Herbal Medicines Journal **2024; in press**
ISSN: 2538-2144

Review Article

Potential Therapeutic Effects of Saffron on Long COVID

Fangqing Xie[1*]

[1]Institute of Applied Physics, Karlsruhe Institute of Technology (KIT), Campus South, 76131 Karlsruhe, Germany

Received: 11.10.2023; Accepted: 13.07.2024

Abstract

Individuals with post-acute COVID-19 syndrome, alternatively called long COVID, have been found to have traces of the virus, viral RNA, and viral proteins. The mechanism behind long COVID is related to a destabilized and hyperactive immune system, impaired oxygen delivery caused by micro-clotting, chronic inflammation, and disruption of cellular energy metabolism. No specific treatment has been developed for long COVID to date. However, traditional Chinese medicine (TCM) suggests that saffron may help activate blood circulation, dissipate blood stasis (thrombosis), and toxins (free radicals). Saffron contains crocin, crocetin, and safranal, which have anti-inflammatory properties, promote blood circulation, scavenge blood clots, and enhance oxygen transport as well as diffusivity. Moreover, safranal has protective effects on the central nervous system (CNS), and is an anti-ischemic agent. Thus, saffron tea may have therapeutic effects on long COVID, either alone or in combination with anti-viral capsules of 1,8-cineole, which is an over-the-counter medicine to combat respiratory diseases.

Keywords: Post-acute COVID-19 syndrome, Thrombosis (micro-clots), Crocus sativus Linn (Saffron), Eucalyptol (1,8-Cineole), SARS-CoV-2

***Corresponding Author:** Fangqing Xie Institute of Applied Physics, Karlsruhe Institute of Technology (KIT), Campus South, 76131 Karlsruhe, Germany. Email: fangqing.xie@kit.edu

Please cite this article as: Xie F. Potential Therapeutic Effects of Saffron on Long COVID. Herb. Med. J. 2024;in press.

Introduction

Around 5% of people infected with SARS-CoV-2 suffer from a prolonged illness called post-acute COVID-19 Syndrome or long COVID (1, 2). Many factors such as acute SARS-CoV-2, injury to one or more organs, the continuous presence of SARS-CoV-2 (3) or its fragments in specific tissues, reactivation of neurotrophic pathogens like herpesviruses due to COVID-19 immune dysregulation, interactions of SARS-CoV-2 with the host's microbiome and virome communities, clotting and coagulation issues, dysfunctional brainstem and vagus nerve signaling, the ongoing activity of primed immune cells, and autoimmunity caused by molecular mimicry between pathogen and host proteins may cause long COVID. Symptoms of long COVID include fatigue, muscle weakness, insomnia, palpitations, chronic rhinitis, dysgeusia, chills, a sore throat, headache (4), neurocognitive, metabolic, cardiovascular, and gastrointestinal determinants, anemia (5), thrombotic and cerebrovascular diseases, dysautonomia, and finally postural orthostatic tachycardia syndrome (6). Some long COVID patients exhibit the diagnostic conditions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) – a neuroinflammation-linked condition with various chronic symptoms, including severe fatigue, musculoskeletal pain, and

post-exertional malaise (4). Patients with long COVID may have various underlying biological drivers for non-mutually exclusive symptoms. Many studies have indicated multi-organ damage associated with COVID-19 in the heart, lungs, liver, kidneys, pancreas, and spleen (6).

1.1. Thromboinflammation

Some long COVID patients suffer damage to the cells and tissues that regulate blood flow. This damage is caused by the viral attack (7). It can lead to hypercoagulation, where platelets and endothelial cells interact with viral agents and inflammatory molecules, blocking small blood vessels and disrupting oxygen delivery (8-10). The theory of persistent microclots was approved by a team in South Africa, which found that such clots can remain in the blood of long COVID patients (11). These micro-clots, which are difficult to dissolve, contain many inflammatory molecules that can worsen clotting and endotheliitis (inflammation of the blood vessels). This can ultimately lead to tissue ischemia and hypoxia (Figure 1) (12), which can cause several of the persistent symptoms observed in long COVID patients. This can also account for the reduction in oxygen consumption observed after a cardiopulmonary exercise test (CPET) (12). Patients with COVID-19 are at increased risk of developing various cardiovascular diseases, including cerebrovascular disorders, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease (13).

The disruption of the circulatory system can cause endothelial dysfunction, leading to downstream impacts like deep vein thrombosis, pulmonary embolism, and bleeding events (6). Microclots are found in patients suffering from both acute COVID-19 and long COVID, which can increase the risk of developing thrombosis and be a potential therapeutic target. Removing and reversing these underlying endotheliopathy (14) is a significant therapeutic procedure that requires controlled clinical studies to determine its efficiency in patients with various comorbidities affecting SARS-CoV-2 infection and COVID-19 severity. The platelet and clotting grading system is a simple and cost-effective diagnostic method for early detection of long COVID, which is a significant factor for effective treatment, especially for decreasing clot burden and platelet hyperactivation (11).

