Review Article

Crocus sativus (saffron) and age-related macular degeneration

Ahmad Shamabadi [1], Hassan Asadigandomani [2], Kimia Kazemzadeh [2], Kimia Farahmand [2], Razman Arabzadeh Bahri [2] and Shahin Akhondzadeh [1]

[1] *Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, Tehran, Iran*
[2] *School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

ABSTRACT

Background: Age-related macular degeneration (ARMD) leads to impaired vision and potential blindness. Globally, it accounts for approximately 9% of vision loss cases, and a projected 288 million individuals will be affected by 2040. Current treatments have limitations such as variable effectiveness, high costs, and potential side effects. Additionally, atrophic ARMD management remains challenging. As saffron has shown promising neuroprotective and antioxidant effects by potentially delaying disease progression, this study aims to review the mechanistic, pre-clinical, and clinical evidence of the effects, safety, and tolerability of saffron in ARMD treatment.

Methods: The Scale for the Assessment of Narrative Review Articles was applied in this narrative review. To find relevant literature, the syntax "(saffron OR crocus) AND (retin* OR "geographic atrophy" OR "choroidal neovascular*" OR "macular degeneration")" was searched in PubMed/MEDLINE. Pre-clinical and clinical original investigations of the effects of saffron in ARMD along with the eligible studies cited in their reference lists were identified and included.

Results: Saffron and its active compounds, crocin and crocetin, have shown promising results in improving visual function and delaying ARMD progression. Several clinical studies have found that daily supplementation with 20–50 mg of saffron or 5–15 mg of crocin for 3–12 months significantly improved best-corrected visual acuity, contrast sensitivity, and retinal function as measured by electroretinogram and microperimetry, with benefits observed in both dry and wet forms of ARMD. The effects were independent of genetic risk factors and maintained during the follow-up periods, suggesting the potential role of saffron as a long-term treatment option. Saffron reduces ARMD progression via anti-angiogenic, neuroprotective, and antioxidant mechanisms. Moreover, saffron is safe and well tolerated.

Conclusions: Although further research is needed to confirm long-term safety and efficacy, current evidence supports the use of saffron or crocin supplements as a safe and tolerable adjunct therapy for ARMD management.

KEYWORDS

saffron, crocus sativus, saffron crocus, age related macular degeneration, macular degeneration, adverse drug reaction, clinical trial, herbal medicine, nutraceuticals, neuroimmunomodulation

Correspondence: Shahin Akhondzadeh, Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, South Kargar Street, Tehran, Iran. Email: s.akhond@neda.net. ORCID iD: https://orcid.org/0000-0002-2277-5101

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INTRODUCTION

Age-related macular degeneration (ARMD) is characterized by impairment of nutrient and waste material transportation between the retina and choroid in the macular region, negatively affecting visual acuity and potentially causing permanent central vision loss in its severe stages [1]. ARMD mainly affects individuals older than 55 years, is the main cause of irreversible blindness in developed countries, and accounts for approximately 9% of all global cases of complete vision loss [2]. In 2040, an estimated 288 million people will be affected by ARMD worldwide [3]. Visual consequences significantly decrease quality of life and increase morbidity in patients with ARMD. Affected individuals are at a greater risk of falling and require assistance if unable to perform routine activities. Vision impairment may also have psychiatric consequences such as depression [4]. The crude disability-adjusted life years for those with ARMD rouse by 46% during the past 30 years because of the longer life expectancy and growing populations [5]. The United States spent over $250 million per year on the diagnosis, treatment, and special care of patients with ARMD, constituting massive resource allocation and expenditures related to factors such as the expanding number of patients and costly available therapies [6].

ARMD is classified into three main stages: early, intermediate, and late. The disease is progressive, and visual complications often appear in the late stage [7]. The late stage is subdivided into atrophic (dry) and exudative (wet) ARMD. Exudative ARMD is more commonly associated with severe vision impairment. Symptoms of atrophic ARMD are the consequence of retinal pigment epithelium (RPE) degeneration and photoreceptor damage. In contrast, exudative ARMD presentations are mainly related to macular neovascularization in response to vascular endothelial growth factor (VEGF) secretion as a compensatory mechanism to repair retinal destruction. VEGF also increases blood vessel permeability, causing extravasation of fluids and plasma components and imbalances in retinal homeostasis, eventually leading to further vision deterioration with hemorrhages caused by these vessel abnormalities [4].

