Prophylactic and Therapeutic use of *Tiryaq Wabayi* in COVID-19 - A Review

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***Abstract*: Corona Virus Disease 2019 is an acute infectious disease caused by a novel corona virus; initially named 2019-nCov, later named SARS-CoV-2, which emerged in Wuhan, China and spread worldwide in very short time period. Clinically, it is characterized by asymptomatic, mild; symptoms of upper respiratory infection or digestive system, moderate; pneumonia, severe; pneumonia with hypoxemia, and critical; severe acute respiratory distress syndrome (ARDS). 49 percent mortality rate was recorded in ARDS affected COVID-19 patients. The definite treatment and specific vaccine for COVID-19 are under investigation yet, the only known measure is prevention includes frequent hand washing, wear face mask, and social distancing etc. *Tiryaq Wabayi* is a Unani pahrmacopeal poly herbal formulation. Although, since ancient times it is recommended as prophylaxis during epidemics by eminent Unani scholars like Galen and Avicenna, but it may be more potential to combat epidemics including COVID-19. This article was aimed to review *Tiryaq-e-Wabayi* with scientific validation on the basis of their ingredients associated with *Mizaj-e-Advia* (temperament of drugs), phytochemical constituents, and pharmacological properties.**

***Keywords*: *Tiryaq Wabayi*, Unani medicine, Epidemic, Immune-stimulant Activity, Anti-viral Activity**

INTRODUCTION

COVID-19 (corona virus disease 2019) is a major health hazards caused by a novel corona virus (initially named 2019-nCov), was discovered to be responsible for the outbreak of unusual series of acute atypical respiratory disease occurred in Wuhan, Hubei province of central China [1]. 2019-nCov was later named SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) due to its high structural homology to the SARS-CoV, which caused the outbreak of SARS in 2003 [2]. It spread rapidly worldwide and became a pandemic as declared by the World Health Organization (WHO) on 11 March 2020 [3]. As per WHO corona virus disease (COVID-19) dashboard, globally, 438,633 new cases and 42,512,186 confirmed cases of COVID-19, including 1,147,301 deaths, while across India, 50,129 new cases, 7,864,811 confirmed cases of COVID-19 with 118,534 deaths, have been reported, up to 2:09 pm CEST, 25 October 2020 [4]. COVID-19 cases were mostly observed among elderly people and children (< 18 years) [5]. Although the Chinese series showed equal number of cases between males and females, the data suggested that more men than women suffered from severe disease and died [6]. Adverse outcomes of COVID-19 were associated with comorbidities, including hypertension, cardiovascular disease, and lung disease. These conditions are more prevalent in men and linked to smoking and drinking alcohol [7]. SARS-CoV-2 is an enveloped, single stranded ribonucleic acid betacoronavirus. This highly contagious pathogen is transmitted by respiratory droplets and aerosols, direct contact of mucous membranes and probably the fecal–oral route [8]. Clinical features of COVID-19 are classified into Asymptomatic; COVID nucleic acid test positive, without any clinical symptoms and signs and the chest imaging is normal, Mild; Symptoms of acute upper respiratory tract infection (fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing) or digestive symptoms (nausea, vomiting, abdominal pain, diarrhea), Moderate; Pneumonia (frequent fever, cough) with no obvious hypoxemia, chest CT with lesions, Severe; Pneumonia with hypoxemia (SpO2 < 92%), and Critical; Acute respiratory distress syndrome (ARDS), may have shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction and acute kidney injury [9]. The mortality rate of COVID-19 increases by up to 49% in patients who develop ARDS [10]. Pathologically, the SARS-CoV-2 attaches to the surface of the epithelial membrane of the oral cavity, the mucosal membranes of the conjunctiva or the otic canal [11]. The spike (S) glyprotein of SARS-CoV2 is cleaved by a cellular enzyme named furin at the S1/S2 site [12]. The activated S protein is primed by the transmembrane protease serine 2 (TMPRSS2) and cathepsin L. and finally attaches to the host cell via receptor binding domains of the Angiotensin Converting Enzyme 2 (ACE2), which is most abundant in type II alveolar cells [13]. After a SARS-CoV-2 attaches to a target cell, the virion releases RNA into the cell, initiating replication of the virus which further disseminates to infect more cells. SARS-CoV-2 produces several virulence factors that promote shedding of new virions from host cells and inhibit immune response [14]. Alveolar macrophages detect cell injury via damaged associated molecular patterns from alveolar cells [14]. They also response to released cytokines from damaged alveolar cells, and secret inflammatory cytokines such as interleukins (IL2, IL-6, IL-7, IL-10), GCSF, IP-10, MCP-1, MIP-1A and TNF-α and other chemokin [11]. Lymphocyte count, lymphocytic T Cells (CD4+ and CD8+) and natural killer (NK) cells significantly reduced in patients with severe COVID-19 [15,16]. Histologically, COVID-19 shows diffuse alveolar damage corresponding to the phase of the disease (acute to fibrotic), divided into 3 main injury patterns: epithelial, vascular and fibrotic [14].

