al-Dam Qawī* (Hypertension), *'Usr al-Bawl* (Dysuria), *Ḥumma* (Fever), *Du'f al-Ishtihā'* (Anorexia), *Waja' al-Fu'ād* (GERD), *Nafkh al-Mi'da* (Flatulence), *Gazīdgi-i-'Aqrab* (Scorpion Sting), *Dard* (Pain), *Ḥaṣāh al-Kulya* (Nephrolithiasis), *Ḥaṣāh al-Mathāna* (Cystolithiasis), *Qūlanj* (Colicky pain), *Baraṣ* (Leucoderma), *Bahaq* (Pityriasis), *Buthūr Labaniyya* (Acne vulgaris), *Waram* (Inflammation)¹⁷⁻¹⁹.

3.2.5 Miqdar-e-Khurak (Dose): 3-5 grams¹⁷⁻¹⁹.

3.2.6 Chemical constituents:

Ajwain seeds contain fiber, carbohydrates, tannins, glycosides, protein, fat, saponins, flavone and mineral matters containing calcium, phosphorous, iron and nicotinic acid. Ajwain fruits yield 2% to 4% essential oil, with thymol as the major constituent (35% to 60%). The constituents other than thymol include *p*-cymene, γ -terpinene, α - and β -pinenes, dipentene, α -terpinene, and carvacrol. Camphene, myrcene, and α -3-carene have also been found in minute quantity in the plant. A yellow, crystalline flavone and a steroid-like substance have been isolated from the fruits. It also contains 6-O- β -glucopyranosyloxythymol, glucoside and reported to produce 25% oleoresin containing 12% volatile oil. The principal oil constituents of *T. ammi* include carvone, limonene and dillapiole^{30,31}.

3.2.7 Pharmacological activities:

Ajwain (*Trachyspermum ammi*) has been reported for antiviral^{32,33}, antimicrobial, insecticidal, anthelmintic³⁴⁻³⁶, antioxidant³⁷⁻³⁹, anti-inflammatory⁴⁰ activities. Besides these, it has also been reported for hypolipidemic, digestive stimulant, antihypertensive, hepatoprotective, antispasmodic, broncho-dilating, antilithiasis, diuretic, abortifacient, galactogogic, antiplatelet-aggregatory, antitussive, antifilarial, gestroprotective, nematocidal activities³¹.

3.2.7.1 Antiviral activity:

A study evaluated cytotoxic and antiviral effect of Ajwain essential oil against Japanese encephalitis virus (JEV). *In vitro* cytotoxic effect was examined in vero cell line by MTT assay method. Plaque assay was used to determine JEV titer and plaque reduction neutralization test (PRNT) was employed to quantify the *in vitro* antiviral activity of ajwain oil. The study demonstrated potent cytotoxic and antiviral effect of Ajwain essential oil. The study reported cytotoxic concentration of Ajwain essential oil as 1 mg/ml by MTT assay. The titer of the virus pool was found to be 50×10^7 PFU/ml. The study demonstrated that 0.5mg/ml of Ajwain oil exhibited 80% and 40% virus inhibition in pre-exposure treatment and post-exposure treatment (antiviral activity), respectively³². Another study has demonstrated potent inhibitory effect of methanolic extract of Ajwain against hepatitis C virus ($>/=90\%$ inhibition at 100 microg/ml)³³.

