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Review article

Saffron: A potential drug-supplement for severe acute respiratory syndrome coronavirus (COVID) management

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2 (COVID-19), came as a significant health care challenge for humans in 2019–20. Based on recent laboratory and epidemiological studies, a growing list of mutations in the virus has the potential to enhance its transmission or help it evade the immune response. To further compound the problems, there are considerable challenges to the availability of effective, affordable, safe vaccines on a mass scale. These impediments have led some to explore additional options available in traditional medicines, especially immune-boosting natural products. Saffron has been used for centuries to treat fever, bronchitis, cold and other immune, respiratory disorders. Herein, we discuss the potential role of saffron during and after COVID-19 infection, focusing on immunomodulation, respiratory, renal, and cardiovascular functions. As a nutraceutical or drug supplement, it can alleviate the magnitude of COVID-19 symptoms in patients. The anti-inflammatory, antioxidant, and other medicinal properties attributed to saffron bioactive compounds can help in both pre-and post-infection management strategies. The abnormalities associated with COVID-19 survivors include anxiety, depression, sleep disturbances, and post-traumatic stress disorder. Saffron can help manage these post-hospitalization abnormalities (sub-acute and chronic) too, owing to its anti-depressant property. It can help common people boost immunity and manage depression, stress and anxiety caused due to prolonged lockdown, isolation or quarantine.

1. Introduction

The respiratory pandemic COVID-19 (Coronavirus disease 2019) is the third epidemic of zoonotic origin to occur in the present century. COVID-19 was declared a pandemic by WHO on 12th March 2020, and its causative agent was named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). Based on information shared on World Health Organization (WHO) and Centres for Disease Control and Prevention, USA (CDC, USA) portals, people suffering from SARS-CoV-2 may possess cough, congestion or runny nose, sore throat, fever or chills, difficulty in breathing or shortness of breath, headache, muscle or body aches, fatigue, loss of smell or taste, vomiting or nausea, diarrhea, and some patients may need hospitalization. The incubation period of COVID-19 ranges from 1 to 14 days, with an average of 5–6 days in most patients. Till 11th April, 2021 nearly 135.70 million people were infected worldwide, out of which about 2.93 million lost their lives (WHO, 2021) while the maximum number of deaths (approx. 5,75,205; 1.8%) were reported in the USA, and the maximum percentage of deaths was 19.5% in Yemen (COVID-19 Stats). Even though most infected individuals suffer only mild to moderate illness, the majority of older and co-morbid patients with diseases like hypertension, diabetes, asthma, etc., develop severe illness and die. The depressed immune function has increased susceptibility to novel coronavirus infection (Brahmbhatt, 2020).

Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses of ~30 kb. Based on their genomic structure, these are divided into 4 genera (α, β, γ, and δ). Only two genera (α and β) infect mammals (Rabi et al., 2020). α coronaviruses (229E and NL63) cause common cold and croup (laryngotracheobronchitis), while β coronavirus examples are SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 (Yuki et al., 2020). Although the vaccine development against SARS-CoV-2 is good news, there are some concerns about the safety, allergic reactions, free-access, affordability, and efficacy against new variants, and the possibility of generating a lethal mutant of the virus in the future. Further, thirty to forty percent of COVID-19 survivors have shown the symptoms of anxiety, depression, sleep disturbances, and post-traumatic stress disorder (Nalbandian et al., 2021). In a large-scale analysis of nearly sixty thousand COVID-19 survivors within 90 d after COVID-19 diagnosis, it has been estimated that the probability of

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occurrence of new psychiatric illnesses is 5.8% constituting predominantly anxiety disorder (4.7%), mood disorder (2%), insomnia (1.9%), dementia (1.6%) (Taquet et al., 2021). It has been further suggested that a multi-disciplinary collaboration is essential for physical and mental health care to survivors of acute COVID-19 (Nalbandian et al., 2021).

Given the issues discussed above, it is high time for people to boost their immune system. No other spice is as intriguing and splendid as saffron (*Crocus sativus* L.). It is associated with Greek gods, hanging gardens of Babylonia, Song of Solomon (Bible) for its essence and aroma. Medical practitioners like Hippocrates and Pliny have used it, and famous women like Cleopatra made its use in cosmetics (Husaini, 2010). Many in vitro and in vivo studies have confirmed the saffron as an antiviral, antioxidant, bronchodilator, anti-inflammatory, and strong immune booster acting on humoral as well as cellular immunity (Bhat et al., 2020; Kadri, 2014; Alam et al., 2020; Alshehri et al., 2017; Chiavaroli et al., 2017; Shahbazi and Bolhassani, 2016).

In this paper, we highlight the properties of saffron (Figure 1) that could help alleviate the symptoms of SARS-CoV-2 infection in light of its pathophysiology, making it a suitable candidate as a drug supplement. The purpose is not to present saffron as a solution to COVID-19, but only to explore its use in the integrated management of COVID-19. It needs to be evaluated for its potential role in the long-term physical and mental health management strategy of COVID-19 patients. The paper highlights its potential use in helping manage depression, stress, and anxiety caused due to prolonged lockdowns and isolation or quarantine of people during pandemics.