To date, there are no specific vaccines or medicines for COVID-19. Treatments are under investigation. Several drugs including lopinavir-ritonavir, remdesivir, Favipiravir, hydroxychloroquine, Dexamethasone and azithromycin have been tested in clinical trials, but none of them have been proven to be a definite therapy yet [17]. Many countries have implemented social distancing and

lockdown to take the edge off further spread of the virus. Here we will review an ancient herbal Unani formulation named Tiryaq-e-Wabayi, with scientific validation on the basis of their ingredients associated with Mizaj-e-Advia (temperament of drugs), phytochemical constituents and pharmacological properties. Although, it is claimed as prophylactic during epidemics, it may be more potential therapeutic to combat COVID-19.

DESCRIPTION OF *TIRYAQ WABAYI*

Literally the meaning of *Tiryaq Wabayi* is the antidote for epidemics, because it is derived from two Arabic words '*Tiryaq'* means antidote and *'Wabayi'* means epidemic diseases [18]. Technically it is a pharmacopeal Unani medicine, specially formulated for the protection from epidemic diseases [19]. Since ancient times, *Tiryaq Wabayi* has been used as prophylaxis during epidemics to protect from cholera, plague, chickenpox and other epidemic diseases by Unani physicians and researchers. According to Galen (129-200AD), whose healthy individuals have used *Tiryaq wabai*, during epidemics; those have saved from epidemic infections. *Tiryaq wabai* contains three ingredients Sibr (*Aloe vera Linn*. Burm. F.), Kurkum (*Crocus sativus* Linn.) and Mur (*Commiphora myrrha* (Nees) Engl.) as principal herbs [19].

According to temperamentology, *Sibr* (Aloe) and *Mur* (Myrrh) have *Haar wa Yabis Ba'darja-e-Dom* (Hot 2° & Dry 2°), and *Kurkum* (Saffron) has *Haar Ba'darja-e-Dom wa Yabis Ba'darja-e-Awwal* (Hot 2° & Dry 1°) temperament (*Mizaj*) in nature [20].

Pharmacologically, *Sibr* (Aloe) possess *Mulayyin* (Laxative), *Mus'hil* (Purgative), *Muqawwi-e-Me'ada* (gastro-protective / stomach tonic), *Muqawwi-e-Kabid* (hepato-protective / liver tonic), *Mudirr-e-Baul wa Haiz* (Diuretic & Emmenagogue), *Mohallil-e-Waram* (Anti-inflammatory) actions [20,21,22]. It is indicated in *Qabz* (constipation), *Su'aal* (cough), *Zukam* (common cold / coryza), *Fudhlat-e-Dimagh* (morbid maters of brain), *Zof-e-Me'ada* (weakness of stomach), *Zof-e-Kabid* (weakness of liver), *Ihtibaas-e-Baul* (Retention of Urine), *Ihtibaas-e-Tamas* (Amenorrhoea) and *Waja-ul-Mafasil* (Arthritis) [20,21]. *Kurkum* own *Muqawwi-e-Qalb* (cardio-protective / cardio-tonic), *Muqawwi-e-Dimagh* (brain tonic), *Muqawwi-e-Aasab* (Neuro-protective / Neuro tonic), *Muqawwi-e-Kabid* (hepato-protective / liver tonic), *Dafey-e-Tashannuj* (Antispasmodic), *Muhallil-e-Auram* (anti-inflammatory), *Dafey-e-Ta'affun* (antiseptic), *Jali* (detergent), properties. It is used in *Zof-e-Qalb* (weakness of heart), *Zof-e-Dimagh* (weakness of brain), *Zof-e-Aasab* (weakness of nerves), *Waja-ul-Aasab* (neuralgia), *Zof-e-Baah* (sexual debility), *Zof-e-Basar* (weakness of eyesight), *Su'aal-e-Tashannuji* (spasmodic cough), *Suda'a*, (headache) *Waja-ul-Mafasil* (arthritis), and *Nazla Medi wa Ma'avi* (stomach & intestinal cold) [20,21]. *Mur* has proposed *Dafey-e-Ta'affun* (antiseptic), *Munaffis wa Mukhrij-e-Balgham* (mucolytic & expectorant), *Muharrik* (stimulant), *Mo'addil* (altering), *Mudirr-e-Baul wa Haiz* (diuretic & Emmenagogue), *Kasir-e-Riyah* (carminative), *Muqawwi-e-Me'ada* (gastro-protective / stomach tonic), *Muhallil* (altering), *Mufatteh* (deobstruent) and *Musakh'khin* (calorific). It is recommended in *Qula'a* (stomatitis), *Su'aal-e-Sho'abi* (chronic Bronchitis), *Ittisa'a-e-Sho'abi* (bronchiectasis), *Su-e-Hazam* (dyspepsia), *Sozish-e-Masana* (cystitis), *Ihtibaas-e-Tamas* (Amenorrhoea), *Waj-ul-Mafasil* (arthritis), *Niqras* (gout), *Irq-un-nisa* (sciatica) and *Auram-e-Balghami* (phlegmatic inflammations) [20,21].

The dosage of *Sibr* is 500 mg, to be administered in the form of *Safoof* (Powder) alone or mixed with honey orally. *Kurkum* (saffron) to be taken in the dose of 1-2gm within the formulation or 3-5 threads alone, after dissolving it into *Arq-e-Gulab* (Rose Distillate), or any appropriate *Arq* (Distillate), orally as well as topically. 2 gm of *Mur* (myrrh) to be administered in the form of *Safoof* (Powder) alone or mixed with honey orally [20,21].