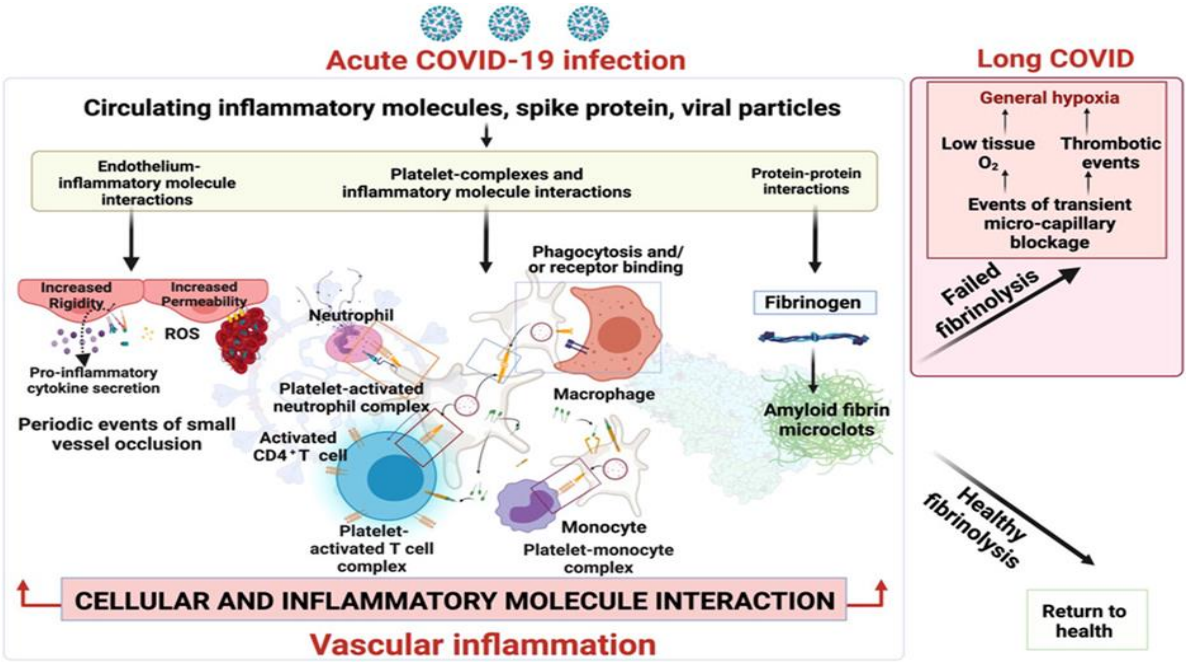

Figure 1. Clotting pathologies in long COVID. ROS, reactive oxygen species, created with BioRender.com. (Open access, courtesy of *Experimental Physiology*) (12).

1.2. Persistent Viral Fragments

Long COVID patients have been found to have

persistent viral fragments in various parts of their body, including the brain, muscles, gut, and lungs (15, 16). These virus fragments are definitively linked to long COVID symptoms, and drive the illness in long COVID patients (4). Viral antigen persistence is believed to reflect incomplete clearance of SARS-CoV-2 rather than subclinical (latent or persistent) infection, as the virus cannot replicate in biopsy-derived tissue. Only some viral transcripts were detected in biopsy specimens from the same patient (15), suggesting that not all patients have persistent viral fragments. Patients with gut antigen persistence who used qPCR exhibited the symptoms of long COVID, while none without evidence of antigen persistence in the gut reported long COVID symptoms. Thus, it could be strongly suggested that viral antigen persistence is effective in long COVID, and it is possible that SARS-CoV-2 antigen persistence, probably in infected tissues beyond the gut, could be effective on host immune responses underlying the long COVID syndrome (15, 17). SARS-CoV-2 antigen persistence in the gut is believed to be the basis for immune perturbation in long COVID (15). The viral proteins and/or RNA have also been found in the reproductive system, cardiovascular system, eyes, lymph nodes, appendix, breast tissue, hepatic tissue, plasma, stool, and urine (6).

1.3. The Haywire Immune System

Analysis of longitudinal measurements of over 6500 serum proteins revealed that individuals with long COVID exhibited evidence of persistent complement-mediated immunopathology associated with thromboinflammation (18). This finding addresses the gap between observed complement-activating features of SARS-CoV-2 and reports of microclots, vascular inflammation, and cardiovascular complications (13, 18). Autopsies of COVID-19 patients have also revealed signs of neurovascular injury accompanied by classical complement component deposition on endothelial cells and platelets (19). Machine learning algorithms have independently identified complement and thromboinflammatory markers as top protein biomarkers of active long COVID (18).

Moreover, in some COVID-19 patients, the immune system may be unable to reset itself to idle after being destabilized by the coronavirus attack(20, 21). Patients with long COVID have highly activated innate immune cells, lack naive T and B cells, and show high levels of the expression of type I IFN (IFN-β) as well as type III IFN (IFN-λ1) that remain persistently high up to 8 months after the infection. An abnormal immune profile was observed in patients with long COVID (21). The damage observed across diverse tissues has mainly been associated with immune-mediated response and inflammation rather than direct infection of cells by the virus.

1.4. Neurological and Cognitive Symptoms

Neurological and cognitive symptoms are significant aspects of long COVID. These symptoms may include sensorimotor symptoms, memory loss, cognitive impairment, paresthesia, dizziness, balance issues, sensitivity to light and noise, loss of (or phantom) smell or taste, and autonomic dysfunction. They often affect the individual's daily activities (6, 22).

Cognitive impairment is a condition that can occur independently of mental health issues like anxiety and depression. An investigation that covered over 1.3 million people suffering from COVID-19 revealed that while mental health conditions like anxiety and depression returned to normal over time, there was a continued risk of cognitive impairment (commonly referred to as "brain fog"), seizures, dementia, psychosis, and other neurocognitive conditions for at least two years (6, 23). Clinical evaluations conducted on pediatric patients with long COVID have revealed that both physical and mental health issues are common not only in children who have recovered from COVID-19 but also in those who are still experiencing long COVID symptoms. However, these issues were more prevalent in the long COVID group (24). Many long COVID patients experience fatigue and cognitive difficulties, which are commonly referred to as "brain fog." Cognitive problems can be caused by tiny clots in the brain that damage small fiber nerve cells and trigger dysautonomia. Therefore, it appears that long COVID symptoms like dysautonomia, brain fog, and fatigue may be linked to neurological issues (20). The tentative mechanisms for these neuropathologies include neuroinflammation, blood vessel damage caused by coagulopathy and endothelial dysfunction, and injury to neurons (6). Furthermore, a comparison of blood samples from 48 patients with long COVID who were

suffering from cognitive impairments and 15 long COVID patients without it indicated higher levels of inflammatory markers in the first group. This phenomenon suggests that chronic inflammation may drive these neurological symptoms (20, 25).

There is ongoing research on how SARS-CoV-2 causes neurological symptoms and cognitive-behavioral changes. Neuroimaging findings have been categorized into different subcategories, including headache and dizziness, cerebrovascular complications after stroke, intracerebral hemorrhage (ICH), cerebral microbleeds (CMBs), encephalopathy, meningitis, encephalitis and myelitis, altered mental status (AMS) and delirium, seizure, neuropsychiatric symptoms, Guillain-Barre syndrome (GBS) and its variants, smell and taste disorders, peripheral neuropathy, mild cognitive impairment (MCI), myopathy, and myositis. The goal is to put together these findings to give a comprehensive understanding of the effect of SARS-CoV-2 on the brain (26).