2. Pathophysiology and physiological immune response to SARS-CoV-2

The immune responses to viral infections are of two types, Innate Immune Response and Adaptive Immune Response. The major components involved in the innate immune response are Toll-like receptors (TLR) (Jiang et al., 2005), RIG-I-like receptors (retinoic acid-inducible protein 1 like) (RLR) (He et al., 2005), Nucleotide-binding and oligomerization Domain (NOD)-like receptors (NLR) (Yu et al., 2020), C-type lectin-like receptor (CLR) (Cui et al., 2019), Dendritic Cell (DC) (Ziebuhr et al., 2000). TLRs recognize pathogen-associated molecular patterns (PAMP) and target viral lipids, lipoproteins, proteins, and nucleic acids in cell membrane (TLR-2 and TLR-4), cytoplasm (TLR-3, TLR7/8), endosome, lysosome, and endocytolysosome. RLRs recognize viral RNA in the cytoplasm and cause induction of type 1 IFN and inflammatory cytokines to block viral replication (reviewed in Florindo et al., 2020). The major components of Adaptive Immune Response are the T cells and the Humoral immune response. In T-cell mediated response, CD4^{+} T cells promote the production of virus-specific antibodies by activating T-dependent B cells, which produce pro-inflammatory cytokines via NF-kB pathway. Cytotoxic CD8^{+} T cells infiltrate into the infected area and eliminate viral infected cells (Lauer et al., 2020). In the humoral immune response, activation of B cells by CD4^{+} T cells, memory, and antibodies secreting cells occur, targeting viral proteins through IgM, IgG, and IgA antibody production (Li et al., 2020; Bai et al., 2020).

The host response to SARS-CoV-2 begins with the initial physiological immune response followed by the pathogenic hyperinflammatory phase. The physiological host response encompasses viral entry, infection, and the early immune phase. It involves the entry of SARS-CoV-2 into alveolar epithelial cells by binding to angiotensin-converting enzyme 2 (ACE2) through surface spike (S) protein-mediated by transmembrane serine protease 2 (TMPRSS2) (Hoffmann et al., 2020). It is then followed by active replication and viral release, causing pyroptosis. Viral-mediated cell death causes the release of various damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). These are recognized by pattern-recognition receptors on alveolar macrophages and endothelial cells. PAMPs are recognized in the extracellular space by Toll-like receptors (TLRs), causing induction of pro-inflammatory cytokine transcription factors such as NF-κβ, while DAMPs are recognized intracellularly by nucleotide-binding domain leucine-rich repeat (NLR) proteins causing activation of inflammasomes and conversion of pro-IL-1β to active-IL-1β (Huang et al., 2020; Schnappauf et al., 2019; Soy et al., 2020). The DAMP/PAMPs recognition causes the release of pro-inflammatory cytokine and chemokine, activation of inflammasomes, and the recruitment of monocytes, macrophages, and virus-specific T cells to eliminate the infected cells (Bohn et al., 2020).

A more severe pathological phase follows the physiological phase in about 20 percent of infectious cases (Parasher, 2020). It is marked by an increased secretion of pro-inflammatory cytokines and chemokines, like interleukins (IL-1, IL-6, IL-8, IL-12, and IL-120), tumour necrosis factors (TNF-α, IFN-β and IFN-λ), C-X-C motif chemokine ligand 10 (CXCL10), macrophage inflammatory protein-1α (MIP-1α), monocyte chemo-attractant protein-1 (MCP-1) and interferon gamma-induced protein 10 (IP-10) (Huang et al., 2020; Zhou et al., 2020a; Qin et al., 2020). The cytokine surge serves as a chemo-attractant for neutrophils, CD4 helper T cells, and CD8 cytotoxic T cells, causing excessive infiltration of immune cells in the lungs. CD4 helper T cells activate B cells for producing virus-specific antibodies, while CD8 T cells kill the virus-infected cells.