Tiryaq Wabayi (TW) is prepared by mixing of micro fine powder of each drug in equal quantity of 12 gram with 120 milliliters of *Arq-e-Gulab* (Rose Distillate) to make pills as the size of Black Chickpea (*Nakhood*) and saved it in air tight container by enveloping the *Warq-e-Nuqra* (Silver Foil) over it [18]. As dosage, one pill to be used on empty stomach at morning or bed time with 120 milliliters of *Arq-e-Gaozaban* or *Arq-e-Badyan*, thrice weekly, during epidemics or pandemics as prophylaxis [19]. As therapeutic, one pill twice daily on empty stomach with 120 milliliters of *Arq-e-Gaozaban* or *Arq-e-Badyan* may be effective in patients with epidemics.

PHYTOCHEMICAL CONSTITUENTS OF PRINCIPAL HERBS

The Aloe vera leaf gel contains about 98% water and the total solid content is 0.66% and soluble solids are 0.56% with some seasonal fluctuation. On dry matter basis aloe gel consists of polysaccharides (53%), sugars (17%), minerals (16%), proteins (7%), lipids (5%) and phenolic compounds (2%). Aloe vera contains 200 potentially active constituents: vitamins; Vitamins A, C and E, thiamine, niacin, riboflavin, vitamin B12, choline and folic acid, minerals; Sodium, potassium, calcium, magnesium, selenium, manganese, copper, zinc, chromium and iron, enzymes; Amylases, lipases, alkaline phophatases, cellulases, catalases and peroxidases, polysaccharides; glucomannose / polymannose, alprogen, C-glucosyl chromone, phenolic compounds; anthraquinones and their derivative Aloin and emodin, Barbaloin, aloeemodin-9-anthrone, lsobarbaloin, Anthrone-C-glycosides, chromones., and organic acids; Amino acids and Salicylic acid, Sterols; cholesterol, Campesterol, βSitosterol, Lupeol, Hormones: Auxins , gibberellins and other like Saponins and Lignin [23].

Characteristic components of saffron are crocin -(responsible for the color), picrocrocin- (up to 4%, responsible for the bitter taste), and safranal- (responsible for odor and aroma). Saffron contains more than 150 volatile and aroma-yielding compounds; consisting of more than 34 components; mainly terpenes, terpene alcohols, and their esters, and non-volatile active components; many are carotenoids including zeaxanthin, lycopene, and various α- and β-carotenes. It also has lipids, starch, phenolic and flavonoid compounds [24,25].

Twelve components: crocin-1, crocin-2, crocin-3, picrocroein, acid form of picrocrocin, HTCC-diglycosil-kaempferol, trans-crocin-4, trans-crocin-2, trans-crocin-3, safranal, crocetin and cis-crocin-3 were isolated from saffron stigmas.[26] New monoterpenoid compounds, crocusatins F, G, H, I, J, K, L together with a new naturally occurring acid, (3S),4-dihydroxybutyric acid, were isolated from aqueous and ethanolic extracts of the stigmas of Crocus sativus (saffron).[27]

The main active constituents of Commiphora myrrha include volatile oil; cuminic aldehyde, eugenol, metacresol, pinene, limonene, diterpenes, and sesquiterpenes, resin (up to 40%); ether soluble portion: α, β and γ commiphoric acids and esters of another resin

acid and two phenolic resins, gums (up to 60%); associated with enzyme oxidase, polysaccharides, and bitter principle. Other constituents include Flavonoids, Alkaloids, Tannins, Glycosides, Steroids, Saponins, Terpenoids (sesquiterpenes, furanosesquiterpenoids), Carbohydrates, 7 Organic compounds; limonene, curzerene, germacrineB, isocericenine, myrcenol, beta selinene, spathulenol, and Minerals; Magnesium, Potassium, Sodium, Manganese, Zinc, Calcium and Phosphorus, Aluminum, Scandium, Chlorine, Arsenic, mercury, lead etc. [28]

PHARMACOLOGICAL STUDIES OF PRINCIPAL HERBS

Antiviral Activity

Several ingredients in Aloe gel are antiviral agent. Lectins, fractions of Aloe vera gel, directly inhibited the cytomegalo virus proliferation in cell culture, perhaps by interfering with protein synthesis [29]. A purified sample of Aloe emodin was effective against infectivity of herpes simplex virus type I and type II and it was capable of inactivating all of the viruses, including varicella zoster virus, influenza virus, and pseudo-rabies virus [23]. In a study of a crude hot glycerin extract of Aloe Vera gel against HSV-2 replication in Vero cell line, the extract shows antiviral activity against HSV-2 not only before attachment and entry of the virus into the Vero cells, but also in post attachment stages of virus replication [30]. Various reports have suggested that *Aloe vera* gel has antiviral activity that prevent virus adsorption, attachment, or entry to the host cell. An in vitro study has shown that crude extract of *Aloe vera* gel has antiviral activity against herpes simplex virus type 2 strains [31]. Anthraquinone derivatives, such as Aloe-emodin, emodin, and chrysophanol, reportedly exhibit antiviral activity wherein their inhibitory mechanism and effect against influenza A virus with reducing virus-induced cytopathic effect and inhibiting replication of influenza A [32]. Preliminary trials have suggested that A. vera consumption may be of help to HIV-infected individuals as it improves the immune system by increasing the CD4 count [33].