The evidence from cerebrospinal fluid and brain tissue implies that immune activation and inflammation within the central nervous system (CNS) contribute to neurological disorders in patients with acute COVID-19. An examination of brain tissue samples from patients who died due to acute COVID-19 revealed only limited detection of SARS-CoV-2 nucleic acid or viral protein in the CNS. This is in line with findings from live patients who underwent CSF testing (3, 4, 22).

It has been found that COVID-19 may damage the blood vessels in the brain, leading to neurological manifestations. This damage may be caused by the activation of endothelial cells and coagulopathy, which can lead to vascular dysfunction, including microbleeds or stroke (22, 26-28). High-field magnetic resonance examination of brain tissue showed microvascular damage in areas related to neurological symptoms of COVID-19. This damage is in line with widespread vascular injury observed in other organs. Researchers found that ischemic infarctions were present in 5.8% of ICU-treated patients six months after critical COVID-19. Moreover, cerebral microbleeds were observed in 39.1% of ICU-treated patients, 28.3% of ward-treated patients, and 17.4% of home-isolated COVID-19 patients, while 22.6% of non-COVID controls also exhibited these microbleeds (28).

Individuals with long COVID experience symptoms that are similar to those of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). ME/CFS is also regarded as a post-infectious syndrome caused by various infectious agents. Since the pathophysiology of ME/CFS is not well understood and no efficient disease-modifying therapies are available, investigations on long COVID may help ME/CFS patients (22).

Long COVID is a condition that occurs after the acute phase of COVID-19. Potential causes of long COVID are currently understood to be related to nervous system pathogenesis, which may include residual immune activation, persistent autoimmune disturbance, endothelial activation, vascular dysfunction, or injury accrued during acute disease (22). Long COVID is possibly due to long-term organ damage during the initial infection. Specific long-lasting inflammatory reactivity caused by organ damage, central nervous system complications, gastrointestinal distress, autoimmunity, endothelial dysfunction, and coagulation dysregulation have all been found to be associated with the development of long COVID pathogenesis (29). Unfortunately, there is currently no particular treatment for long COVID at present. The symptoms of long COVID are related to impaired oxygen delivery due to micro-clotting and disruption of cellular energy metabolism. Treatment strategies that address these underlying mechanisms are still being developed (1, 12).

2. Utilization of Saffron in Ethnopharmacology

Saffron, which is the dried stigma of Crocus sativus L., has been used for centuries in traditional medicine for its healing features and for treating several pathological disorders (30). The use of saffron can be traced back to the Minoan civilization of 1550 B.C. in Egypt, inscribed in the Papyrus Eber. During the reign of Ashurbanipal (7th century B.C.), the Assyrians first documented the therapeutic significance of saffron in their botanical dictionary. In traditional Persian medical literature, saffron (C. sativus "Hausknechtii") was extensively cultivated and used for medicinal purposes in ancient Persia. Ancient Persians also practiced saffron bathing to relieve fatigue or to cool off. Alexander the Great later promoted the saffron-bathing practice to Greek soldiers (356 B.C.–323 B.C.) during their Asian campaigns (31). The healing features of saffron were also described in Materia Medica, Pedanio Dioscorides, a Greek medical practitioner of the first century A.D.(32). Saffron was introduced to China through the Silk Road in the Western Han Dynasty (202 B.C.–8 B.C.). Firstly treated as a precious spice, it later became a highly efficient gynecological medicine in traditional Chinese Medicine (TCM) (31, 33).

The main chemical constituents of saffron are crocin, crocetin, and safranal, which have a wide spectrum of biological activities, including antigenotoxic, antioxidant, anticancer, anti-inflammatory, antiatherosclerotic, antidiabetic, antihyperlipidemic, antidegenerative, antidepressant, and anti-anxiolytic properties (34-37). Saffron has been used in the treatment of several disorders, including bronchitis, asthma, cephalalgia, pharyngoplasty, vomiting, fever, epilepsy, inflammations, skin diseases, septic inflammations, stimulating circulation, neurological disorders, cardiovascular diseases, cardiac ischemia, hypotensive, cancer, type 2 diabetes, hypoglycemic, erection dysfunction, infertility, premenstrual syndrome, and primary dysmenorrhea (32, 36-40).

3. Saffron's Most Bioactive and Medicine-Benefiting Constituents: Crocin, Crocetin, and Safranal

Saffron is a herb with almost 70 bioactive constituents, making it unique. This herb's main constituents are crocin, picrocrocin, crocetin, and safranal, which give saffron its unique color and taste (41, 42). These four constituents determine the quality of saffron, with higher percentages indicating better quality and, as a result, stronger properties (33). The yellow-orange color of saffron comes from a-crocin, while the spicy taste comes from the bitter picrocrocin. The main aroma-active constituent is safranal. Figure 2 illustrates the molecular structures of three constituents in saffron that have medicinal benefits, namely crocin, crocetin, and safranal.

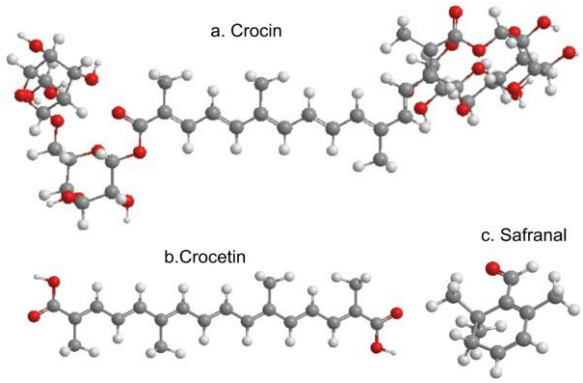

Figure 2. Molecular Structures of the Three Most Bioactive Constituents of Saffron: (a) Crocin, (b) Crocetin, (c) Safranal.