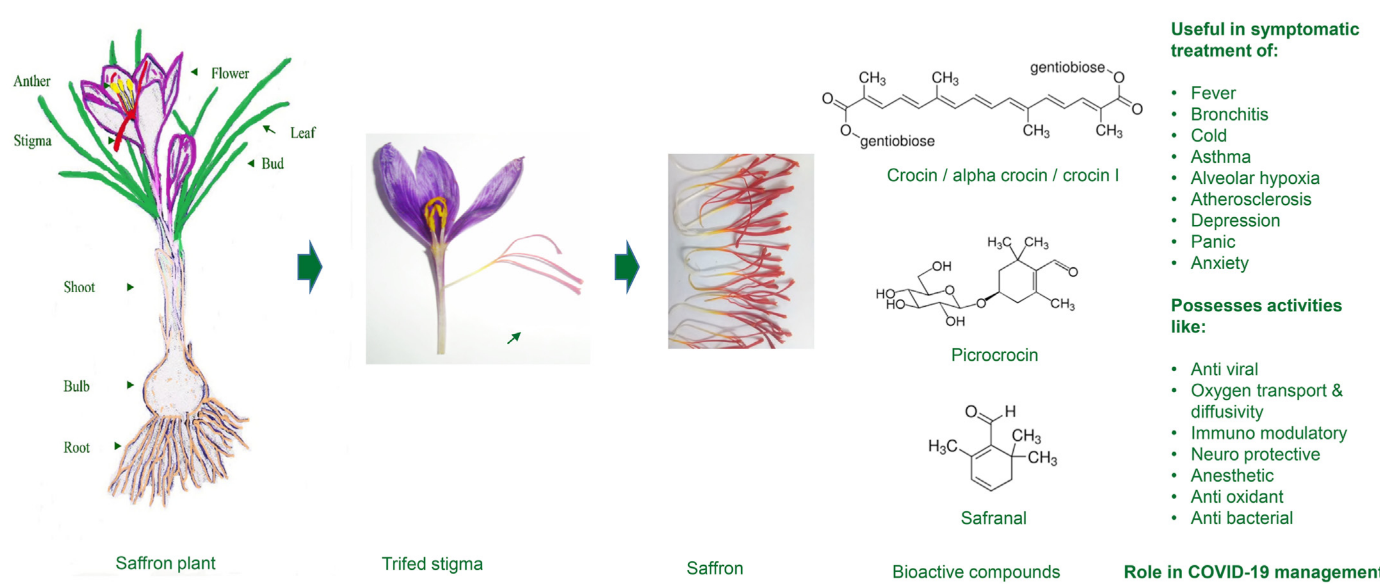

Figure 1. Saffron stigma bioactive compounds with therapeutic value useful for COVID-19 management.

In addition to ACE2, SARS-CoV-2 can also bind to dendritic-cell specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) and DC-SIGN-related protein (DC-SIGNR, L-SIGN) (Jeffers et al., 2004; Marzi et al., 2004; Yang et al., 2004). DC-SIGN is highly expressed on dendritic cells and macrophages. Dendritic cells (DCs) are involved in phagocytosis of virus in the lungs. After phagocytosis, DCs migrate to lymphoid organs and activate antigen-specific T cells, which move into the lungs and destroy virus-infected alveolar cells. DCs, macrophages, pathological cytotoxic T cells derived from CD4 helper T cells help fight the virus, but eventually cause lung inflammation and injury [Fang et al., 2012; Small et al., 2001]. The host cells undergo apoptosis releasing new viral particles. The cycle of infection and apoptosis continues, leading to the loss of pneumocytes which are involved in the gas exchange between the alveoli and blood. This causes diffuse alveolar damage, and eventually results in an acute respiratory distress syndrome (Bohn et al., 2020). This may then progress to activation of a procoagulant response, multiple organ failure and death, especially in old aged, immune-compromised, or with underlying pathology (Gautam et al., 2020) (Figure 2).

While uncontrolled immunity causes pulmonary tissue damage and reduced lung capacity, immune insufficiency or misdirection increases viral replication and tissue damage. Therefore, the induction of a balanced host immune response against SARS-CoV-2 is critical for controlling its infection (Florindo et al., 2020). Some herbs are traditionally known to contain components that stabilize the functioning of innate immunity (macrophages, neutrophils, and dendritic cells) as well as acquired immunity (T cells and B cells).

3. A brief description of saffron medicinal properties

The healing properties of saffron are recorded in Materia Medica by Pedanio Dioscorides, a Greek medical practitioner of the first century A.D. Physicians like Hippocrates and Pliny have used it in cases of excessive drunkenness, loss of male potency, and as an aphrodisiac. Modern medicine has acknowledged several therapeutic effects and pharmaceutical applications of saffron.

Medicinal properties of saffron are attributed to the presence of volatile as well as non-volatile aroma yielding compounds. The red stigmas of *Crocus sativus* accumulate different bioactive compounds amongst which safranal, crocin, campherol, picrocrocin, crocetin, α- and β-carotenes are of prime importance. The ability to synthesize these compounds is not common across species. Picrocrocin and crocin have been detected only in saffron (*Crocus* species), *Buddleja* (Liao et al., 1999), and *Gardenia* (Pfister et al., 1996).

Research on the physicochemical and biochemical properties of saffron along with the bioactivity of its compounds, has confirmed its role in pharmacognosy (Table 1). A vast number of papers have been published focusing on cancer, antioxidant properties, sedative effect, neuronal injury, etc. (reviewed in Premkumar and Ramesh, 2010; Licón et al., 2010; Mokhtari-Zaer et al., 2020). Saffron and its constituents are considered an efficient treatment for coronary artery diseases, neurodegenerative disorders, bronchitis, asthma, diabetes, fever, and colds (Boskabady and Farkhondeh, 2016). It is a promising natural medicine in treating metabolic syndrome (Razavi and Hosseinzadeh, 2017). It is a potent natural antioxidant used in folk medicine to treat cold, scarlet fever, and asthma (Boskabady and Farkhondeh, 2016; Boskabady et al., 2019). Several in vivo studies have confirmed the antioxidant and anti-inflammatory role of ethanol or aqueous extracts of saffron, safranal, and crocin (Hosseinzadeh and Younesi, 2002; Hosseinzadeh and Ghenaati, 2006). Chatterjee et al. (2005) reported crocin to be a more potent antioxidant agent than α tocopherol. Reduction of blood bilirubin level and decreased blood cholesterol and triglycerides after using crocetin and crocin have also been reported (Nair et al., 1991). The anticancer properties of saffron have also been reported (Duke et al., 1987; Abdullaev and Espinosa-Aguirre, 2004).

