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Saffron for *"toning down"* COVID-19-related cytokine storm: Hype or hope? A mini-review of current evidence

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ABSTRACT

Aim: To assess the potential role of saffron in downregulating inflammation and cytokine storm during COVID-19.

Main findings: Three main compounds of saffron, i.e., crocetin esters, picrocrocin, and safranal, present strong antioxidant and anti-inflammatory action for several disease states (e.g., Alzheimer's, cancer, and depression) but have also been studied in COVID-19. In particular, based on our comprehensive review of both *in vitro* and *in silico* studies, saffron's essential oils and other constituents appear to have both immunomodulatory and anti-asthmatic actions; these actions can be particularly helpful to treat patients with respiratory symptoms due to COVID-19. Moreover, crocin appears to reduce the COVID-19-related cytokine cascade and downregulate angiotensin-converting enzyme 2 (*ACE2*) gene expression. Last, *in silico* studies suggest that saffron's astragalin and crocin could have inhibitory actions on SARS-CoV-2 protease and spike protein, respectively.

Conclusion: Saffron represents a promising substance for toning down cytokine storm during COVID-19, as well as a potential preventive treatment for COVID-19. However, appropriate randomized clinical trials, especially those using biomarkers as surrogates to assess inflammatory status, should be designed in order to assess the clinical efficacy of saffron and allow its use as an adjunct treatment modality, particularly in resource-poor settings where access to drugs may be limited.

1. Introduction

COVID-19 represents the most important pandemic of the 21st century so far. Among the many features of infection, the clinical manifestations and biological underpinnings linked to inflammatory processes have received significant attention [1]. In particular, the lung injury caused by SARS-CoV-2 activates inflammatory T cells and monocytes that start to produce interleukins such as Interleukin-1, -6, -8, -10. The production of the latter leads to cytokine release syndrome that causes injuries to multiple organs such as the liver, heart, kidney, and brain [2].

There are several therapeutic options for managing COVID-19, such as remdesivir, convalescent plasma, supportive care, monoclonal antibodies, interleukin-6 (IL-6) receptor inhibitors, Janus Kinase inhibitors, and corticosteroids [3]. Regarding the latter, the targeted glucocorticoid receptor regulates several thousand genes), thus providing a solid evidence as a treatment for COVID-19 [4–6]. Moreover, monoclonal antibodies have shown promising results, especially those targeting different proteins of SARS-CoV-2, but have been linked to reduced emergence of novel viral variants [7].

Considering that a major part of the world's population depends on phytomedicine (e.g., 80% of the population in Africa), we briefly review the evidence status regarding anti-inflammatory actions of saffron on COVID-19, following similar reviews with other phytochemical products

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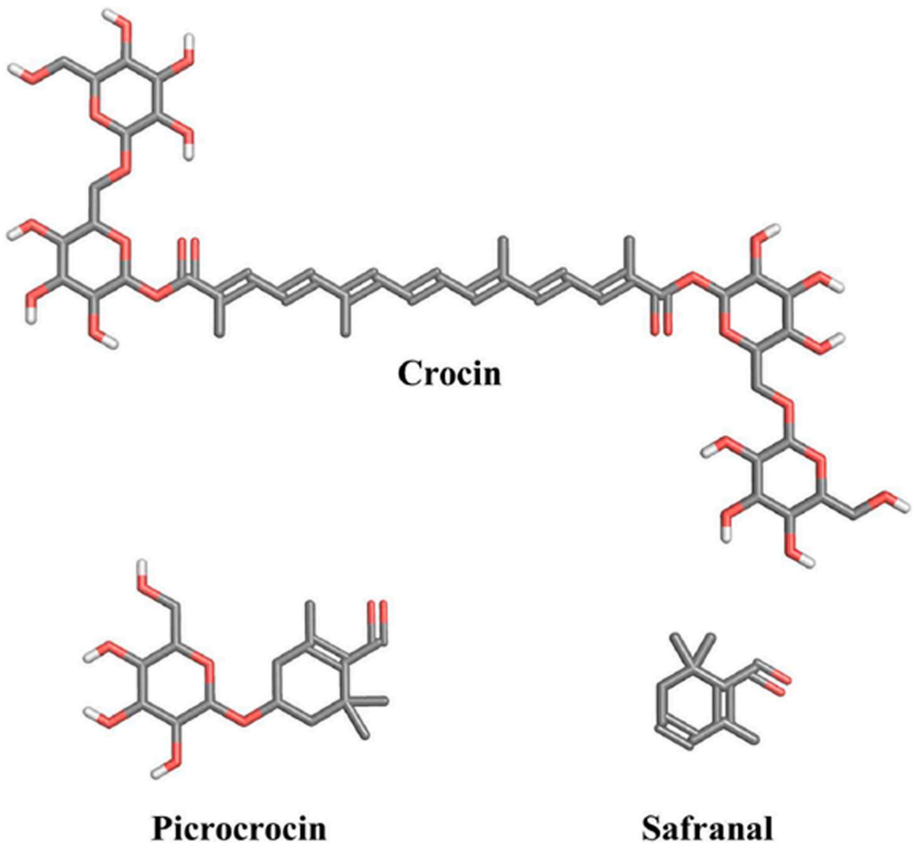