3.2.7.2 Antimicrobial, insecticidal, anthelmintic activities:

A number of research studies have demonstrated significant antimicrobial effect against a wide range of bacteria and fungi, both sensitive and resistant. Ajwain essential oil has been reported to exhibit remarkable activity against vaginal pathogens including *Candida spp.*, *Gardnerella vaginalis*, *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus agalactiae* and *Lactobacillus acidophilus* and *Trichomonas vaginalis*³⁴. Ajwain essential oil fractions, γ -terpinene, ρ -cymene and thymol exhibited potent antibacterial and antifungal activity³⁵. Ajwain essential oil possessed remarkable antibacterial activity against three Gram (-) bacterial strains (*E. coli*-MTCC 443, *P. vulgaris*-MTCC 1771, and *K. pneumoniae*-MTCC number 7028) and three Gram (+) bacterial strains (*S. aureus*-MTCC 3381, *B. subtilis*-MTCC 10619, and *B. megaterium*-MTCC 2412). It also exhibited potent insecticidal activity against *Plodia interpunctella*³⁶. Ajwain extracts have also been reported for potent anthelmintic activity against *Ascaris lumbricoides* and *Haemonchus contortus*. It is suggested that Ajwain exert anthelmintic activity by interference with the energy metabolism of parasites through potentiation of ATPase activity and thus loss of energy reserves. The plant has also been reported to possess cholinergic activity with peristaltic movements of the gut, thus helping in expulsion of intestinal parasites which might also be a contributory factor to its anthelmintic activity³¹.

3.2.7.3 Antioxidant activity:

Ajwain extract and essential oils have been reported to possess significant antioxidant activity. Pre-feeding of ajwain extract in hexachlorocyclohexane (HCH)-induced oxidative stress and toxicity in rats resulted in increased GSH, GSH-peroxidase, G-6-PDH, SOD, catalase, glutathione S-transferase (GST) activities and decreased hepatic levels of lipid peroxides³⁷. Antioxidant activity of Ajwain essential oil determined by the DPPH and superoxide scavenging methods revealed significant antioxidant activity³⁸. *In vitro* radical scavenging and antioxidant capacities of Ajwain

essential oil and its main components were investigated and an antioxidant enzyme response to Ajwain essential oil at the gene expression levels was determined. The inhibitory effects of Ajwain essential oil and its main components on superoxide and nitric oxide production and NADH oxidase (NOX) and nitric oxide synthase (NOS) expression examined in lipopolysaccharide (LPS)-stimulated macrophages. Ajwain essential oil and thymol displayed a robust antioxidant activity while γ -terpinene and p -cymene have presented a few antioxidant activities. Ajwain essential oil at 10 μ g/mL strongly reduced NO but potentially increased reactive oxygen species (ROS) in LPS-stimulated macrophages. Ajwain essential oil significantly decreased inducible nitric oxide synthase (iNOS) mRNA expression but upregulated NOX mRNA in LPS-stimulated macrophages at 10 μ g/mL. Ajwain essential oil had strong synergism with LPS to enhance ROS, a condition that is suitable against tumors propagation. It was observed that the thymol at 10 μ g/mL significantly reduced NO, and ROS production and expression of iNOS mRNA and NOX mRNA in LPS-stimulated macrophages, however, γ -terpinene and p -cymene did not exhibited such activities. Thymol was found to be the most promising compound responsible for antioxidant activity of Ajwain essential oil, however, the strong synergism between all monoterpenes and monoterpenoids components of essential oils may also have contributed enough to the presentation of its biological action³⁹.

3.2.7.4 Anti-inflammatory activity:

A study investigated the anti-inflammatory effect of aqueous extract of Ajwain seed on type II collagen-induced arthritis (CIA) in Wistar rats. The study demonstrated a significant increase in paw thickness, arthritis score, and *COX2* and *iNOS* mRNA levels in CIA treated group compared to those of the normal group. Treatment with standard drug 'ibuprofen' and aqueous extract of Ajwain seed alone or in combination significantly reduced the studied variables. Ibuprofen-treated group showed higher rate of reduction in the paw thickness, arthritis score, and *iNOS* mRNA level than the Ajwain extract-treated group, however, treatment with Ajwain extract reduced *COX2* mRNA level more than ibuprofen. The study suggested that the aqueous extract of Ajwain can be used alone or in combination with ibuprofen to treat RA⁴⁰.