4. Saffron in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) management

Coronavirus is known to act more severely on individuals with weak immunity. The major pathway of cell destruction in COVID-19 patients is mostly immune-mediated apoptosis. Therefore a robust immune system can help reduce the severity of the viral infection and subsequent disease response. Since ACE2 receptor is found in multiple organs viz. oral and nasal mucosa, lungs, stomach, intestine, bladder, heart, and kidney (Zhou et al., 2020b; Xu et al., 2020; Donoghue et al., 2000), cell-mediated immunity causes damage through cytokine storm (Williams and Chambers 2014; Cameron et al., 2008). It could be helpful if inflammation is suppressed during this severe stage (Shi et al., 2020). Immunity-boosting medicinal plants can help during the early non-severe stage, while herbs with anti-inflammatory and anti-thrombotic properties can help during a later or severe stage (Gautam et al., 2020). The potential role of saffron and its constituents and the possible action mechanism is described under relevant heads in the following sub-sections.

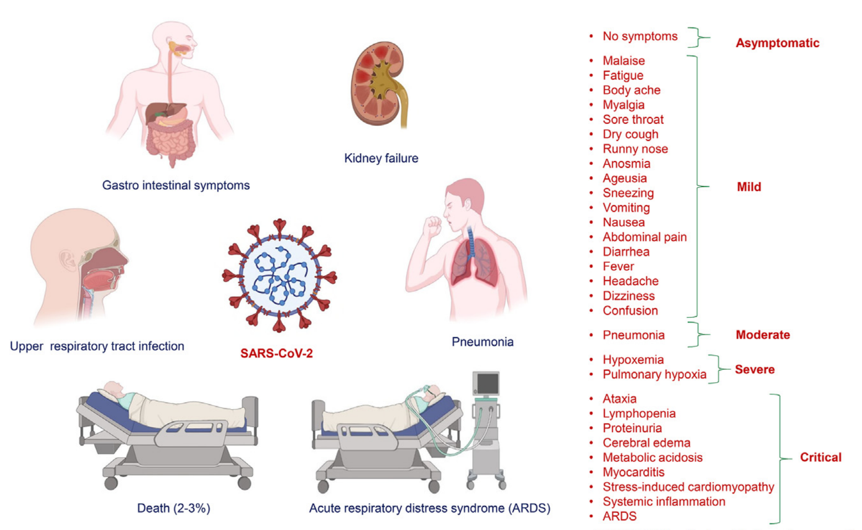

Figure 2. SARS-CoV-2 symptoms and pathophysiology based on disease severity.

Table 1. Active ingredients of saffron and the rationale of their use as nutraceuticals.

Component/active ingredient	Medicinal role	Reference
Saffron extract	• Anxiolytic and hypnotic effects; animal model • Significant improvement in memory skills; animal model • Found to be as effective as donezepril in treatment of Alzheimer's disease; clinical study • Induced plaque stability, better glycaemic control and amelioration in a dose-dependent manner; animal model. • Effective against skin neoplasia; clinical study • Can be used in second-degree burn wound due to its increased re-epithelialization in burn wounds; animal model • Relief from painful dysmenorrhoea due to decrease in uterine contractions; clinical study • Significant improvement in memory skills; animal model • Potent cytotoxic effect on human and animal adenocarcinoma cells; animal model • Its strong antioxidant properties by scavenging the ROS may help pancreatic cells in increased insulin secretion and reduce elevated blood glucose levels; animal model • Anti-tumor activity (cytotoxic to TC-1 cells); Cell line model • Increases Bcl2/Bax ratio expression thereby protecting against endothelial cells apoptosis; in vitro cell culture model	Hosseinzadeh and Noraei (2009); Hosseinzadeh et al. (2012); Akhondzadeh et al. (2010); Christodoulou et al. (2014); Abdullaev (2002); Khorasani et al. (2008); Lequerc (1973); Hosseinzadeh et al. (2012); Garc-Olmo et al. (1999); Kianbakht and Ghazavi (2011); Khavari et al. (2015); Xu et al. (2007)
Picrocrocin	• Sedative effect on lumbar pains and spasms; clinical study • Anti-tumor activity (cytotoxic to TC-1 cells); Cell line model • Prevent learning and memory decline via neuronal protection; animal model • Protection against hexachlorobutadiene-induced (HCBD) nephrotoxicity; animal model • Anti-V mediators; in vitro and animal model	Lequerc (1973); Khavari et al. (2015); Baluchnejadmojarad et al. (2019); Boroushaki et al. (2007); Alayunt et al. (2019); Ahmad et al. (2005); Patel and Bhutani (2014)
Carotenoids	• Potent antioxidant activity; in vitro model • Marked improvement in skin texture; animal model • Cytotoxic effect on cancerous cells due to interaction with topoisomerase II, an enzyme regulating cellular DNA and proteins synthesis; in vitro model • Enhanced ex vivo macrophage yeast phagocytic ability; animal model • Neuroprotective agent against Methamphetamine-induced neurodegeneration; animal model • Anti-inflammatory effect through reduction of LPS-induced pro-inflammatory mediators; animal model • Antioxidant; animal model	Kanakis et al. (2009); Das et al. (2010); Molnar et al. (2000); Bakshi et al. (2016); Mozaffari et al. (2019); Patel and Bhutani (2014); Yarijani et al. (2017)