3.1. Crocin

Crocin is a carotenoid synthesized in the flowers of Crocus sativus L. and gardenia plants. Saffron contains six different types of crocin, each with a distinct glycosyl ester. The most abundant type is trans-crocin-1, which has a high water solubility (43, 44). Crocin has been found to have numerous medicinal benefits, including anti-inflammatory, antioxidative, antidepressant, anticonvulsant, analgesic, anti-cancer, and other therapeutic properties. It can impact various bodily systems such as the cardiovascular, immune, respiratory, genital-urinary, and central nervous systems. Research on crocin's biological and pharmacological properties has been conducted both in vitro and in vivo. It interacts with various cellular signaling pathways, and has been found to improve memory and act as an anxiolytic, aphrodisiac, and neuroprotective agent. Crocin is effective in controlling pathological conditions such as oxidative stress, inflammation, metabolic disorders, neurodegenerative disorders, and cancer. It has also been found that crocin protects the cardiovascular system by inhibiting toll-like receptors (45). Crocin has therapeutic effects on autoimmune diseases (46) and can improve the ethanol-induced impairment of learning behavior in mice (47).

3.2. Crocetin

Crocetin is a natural aglycone found in saffron and the fruit of Gardenia jasminoides J. Ellis of Rubiaceae, as illustrated in Figure 3. It can also be produced as a bioactive metabolite by the hydrolysis of crocin in biological systems. Modern pharmacological investigations have shown that crocetin possesses various properties, including cardioprotective, hepatoprotective, neuroprotective, antidepressant, antiviral, anticancer, atherosclerotic, antidiabetic, kidney protection, ocular pathologies, and memory-enhancing properties.

Figure 3. Original plants and medicinal materials of *Crocus sativus* L. and *Gardenia jasminoides* Ellis (48). (A) *C. sativus* L. flower (the picture comes from http://www.plantsoftheworldonline.org/); (B) dried stigmas of *C. sativus* L.; (C) the fruits of *G. jasminoides* Ellis. (The picture comes from http://www.360doc.com); (D) dried fruits of *G. jasminoides* Ellis. (Open access, Courtesy of Frontiers in Pharmacology).

Crocetin can act through various mechanisms such as improving the rate of oxygen transport and diffusivity, inhibiting pro-inflammatory mediators, protecting cells from reactive oxygen species (ROS) damage, and stimulating apoptosis in cancer cells (48). Studies have investigated the impact of crocetin on platelet activity and thrombosis. It has been found that crocetin can reduce collagen-induced platelet aggregation in rats. The beneficial effects of crocetin on platelet activity and thrombosis formation may be related to the inhibition of Ca^{2+} elevation in stimulated platelets (49).

Generally, crocetin has shown the highest efficacy in gastrointestinal transport. It is known that crocetin can pass through the intestinal barrier. As it has been indicated in several studies, crocetin can be quickly absorbed into the blood via the gastrointestinal tract, reaching peak plasma concentration for a short period. After oral administration, crocetin derived from saffron-extracted crocin was more bioavailable than pure crocetin, indicating the greater bioavailability of crocin into enterocytes for later absorption than that of crocetin (48, 50).

3.3. Safranal

Safranal is a compound responsible for the unique odor of saffron. It is produced from picrocrocin through hydrolysis. Esmaeilzadeh *et al*. conducted a review study in which they reported that most studies on safranal are related to its effects on the central nervous system (CNS). These effects include antianxiety, analgesic, anticonvulsant, anti-ischemic, and anti-tremor effects, as well as memory enhancement, and protective effects against neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases. Other impacts of safranal include antiasthmatic, antihypertensive, anti-aging, and anticataract properties. Furthermore, safranal has been shown to have protective effects against metabolic syndrome and diabetic nephropathy. Safranal's pharmacological effects involve various mechanisms such as antioxidant, anti-inflammatory, antiapoptotic, regulatory, and muscle relaxation effects on the genes and protein expression related to the oxidative stress signaling pathways, inflammation, apoptosis, proliferation, etc. (51).

4. Potential Therapeutic Effects of Saffron on Long COVID

Traditional, complementary, and integrative medicine (TCIM) can significantly address global health challenges. By combining empirical data and experiential wisdom with a safety-assured scientific approach, TCIM can enhance health outcomes and provide culturally sensitive health services. Saffron has been the most expensive spice in the world for over 5000 years, and has been used as a traditional medicine in Ethnopharmacology. Ethnopharmacology uses saffron to treat ailments such as bronchitis, cephalalgia, pharyngoplasty, vomiting, fever, epilepsy,

inflammations, skin diseases, septic inflammations, and stimulating blood circulation (31, 32, 37). The most bioactive and medicine-benefiting constituents of saffron are crocin, crocetin, and safranal. These active constituents have exhibited anti-thrombotic, anti-inflammatory, immunomodulatory, and anti-depressant effects, which may provide therapeutic benefits for long COVID.

4.1. Anti-Thrombotic Effects of Scavenging Micro-Clots in the Blood of Long COVID Patients

Some studies suggest a persistent virus is linked to long COVID symptoms (4). Platelets and endothelial cells may interact with viral products and inflammatory molecules, causing hypercoagulation, which can lead to micro-clots blocking small blood vessels. They affect oxygen delivery, and ultimately cause systemic tissue ischemia as well as hypoxia (8-10, 12). In the 2020 edition of Chinese pharmacopoeia, saffron was shown to activate blood circulation, dissipate blood stasis, scavenge toxins in blood, and disperse depression (52). Gardenia fruits mashed with rice wine are applied locally to reduce swelling, relieve pain, and promote blood circulation for patients with acute sprains and contusions (53). Blood clots frequently form in bruised regions with sprains and contusions (54). Both saffron and gardenia fruits contain crocetin, which has been found to reduce collagen-induced platelet aggregation and prevent thrombosis (48, 55). Network pharmacology analysis showed that saffron has significant anti-thrombotic effects (56), particularly in the arterial part, making it a suitable supplement and complementary therapy for preventing or mitigating cardiovascular disease risk factors (57). Moreover, safranal, a component of saffron, has been shown to have anti-ischemic effects (51). A combination of safranal and crocetin is believed to synergistically scavenge micro-clots in patients with long COVID (58).

4.2. Anti-Inflammatory and Immunomodulatory Effects of Saffron on Long COVID

The present evidence suggests that inflammation and autoimmunity are the primary causes of long COVID (29). Some COVID-19 patients experience an overactive immune system that cannot reset itself to a resting state after being attacked by the virus (20, 21). Furthermore, long COVID patients with cognitive impairments have been found to have higher levels of inflammatory markers in their blood (20, 25). The underlying causes of long COVID symptoms are impaired oxygen delivery due to micro-clotting, disruption of cellular energy metabolism, a revved-up and destabilized immune system, and chronic inflammation.