Crocin and picrocrocin; a major chemical component of saffron, indicated significant anti-HSV-1 and also anti-HIV-1 activities. It is studied that Crocin inhibited the HSV replication at before and after entry of virions into Vero cells. Indeed, crocin carotenoid suppressed HSV penetration in the target cells as well as disturbed virus replication after entry into the cells. Picrocrocin was also effective for inhibiting virus entry and also its replication [34].

In a study to investigate antibacterial, antifungal and antiviral activities of Commiphora myrrha and commiphora Africana essential oils, the pure myrrha oil shows high antiviral activity while the ethanol oil shows moderate antiviral activity [35].

Immuno-stimulatory & Immuno-modulatory Activity

Itrat *et al* studied to evaluate the immune (particularly cell mediated immunity) stimulating effect of *Tiryaq wabayi* in elderly. The result showed statistically significant increase in TLC ($P < 0.001$), lymphocyte percentage ($P < 0.001$), ALC ($P < 0.001$), CD4 count ($P < 0.001$) in comparison to control group, but increase in CD8 count was not statistically significant. No major adverse effect was observed throughout the study [36].

Aloe vera has been universally demonstrated to result in marked increase in phagocytic and proliferative activity of the reticuloendothelial system [37]. Jyotsana *et al* showed a significant increase in total white blood cell and macrophage count upon administration of Aloe vera extract [38]. The immunomodulatory activities of the polysaccharides of Aloe vera have been attributed to activation of macrophage cells to generate nitric oxide, secrete cytokines (e.g. tumour necrosis factor-alpha or TNF-α, interleukin-1 or IL-1, interleukin-6 or IL-6 and interferon-γ or INF-γ) and present cell surface markers [37]. Some immunomodulatory effects were shown to be associated with glycoproteins, namely lectins, found in Aloe gel [37]. *Aloe vera* extract produces stimulatory effect on the humoral and cell mediated immune response. It is showed that Pyrogallol-induced suppression of humoral as well as cell mediated immune response was significantly attenuated by daily oral treatment with *Aloe vera* extract, it is studied that *Aloe vera* extract at the dose of 100 mg/kg, was found to suppress delayed type hypersensitivity reaction induced by Sheep Red Blood Cells (SRBCs) in mice. It reveals effect of drug on T-lymphocytes and other cell types required for expression of humoral response to SRBCs, as evidenced by marked increase in haemagglutination titers in mice was also observed [39]. In another study regarding The effect of Aloe vera extract on humoral and cellular immune response in rabbit, A. vera treatment produced a significant increase in the blood CD4+ after 14 and 21 days, respectively ($P<0.05$) and CD8+ lymphocytes after 7, 14 and 21 days ($P<0.05$), while serum IgM and Serum IgG concentrations increased significantly on days 7, 14 and 21 ($P<0.05$), when compared with the control group [40].

The immune-modulatory activity of *Crocus sativus* was studied on Th1 and Th2 limbs of the immune system. Oral administration of alcoholic extract of *Crocus sativus* (ACS) at graded dose levels (1.56-50 mg/kg, po), potentiated the Th2 response of humoral immunity, causing significant increases in agglutinating antibody titre in mice at a dose of 6.25 mg/kg and an elevation of CD19(+) B cells and IL-4 cytokine, a signature cytokine of Th2 pathway. Appreciable elevation in levels of IgG-1 and IgM antibodies of the primary and secondary immune response was also observed. However, ACS showed no appreciable expression of the Th1 cytokines IL-2 (growth factor for CD4(+) T cells) and IFN-γ (signature cytokine of Th1 response). A significant modulation of immune reactivity was observed in all the animal models [41]. The effects of three concentrations of macerated extract of Crocus sativus, dexamethasone, and saline were evaluated on cell viability and production of cytokines, including interleukin (IL)-4, IL-10, and interferon –γ (IFN-γ) were evaluated. In cells stimulated with phytohemagglutinin (PHA), different concentrations of the extract significantly inhibited cell viability of lymphocytes ($P<.001$ for all concentrations). High concentrations of the extract (500 µg/mL) also inhibited secretion of IFN-γ in stimulated cells and IL-10 secretion in both stimulated and non stimulated cells ($p<0.05$ for all cases). The effects of high and low concentrations of the extract (500 and 50 µg/ml, respectively) on IL-4 secretion were lower than that of dexamethasone ($P<.05$ to $P<.001$). The extract showed a stimulatory effect on IFN-γ and IL-4 secretion in non stimulated cells. The ratios of IFN-γ to IL-4 in the presence of all concentrations of saffron on stimulated cells were significantly higher than for the control group ($P<.05$ to $P<.01$) [42].

Myrrh and its bioactive molecules have been shown to have potential effects on the functions of white blood cells and immuno-modulatory activities. However, few studies have reported these effects [43]. Microscopic examination of blood smear from myrrh-treated rats with skin injury, showed an elevated count of middle-sized lymphocytes and neutrophils that were characterized with well-defined nuclear lobules and rich-granules cytoplasm. Furthermore, the microscopic examinations of the spleen and lymph nodes of myrrh treated rats with skin injury, showed an increased thickness of lymphatic sheath around the arterioles in the white pulp that was associated with high density of the medium-sized lymphocytes in the secondary lymphoid follicles in the lymph nodes with engorged sinusoids [43].