3.3 Kafoor (*Cinnamomum camphora*)

3.3.1 Overview:

Kafoor (camphor) is a well acclaimed Unani drug used for a number of pathological conditions since ages. Camphor is a waxy, white crystalline substance derived from the wood of camphor laurel (*Cinnamomum camphora* L.) tree through steam distillation. Its therapeutic values are clearly defined in classical Unani literature. It acts as resolvent, rubefacient, counter-irritant and has anti-inflammatory and mild analgesic action. It is one among the major ingredients of different liniments used for the treatment of neuralgia, fibrositis and other similar conditions. It is also used as expectorant and has irritant and carminative properties when ingested. It has also been used in many skin disorders. The drug has shown diverse biological and pharmacological activities^{41,42}.

3.3.2 Mizaj (Temperament): Barid Yabis (Cold Dry)¹⁷⁻¹⁹.

3.3.3 Afaal (Action):

Externally: *Dāfi'-i-Ta'affun* (Antiseptic), *Muħarrik* (Stimulant), *Muħammir* (Rubefacient), *Mubarriid*

(Refrigerant), *Mukhaddir* (Anaesthetic), *Musakkin-i-Alam* (Analgesic)¹⁷⁻¹⁹.

Internally: *Mu'arriq* (Diaphoretic), *Muqawwi-i-Mi'da* (Stomachic), *Mufarriḥ* (Exhilarant), *Muqawwi-i-Qalb* (Cardiac Tonic), *Dāfi'-i-Ḥummā* (Antipyretic), *Qābiḍ* (Astringent), *Dāfi'-i-Tashannuj* (Antispasmodic), *Munaffith-i-Balgham* (Expectorant), *Tiryāq-i-Hayḍa* (anti-cholera), *Kāsir-i-Riyāḥ* (Carminative)¹⁷⁻¹⁹.

3.3.4 Istemal (Therapeutic uses):

Externally- *Waja' al-Khāshira* (Lowbackache), *Waja' al-Mafāsil* (Polyarthrititis), *Dhāt al-Janb* (Pleurisy), *Dhāt al-Ri'a* (Pneumonia), *Waja' al-Asnān* (Toothache), *Waja' al-Udhun* (Otagia), *Sozish-i-Jild* (Burning Sensation of Skin), *Ramad* (conjunctivitis), *Qulā'* (Stomatitis), *Ru'āf* (Epistaxis), *Ṣudā'* (Headache)¹⁷⁻¹⁹.

Internally- *Nafkh al-Mi'da* (Flatulence), *Hayḍa* (Food poisoning), *Diq* (Tuberculosis), *Dāfi'-i-Aṭāsh* (Anti-Thirst), *Kathra al-Ihtilām* (Nocturnal emission), *Jarayān* (Spermatorrhoea), *Gazīdgi-i-'Aqrab* (Scorpion Sting), *Nazla* (Catarrh), *Zukām* (coryza), *Munawwim* (Sedative), *Ishāl* (Diarrhea), *Su'āl* (Cough), *Ḥumma* (Fever), *Ḍiq al-Nafas* (Bronchial Asthma), *'Usr al-Bawl* (Dysuria), *Ḥurqa al-Bawl* (Burning micturition), *'Usr al-Tamth* (Dysmenorrhoea), *Khafaqān* (Palpitation)¹⁷⁻¹⁹.

3.3.5 Miqdar-e-Khurak (Dose): Oral - 1-3Ratti (125mg - 375mg)^{17,18}.

3.3.6 Chemical constituents of *C. camphora*:

Fractionation of the camphor-free oil obtained from *C. camphora* provides an oil rich in safrole (80% or more), usually called Chinese sassafras oil. *C. camphora* is a well-known chemotype; on distillation, the wood from different groups of trees may yield camphor, linalool, safrole or cineole as the major chemical. The use of *C. camphora* as a source of leaf oil has expanded in recent years, and it is now an important source of natural linalool (which is still preferred over the synthetic form for some fragrant applications). Major oil constituents of *C. camphora* include camphor, linalool, camphene, safrole, borneol, dipentene, terpeneol and cineole^{41,42}.