ARMD treatment is based on the disease stage; however, prevention is important in this regard. Evidence has identified smoking as a risk factor for the occurrence and progression of ARMD, and the risk may persist up to 20 years after smoking cessation [8]. Investigations on the effect of various dietary supplements suggested a small effect size in decelerating disease progression only in the intermediate stage [9]. Retinal laser therapy, as another potential treatment modality, has yielded no positive effect in the intermediate stage of ARMD [10].

In 2005, clinical evidence supported another treatment modality for exudative ARMD [11]. Intravitreal injection of anti-VEGF effectively sustains visual acuity in >70% of treated eyes, and approximately 20% experience an improvement in visual acuity after initial applications [12]. Anti-VEGF medications have been approved by the United States Food and Drug Administration, including ranibizumab, aflibercept, and brolucizumab, each with different therapeutic doses, frequencies of administration, and durations of treatment [2, 13, 14]. Generally, a monthly anti-VEGF injection is recommended for three consecutive months, followed by a treat-and-extend regimen [15]. Owing to treatment costs [13], this approach may be unsuitable for every affected individual. Additionally, multiple factors contribute to treatment outcomes, including time of diagnosis and treatment initiation, cost-effectiveness, adverse effects of injections such as endophthalmitis [16], patient adherence, and individual response to treatment [13]. Accordingly, individualized management strategies are of great interest [17].

Dry ARMD management is more challenging [18]. Recent studies have emphasized the role of complement pathway inhibitors, antioxidants, and neuroprotective agents in inhibiting retinal cell degeneration [19-22]. Neuroprotection can decrease the apoptosis associated with ARMD pathophysiology [23, 24]. Furthermore, the oxidative process and production of reactive oxygen species (ROS) are related to disease onset and progression [25, 26]. Additional studies with larger cohorts are necessary to clarify treatment efficacy, monitoring of disease progression, and prognosis determination [27].

Saffron is the dried stigma of a flowering plant, *Crocus sativus*, which mainly grows in the European-mediterranean region and Asia, and has been used in several therapeutic agents since the 16th century and is prominent in pharmacology and pharmacotherapy [28, 29]. Saffron comprises several metabolites, including carotenoids such as α-crocetin, glycoside crocin, picrocrocin, and aglycone-safranal, along with zeaxanthin and lycopene as antioxidants [30]. These bioactive components are responsible for the pharmacological features of saffron. Many studies on saffron metabolites reported an anti-apoptotic effect via inhibition of caspase-mediated apoptosis pathways, which are complicit in retinal damage [31-33].

Saffron act as antioxidants by depleting free radicals in oxidative stress [34, 35]. Moreover, the neuroprotective effect of saffron is mediated through safranal and crocetin as anti-apoptotic, anti-inflammatory, and antioxidant agents, preventing neuronal loss in neurodegenerative diseases such as Parkinson and Alzheimer's diseases [30, 36, 37]. Additionally, crocin and crocetin enhance retinal blood flow and oxygen diffusion, which inhibits VEGF production and neovascularization [38]. Several studies have reported that oral saffron supplements are safe and well tolerated [39-41].

The specific effects of saffron on the pathophysiology of ARMD and other diseases drew attention to its potential therapeutic and adjunctive roles in different ARMD stages [42]. Applying the Scale for the Assessment of Narrative Review Articles [43], this study reviews the mechanistic, pre-clinical, and clinical evidence of the effects, safety, and tolerability of saffron in ARMD treatment. As these characteristics are investigated, it is essential to explore how they translate into practical applications and patient outcomes in ARMD management. Understanding the clinical implications of saffron administration will provide a comprehensive view of its role in enhancing retinal health and preserving vision in this cohort.

METHODS

To find relevant literature for this narrative review, the syntax "(saffron OR crocus) AND (retin* OR "geographic atrophy" OR "choroidal neovascular*" OR "macular degeneration")" was searched in PubMed/MEDLINE. Original pre-clinical and clinical studies investigating the effects of saffron in ARMD were identified. Eligible articles comprised original studies without restrictions on type and design. Articles in the reference lists of included studies, if relevant, were further reviewed and cited.