Anti-oxidant Activity

Aloe contains substantial amounts of antioxidants including a-tocopherol (vitamin E), carotenoids, ascorbic acid (vitamin C), flavonoids, and tannins [44]. Administration of ethanolic extract of Aloe gel on tissue antioxidants led to reduction in blood glucose level in diabetic rats, which helps to prevent excessive formation of free radicals through various biochemical pathways and also reduces the potential glycation of the enzymes [45,46,47]. In vitro and in vivo antioxidant potentials of a polysaccharide isolated from Aloe gel were investigated. It is suggested that *Aloe vera* polysaccharides exhibited a protective effect against 2, 20 –azobis (2- amidinopropane) dihydrochloride-induced oxidative stress and cell death in kidney epithelial cells (Vero cells) as well as in an in vivo zebra fish model [48].

The antioxidant activity of saffron is mainly attributed to carotenoid and flavonoid compounds, notably glycosides of crocin and kaempferol. Protocatechuic acid, kaempferol, and kaempferol 7-O-beta-d-glucopyranoside isolated from Crocus sativus were more effective in scavenging alpha, alpha-diphenyl-beta-picrylhydrazyl (DPPH) radicals than alphatocopherol [49]. The antioxidant activity of saffron stigmas was evaluated after extraction with different solvents. It is showed that the free radical scavenging and ferric reducing power activities were higher for the methanolic extract of saffron stigma at a concentration of 300 µg/ml, with values of 68.2% and 78.9%, respectively, as compared to the corresponding boiling water and ethanolic extracts, but the activities were lower than those of antioxidant standards such as BHT and α-tocopherol [50]. The effect of aqueous saffron extract (*Crocus sativus*) and its active constituent, crocin on oxidative stress was evaluated following renal ischemia-reperfusion injury (IRI) in rats. it is resulted that the aqueous extract also reduced lipid per oxidation products (from 85.8 ± 5.4 to 15.9 ± 2.6 nmol/g tissue, $p<0.001$; 80 mg/kg) and increased antioxidant power (from 2.98 ± 0.11 to 5.97 ± 0.56 micromol/g tissue, $p<0.001$; 80 mg/kg) in ischemia-reperfusion injured rat kidneys [27].

The methanolic extract of saffron and its components such as safranal, crocin etc. were reported to possess radical scavenging activity, suggesting its use as a cosmetic to treat age related disorders, as a food supplement etc. [51,52]. Crocin was found to possess greater antioxidant capacity than alpha-tocopherol in neuronally differentiated pheochromocytoma cells deprived of glucose, whose absence caused peroxidationof t heir cell membrane lipids and decreased intercellular superoxide dismutase activity. These effects were reversed by crocin, promising it as a unique and potent antioxidant that combats oxidative stress in neurons [53]. Further it was also said to increase the levels of various enzymes such as the glutathione reductase, glutathione-S-transferase and also maintains the functional levels of other antioxidants suggesting it as a potential antioxidant [51]. Myrrh ethanol extract with high phenolic and flavonoid contents and low IC50 showed higher antioxidant activity [54].

Anti-inflammatory Activity

Aloe vera directly inhibits the cyclooxygenase pathway and reduces prostaglandin E2 production, which plays an important role in inflammation [55]. A study suggests that Aloe as a whole has anthraquinones (aloin) and chromone (aloesin) components, and Aloe gel has pharmacological activity to alleviate inflammatory responses in inflammatory bowel disease [56]. A recent clinical study evaluated the therapeutic effect of Aloe gel wherein 2% oral gel is not only effective in decreasing the pain score and wound size in recurrent aphthous stomatitis patients but also decreasing the aphthous wound healing period [57].

Saffron has been suggested as therapeutic herbal agents to avoid damages induced by neutrophil cells as the central cells in acute inflammatory processes. Within inflammatory processes, it is observed an increase in the number, mobility, lifespan, tissue influx ability and phagocytic activity of neutrophil cells [58,59]. Tamaddonfard *et al.* investigated the anti-inflammatory activity of crocins (25, 50, and 100 mg/kg) and safranal (0.5, 1, and 2 mg/kg) by decreasing the number of neutrophils count, infiltration of neutrophils in paw tissues and inflammatory pain responses in an animal model study. [60] Accordingly, safranal (0.1, 0.5 and 1 ml/kg IP for 3 weeks) and saffron (100 mg daily for 6 weeks) did not have any significant effects on the count of WBC. Although, crocin (25, 50, and 100 mg/kg) and safranal (0.5, 1, and 2 mg/kg) could decrease immune cells in paw tissues of animals [60].