3.3.7 Pharmacological activities:

Kafoor (*C. camphora*) has been reported to exhibit several biological activities such as antiviral⁴³, antimicrobial^{43,44}, insecticidal⁴⁵, antitussive^{46,47}, anti-inflammatory and antioxidant⁴⁸, anti-allergic⁴⁹, antimutagenic and anticancer⁴³ activities.

3.3.7.1 Antiviral, antimicrobial, insecticidal activities:

Camphor has been used as a fumigant during the outbreak of plague, also known as Black Death that spread through Europe in the 14th century, as well as during outbreaks of small pox and cholera. Essential oils of several species containing camphor have been reported to possess potent antiviral, antimicrobial and antitussive activities. Essential oil of *Salvia Fruticosa* 'The Greek sage' and its main components (1,8-cineole, α - β -thujone and camphor) exhibited highly promising virucidal activity against herpes simplex virus-1 (HSV-1). Essential oil of Lavender cotton (*Santolina insularis*), rich in camphor has been reported to deactivate HSV-1 and HSV-2 by inhibiting cell to cell transmission of both the viruses⁴³.

Essential oils of different species containing camphor exhibited marked inhibitory activity against various bacterial and fungal strains. A study demonstrated prominent antibacterial activity and quorum-sensing inhibitory activity

of *C. camphora* essential oil (EO) against *Chromobacterium violaceum*. It significantly inhibited the formation of biofilm and swarming movement and decreased the production of violacein and biofilm biomass in *C. violaceum*. In addition, it also downregulated the expression of the acyl-homoserine lactones (AHL) synthesis gene (*cviI*) and transcription regulator (*cviR*), and exhibited inhibitory effects on the expression of QS-regulated virulence genes⁴⁴. The essential oils extracted from the stem barks, leaves, and fruits of *C. camphora* (L.) are reported to possess strong fumigant toxicity against *Tribolium castaneum* and *Lasioderma serricorne* adults measured by seal-spaced fumigation⁴⁵.

3.3.7.2 Antitussive activity:

Menthol and other aromatic vapors have been widely used in the symptomatic treatment of upper respiratory tract infections. A study investigated the action of aromatic vapors (menthol, camphor and cineole) in different doses on the chemically induced cough reflex in conscious guinea-pigs. Menthol possessed the most effective antitussive effect and produced a significant 28 and 56% reduction in cough frequency. Camphor gave a significant 33% reduction, while cineole, at the concentrations used, showed no significant effect⁴⁶. A study examined antitussive effect of camphor and synthesized camphor lactam in citric acid-induced cough in guinea pig model. The result revealed significant reduction in cough response induced by citric acid and also increased latency to initial cough response at different concentrations. It was observed that the slight modification in chemical structure of camphor resulted in increased antitussive effect as it significantly increased cough latency and decreased cough frequency⁴⁷.

3.3.7.3 Anti-inflammatory, antioxidant activity:

A study investigated the inhibitory effects of different extract of *C. camphora* on various pro-inflammatory mediators to explore its potential anti-inflammatory mechanisms. Result revealed that the hexane and ethyl acetate (EtOAc) extracts significantly blocked the production of interleukin (IL)-1 beta, IL-6 and the tumor necrosis factor (TNF)-alpha from RAW264.7 cells stimulated by lipopolysaccharide (LPS) up to 20-70%. The hexane and EtOAc extracts (100 microg/ml) also inhibited nitric oxide (NO) production in LPS/interferon (IFN)-gamma-activated macrophages by 65%. The methanol extract and two other fractions prepared by solvent partition with n-butanol (BuOH) and EtOAc at 100 microg/ml exhibited strong suppressant effect on prostaglandin E(2) production in LPS/IFN-gamma-activated macrophages up to 70%. Hexane, BuOH and EtOAc extracts (100 microg/ml) also inhibited the functional activation of beta1-integrins (CD29) assessed by U937 homotypic aggregation up to 70-80%. Further, EtOAc and BuOH extracts were tested for their antioxidant effect by using 1,1-diphenyl-2-picrylhydrazyl (DPPH) and xanthine oxide (XO) assays and displayed strong anti-oxidative activity with IC(50) values of 14 and 15 microM, respectively. It was suggested that the possible mechanism involve in the anti-inflammatory actions of *C. camphora* may be the modulation of cytokine, NO and PGE(2) production and oxidative stress⁴⁸.