Fig. 1. Chemical structures of Crocin, Picrocrocin and Safranal from saffron.

[8–11]. These findings could stimulate further research in the field, especially for use in countries where access to healthcare and medications are limited.

2. Overview of saffron and its biological activities

Medicinal use of saffron can date back thousands of years, with the earliest evidence of the plant depicted on artifacts from the Aegean Bronze Age around 3,000–1,100 BC [12,13]. Saffron is used to treat various ailments as part of traditional medicine practiced in a number of countries and cultures [13]. Traditional applications of saffron range from treating skin or metabolic conditions (such as erysipelas and diabetes in traditional Iranian medicine or acne in traditional Greek medicine to sexual dysfunction, as saffron is believed to possess aphrodisiac properties [14–16]. Saffron historically makes up part of both the Unani Medicine, which used saffron as an antidote during periods of *Amra-z-e-Waba* (a term applied to denote rather fatal epidemics) [17], and Persian Medicine. Of note, textual searches for compounds with potential actions against respiratory diseases have increased in light of the COVID-19 [18].

The dried stigma is the portion of the *Crocus sativus* saffron flower used for culinary and medicinal purposes [13]. Among the over 150 chemical compounds identified in the stigma, the three main compounds are crocetin esters, picrocrocin, and safranal (**Fig. 1**) [19–22]. The intense yellow color of saffron is attributed to the crocetin esters called crocins, which are glycosylated carotenoids. The latter vary in form and concentration depending on the saffron quality, and they can make up between 25 and 35% of total dry saffron weight [19,20]. The bitter taste of saffron is due to picrocrocin, a precursor of safranal, [19,20]. Over 40 compounds are responsible for the aroma of saffron, of which the major compound is safranal [19,22,23]. The concentration of safranal is minimal in fresh stigmas, and is generated during the dehydration and preservation process from picrocrocin [14,19].

A number of studies have investigated the effects of crocins on diseases such as Alzheimer's disease, cancer, and depression [13,16,20]. The digentibiosyl ester of crocetin, *trans*-crocin-4, was demonstrated *in vitro* to interrupt the aggregation process of β-amyloid protein, a process implicated in Alzheimer's disease progression [24–26]. This crocin was found to alter the aggregation pathway by directly binding to the plaque-forming fragment of β-amyloid [24]. These findings suggested that crocin can affect pathogenic aggregation in Alzheimer's disease directly through interaction with β-amyloid [24]. In another study investigating the effects of crocin on DNA damage in mice, *trans*-crocin-4 was found to significantly decrease DNA damage induced by methyl methanesulfonate, a known DNA alkylating agent [27]. Crocin reduced injury in mice liver and spleen about 4.7- and 6.6-fold, respectively, as determined by microscopic analysis of cell nuclei [27]. Crocin was also examined in a randomized, controlled clinical trial of 40 multiple sclerosis patients with primary endpoints of reduced inflammation and DNA damage [28]. Levels of inflammation biomarkers, tumor necrosis factor-α (TNF-α) and interleukin-17, and DNA damage, measured by an oxidation biomarker, were significantly diminished after 4 weeks of treatment with crocin compared to the placebo-treated group [28]. These results indicate that crocin exhibits anti-inflammatory and anti-oxidative actions [15] with the potential to attenuate disease progression or reduce the side-effects of antineoplastic agents [13,27,29].