Carotenoids that can impact immunity are abundant in saffron. A randomized, double-masked, placebo-controlled clinical trial involving healthy men aged 21.4 ± 0.8 years indicated that the sub-chronic daily use of 100 mg saffron has transient immunomodulatory effects without any adverse effect (59). Its main active components such as crocins, crocetin, and safranal have been shown to have protective effects against immune diseases, anti-inflammatory activities, and molecular mechanisms on the immune system. Moreover, saffron is known to inhibit key pro-inflammatory enzymes such as myeloperoxidase (MPO), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), phospholipase A2, and prostanoids, while also enhancing antioxidant capacity and acting as a free radical scavenger. As an anti-inflammatory and immunomodulatory agent, it modulates inflammatory mediators, humoral immunity, and cell-mediated immunity responses. In summary, saffron is a health-promoting agent with significant benefits in immune-related disorders (60-62).

4.3. Antidepressant Effects of Saffron on Long COVID

Saffron has been found to have beneficial impacts against several human neurological disorders, including depression, anxiety, and sleeping alterations (63). Its antidepressant effects have been investigated in several studies, and a recent meta-analysis approved its efficiency for the treatment of major depression. So far, research has confirmed the beneficial effects of the use of saffron in the treatment of mild-to-moderate depression (64). In various double-blind, placebo-controlled, single-center, and randomized trials, saffron was found to produce significantly better outcomes than the placebo or similar outcomes to fluoxetine and imipramine (antidepressant medications) in the treatment of mild-to-moderate depression (65-68). Saffron's therapeutic effects are due to its bioactive molecules, particularly crocins, which have been shown to act as a monoamine oxidase type A and B inhibitor. Moreover, saffron inhibits the reuptake of monoamines,

exhibits N-methyl-D-aspartate antagonism, and improves brain-derived neurotrophic factor signaling (69).

4.4. Scavenging the Persistent SARS-CoV-2 and Its Fragments with 1,8-Cineole and Saffron

Scientific evidence suggests that 1,8-cineole is effective against RNA and DNA viruses (70, 71). A literature review showed that 1,8-cineole could combat several viruses, including HSV-1/HSV-2, SARS-CoV-1, E7 and E19, Coxsackie virus B1/B3, and JUNV (72). It is important to note that SARS-CoV-1 shares 96% genetic similarity with SARS-CoV-2. Some patients who have recovered from acute COVID-19 still have traces of the virus (15). 1,8-cineole is a compound with multiple benefits against SARS-CoV-2 and can target different parts of the virus (73, 74). Moreover, SARS-CoV-2 may dysregulate the host immune response during acute COVID-19 as if it allows previously harbored pathogens such as herpesvirus (HSV) to reactivate, infect new body sites, and cause new chronic symptoms (4). Recent studies have suggested that saffron extract and its major ingredients, crocin, and picrocrocin, may also have antiviral activity against HSV. These compounds could be promising anti-HSV agents for herbal therapy against viral infections. Monoterpenes aldehyde showed higher anti-HSV effects after the virus penetrated the cells. These sugar-containing compounds extracted from saffron were shown to be effective antiherpetic drug candidates (75). Therefore, 1,8-cineole alone or combined with saffron could regulate host microbiome/virome balance through their antimicrobial and antiviral activities.

Figure ٤. Saffron (1 g) Tea with Boiled Water (300 ml).

4.5. Metabolization

In Chinese pharmacopoeia (52), it is recommended to decoct or soak saffron (1-3g) in boiling water for oral administration, as displayed in Figure 4.

Daily doses of up to 1.5 g of saffron are safe (76). The most beneficial and bioactive constituents of saffron are safranal (150.21 g/mol), crocin (976.96 g/mol), and crocetin (328.402 g/mol). Due to their chemical volatility characteristic, these constituents are small aromatic volatile molecules that can add therapeutic value to saffron. Crocetin was quickly absorbed into the blood circulation when orally given and was found in plasma as an intact free form and as glucuronide conjugates (crocetin-monoglucuronide and -diglucuronide). In mice plasma, crocetin and its glucuronide conjugates were found in crocin-administered samples, while intact crocin (glycoside forms) was not found. These results suggest that orally administered crocin is hydrolyzed to crocetin before or during intestinal absorption, and absorbed crocetin is partly metabolized to mono- and diglucuronide conjugates. Pharmacological investigations of safranal (29) have shown that it has several drug-like attributes such as adherence to Lipinski's rule of five, optimum lipophilicity, high permeability, low blood-to-plasma ratio, less to moderate propensity to interact with P-glycoprotein or breast cancer-resistant protein transporters, and high plasma protein binding, which are common to most of the marketed drugs. These attributes were confirmed using in vitro and ex vivo models (77). Based on the documents cited in Sections 3 and 4, saffron or its most beneficial and bioactive constituents such as safranal, crocin, and crocetin, should be considered promising therapeutic candidates against long COVID. However, systematic clinical studies are required to confirm their beneficial impacts on humans.

5. Toxicity and Safety

Saffron contains three most bioactive components beneficial for medicinal purposes, i.e. crocin, safranl, and crocetin. Crocin is considered to be a low-toxic agent. Safranal is also safe to use when taken orally, but it may have some toxicity when given intraperitoneally (32). Crocetin can selectively target cancer cells and is promising for cancer prevention. It has negligible

toxicity towards normal cells and is non-toxic when taken orally (48).

However, it is essential to consume saffron cautiously. It can cause rhythmic uterine contractions, which can lead to miscarriages in pregnant women if taken in large doses. During menstruation, saffron can cause abdominal pain, diarrhea, and depletion of circulating blood volume due to uterine contractions. Therefore, saffron is not recommended for pregnant women and those experiencing heavy bleeding during menstruation (78). Overdosing can lead to abortions with a high risk of maternal death.

Consuming high doses of saffron can also cause narcotic and ecstasy effects, leading to temporary paralysis. Patients who have just undergone surgery or have obvious bleeding wounds should not take saffron as it may hinder wound healing and even worsen bleeding (31, 79). Saffron tea should be avoided by long COVID patients who have cerebral microbleeds (26).