3.3.7.4 Anti-allergic activity:

Immunoglobulin E (IgE) is known to play an important role in allergic diseases. A study demonstrated that methanol extract of leaves of the camphor tree reduced the amount of IgE secreted by human myeloma U266 cells. Upon fractionation of methanol extract by extraction with organic solvents, it was observed that the ethyl acetate fraction had the highest activity. The fraction was further separated into

several subfractions by preparative TLC and dimethylmatairesinol was identified as the main component of one of the active subfractions. The study suggested *C. camphora* extract and its component including dimethylmatairesinol as a potent anti-allergic agent⁴⁹.

4. Plausible role of Arq Ajib in combating COVID-19

The use of medicinal plants complements an interesting approach for treating numerous diseases. It has gained a notable attention in recent decades as the medicinal plants contain a vast array of biologically active compounds which are proved to have promising effects in treating viral, bacterial and fungal infections and a number of other afflictions^{8,9}. In current situation, where definitive therapeutic candidates have not been developed and approved for managing COVID-19, herbal preparations are widely utilized in the community as a preventive measure. Besides repurposing of the existing antiviral drugs, scientists are exploring both the conventional and traditional systems to develop novel drugs for the prevention and cure of the current pandemic. It is hypothesized that the medicinal plants with antiviral, anti-inflammatory and immunomodulatory activities may have the potential to prevent and mitigate the prevailing situation caused by SARS-CoV-2⁵⁰.

Ingredients of Arq Ajib and their phytoconstituents are proved to exhibit wide-ranging biological activities including antiviral, Anti-inflammatory and immunomodulatory activities. These ingredients have exhibited potent inhibitory effects on herpes simplex type 1 & 2 (HSV-1 & 2), vesicular stomatitis (VSV), Japanese encephalitis virus (JEV) and hepatitis C virus as detailed in the above discussion. Essential oils of eucalyptus, tea tree and thyme have been reported to exhibit potent inhibitory effect on HSV-1 and reduced viral infectivity by >96%, whereas their monoterpene compounds including α -terpinene, γ -terpinene, α -pinene, *p*-cymene, terpinen-4-ol, α -terpineol, thymol and citral inhibited HSV-1 by about >80%. Both the essential oil and monoterpenes exhibited high inhibitory effects on HSV via direct inactivation of free virus particles and possessed moderate effect when added to the host cells at pre and post attachment stage of virus to the host cells. It is interesting to note that the mixtures of monoterpenes in essential oil exhibited a ten-fold higher selectivity index and lower toxicity compared to its isolated single monoterpenes⁵¹. It supports the concept of synergy in plant-based drugs which is attributed to diverse chemical compounds with similar effects present in the drug⁵².

Camphene 'a camphor derivative' exhibited a high level *in-vitro* and *in-vivo* inhibitory activity against influenza A and B viruses by inhibiting viral hemagglutinin (HA) 'an antigenic glycoprotein, responsible for the viral entry to host cells' and viral replication on early stages⁵³. Menthol has been reported to have direct virucidal effects on herpes simplex virus 1 and 2 via suppression of viral entry to host or interference with the viral envelope. It has also exhibited antiviral effects against Cocksackievirus B, by stimulating transient receptor potential cation channel subfamily M member 8 (TRPM8) and lowering the levels of mitochondrial fission during infection⁵⁴. Quercetin 'a flavonoid compound' widely distributed in vegetables, fruits and various medicinal plants including *Mentha arvensis*, presents a compelling approach in treating various diseases and improving human health and wellbeing⁵⁵. It is a potent inhibitor of a wide spectrum of Influenza A virus strains (H1N1, H3N2 and H5N1). It exhibits its antiviral effects by interacting with viral HA, thus restricting the viral entry to

the host cells. Quercetin is considered to be safe and effective antiviral compound as it targets influenza viral particles and has no untoward effects on the host cell⁵⁶. Recently, quercetin from *Aloe vera* exhibited a high binding affinity with RNA-dependent RNA-polymerase of SARS-CoV-2⁵⁷, which suggests quercetin as a potential inhibitor of SARS-CoV-2.