The effect of picrocrocin on DNA damage appeared to be minimal, though it decreased the proliferation of human adeno- and hepatocarcinoma cell lines [30]. Reports on the actions of the deglycosylated form of picrocrocin, safranal, have been more extensive and highlighted its potential anticancer properties [31,32], as well as its effects in relieving depression, hunger, and inflammation [19,33]. Safranal was shown to exhibit anti-tumor activities against a neuroblastoma cell line by inhibiting cell proliferation and inducing apoptosis

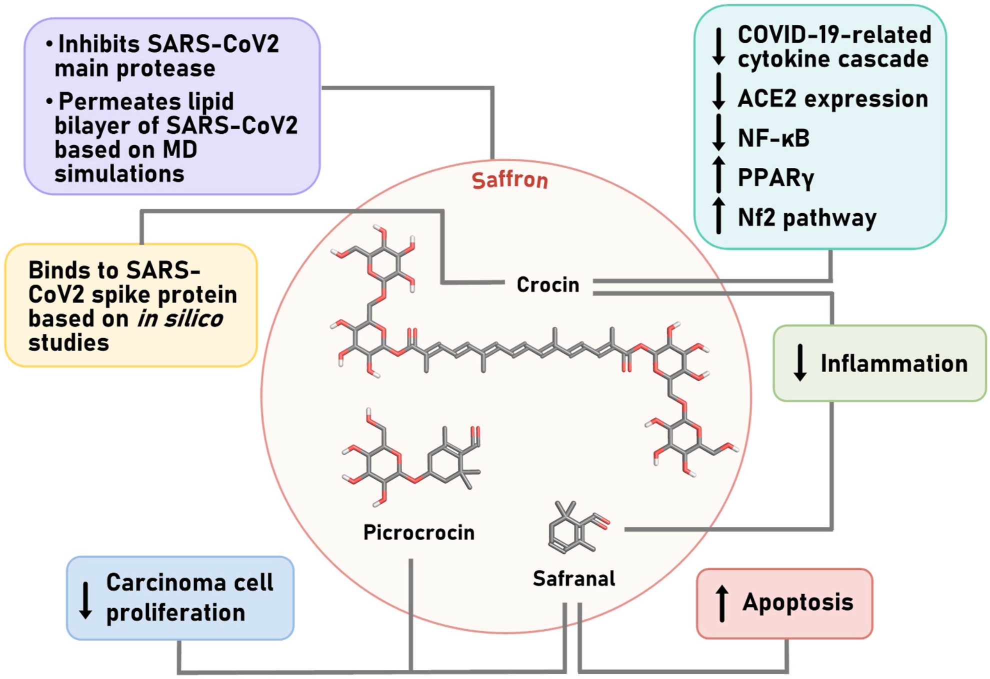

Fig. 2. Actions of Crocin, Picrocrocin and Safranal in COVID-19. **Abbreviations**: ACE-2: Angiotensin-converting enzyme 2; COVID-19: Coronavirus Disease; MD: Molecular Dynamics; Nf2: Neurofibromatosis Type 2 Protein; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PPARγ: Peroxisome proliferator-activated receptor gamma; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

[32]. A study using hepatocellular carcinoma cell lines demonstrated that safranal promotes cytotoxicity and apoptosis, through inhibition of DNA repair mechanisms and induction of endoplasmic reticulum stress [31]. These results indicate that the pro-apoptotic activity of safranal is mediated via up-regulation of cell-death proteins [31]. In addition to the anti-tumor activity attributed to safranal, anti-inflammatory properties have also been ascribed [33]. Using a colitis mouse model, researchers demonstrated that symptoms of inflammation were alleviated upon treatment with safranal [30]. Levels of interleukin-6 and TNF-α were reduced in safranal-treated mice, along with less crypt damage and macrophage infiltration in colon tissue compared to untreated mice [28]. These findings emphasize the potential of saffron-derived compounds in treating a number of conditions. We briefly expand on current research investigating saffron and its effects on inflammation associated with COVID-19, following a comprehensive search and presentation of the pertinent literature (**Supplementary File**). Fig. 2 depicts the potential actions of crocin, picrocrocin and safranal in COVID-19.