4.1. Ethnobotanical use in epidemics

Saffron has been included by Unani medicine among the drugs used during the epidemic. Stamen of saffron can be used as a fumigant for sanitizing the environment due to the antimicrobial activity of its volatile oils. Ibn-Rushd (1126–1198 CE), a great scholar born in Spain commonly known by the name Averroes, describes a medicine that he claims a savior during an epidemic as '*whoever has used this formulation during an epidemic remained protected from it*.' The composition of this medicine is as follows: Two parts of saffron along with *Aleovera* L. and *Commiphora myrrha* Nees Engl. one part each (Nikhat and Fazil 2020). Both traditional and experimental evidence suggests the possible therapeutic effect of saffron and its constituents on various aspects of health, which can be helpful in the management of SARS-CoV-2 pandemic as well (Table 2). Ancient Iranian physician, Avicenna, has stated that saffron oil can facilitate breath and strengthen the respiratory organs. Four cumulative concentrations of a hydro-ethanolic extract of saffron and its constituent safranal were tested on guinea pig tracheal smooth muscle, and the effect was found to be comparable to that of theophylline (Boskabady and Aslani, 2006; Boskabady et al., 2019; Mokhtari-Zaer et al., 2015). Even saffron petal extract (SPE) has been found useful through photochemical analysis, revealing the presence of flavonoids, anthocyanins, and tannins. The SPE was injected intra-peritoneally to rats for 14 days, and the results showed an increase in the number of white blood cells and antibody response without any alteration in hematological parameters (Babaei et al., 2014).

4.2. As immunity booster

Currently, immunomodulatory drugs that target interleukins, like tocilizumab (an IgG1 monoclonal antibody against IL-6 receptor) are reported to be beneficial in moderate-to-severe cases of SARS-CoV-2 infection. Bioactive constituents of saffron can affect both cellular and humoral immunity functions, which can be quite beneficial (Table 2). Immunomodulation by these saffron components can help as a management strategy against SARS-CoV-2. Its immunomodulatory activity may involve direct targeting of Toll-like receptors (TLRs), attributed to nuclear factor (NF-κB), activator protein 1 (AP-1), and downstream signaling pathways (reviewed in Zeinali et al., 2019; Boskabady et al., 2020). A randomized, double-blind placebo-controlled clinical trial has been conducted to determine the immunomodulatory effects of saffron. It was observed that saffron increases the IgG level and decreases the IgM level compared with baseline and placebo. Furthermore, it increases the percentage of monocytes in comparison to placebo. Hence, the sub-chronic daily use of 100 mg saffron was suggested to have temporary immune-modulatory activities without any adverse effects (Kianbakht and Ghazavi, 2011). Saffron has been shown to enhance IFN-γ to IL-4 ratio in human lymphocytes and thereby affect Th1 and Th2 balance in them (Boskabady et al., 2011). These properties could aid in modulating the immune response during SARS-CoV-2 infection. A study on sensitized guinea-pigs has shown that the total and differential count of white blood cells (WBC) gets affected positively by the saffron extract and safranal (Bayrami and Boskabady, 2012). Azithromycin is a preferred antibiotic in SARS-CoV-2 management due to its

Table 2. Saffron as a drug-adjuvant or supplement in Covid-19 pandemic management.