RESULTS and DISCUSSION

Mechanistic insights and pre-clinical evidence

ARMD is assumed to have underlying inflammatory and oxidative mechanisms that result in retinal cell apoptosis [37]. Studies have demonstrated the beneficial effects of crocetin, the primary active compound in saffron, in reducing the progression of mild-to-moderate ARMD [36, 44-46]. Crocetin delays ARMD progression through two main pathways: anti-angiogenesis and neuroprotection [45, 47, 48]. Anti-angiogenesis is the inhibition of abnormal blood vessel formation, which can impair vision in patients with ARMD [49]. Neuroprotection involves safeguarding retinal cells from damage and degeneration, primarily by combating oxidative stress and reducing inflammation. These protective actions aid in maintaining retinal health and preventing further deterioration [45]. Additionally, the antioxidant properties of crocetin neutralize ROS, reducing oxidative damage in retinal tissues. Overall, the multi-faceted properties of crocetin highlight its potential as a therapeutic agent in managing ARMD [36].

In neovascular ARMD (nARMD), choroidal neovascularization (CNV) is a hallmark of disease progression, driven by the overexpression of VEGF and its receptors [50]. Current treatments, such as anti-VEGF agents, inhibit these pathways, reducing abnormal blood vessel growth and vascular permeability [50, 51]. Pre-clinical evidence has shown that saffron and its bioactive compound crocetin can modulate VEGF activity through alternative mechanisms, suggesting a potential complementary or novel therapeutic role in managing nARMD [48, 49, 52, 53].

The anti-angiogenic effects of crocetin was demonstrated in CNV and other diseases, such as gastric cancer [52]. For instance, crocetin reduces the expression of Sonic hedgehog and VEGF in malignant cells, thereby inhibiting their proliferation and angiogenesis [52]. In addition to the key role of VEGF in ARMD pathogenesis, the Sonic hedgehog pathway is crucial in retinal development, degenerative changes, and angiogenesis [54-56]. Therefore, inhibiting this important pathway may have a significant role in preventing CNV, and consequently, nARMD.

VEGF signaling primarily operates through the activation of VEGF receptor 2 (VEGFR2) on endothelial cells, triggering their proliferation and migration, and ultimately forming new blood vessels [57]. Thee VEGF/VEGFR2 signaling pathway is a key pathophysiological factor in the occurrence of CNV, making it a novel therapeutic target [58]. Zhao et al. demonstrated that crocetin effectively inhibited angiogenesis by targeting the VEGF/VEGFR2 signaling pathway, suggesting it as a potential treatment option for nARMD [49]. Crocetin disrupts VEGF binding by adhering to the VEGFR2 binding site through hydrophobic interactions and a hydrogen bond, thereby exerting its anti-angiogenic effects [49].

Matrix metalloproteinases (MMPs) are a group of enzymes that degrade components such as elastin, gelatin, and types I, IV, and V collagen. MMP levels increase under pathological conditions [59]. MMP-2 and MMP-9 accumulate

in the Bruch's membrane of eyes affected by ARMD, indicating a potential local enzymatic imbalance [60, 61]. Furthermore, studies using cell cultures have highlighted the role of MMP-2 and MMP-9 in CNV progression [62, 63]. Crocin and crocetin reduced the gene expression levels of MMP-2 and MMP-9, which are involved in inflammation and angiogenesis [47]. Thus, the reduction in levels of enzymes such as MMP-2 and MMP-9 may contribute to the protective effects of saffron on ARMD.