The aqueous and ethanolic extracts of saffron stigmas and petals were reported to posses antinociceptive and anti-inflammatory activity both of, acute and chronic as evidenced by effects in writhing test, xylene induced ear oedema in mice and formalin-induced edema in the rat paw [51]. The preventive effect of the aqueous extract of saffron was studied against diazinon (DZN) -induced rise of several specific inflammation, oxidative stress and neuronal damage in rats. Vitamin E (200 IU/kg) and the aqueous extract of saffron at doses 50, 100 and 200 mg/kg were injected intraperitoneally three times per week alone or with DZN (20 mg/kg/day, orally) for 4 weeks. Red blood cell (RBC) cholinesterase activity was inhibited by DZN and this effect was not affected by vitamin E or saffron plus DZN. The levels of serum tumor necrosis factor-α (inflammation marker), direct 8-iso-prostaglandin F2α (oxidative stress marker) and soluble protein-100 β (S100β, neuronal damage marker) were increased significantly by DZN. The saffron extract inhibited the effect of DZN on these biomarkers levels. However, vitamin E was able to only reduce 8- iso-prostaglandin F2α and S100β levels [50,61]. Saffron stigma and petal extracts exhibited antinociceptive effects in chemically induced pain test as well as acute and/or chronic anti-inflammatory activity, and these effects might be due to the presence of flavonoids, tannins, anthocyanins, alkaloids, and saponins [24,62].

The anti-inflammatory effects of guggulsterone (GS), which is a chemical constituent, found at high levels in Commiphora myrrha, were assessed. GS has been shown to attenuate the development of cerulein-induced acute pancreatitis in mice, by inhibiting the infiltration of neutrophils in the pancreas and reducing the levels of inflammatory mediators such as tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β) [63,64]. Researchers indicated that the extract of Myrrh inhibits the production of CXCL13 and TNFα by suppressing chemokine gene expression in activated human macrophages [65]. Myrrh inhibited LPS-induced productions of inflammatory mediators in septic mice by decreasing NO, PGE2, IL-1β, IL-6, and TNF-α [66]. Myrrh attenuates ammonia-induced inflammation in hyperammonemic rats by suppressing TNF-α [67]. Myrrh inhibits paw edema in mice induced by formalin by decreasing PGE2 [68]. Myrrh attenuates the upregulation of inflammatory biomarkers in an ulcerative colitis rat model by suppressing TNF-α , IL-1β, IL-6, PGE2, and by increasing NO, and IL-10 [69].

Hepato-protective Activity

Isolated phytosterols, namely lophenol and cycloartanol, have the ability to induce the downregulation of fatty acid synthesis and a tendency for upregulation of fatty acid oxidation in the liver, which favors the reduction in intra-abdominal fat and improvement of hyperlipidemia. Further, addition to sterol regulatory element-binding transcription factor 1/peroxisome proliferator activated receptor (PPAR)-a ratio was decreased; metabolic syndrome-related disorders were improved and liver steatosis in Aloe-sterol-treated Zucker diabetic fatty rats.[70] Saito et al showed that *Aloe vera* gel extract prevents ethanol-induced fatty liver by suppressing mRNA expression of lipogenic genes in the liver [71].

Crocin possessed hepato-protective effects against aflatoxin B1 hapatotoxicity via the reduction of hepatic (AST, ALT, ALP and γ-GGT) and via its antioxidant activity in rats [50,72]. The effect of aqueous extract of Crocus sativus stigmas (CSE) and crocin (trans-crocin 4) was examined on methyl methane sulfonate (MMS)-induced DNA damage in multiple mice organs. A significant increase in the tail DNA was seen in nuclei of different organs of MMS-treated mice. In control groups, no significant difference was found in the tail DNA between CSE- or crocin-pretreated and saline-pretreated mice. The MMS-induced DNA damage in CSE-pretreated mice (80 mg/kg) was decreased between 2.67-fold (kidney) and 4.48-fold (lung) compared to those of MMS-treated animals alone (p0.05 as compared with MMS treated group. Crocin also significantly decreased DNA damage (between 4.69-fold for liver and 6.55-fold for spleen, 400 mg/Kg) [73].

To investigate the hepatoprotective activity of *Commiphora myrrha* ethanol extract against d-galactosamine/lipopolysaccharide (d-GalN/LPS)-induced acute hepatic injury in rats, it is suggested that *Commiphora myrrha* considerably reduces the oxidative stress of d-GalN/LPS-induced hepatic injury via multiple pathways including a down regulation of inflammatory mediators and cytokines. Such a property might be sufficient to combat cellular damage caused by various conditions that resemble fulminant hepatitis and could be of a potential clinical application [74].

Anti-microbial Activity

Aloe vera has been described as an antibacterial agent. The Aloe protein of 14 kDa from the Aloe leaf gel was isolated and the purified Aloe protein exhibited potent antifungal activity against Candida paraprilosis, Candida krusei, and Candida albicans [75]. Aloe has anthraquinones as an active compound, which is structural analogue of tetracycline. The anthraquinones acts like tetracycline that inhibits bacterial protein synthesis by blocking the ribosomal A site (where the aminoacylated tRNA enters). Therefore, the bacteria cannot grow in the media containing A. vera extract. Pandey and Mishra established the susceptibility of Gram-positive and Gramnegative bacteria to an extract of the inner gel of *Aloe vera* [76]. Polysaccharides of *Aloe vera* gel have been attributed direct bacterial activity through the stimulation of phagocytic leucocytes to destroy bacteria [77]. *Aloe vera* contains pyrocatechol a hydroxylated phenol, known to have toxic effect on microorganisms [78]. A recent study demonstrated that the Aloe inner gel expresses antibacterial properties against both susceptible and resistant Helicobacter pylori strains and impact on the antimicrobial resistance phenomenon of H. pylori, proposing the *Aloe vera* inner gel as a novel effective natural agent for combination with antibiotics for the treatment of H. pylori gastric infection [79].