Role	Remarks	Reference
Immunomodulation	• Modulate total and differential leukocyte counts; animal model • Increases level of serum immunoglobulins and circulating antibody titre, and phagocytic index; animal model • Modulates innate immunity (macrophage, neutrophils, NK cells) and acquired immunity (inflammatory and anti-inflammatory cytokines, B cell, and Th1/Th2) components; animal model • Decreases levels of TNFa, IL-1b, and IL-4 but increases the levels of IL-10 and IFN-g in the plasma and serum; animal model • Promotes macrophage activation significantly; cell line model • Decreases protein expression levels of MMP-1, MMP3, MMP-9 MMP-13, HAases, tryptase, and Hsp70; animal model • Suppresses the proliferation and expression of NF-kB and increases Nrf2 expression in asthma; animal model • Elevates the levels of IgG-1 and IgM antibodies; animal model • Effective in the prevention of symptomatic EAE by inhibition of oxidative stress and leukocyte infiltration to the CNS; animal model • Significant decrease in airway hyper-reactivity and inflammation as well as levels of BALF interleukins (IL-4, IL-5, IL-13), lung eosinophil peroxidase, tryptase and serum OVA-specific IgE; animal model • Decreases LPS-induced mRNA and the protein expressions of interleukin-6 (IL-6), MCP-1, and TNF-α in lung tissue; animal model • Decreases activities of EPO and MPO; animal model • Decreases phospho-IκB expression and NF-κB activity in LPS-induced lung tissue alteration; animal model • Inhibits the expression of CXCL8, eotaxin, p-ERK, p-JNK, and p-p38 protein; animal model • Increases HO-1 protein expression in the colon tissues thereby having protective effect on Nrf-2 pathway; animal model; animal model	Mokhtari-Zaer et al. (2020); Vijayabhargava and Asad (2011); Boskabady et al. (2020); Ghazavi et al. (2009); Escribano et al. (1999); Bani et al. (2011); Yang et al. (2012); Ding et al. (2015); Singh et al. (2020)
Respiratory function	• May be used for relief from symptoms of asthma due to bronchodilatory effect; clinical study • Ability of increasing the speed of oxygen transport and diffusivity. Beneficial therapeutic candidate for alveolar hypoxia, haemorrhages, tumours and arthritis; in vitro and animal models • Suppression of airway inflammation and hyper-reactivity; animal model • Treating respiratory disorders mostly chronic bronchitis; animal model • Reduces the severity of an ovalbumin (OVA)-induced asthma; animal model • Increases the levels of TIPE2 and Foxp3 in Treg cells and the number of Treg cells and hence mitigate the severity of asthma; animal model	Bayrami and Boskabady (2012); Frank (1961); Di Luccio and Gainer (1980); Giaccio (2004); Xiong et al. (2015); Yang et al. (2012); Ding et al. (2015)
Renal function	• Lowered lipid peroxidation levels in liver and kidney of diabetic rats; animal model • Protective against renal damages from ischemia-reperfusion (I/R); animal model	Kianbakht and Ghazavi (2011); Yarijani et al. (2017)
Cardio-vascular	• Cardioprotective effect by maintaining the redox status of the cell; animal model • Atheroprotective mechanism due to its ability to increase the plasma oxygen diffusivity; animal model • Improves cardiac function (cardio protective potential) due to crocin pre-treatment; animal model • Improved left ventricular functions, decreased infarct size and overall haemodynamic status of the myocardium; animal model	Goyal et al. (2010); Gainer et al. (1993); Bharti et al. (2012)
Anxiety and depression	• Effectiveness similar to chemically synthesized drugs in case of depression (anti-depressant) and epilepsy (anticonvulsant); clinical study • Significant improvement in memory skills; animal model • Aqueous extract when administered intraperitoneally reduced the side effects of electroshock stress; animal model • Aqueous extract reduces stress-induced anorexia; animal model. • Ameliorate insomnia by binding to benzodiazepines; animal model • Muscle relaxation; animal model • Modulate the activities of human monoamine oxidases (hMAO-A and hMAO-B isoforms), a highly promising hMAO-B inhibitor; in vitro and in silico	Akhondzadeh et al. (2004); Basti et al. (2007); Hosseinzadeh et al. (2012); Halataei et al. (2011); Hosseinzadeh and Noraei (2009); De Monte et al. (2014)

anti-inflammatory action, and the prevention of secondary bacterial infection (Parasher 2020). Saffron has been shown to reduce inflammation by inhibiting cyclooxygenase enzyme activity (Rahmani et al., 2017). This property can help tackle excessive lung inflammation in SARS-CoV-2 patients due to the release of pro-inflammatory cytokines and chemokines.

4.3. In respiratory problems

In traditional medicine, saffron has been used to treat fever, bronchitis, cold, pertussis, asthma, and respiratory function improvement. Safranal, a major component of saffron, might be useful in treating respiratory disorders, mostly chronic bronchitis. It has significant therapeutic effects on lung pathology and tracheal hyper-responsiveness (Boskabady et al., 2012, 2014). Saffron can be useful in SARS-CoV-2 management as it has been shown to inhibit the release of inflammatory cytokine, and production of nitric oxide and nitrite (Boskabady et al., 2014), endotheline-1, and total protein secretion (Gholamnezhad et al., 2013), and the recruitment of inflammatory cells to the lungs in sensitized guinea pigs (Mahmoudabady et al., 2013). Additionally, it sedates coughing through an anesthetic effect on the vagal nerves of the alveoli (Giaccio, 2004). Byrami et al. (2013) demonstrated the preventive effects of the saffron extract on tracheal responsiveness and plasma levels of IL-4, IFN-γ, total nitric oxide, and nitrite in sensitized guinea-pigs. The saffron extract was reported to show a preventive effect on tracheal responses, serum levels of inflammatory mediators and also showed increased Th1/Th2 balance. The SARS-CoV-2 infection causes loss of pneumocytes, which are involved in the gas exchange between the alveoli and blood. In an earlier study, crocetin has shown the most remarkable effect due to its ability to increase the speed of oxygen transport and diffusivity *in vivo* as well as *in vitro* (Frank, 1961). It can be useful in hemorrhages, alveolar hypoxia, atherosclerosis, tumors and may help SARS-CoV-2 patients.

Bukhari et al. (2015) evaluated the antioxidant potential of saffron in normal human bronchial epithelial cells (NHBE) and the anti-inflammatory potential of safranal in a murine model of asthma. In bronchial epithelial cells, safranal significantly reduced oxidative stress via iNOS reduction and prevented apoptosis in these cells, which could be useful in reducing the immune-mediated cell destruction in COVID-19 patients. This safranal mediated iNOS inhibition attenuated asthmatic features in the murine model of allergic asthma (Table 2).