Impairment of the antioxidant defense system accelerates aging in RPE cells, leading to their degeneration and the onset of ARMD due to ROS accumulation [64, 65]. Natural antioxidant compounds can partially prevent RPE cells degeneration by reducing oxidative stress and enhancing the antioxidant defense mechanisms [66-68]. Additionally, the antioxidant effects of crocetin were investigated in several studies [69, 70]. Karimi et al. [71] demonstrated that the administration of crocetin in an *in vitro* RPE model subjected to oxidative stress induced by tert-butyl hydroperoxide effectively prevented lipid peroxidation, protected the cell membrane from damage, reduced the release of cytosolic contents, and maintained cytoskeletal organization [71]. Other potential beneficial effects of saffron on ARMD include the enhancement of anti-ROS compounds and anti-apoptotic genes as well as the inhibition of pro-apoptotic factors. For instance, Demirci Kucuk et al. [72] concluded that crocetin improved cell viability, increased superoxide dismutase and glutathione levels, and decreased malondialdehyde levels after H2O2-induced damage. Crocetin also reduced pro-apoptotic Bax and Nrf2 expression while increasing anti-apoptotic Bcl-2 expression and decreasing ROS levels [72].

Saffron reduces ARMD progression via anti-angiogenic, neuroprotective, and antioxidant mechanisms and has shown promising effects [45, 47-49]. Additionally, saffron counteracts the VEGF cascade, a key factor in nARMD pathogenesis, by disrupting VEGF/VEGFR2 binding and reducing the expression of MMP-2 and MMP-9 [47]. Its antioxidant effects also protect RPE cells from oxidative stress-induced degeneration [45].

Clinical evidence

Our literature review identified nine eligible clinical studies, the characteristics of which are detailed in Table 1 [42, 44, 46, 73-78]. In a randomized, double-blind, placebo-controlled crossover trial [44], 100 adults with mild-to-moderate ARMD with vision > 20/70 Snellen equivalent in at least one eye received either oral saffron supplementation (20 mg/day) or placebo for 3 months, followed by crossover for another 3 months. Compared to placebo, saffron supplementation modestly improved best-corrected visual acuity and multifocal electroretinogram (ERG) response density and latency, with similar benefits observed in participants already receiving age-related eye disease study (AREDS) supplements. The study concluded that saffron supplementation may provide additional visual benefits for patients with ARMD, and longer-term supplementation may yield greater improvements considering the chronic nature of this disease [44].

Marangoni et al. [73] investigated the effects of saffron supplementation on early ARMD and whether these effects were influenced by specific genetic risk factors: age-related maculopathy susceptibility 2 (*ARMS2*) and complement factor H (*CFH*). Over an average treatment period of 11 months, 33 patients received 20 mg/day of saffron, yielding significant improvements in focal ERG (fERG) amplitude and sensitivity after 3 months, benefits that were maintained during the follow-up. The study found no significant differences in functional improvements based on the patients *CFH* or *ARMS2* genotypes, suggesting that the beneficial effects of saffron are independent of these genetic risk factors [73]. Likewise, Broadhead et al. [42] evaluated the long-term effects of saffron supplementation (20 mg/day) over 12 months in patients with mild-to-moderate ARMD and vision > 20/70 Snellen equivalent in at least one eye. In this open-label extension trial involving 93 participants, the researchers found significant improvements in multifocal ERG (mfERG) response density, particularly in the central rings associated with visual function, indicating preserved retinal function. Although the best-corrected visual acuity declined slightly, the study concluded that saffron supplementation may benefit retinal health without significant adverse events, suggesting its potential role as a long-term treatment option for ARMD, independent of other agents such as AREDS supplements [42].

A longitudinal follow-up study by Piccardi et al. [74] assessed the long-term effects of saffron supplementation (20 mg/day) on central retinal function in 29 patients with bilateral early ARMD over 14 months. The study found significant improvements in retinal flicker sensitivity, measured by fERG, with mean sensitivity increased by 0.3 log units after 3 months and maintained throughout the follow-up period. Additionally, visual acuity was improved by two Snellen lines, indicating sustained benefits from saffron supplementation. Thus, saffron may induce long-term enhancements in macular function, supporting its potential as a management option for early ARMD [74]. In addition,

Falsini et al. [75] explored the impact of saffron supplementation (20 mg/day) on retinal flicker sensitivity in patients with bilateral early ARMD over a 12-month follow-up. Involving 25 participants, the research utilized fERG to measure changes in retinal function at 3-month intervals. Visual acuity and fERG sensitivity significantly improved, with mean visual acuity increasing by two Snellen lines and fERG sensitivity improving by 0.3 log units. These enhancements were maintained throughout the follow-up, suggesting that saffron supplementation can lead to sustained improvements in macular function for individuals with early ARMD [75].