Conclusion

Saffron is used in traditional Chinese medicine (TCM) to activate blood circulation, dissipate blood stasis (thrombosis), and remove toxins (free radicals) from the blood (52). The major components of saffron that are beneficial for health are crocin, crocetin, and safranal. Crocin is effective in controlling various pathological conditions such as oxidative stress, inflammation, metabolic disorders, neurodegenerative disorders, and cancer. It also protects the cardiovascular system (45). Conversely, crocetin can help promote blood circulation, reduce swelling and pain, and scavenge blood clots (53, 54). It has been shown that safranal can protect the central nervous system and has anti-ischemic properties (51). Saffron's bioactive constituents can also affect cellular and humoral immunity functions, which may be beneficial. Its immunomodulatory activity can directly target toll-like receptors (TLRs) and downstream signaling pathways (80), which include nuclear factor (NF-κB) and activator protein 1 (AP-1). For long COVID patients who still have viral RNA, viral proteins, and even traces of the SARS-CoV-2 virus (15), Soledum Forte 200 mg capsule (1,8-cineole) with its antivirus property for respiratory diseases can be used to eliminate the rest of the virus (74, 81). Combining saffron tea with Soledum Forte 200 mg capsules, an over-the-counter medicine in Germany, can provide therapeutic benefits for long COVID patients.

Acknowledgements

The author would like to thank Jin Wu and Elaine Qinyi Xie for their valuable discussions. The Werner Siemens Foundation funded the author through the Center for Single-Atom Electronics and Plasmonics.

Funding

None.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Hanson SW, Abbafati C, Aerts JG, Al-Aly Z, Ashbaugh C, Ballouz T, et al. Estimated global proportions of individuals with persistent fatigue, cognitive, and respiratory symptom clusters following symptomatic COVID-19 in 2020 and 2021. Jama. 2022;328(16):1604-15.
2. WHO Expert Meeting on Evaluation of Traditional Chinese Medicine in the Treatment of COVID-19: WHO; 2022 [Available from: https://www.who.int/publications/m/item/who-expert-meeting-on-evaluation-of-traditional-chinese-medicine-in-the-treatment-of-covid-19.
3. Ghafari M, Hall M, Golubchik T, Ayoubkhani D, House T, MacIntyre-Cockett G, et al. Prevalence of persistent SARS-CoV-2 in a large community surveillance study. Nature. 2024:1-8.
4. Proal AD, VanElzakker MB. Long COVID or post-acute sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent symptoms. Frontiers in microbiology. 2021;12:1494.
5. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature. 2021;594(7862):259-64.
6. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nature Reviews Microbiology. 2023;21(3):133-46.
7. Pretorius E, Vlok M, Venter C, Bezuidenhout JA, Laubscher GJ, Steenkamp J, et al. Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. Cardiovascular diabetology. 2021;20(1):1-18.
8. Fogarty H, Townsend L, Morrin H, Ahmad A, Comerford C, Karampini E, et al. Persistent endotheliopathy in the pathogenesis of long COVID syndrome. Journal of thrombosis and haemostasis. 2021;19(10):2546-53.
9. Gavriilaki E, Eftychidis I, Papassotiriou I. Update on endothelial dysfunction in COVID-19: severe disease, long COVID-19 and pediatric characteristics. Journal of Laboratory Medicine.