4.4. Antiviral role

Antiviral drugs like remdesivir and favipiravir have shown some efficacy in SARS-CoV-2 management (Parasher 2020). There exists strong scientific evidence for the antiviral effects of saffron (Table 2). Antiviral (anti-HSV-1 and anti-HIV-1) effect of saffron has been tested, and it was found that the saffron extract shows mild activity while crocin and picrocrocin indicated significant anti-HSV-1 and anti-HIV-1 activities. Both crocin and picrocrocin were found to be effective for inhibiting the virus entry as well as its replication. Further, it has been suggested that crocin and picrocrocin are promising anti-HSV and anti-HIV agents for herbal therapy against viral infections (Soleymani et al., 2018). Crocin and picrocrocin prevented the virus from entering the Vero cell, which disrupted the virus entry mechanism.

Recently, in silico analysis for pharmacokinetic, toxicological, and ADMET (absorption, distribution, metabolism, excretion, and toxicity) parameters of saffron bioactive molecules indicated that crocetin has a high drug score against SARS-CoV-2 (Kordzadeh et al., 2020). It was elucidated that crocin and crocetin possess a high binding affinity towards the main protease (PDB ID: 6M03) of SARS-CoV-2, and crocetin shows translocation through lipid bilayer as a drug molecule.

4.5. Depression and anxiety management

There are several long-term residual effects of SARS-CoV-2 infection. According to a post-hospitalisation COVID-19 study, four in five patients with COVID-19 have persistent symptoms and continue to experience negative impacts on their physical and mental health, as well as ability to work (UKRI). The long-term effects include fatigue, dyspnea, cognitive problems, depression, sleep abnormalities, and deterioration in the quality of life (Carfi et al., 2020; Tenforde et al., 2020; Huang et al., 2021; Chopra et al., 2020). These long-term effects can be categorized into: (1) subacute abnormalities present from 1–3 months beyond acute COVID-19; and (2) chronic abnormalities persisting beyond 3 months of the onset of acute COVID-19 (Greenhalgh et al., 2020; Shah et al., 2021). Saffron can be a suitable candidate for the management of anxiety, depression, neuropsychiatric disorders and the other long-term effects including subacute and chronic abnormalities of SARS-CoV-2 infection. This can be exemplified by many earlier safety studies of saffron where double-blind randomized trials focused on the patients with neuropsychiatric problems (Table 3). It has been reported to be more effective than placebo or almost equivalent to the therapeutic doses of fluoxetine and imipramine (Kafi et al., 2018; Gohari et al., 2013; Qadir et al., 2020) (Tables 2 and 3). Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) anti-depressant, helpful as a drug for people with depression, anxiety, panic, or obsessive-compulsive symptoms (Meltzer et al., 1979). Imipramine is a tricyclic anti-depressant (TCA) used mainly in treating depression, anxiety, panic disorder, and bedwetting (Post et al., 1974).

Human monoamine oxidase (hMAO) enzymes hMAO-A and hMAO-B are two important targets for treating neuropsychiatric and neurodegenerative diseases. hMAO-A isoform regulates serotonin, epinephrine, and norepinephrine metabolism, and hMAO-B metabolizes benzylamine and phenethylamine, while both isoforms are involved in the metabolism of dopamine. In an interesting study, the artificially designed chemical derivatives of safranal were shown to modulate the activities of these enzymes, and one such derivative was exceptionally potent and highly promising hMAO-B inhibitor (De Monte et al., 2014).

5. Potential as a drug adjuvant

Twenty-one percent (21%) of the trials on COVID-19 management have focussed on non-vaccine approaches like immunomodulatory (18%) and dietary supplementation (3%). There are many immune modulator based treatments in development like AT-100 (recombinant human surfactant protein D, rhSP-D reduces inflammation and modulates lung immune response), BPI-002 (small molecule as a potent T cell co-stimulator), 7HP-349 (small-molecule integrin activator as an oral adjuvant), Brilacidin (defensin mimetic candidate), PRTX-007 (oral small molecules which activate toll-like receptor 7) (Florindo et al., 2020).

Saffron is power-packed with B vitamins, vitamin C, carotenoids, and phytochemicals, which boost immunity. Saffron constituents are patented in several polyherbal drug formulations used for the treatment of cardiovascular and central nervous system diseases as well as for boosting immune function and depression treatment (Mohajeri et al., 2020). Clinical trials show that if saffron extract is administered @ 20–200 mg/day for ten days to several weeks, it is effective in patients suffering from Central Nervous System (CNS) diseases like Alzheimer's and psychological disorders like depression (Abdullaev, 2002; Abdullaev and Espinosa-Aguirre, 2004; Bakshi et al., 2010; Bathaie and Mousavi, 2010; Rezaee and Hosseinzadeh, 2013; Lopresti and Drummond, 2014; Farokhnia et al., 2014; Bhandari, 2015; Pitsikas, 2015). The most common effective doses of saffron (30–50 mg/day) used in clinical studies are considered safe and are noticeably lower than the toxic doses (>5 g/day) (Mehri et al., 2020). Doses higher than 10 g/day induce abortion and lead to vomiting, vertigo, dizziness, hematuria, bleeding in the uterus and gastrointestinal mucosa (Schmidt et al., 2007).