The extracts of *Crocus sativus* and *Crocus cassia* exhibit promising antibacterial activities against clinical isolates of S. aureus, E. coli, P. aeruginosa, Enterococcus, S. pyogenes and K. pneumoniae. Based on the results of the MIC assay, the methanolic extract of *Crocus cassia* was more effective than the methonalic extract of *Crocus sativus* against the tested pathogens [80].

The hydroalcoholic extract, and ethanolic and chloroformic fractions of *Crocus sativus* had antimicrobial effects, despite its petroleum etheric fraction and distillate. The best effect of hydroalcoholic extract was on Strep. sanguinis with the MIC and MBC of 31.25 mg/ml both. Maximum inhibitory effect of ethanol fraction was on Strep. sanguinis with MIC and MBC of 7.81 and 15.62 mg/ml respectively. Chloroform fraction presented most effect on Strep. sanguinis presenting MIC and MBC of 7.8 mg/ml. The hydroalcoholic extract of saffron in concentrations of 500 mg/ml and 1000 mg/ml showed inhibitory effects on the growth and proliferation of streptococcus mutans, streptococcus sanguinis, and streptococcus sobrinus in cup-plate method [81].

A study to evaluate the antimicrobial activity of various extracts of *Commiphora myrrha* was conducted by adopting the cup-plate agar diffusion method. Methanolic and aqueous extracts of the resin of myrrh at concentration of 100 mg/ml was found to be more active against Gram- negative bacteria (Proteus vulgaris; Klebsiella pneumoniae; Escherichia coli and Pseudomonas aeruginosa) and Gram- positive bacteria (Bacillus subitilis), and also showed high antifungal activity against (Candida albicans and Aspergillus niger). While chloroform extract of the resin showed moderate activity towards Gram- positive and Gram- negative bacteria ,as well as against Candida albicans, whereas the same extract revealed high antifungal activity against Apergillus Niger. It was concluded that Methanolic, chloroform and aqueous extracts of *Commiphora myrrha* resin revealed that the selected entire plant had a significant potential effect capable to inhibit the growth of both bacterial and fungal standard species [82].

Cardio-protective Activity

Crocetin, the main active constituent of saffron was found to decrease the level of cardiac marker - lactate dehydrogenase activity and also increase mitochondrion potential in a cardiac myocyte treated with noradrenaline, suggesting its cardioprotective action

[83]. Saffron was also showed
to possess calcium antagonistic activity. This antagonistic activity wasthrough the blockade of extracellular Ca (2+) influx throug h receptor-operated Ca (2+) channels and potential - dependent
Ca (2+) channels.[84] In another study, crocetin by its strong antioxidant activity prevented the cardiac hypertrophy induced by n orepinephrine by increasing the levels of the antioxidant enzymes such as myocardial superoxide dismutase, catalase, glutathione peroxidase and also significantly improved the myocardial pathological histological changes induced by norepinephrine [85].

Anti-tussive Activity
The ethanolic extract of *Crocus sativus*
and its constituent safranal, was found to reduce the number of cough in guinea pigs when injected intra peritoneally where a neb ulized solution of citric acid (20%) was used to induce cough [86].

Smooth Muscles Relaxant
The relaxant effect of saffron on smooth muscle was evident as shown in guinea pig tracheal chain experiment.
The relaxation produced with the aqueous-ethanolic extract and
safranal in comparison with saline as negative control, and theophylline, was comparable to or even higher than that relaxation produced with theophylline suggesting its use in the treatment of various respiratory disorders like asthma etc. [87].

Neuro-protective Effects
The protective effect of aqueous extract of *Crocus sativus* on neurotoxicity induced by aluminuim chloride (AlCl3) was evaluated in mice. The authors conclude that the biochemical and molecular studies revealed the neurotoxicity of AlCl3 in the brains of mice. In addition, there was an ameliorative change with saffron extract and honey syrup against AlCl3 neurotoxicity. The obtained molecular results suggested that AlCl3 made induction for BCL-W gene, which was an anticancer gene or belonged to the DNA repair system in the brain cells, as well as for R-spondin and inositol polyphosphate 4-phosphatase genes, which helped in cell proliferation [88].
The neuro-protective effect of saffron extract, its active component crocin and gamma-glutamylcysteinylglycine (GSH) was studied in glucose-induced neurotoxicity, using PC12 cells as a suitable in vitro model of diabetic neuropathy. Cell viability was quantitated by MTT assay. ROS was measured using DCF-DA by flow cytometry analysis. The result showed that glucose (13.5 and 27 mg/ml) reduced the viability of PC12 cells after 4 days. Saffron extract (5 and 25 mg/ml), crocin (10 and 50 muM) and GSH (10 muM) decreased this toxicity. Glucose toxicity was associated with increased ROS production which reduced by saffron, crocin and GSH pretreatment. The results suggested that saffron and its carotenoid crocin could be potentially useful in diabetic neuropathy treatment [89].
The preventive effect of the aqueous extract of saffron was studied against diazinon (DZN) -induced rise of several specific inflammation, oxidative stress and neuronal damage in rats. The saffron extract inhibited the effect of DZN on these biomarkers levels [90].