Notably, an open-label, pilot trial by Majeed et al. [76] evaluated the effects of Macumax®, a dietary supplement containing saffron, in patients with early stage, dry-type ARMD. The study formulation comprised a capsule containing ZeaLutein® (lutein: 5 mg + zeaxanthin: 1 mg + piperine: 2 mg; 100 mg), bilberry extract (20 mg), saffron extract (5 mg), and zinc monomethionine (7.5 mg). Over 90 d, 20 participants received 20 mg of Macumax® daily. After treatment, subjective symptoms improved, including vision scores. Significant changes in diminished and distorted vision scores were detected from day 60 of treatment. Regarding objective symptoms, abnormal Amsler's grid aberration scores improved significantly from 77.5% of participants initially to 40% on day 90. Thus, Macumax® supplementation is safe and eye health remained unchanged; consequently, Macumax® supplementation may provide visual benefits for patients with dry ARMD, with no serious adverse events [76].

Lashay et al. [46] investigated the short-term effects of saffron supplementation (30 mg/day) in 60 patients with wet or dry ARMD in a randomized, double-blind, placebo-controlled trial. Over 6 months, the researchers assessed changes in retinal function using mfERG measurements and macular thickness using optical coherence tomography (OCT). At study completion, the decrease in macular thickness was not significant in eyes with dry AMD, yet these eyes displayed a significant improvement in ERG amplitude 3 months post-treatment. In contrast, they found a significant decrease in macular thickness in eyes with wet AMD. Likewise, a significant improvement in ERG amplitude was detected in eyes with wet AMD 3 months post-treatment; however, these changes decreased at 6 months. The study concluded that saffron supplementation is a promising therapeutic option to improve visual function in individuals with ARMD, although further research is needed to confirm these findings and explore long-term effects [46].

In a clinical trial involving 31 participants, Piccardi et al. [77] examined the effects of saffron, known for its antioxidant properties, on central retinal function in patients with *ABCA4*-related Stargardt disease/fundus flavimaculatus. The researchers administered saffron supplementation (20 mg/day) for 6 months, and assessed changes in visual function and retinal sensitivity measurements. Saffron supplementation stabilized both parameters, suggesting that saffron may help preserve retinal function in individuals with this genetic form of macular dystrophy, affirming the potential role of saffron as a therapeutic option for managing retinal degeneration associated with *ABCA4* mutations [77].

Finally, Sepahi et al. [78] evaluated the effects of crocin, a bioactive compound derived from saffron, on 101 eyes with refractory diabetic maculopathy in a randomized, double-blind, placebo-controlled clinical trial. Over 3-months, 60 patients received either oral crocin or placebo. Compared to placebo, crocin 15 mg/day oral supplementation significantly improved best-corrected visual acuity and reduced central macular thickness, suggesting that crocin may have anti-inflammatory and neuroprotective effects in the treatment of refractory diabetic macular edema. Thus, crocin is a promising adjunct therapy for managing diabetic maculopathy, although further research is needed to confirm these findings and explore long-term effects [78].

Several clinical studies have investigated the effects of saffron supplementation on ARMD and other macular pathologies [42, 44, 46, 73-78]. Saffron supplementation (20–30 mg/day) modestly improves visual acuity, mfERG response, and retinal sensitivity in patients with mild-to-moderate ARMD, with benefits observed within 3 months and maintained for up to 15 months [42, 44, 46, 75, 76]. The effects of saffron are independent of genetic risk factors [73] and may provide additional benefits when administered alongside other adjuncts such as AREDS supplements [44]. Furthermore, saffron supplementation has demonstrated potential effectiveness in managing other macular diseases such as Stargardt disease [77] and refractory diabetic macular edema [78], suggesting broader therapeutic applications in retinal health.