2021;45(6):293-302.
10. Grobler C, Maphumulo SC, Grobbelaar LM, Bredenkamp JC, Laubscher GJ, Lourens PJ, et al. Covid-19: the rollercoaster of fibrin (ogen), d-dimer, von willebrand factor, p-selectin and their interactions with endothelial cells, platelets and erythrocytes. International journal of molecular sciences. 2020;21(14):5168.
11. Pretorius E, Venter C, Laubscher GJ, Kotze MJ, Oladejo SO, Watson LR, et al. Prevalence of symptoms, comorbidities, fibrin amyloid microclots and platelet pathology in individuals with Long COVID/Post-Acute Sequelae of COVID-19 (PASC). Cardiovascular diabetology. 2022;21(1):148.
12. Astin R, Banerjee A, Baker MR, Dani M, Ford E, Hull JH, et al. Long COVID: mechanisms, risk factors and recovery. Experimental physiology. 2023;108(1):12-27.
13. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nature medicine. 2022;28(3):583-90.
14. Chang JC. Molecular Pathogenesis of Endotheliopathy and Endotheliopathic Syndromes, Leading to Inflammation and Microthrombosis, and Various Hemostatic Clinical Phenotypes Based on "Two-Activation Theory of the Endothelium" and "Two-Path Unifying Theory" of Hemostasis. Medicina. 2022;58(9):1311.
15. Zollner A, Koch R, Jukic A, Pfister A, Meyer M, Rössler A, et al. Postacute COVID-19 is characterized by gut viral antigen persistence in inflammatory bowel diseases. Gastroenterology. 2022;163(2):495-506. e8.
16. Stein SR, Ramelli SC, Grazioli A, Chung J-Y, Singh M, Yinda CK, et al. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. Nature. 2022;612(7941):758-63.
17. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nature medicine. 2020;26(7):1017-32.
18. Cervia-Hasler C, Brüningk SC, Hoch T, Fan B, Muzio G, Thompson RC, et al. Persistent complement dysregulation with signs of thromboinflammation in active Long Covid. Science. 2024;383(6680):eadg7942.
19. Lee MH, Perl DP, Steiner J, Pasternack N, Li W, Maric D, et al. Neurovascular injury with complement activation and inflammation in COVID-19. Brain. 2022;145(7):2555-68.
20. Couzin-Frankel J. Clues to long COVID. Science. 2022;376(6599):1261-5.
21. Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CML, Patel SK, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nature immunology. 2022;23(2):210-6.
22. Spudich S, Nath A. Nervous system consequences of COVID-19. Science. 2022;375(6578):267-9.
23. Taquet M, Sillett R, Zhu L, Mendel J, Camplisson I, Dercon Q, et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. The Lancet Psychiatry. 2022;9(10):815-27.
24. Buonsenso D, Camporesi A, Morello R, De Rose C, Fracasso M, Valentini P. Paediatric long COVID studies should focus on clinical evaluations that examine the impact on daily life not just self-reported symptoms. Acta Paediatrica (Oslo, Norway: 1992). 2024.
25. Merad M, Blish CA, Sallusto F, Iwasaki A. The immunology and immunopathology of COVID-19. Science. 2022;375(6585):1122-7.
26. Ghaderi S, Olfati M, Ghaderi M, Hadizadeh H, Yazdanpanah G, Khodadadi Z, et al. Neurological manifestation in COVID-19 disease with neuroimaging studies. American Journal of Neurodegenerative Disease. 2023;12(2):42.
27. Lee M-H, Perl DP, Nair G, Li W, Maric D, Murray H, et al. Microvascular injury in the brains of patients with Covid-19. New England Journal of Medicine. 2021;384(5):481-3.
28. Ollila H, Pihlajamaa J, Martola J, Kuusela L, Blennow K, Zetterberg H, et al. Brain magnetic resonance imaging findings six months after critical COVID-19: A prospective cohort study. Journal of Critical Care. 2024;80:154502.
29. Haque A, Pant AB. Long Covid: Untangling the Complex Syndrome and the Search for Therapeutics. Viruses. 2022;15(1):42.
30. Abu-Izneid T, Rauf A, Khalil AA, Olatunde A, Khalid A, Alhumaydhi FA, et al. Nutritional and health beneficial properties of saffron (Crocus sativus L): a comprehensive review. Critical reviews in food science and nutrition. 2022;62(10):2683-706.
31. Dai R-C, Nabil WNN, Xu H-X. The history of saffron in China: From its origin to applications. Chinese Medicine and Culture. 2021;4(4):228-34.
32. Christodoulou E, Kadoglou NP, Kostomitsopoulos N, Valsami G. Saffron: a natural product with potential pharmaceutical applications. Journal of Pharmacy and Pharmacology. 2015;67(12):1634-49.
33. Asgari M, Yu Q, Abdi M, Du G-L, Shen Y-H. Survey of the History and Applications of Saffron. Chinese Medicine and Culture. 2022;5(1):31-8.
34. Mirhadi E, Nassirli H, Malaekeh-Nikouei B. An updated review on therapeutic effects of nanoparticle-based formulations of saffron components (safranal, crocin, and crocetin). Journal of Pharmaceutical Investigation. 2020;50:47-58.
35. Moghaddasi MS. Saffron chemicals and medicine usage. J Med Plants Res. 2010;4(6):427-30.
36. Srivastava R, Ahmed H, Dixit RK, Saraf S. Crocus sativus L.: a comprehensive review. Pharmacognosy reviews. 2010;4(8):200.
37. Cerdá-Bernad D, Valero-Cases E, Pastor J-J, Frutos MJ. Saffron bioactives crocin, crocetin and safranal: Effect on oxidative stress and mechanisms of action. Critical Reviews in Food Science and Nutrition. 2022;62(12):3232-49.
38. Xing B, Li S, Yang J, Lin D, Feng Y, Lu J, et al. Phytochemistry, pharmacology, and potential clinical applications of saffron: A review. Journal of Ethnopharmacology. 2021;281:114555.
39. Lu C, Ke L, Li J, Zhao H, Lu T, Mentis AFA, et al. Saffron (Crocus sativus L.) and health outcomes: A meta-research review of meta-analyses and an evidence mapping study. Phytomedicine. 2021;91:153699.
40. Moshiri M, Vahabzadeh M, Hosseinzadeh H. Clinical applications of saffron (Crocus sativus) and its constituents: a review. Drug research. 2014:287-95.
41. Hosseini A, Razavi BM, Hosseinzadeh H. Pharmacokinetic properties of saffron and its active components. European Journal of Drug Metabolism and Pharmacokinetics. 2018;43:383-90.
42. Masoodi MH, Rehman MU. Edible Plants in Health and Diseases: Volume II: Phytochemical and Pharmacological Properties: Springer Nature; 2022.
43. Liakopoulou-Kyriakides M, Kyriakidis D. Croscus sativus-biological active constitutents. Studies in natural products chemistry. 2002;26:293-312.
44. Xi L, Qian Z. Pharmacological properties of crocetin and crocin (digentiobiosyl ester of crocetin) from saffron. Natural Product Communications. 2006;1(1):1934578X0600100112.
45. Boozari M, Hosseinzadeh H. Crocin molecular signaling pathways at a glance: A comprehensive review. Phytotherapy Research. 2022;36(10):3859-84.
46. Korani S, Korani M, Sathyapalan T, Sahebkar A. Therapeutic effects of Crocin in autoimmune diseases: A review. BioFactors. 2019;45(6):835-43.
47. Soeda S, Ochiai T, Shimeno H, Saito H, Abe K, Tanaka H, et al. Pharmacological activities of crocin in saffron. Journal of Natural Medicines. 2007;61:102-11.
48. Guo Z-L, Li M-X, Li X-L, Wang P, Wang W-G, Du W-Z, et al. Crocetin: a systematic review. Frontiers in Pharmacology. 2022;12:745683.
49. Yang L, Qian Z, Yang Y, Sheng L, Ji H, Zhou C, et al. Involvement of Ca2+ in the inhibition by crocetin of platelet activity