SARS-CoV-2 infection first affects the lung epithelial cells leading to subsequent inflammatory processes and release of various pro-inflammatory mediators. Recent reports have shown a highly elevated level of pro-inflammatory cytokines including interleukin-2 (IL-2), IL-6, IL-7, IL-10 and tumor necrosis factor alpha (TNF α) in severely ill COVID-19 cases. Drugs having anti-inflammatory and immunomodulatory activities with the ability to inhibit or modulate these pro-inflammatory cytokines may prove as a potent preventive measure and effective therapeutic candidate for COVID-19^{50,58}. Different extracts and essential oil (EO) of *C. camphora* with camphor as major compound have exhibited potent inhibitory effects on various inflammatory cytokines including IL-6, IL-18, IL-1 β and TNF- α ^{48,59}. Quercetin has been reported to exhibit strong anti-inflammatory effects on different cell types and also has modulatory and regulatory effects on inflammation and immunity. It has potent inhibitory effects on the production of IL-1 α , IL-4, IL-6, IL-8, and TNF- α . It limits inflammation by inhibiting cyclooxygenase (COX) and lipoxygenase (LOX) enzymes which are known to produce inflammation⁵⁵. There are two types of immune responses that occur during an infection; the Th-1 type response which is down-regulated and Th-2 type immune response which is up regulated⁶⁰. Quercetin exerts its immunomodulatory effects via induction of Th-1 derived interferon- γ (IFN- γ), and down-regulation of Th-2 derived IL-4⁵⁵. A herbal commercial drug containing menthol and menthone (major compounds of *Mentha* species) have been reported for immunomodulatory and antiparasitic activities in Balb/c mice SPF (Specific Pathogens Free) infected with *Schistosoma mansoni* and exerted a down-regulating effects on IL-4 and IL-10⁶⁰.

The afore cited evidences support the hypothesis that Arq Ajib may have direct or indirect effects on SARS-CoV-2, as the ingredients of Arq Ajib and their phytocompounds exhibit potent antiviral, anti-inflammatory and immunomodulatory activities. The combined effects of phytocompounds present in the formulation may yield a synergistic effect with potentially enhanced biological activities. Moreover, the formulation may also prove beneficial in providing symptomatic relief in patients affected with COVID-19, as the formulation ingredients and their phytocompounds have been reported to exhibit anti-allergic, antitussive and bronchodilatory activities^{46,47,49,61-63}. Hence, it is rational to state that the formulation may prove effective in augmenting the immune status, alleviating inflammatory responses and suppressing the virulence of SARS-CoV-2.

5. Conclusion

Arq Ajib is a well acknowledged Unani formulation offering an interesting approach in alleviating numerous diseases. The formulation ingredients and their phytocompounds have shown potent inhibitory effects against a number of viruses. Further, they exhibit significant anti-inflammatory, immunomodulatory, antitussive, bronchodilatory and various other biological activities. In the current situation of COVID-19, when the treatment options are limited and exhaustive search for potent therapeutic candidates is in progress, Arq Ajib may play a decisive role in augmenting the immune status of

individuals, protecting them from infection and alleviating the symptoms of infected individuals. Based on the above discussion, it may be concluded that the formulation may prove potential for the development of novel drug candidate for COVID-19. Thus, a detailed evaluation of toxicity and efficacy profile of the formulation is highly essential to ascertain the exact effects of the formulation.

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