Table 1. Characteristics of the nine included clinical studies on oral supplementation of saffron or saffron-derived bioactive compounds

Author (Year)	Study design	Sample size, n	Working diagnosis	Dosage	Duration, m	Main outcomes
Broadhea et al. (2019) [44]	Randomized, double-blind, placebo-controlled trial.	100	Mild to moderate ARMD.	20 mg/d.	3	Modest improvement in BCVA and mfERG response density and latency.
Marangoni et al. (2013) [73]	Longitudinal, interventional study.	33	Bilateral early ARMD.	20 mg/d.	11	Significant improvements in fERG sensitivity and amplitude. The improvements in retinal function remained stable throughout the follow-up period. No significant differences in the clinical and fERG improvements were observed across different variants of the *CFH* or *ARMS2* genes.
Broadhead et al. (2024) [42]	Open-label, single-arm extension trial.	93	Mild to moderate ARMD.	20 mg/d.	12	Mean mfERG response density was significantly higher in rings 1 and 2 as well as overall. No significant changes in mfERG response density in rings 3–6 and latency in any of the rings.
Piccardi et al. (2012) [74]	Longitudinal, interventional, open-label study.	29	Bilateral early ARMD.	20 mg/d.	14	Retinal sensitivity, or the reciprocal value of the estimated fERG amplitude threshold, was the main outcome. Retinal flicker sensitivity significantly improved, as measured by fERG, with mean sensitivity increased by 0.3 log units after 3 months and maintained throughout the follow-up. Visual acuity improved by two Snellen lines.
Falsini et al. (2010) [75]	Randomized, double-blind, placebo-controlled, crossover trial.	25	Bilateral early ARMD.	20 mg/d.	3	Patients' fERG amplitudes increased significantly compared to both baseline and placebo. Decreased fERG thresholds compared to baseline. Placebo supplementation did not result in significant changes in fERG amplitude or threshold. Conclusion: Short-term saffron supplementation improves retinal flicker sensitivity in patients with AMD.
Majeed et al. (2021) [76]	Open-label trial.	40	Early-stage dry-type ARMD.	5 mg/d.	3	Improvement in subjective visual symptoms such as diminished and distorted vision scores. At the start of the study, 77.5% of participants had abnormal Amsler grid aberration scores; by day 90 of saffron treatment, only 40% of patients had abnormal Amsler grid aberration scores.
Lashay et al. (2016) [46]	Randomized, double-blind, placebo-controlled trial.	60	Wet (30 patients) and dry (30 patients) ARMD.	30 mg/d.	6	In patients with dry AMD, no statistically significant difference in macular thickness measured by OCT between the saffron and placebo groups were detected at 6 months. However, a statistically significant improvement in ERG amplitude was detected in the saffron group compared to placebo at 3 months. In patients with wet AMD, a significant decrease in macular thickness was determined in the saffron group compared to placebo at the 6-months follow-up, and a significant improvement in ERG amplitude were detected in the saffron group compared to the placebo group at 3 months. However, these ERG improvements decreased by 6 months.
Piccardi et al. (2019) [77]	Randomized, double-blind, placebo-controlled trial.	31	ABCA4-related STG/FF.	20 mg/d.	6	After saffron supplementation, fERG amplitude remained unchanged from the baseline. After placebo supplementation, fERG amplitude tended to decrease from baseline fERG timing and visual acuity was unchanged throughout the follow-up.
Sepahi et al. (2018) [78]	Randomized, double-blind, placebo-controlled trial.	60	Refractory DME.	5 or 15 mg/d crocin.	3	Crocin 15 mg tablets yielded significant improvements in HbA1c, CMT, and BCVA compared to that of the placebo group. Crocin 5 mg tablets also yielded clinical improvements in these parameters; however, the differences were not statistically significant.

Abbreviations: ARMD, age-related macular degeneration; BCVA, best-corrected visual acuity; mfERG, multifocal electroretinogram; fERG, flicker electroretinogram; OCT, optical coherence tomography; STG/FF, stargardt disease/fundus flavimaculatus; and DME, diabetic macular edema.

Limitations of current evidence

The studies on saffron supplementation for ARMD and other macular pathologies exhibit several limitations that should be considered when interpreting their findings. First, many of these studies had relatively small sample sizes [42, 44, 46, 73-78], limiting the generalizability of the results. For instance, trials involving 20 to 100 participants [42, 44, 46, 73-78] may not adequately represent the broader population of individuals with ARMD and other macular diseases, potentially leading to skewed outcomes or insufficient statistical power to detect differences [79]. Additionally, the duration of most studies was relatively short, typically ranging from 3 to 14 months [42, 44, 46, 73, 75-78], which is insufficient to detect the long-term effects or progression of ARMD, raising questions regarding the sustainability of the observed benefits and whether longer treatment periods would yield different results.