and thrombosis formation. Journal of agricultural and food chemistry. 2008;56(20):9429-33.
50. Asai A, Nakano T, Takahashi M, Nagao A. Orally administered crocetin and crocins are absorbed into blood plasma as crocetin and its glucuronide conjugates in mice. Journal of Agricultural and Food Chemistry. 2005;53(18):7302-6.
51. Esmaeilzadeh D, Moodi Ghalibaf A, Shariati Rad M, Rezaee R, Razavi BM, Hosseinzadeh H. Pharmacological effects of Safranal: An updated review. Iranian Journal of Basic Medical Sciences. 2023.
52. Saffron. Chinese Pharmacopoeia. 2020 Edition ed. p. 134-5.
53. Gardenia fruits. Chinese Pharmacopoeia. 2020 Edition ed. p. 259-60.
54. Thorsson O, Lilja B, Nilsson P, Westlin N. Immediate external compression in the management of an acute muscle injury. Scandinavian journal of medicine & science in sports. 1997;7(3):182-90.
55. Tsantarliotou MP, Poutahidis T, Markala D, Kazakos G, Sapanidou V, Lavrentiadou S, et al. Crocetin administration ameliorates endotoxin-induced disseminated intravascular coagulation in rabbits. Blood Coagulation & Fibrinolysis. 2013;24(3):305-10.
56. Jiang J, Lin S, Li Q, Jiang S, Hu Y, Jiang Y, et al. Comparative studies of the anti-thrombotic effects of saffron and HongHua based on network pharmacology. Tropical Journal of Pharmaceutical Research. 2020;19(7):1441-8.
57. Sinakosa ZM, Geromichalosb GD. The effect of saffron (Crocus sativus) carotenoids on hemostasis and atherosclerosis. Next Generation Sequence & Application. 2016;3:127.
58. Zamani M, Zarei M, Nikbaf-Shandiz M, Gholami F, Hosseini AM, Nadery M, et al. The effects of saffron supplementation on cardiovascular risk factors in adults: A systematic review and dose-response meta-analysis. Frontiers in Nutrition. 2022;9:1055517.
59. Kianbakht S, Ghazavi A. Immunomodulatory effects of saffron: A randomized double-blind placebo-controlled clinical trial. Phytotherapy Research. 2011;25(12):1801-5.
60. Zeinali M, Zirak MR, Rezaee SA, Karimi G, Hosseinzadeh H. Immunoregulatory and anti-inflammatory properties of Crocus sativus (Saffron) and its main active constituents: A review. Iranian Journal of Basic Medical Sciences. 2019;22(4):334.
61. Poma A, Fontecchio G, Carlucci G, Chichiricco G. Anti-inflammatory properties of drugs from saffron crocus. Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Inflammatory and Anti-Allergy Agents). 2012;11(1):37-51.
62. Boskabady MH, Farkhondeh T. Antiinflammatory, antioxidant, and immunomodulatory effects of Crocus sativus L. and its main constituents. Phytotherapy Research. 2016;30(7):1072-94.
63. Cerdá-Bernad D, Costa L, Serra AT, Bronze MR, Valero-Cases E, Pérez-Llamas F, et al. Saffron against neuro-cognitive disorders: an overview of its main bioactive compounds, their metabolic fate and potential mechanisms of neurological protection. Nutrients. 2022;14(24):5368.
64. Lopresti AL, Drummond PD. Saffron (Crocus sativus) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. Human Psychopharmacology: Clinical and Experimental. 2014;29(6):517-27.
65. Akhondzadeh S, Fallah-Pour H, Afkham K, Jamshidi A-H, Khalighi-Cigaroudi F. Comparison of Crocus sativus L. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial [ISRCTN45683816]. BMC complementary and alternative medicine. 2004;4:1-5.
66. Noorbala A, Akhondzadeh S, Tahmacebi-Pour N, Jamshidi A. Hydro-alcoholic extract of Crocus sativus L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. Journal of ethnopharmacology. 2005;97(2):281-4.
67. Basti AA, Moshiri E, Noorbala A-A, Jamshidi A-H, Abbasi SH, Akhondzadeh S. Comparison of petal of Crocus sativus L. and fluoxetine in the treatment of depressed outpatients: a pilot double-blind randomized trial. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2007;31(2):439-42.
68. Akhondzadeh S, Tahmacebi-Pour N, Noorbala AA, Amini H, Fallah-Pour H, Jamshidi AH, et al. Crocus sativus L. in the treatment of mild to moderate depression: a double-blind, randomized and placebo-controlled trial. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2005;19(2):148-51.
69. Siddiqui SA, Ali Redha A, Snoeck ER, Singh S, Simal-Gandara J, Ibrahim SA, et al. Anti-depressant properties of crocin molecules in saffron. Molecules. 2022;27(7):2076.
70. Reichling J, Schnitzler P, Suschke U, Saller R. Essential oils of aromatic plants with antibacterial, antifungal, antiviral, and cytotoxic properties–an overview. Complementary Medicine Research. 2009;16(2):79-90.
71. Wińska K, Mączka W, Łyczko J, Grabarczyk M, Czubaszek A, Szumny A. Essential oils as antimicrobial agents—myth or real alternative? Molecules. 2019;24(11):2130.
72. Tshibangu DS, Matondo A, Lengbiye EM, Inkoto CL, Ngoyi EM, Kabengele CN, et al. Possible effect of aromatic plants and essential oils against COVID-19: Review of their antiviral activity. Journal of Complementary and Alternative Medical Research. 2020:10-22.
73. Asif M, Saleem M, Saadullah M, Yaseen HS, Al Zarzour R. COVID-19 and therapy with essential oils having antiviral, anti-inflammatory, and immunomodulatory properties. Inflammopharmacology. 2020:1-9.
74. Xie f. Repurposing of 1,8-cineole gastric-resistant capsules for patients suffering from COVID-19. Research Gate. 2023.
75. Soleymani S, Zabihollahi R, Shahbazi S, Bolhassani A. Antiviral effects of saffron and its major ingredients. Current drug delivery. 2018;15(5):698-704.
76. Schmidt M, Betti G, Hensel A. Saffron in phytotherapy: pharmacology and clinical uses. Wiener Medizinische Wochenschrift (1946). 2007;157(13-14):315-9.
77. Dogra A, Kotwal P, Gour A, Bhatt S, Singh G, Mukherjee D, et al. Description of druglike properties of safranal and its chemistry behind low oral exposure. ACS omega. 2020;5(17):9885-91.
78. Dashti-Rahmatabadi M, Nahangi H, Oveisi M, Anvari M. The effect of Saffron decoction consumption on pregnant Mice and their offspring. SSU_Journals. 2012;19(6):831-7.
79. Modaghegh M-H, Shahabian M, Esmaeili H-A, Rajbai O, Hosseinzadeh H. Safety evaluation of saffron (Crocus sativus) tablets in healthy volunteers. Phytomedicine. 2008;15(12):1032-7.
80. Husaini AM, Jan KN, Wani GA. Saffron: A potential drug-supplement for severe acute respiratory syndrome coronavirus (COVID) management. Heliyon. 2021;7(5).
81. Colalto C. Volatile molecules for COVID-19: A possible pharmacological strategy? Drug Development Research. 2020;81(8):950-68.