More than 109.20 million people have so far recovered from COVID-19 infection, out of which 32.76–43.68 million (30–40 %) survivors may be suffering the symptoms of anxiety, depression, sleep disturbances, and post-traumatic stress disorder. The development of a saffron-based formulation and its commercialization can help provide these people an over-the-counter medication for effective management of the long-term adverse effects of COVID-19. One example of a patented commercial saffron nutraceutical product (for macular degeneration) is 'Saffron, 2020'. It combines saffron with vital eye health nutrients such as lutein and zeaxanthin, antioxidant vitamins (A, B_2, C, and E), resveratrol, and zinc (Saffron 2020). Microarray studies on this product depict that its efficacy is not only because of the

Table 3. Clinical studies on safety and dosage of saffron in patients suffering from neuro-psychiatric disorders/diseases.

Constituent	Dosage/day	Duration of dosage (weeks)	Neuro-psychiatric disorder/disease	Remarks	References
Saffron capsule	30 mg/day, BID	4	Patients with depression	No significant differences in the frequency of adverse effects between saffron and placebo groups	Mansoori et al., (2011); Shahmansouri et al., (2014); Noorbala et al., (2005); Akhondzadeh et al., (2005); Ghajar et al., (2017); Mazidi et al., (2016); Akhondzadeh-Basti et al. (2007); Lopresti et al. (2018); Esalatmanesh et al., (2017); Tabeshpour et al., (2017); Kashani et al., (2017); Akhondzadeh et al., (2010a); Akhondzadeh et al., (2010b); Mousavi et al., (2015)
Saffron Capsule	30 mg/day, BID	6	Patients with depression	No significant differences in the frequency of adverse effects between saffron and fluoxetine groups	
Hydroalcoholic extract of saffron	30 mg/day, BID	6	Patients with depression	No significant differences in the frequency of adverse effects between saffron and fluoxetine groups	
Saffron capsule	30 mg/day, TDS	6	Patients with depression	Dry mouth and sedation was significantly more frequent in the Imipramine group than saffron group	
Saffron capsule	30 mg/day, BID	6	Patients with depression	No significant differences in the frequency of adverse effects between saffron and citalopram groups	
Saffron Capsule	50 mg/day, BID	12	Patients with anxiety and depression	Side effects were rare	
Saffron Capsule	30 mg/day, BID	8	Depressed outpatients	No significant differences in the frequency of adverse effects between saffron and fluoxetine groups	
Saffron extract	14 mg/day, BID	8	Teenagers with anxiety or depressive symptoms	Headache occurred more frequently in the placebo group than in the saffron group	
Saffron	30 mg/day, BID	10	Patients with obsessive-compulsive disorder	No significant differences in the frequency of adverse effects between saffron and fluvoxamine groups	
Saffron	30 mg/day, BID	8	Women with postpartum depression	No significant differences in the frequency of adverse effects between saffron and placebo groups	
Saffron	15 mg/day, BID	6	Women with postpartum depression	No significant differences in the frequency of adverse effects between saffron and fluoxetine groups	
Saffron capsule	30 mg/day, BID	16	Patients having Alzheimer's disease	No significant differences in the frequency of adverse effects between saffron and placebo groups	
Saffron capsule	30 mg/day, BID	22	Patients having Alzheimer's disease	Vomiting occurred significantly more frequently in the donepezil group than in the saffron groups	
Saffron aqueous extract and crocin	15 mg/day, BID	12	Patients having Schizophrenia	No toxic effect on thyroid, liver, kidney, and hematologic systems	

antioxidant action of crocins but also due to the activation of multiple pathways (Marco et al., 2019).

6. Conclusion

In the absence of effective allopathic drugs and the mass availability of effective, safe, and affordable vaccines for 7.8 billion people, World Health Organisation (WHO) guidelines on social distancing, wearing masks, frequent handwashing are an essential management strategy. Given the rising number of cases, the emergence of new mutants of the novel coronavirus, and repeated lockdowns in several parts of the world, there is a lot of confusion and distress among the common people. Even though 80.4 % (109.20 million) of the infected people recovered, 30–40 % (32.76–43.68 million) of those who recovered may suffer from anxiety, depression, sleep disturbances, and post-traumatic stress disorder for up to even six months. Saffron is a natural product that could help alleviate the symptoms of severe acute respiratory syndrome coronavirus 2 (COVID-19) patients and manage the post-covid long-term sub-acute and chronic abnormalities associated with COVID-19 patients. Saffron can be used to manage stress and anxiety during prolonged lockdown, isolation, and quarantine. Its efficacy in depression management is comparable with drugs like fluoxetine, imipramine, citalopram. It is a potential adjuvant in the form of an immunity-supplement and anti-depressant in future drug formulations. Detailed research on dosage, method of administration, efficacy, etc., needs to be undertaken to explore the potential of saffron in managing the health issues arising because of the COVID-19 pandemic.

Declarations

Author contribution statement

AMH (1st author) conceived, conceptualized, analysed, presented and wrote the paper, with significant inputs from KNJ (2nd) and GAW (3rd) in the preparation of tables and literature review.

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The authors declare no conflict of interest.

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