Furthermore, variations in study design, such as differences in dosing regimens, participant demographics, and inclusion/exclusion criteria, complicate comparisons across studies. For instance, some studies included participants already receiving other agents such as AREDS supplements [42, 44]; thus, confounding the results by introducing additional variables affecting visual function. Furthermore, the reliance on subjective measures such as best-corrected visual acuity [42, 44, 76] and objective measures such as mfERG [42, 46] may introduce variability in outcomes owing to individual differences in perception and reporting. Finally, although safety profiles were generally reported as favorable [42, 44, 46, 73-78], the lack of long-term data regarding safety and potential side effects associated with prolonged saffron use warrant further investigation to ensure a comprehensive understanding of its therapeutic implications. Overall, these limitations highlight the need for large-scale, multicenter, preferably multinational, longer-term, and more rigorously controlled studies to better establish the efficacy and safety of saffron supplementation in ARMD treatment.

Safety and tolerability

Multiple adverse events have been associated with saffron consumption, such as pedal edema, altered appetite, subconjunctival hemorrhage, nausea, dizziness, fatigue, dry mouth, decreased partial thromboplastin time, decreased amylase levels, and mixed white blood cells. However, these signs and symptoms were reported as not serious, with no statistically significant difference in frequency compared with that of placebo or other medications [39, 80]. Toxic side effects may develop with daily saffron doses of > 5 g [81].

Regarding the consumption of saffron in ARMD, none of the included articles reported significantly higher rates of adverse events post-saffron use [42, 44, 46, 73-78]. In a study by Broadhead et al. [42], 14 patients experienced adverse events and two died. However, the deaths were unrelated to saffron consumption, and the difference in adverse event frequencies between the saffron and control groups was not significant. In summary, all nine studies revealed that the oral supplementation of saffron was safe and well tolerated [42, 44, 46, 73-78].

This review summarizes the current literature addressing the treatment outcomes, efficacy, and safety of saffron in managing ARMD. However, various limitations of this review should be noted. First, not many clinical studies were found. The literature pertaining to specific applications of saffron in ARMD was scarce, even using a rigorous search procedure. The limited number of studies affected our capacity to reach firm conclusions, and a more extensive body of data would offer a more solid foundation for inference. Another potential limitation is the use of only one database, which may have restricted the scope of included studies and omitted relevant research sources. Furthermore, our extensive search covered various subjects about the application of saffron in the treatment of other macular diseases. Although the health benefits of saffron in various circumstances were heavily researched, there is a notable dearth of studies explicitly examining its use in ARMD. As many of the prior studies did not specifically target ARMD, the thorough investigation and validation of the therapeutic benefits of saffron in this specific disease were challenging to discover. Moreover, our ability to conduct meta-analysis was hindered by the limited accessible research on saffron in ARMD. Meta-analyses are essential to provide more comprehensive insights and reliable conclusions from the gathered data. This lack of statistical support emphasizes the necessity for more in-depth, targeted research on saffron use in ARMD to facilitate more reliable and quantitative assessments

CONCLUSIONS

Saffron and its active compounds, crocin and crocetin, have shown promising results in improving visual function and delaying disease progression in ARMD. Several clinical studies have found that daily supplementation with 20–50 mg of saffron or 5–15 mg of crocin for 3–12 months significantly improved best-corrected visual acuity, contrast

sensitivity, and retinal function as measured by ERG and microperimetry, with benefits observed in both dry and wet ARMD. The effects were independent of genetic risk factors and were maintained throughout the follow-up periods, suggesting the potential role of saffron as a long-term treatment option. Saffron may delay the progression of ARMD through anti-angiogenic, neuroprotective, and antioxidant mechanisms. While further research is needed to confirm long-term safety and efficacy, current evidence supports the use of saffron or crocin supplements as a safe and tolerable adjunct therapy for ARMD. Long-term studies may provide deeper knowledge of the possible advantages and uses of saffron in ARMD treatment, improving the dependability, reliability, and clarity of findings.

ETHICAL DECLARATIONS

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