3. Current evidence on saffron in COVID-19-related cytokine storm

Saffron appears to be an important component of a diet with anti-inflammatory actions, as assessed on the basis of the dietary inflammatory index, alongside other ingredients such as turmeric, vitamin C, bromelain, and omega-3 fatty acids [11,34,35]. Of note, in addition to saffron, honey has been suggested as an important natural product with anti-inflammatory actions against COVID-19 [36]. Besides saffron, clove, garlic, galangal, licorice, and rhubarb in Persian Medicine, as well as fragrant herbs (which are used as sprays and fumigants), vinegar, and other compounds in Unani Medicine, have been traditionally used in diseases which are clinically similar to SARS-CoV-2 infection [37–40].

Principally, saffron's essential oils and other constituents appear to exhibit both immunomodulatory and anti-asthmatic actions. Saffron has been considered an immune-boosting component, which may be useful in patients with COVID-19 and a weak immune system [41]. The immune-promoting action of saffron could be attributed mostly to its activity on Toll-like receptors, other inflammatory signaling pathways, increasing the levels of IgG, Th1–Th2 ratio, and less to a direct antiviral action on SARS-CoV-2 [41]. Nonetheless, recent *in silico* studies demonstrated that crocin-1 showed strong hydrogen bonding with the SARS-CoV-2 Receptor Binding Domain/ACE2 complex, implying a direct antiviral action of crocin-1 [42]. Moreover, based on additional *in silico* studies including molecular docking, saffron's astragalin was shown to inhibit the main protease rather than the spike protein of SARS-CoV-2, while crocetin exhibits high affinity for the spike protein as well as the main protease, as well as the ability to permeate the lipid bilayer based on molecule dynamics simulations [18,43,44].

Based on the antioxidant, anti-inflammatory properties of saffron, and experimental evidence, some investigators have proposed that crocin may: *a)* reduce the COVID-19-related cytokine cascade, *b)* lead to the upregulation of Peroxisome proliferator-activated receptor-gamma (PPARγ) and downregulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and *c)* downregulate ACE2 gene expression through activation of the Nf2 pathway [45]. Thus, researchers have called for future clinical trials in the field [45].

In addition, a plausible role of saffron on reducing anxiety and depression, most likely through inhibition of monoaminoxidase-b, has been proposed [41,46]. Therefore, the potential benefits of saffron could hold promise during the COVID-19 pandemic, particularly in the treatment of psychiatric and neurologic sequelae of the post-COVID syndrome [47].

Last, the broader importance of saffron has been re-appreciated during the pandemic's parallel efforts to address other medical emergencies, such as stroke, myocardial infraction, and other ischemic conditions. Of note, trans-sodium crocetinate, a successor of its prodromic molecule, crocin, is currently tested in clinical trials for its oxygen diffusion enhancement capability, as well as its potential to act as radiosensitizer for cancer treatment [48].

4. Conclusion

In summary, saffron is a promising, anti-inflammatory and anti-viral herbal medicine and may have an important role in the prevention of severe COVID-19; however, extensive studies and clinical trials are required before any use in clinical practice. We observed that saffron is consistently contextualized with other herbal medicine products to treat clinical symptoms that are similar, more or less, to those observed during COVID-19. Further research towards use of a combination of medications including saffron are needed to determine its efficacy and safety in treating and/or preventing COVID-19. The active saffron compounds present promising pharmacological agents and may serve as templates for the design of novel anti-viral (semisynthetic) compounds.

CRediT authorship contribution statement

Alexios-Fotios A. Mentis: Writing – original draft, conceived and designed the study. **Maria Dalamaga:** developed the search strategy, conceived and designed the study, revised the draft for important intellectual content. **Cuncun Lu:** developed the search strategy, conceived and designed the study, revised the draft for important intellectual content. **Moschos G. Polissiou:** Writing – original draft, conceived and designed the study, All author approved the final version of the manuscript.

Declaration of competing interest

None to be declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2021.100111.

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