DISCUSSION
The beneficial actions of *Tiryaq Wabayi* can be attributed to the presence of phyto-chemical constituents in its ingredients, and complex spectrum of pharmacological actions including antiviral, anti-inflammatory, anti-oxidants, immune stimulant / immune-modulators, hepato-protective, neuro-protective properties.
Lectins and Anthraquinone derivatives; Aloe-emodin, emodin, and chrysophanol in *Aloe vera*, and crocin and picrocrocin in Saffron of *Tiryaq Wabayi*, may prevents SARS-CoV-2 adsorption, attachment, or entry to the host cell, and may inactivate post attachment stages of SARS-CoV-2 replication [23,32]. *Mulayyin* (Laxative) and *Mus'hil* (Purgative) activities of *Sibr* (Aloe), and *Dafey-e-Ta'affun* (antiseptic) activity of *Kurkum* (saffron) may also facilitate its anti-viral property [20,21].
Aloe, Saffron, and Myrrh of *Tiryaq Wabayi* can fight against SARS-CoV-2, to stimulate humoral and cellular immunity by activating macrophages, producing nitric oxide, secreting IL-4 cytokine and elevating IgI, IgM and IgG [37,41,42]. This immune enhancing effect may accelerated due to *Muqawwi-e-Me'ada* (gastro-protective), *Muqawwi-e-Kabid* (hepato-protective) activities of *Sibr* (Aloe), *Muqawwi-e-Qalb* (cardio-protective), *Muqawwi-e-Dimagh* (Encephalo-protective), *Muqawwi-e-Aasab* (Neuro-protective) activities of *Kurkum* (Saffron), and *Muharrik* (stimulant), *Mo'addil* (altering) properties of *Mur* (myrrh) [20,21].
The principal herbs of *Tiryaq Wabayi* can exhibit a protective effect against SARS-CoV-2 induced cell death in lung epithelium by preventing excessive formation of free radicals and reducing lipids per oxidation as antioxidant drug [44,49,54]. Because of *Muhallil-e-Auram* (anti-inflammatory) property, they may resolve SARS-CoV-2 induced pneumonia; is a common pathological condition of acute respiratory distress syndrome (ARDS) and major cause of death, by inhibiting the infiltration of neutrophils, by suppressing NO, PGE2, TNF-α, IL-1β, IL-6, in the lungs [10,21,55,60,66].
Sibr (Aloe) and *Kurkum* (Saffron) in *Tiryaq Wabayi* has *Muqawwi-e-Kabid* (hepato-protective) effect, and *Mur* (Myrrh) has *Kasir-e-Riyah* (carminative), *Muqawwi-e-Me'ada* (gastro-protective) effects [20,21]. Because of these actions, TW may protect the liver from SARS-CoV-2 induced toxicity by down regulating fatty acid synthesis and up regulating fatty acid oxidation, and decreasing DNA damage in liver [70,72,74].
High antimicrobial and antifungal activities of the principal herbs of *Tiryaq Wabayi* may inhibit the growth of Gram-positive bacteria, Gram-negative bacteria and Candida albicans and Aspergillus niger; are developed as secondary infections in the lung of some patients affected with SARS-CoV-2 [5,76,81,82].

Muqawwi-e-Qalb (cardio-protective), *Muqawwi-e-Dimagh* (encephalo-protecive), and *Muqawwi-e-Aasab* (Neuro-protective) effects of *Kurkum* (Saffron), and *Muqawwi-e-Me'ada* (gastro-protective) activity of *Sibr* (Aloe) and *Mur* (Myrrh), may prevent the organ from SARS-CoV-2 induced toxicity [20,21]. Cardio-protective activity of *Kurkum* (Saffron) may cure myocardial injury and heart failure; are severe critical complication in COVID-19 patients. [9, ,83] Neuro-protective effect of *Kurkum* (Saffron) may also prevent from or treat shock and encephalopathy; are critical complication in patients with COVID-19, by reducing oxidative stress in neurons [9,90].

Anti tussive and smooth muscle relaxant activities of *Kurkum* (Saffron) and *Munaffis wa Mukhrij-e-Balgham* (mucolytic & expectorant) properties of *Mur* (Myrrh) in *Tiryaq Wabayi*, may relieved in persistent cough and pulmonary congestion; are the major clinical presentation of acute respiratory distress syndrome (ARDS), frequently developed in SARS-CoV-2 disease, and causes high rate of mortality [10,20,22,86,87]. *Mudirr-e-Baul* (diuretic) effect of *Sibr* (Saffron) and *Mur* (Myrrh) in *Tiryaq Wabayi* may prevent from or cure acute renal injury; is a severe critical complication in patients with Covid-19 [9,20,22].

CONCLUSION

It is concluded that *Tiryaq Wabayi* is a polyherbal formulation with proven safety and efficacy of its ingredients, associated with multi-pharmacological properties. *Sibr* (Aloe), *Kurkum* (Saffron) and *Mur* (Myrrh) in *Tiryaq Wabayi* has potent antiviral, anti-inflammatory, anti-oxidants, immune stimulant / immune modulators, hepato-protective, neuro-protective activities. Hence, it can be used as prophylaxis to protect from COVID-19 during epidemics and as therapeutic to combat COVID-19 and its complication. Furthermore, scientific and clinical studies of *Tiryaq Wabayi* are needed to evaluate its efficacy in patients with COVID-19.

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