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REVIEW

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Saffron's promise: a systematic review of its role in Alzheimer's treatment

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Abstract

Alzheimer's disease (AD) is the most common form of dementia, which can be debilitating and affect the patients' quality of life. Saffron (*Crocus Sativus* L.) is a plant growing in various countries with potential anti-inflammatory, and antioxidant effects. This study aims to systematically review the role of saffron as a therapeutic agent or supplementation in patients with AD. We searched PubMed, Scopus, Embase, and Web of Science databases on 5/1/2023. Clinical studies that reported the effectiveness and/or safety of saffron in patients with AD are considered for inclusion. 565 studies were identified in the initial comprehensive search, and finally, only 4 studies met the eligibility criteria. All the studies were conducted in Iran. Studies showed that saffron has comparable efficacy in cognitive outcomes with approved drugs for AD, donepezil, and memantine; however, supplementation with saffron does not add beneficial effects in this regard. There were no considerable safety issues. Saffron is suggested as a potential herbal therapeutic agent in AD based on limited available evidence. Limitations of the evidence such as the small sample sizes as well as the skimp number of the included studies suggested prudence in clinical recommendations based on the findings of this study; however, this systematic review shed light on the necessity of conducting future trials on this topic.

Keywords Alzheimer disease, Crocus, Systematic review

Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia that usually affects individuals aged 65 years and above, comprising 60–80% of all dementia cases [1]. The global prevalence of dementia is approximated to be 24 million, with projections indicating that it will double every 20 years until 2040 [2]. An estimated 6.7 million Americans aged 65 and above are living with AD, with 73% of them being 75 years or older. Roughly, 1 in 9 individuals in the 65 and above age category have AD. [3]. The increase in AD prevalence also has been observed in community-based studies conducted in Japan and China over recent decades [4, 5]. The onset of AD is slow and the risk of developing AD is about 5–10% at the age of 65 and doubles every 5 years thereafter. The clinical course of the disease is characterized by a gradual decline in cognitive function, difficulty in carrying out daily tasks,

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and persistent changes in behavior and personality [1, 6]. Given the multitude of risk factors, the most likely explanation for the development of sporadic AD is a dynamic and epigenetic process that occurs throughout one's life, particularly as humans live longer lives [7, 8]. The inflammatory process and oxidative stress are potential mechanisms involved in the development of AD [9–11]. There is increasing emphasis on exploring natural products as potential therapeutics for AD [12].

Some studies evaluated the effect of herbal medicine in patients with cognitive impairment. As a result, herbal medicine could play a crucial role in treating AD. Herbal medicine may improve the behavioral and psychiatry symptoms of dementia, especially in combination with other common drugs in AD [13]. However, there is no approved herbal medicine in AD, and more studies are required to evaluate the different kinds of herbal medicine in various stages of dementia [14].

For instance, curcumin showed significant improvements in cognitive function, decreasing neurodegeneration, and improving muscle health in the older adults [15]. Other herbal drugs were also investigated. A comprehensive evaluation of eleven research indicated that *Ginkgo biloba* enhances cognitive ability, neuropsychiatric behavioral, and functional skills in AD. Notable enhancements were recorded in the results from the Mini-Mental State Examination (MMSE), Short Cognitive Performance Test (SKT), and Neuropsychiatric Inventory (NPI). The bulk of synthesized clinical trials indicate that *Ginkgo biloba* exhibits promising promise for treating dementia [16]. Another herbal supplement which is proven to be effective in cognitive function is *Bacopa monnieri*. Neto and colleagues demonstrated that *Bacopa monnieri* can reduce nuclear factor-κB phosphorylation, improve emotional behaviors, cognitive abilities, hyperactivity, sleep routine, depression, attention deficit, learning problems, memory retention, and psychiatric behaviors. Moreover, *Bacopa monnieri* decreases the amount of pro-inflammatory biomarkers and oxidative stress. The authors suggest that *Bacopa monnieri* can be used in combination with other drugs to alleviate AD symptoms [17].

Saffron, another herbal complementary, also known as *Crocus sativus* L., is a plant belonging to the Iridaceae family and is grown in various countries such as Iran, Spain, India, and Greece [18, 19]. For centuries, saffron has been used as a food additive and has a long history of therapeutic use [20, 21]. It is known as an expensive agent due to its medicinal use in the treatment of various disorders [22–25]. The saffron extract contains over 300 components, with crocetin, crocin, and safranal being the main bioactive components [26, 27]. Saffron is safe at pharmacological doses, with no evidence of potential toxicity or tissue damage. The recommended safe dose is 1.5 g per day, while doses above 5 and 20 g/kg may be toxic and fatal, respectively [18, 28, 29]. However, the effective doses used in studies are below toxic levels, indicating that saffron has a wide therapeutic index [30, 31]. This issue is the main aspect that prompted us to investigate saffron as a safe treatment for cognitive dysfunction in AD. Animal studies have provided evidence of saffron antidiabetic, anti-inflammatory, anti-atherosclerotic, anti-tumor, immunomodulatory, and antioxidant effects [32–34]. Besides, human studies have brought saffron consumption in AD patients to a challenge and the outcomes are not the same and can be discussed [35–39]. This systematic review aims to evaluate the existing clinical literature on the effect of saffron, as the main therapeutic agent or as the supplementation on AD.

Methods

This systematic review was conducted based on the methods mentioned in the Cochrane Handbook for Systematic Reviews of Interventions [40] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) statement [41].

Inclusion and exclusion criteria

The inclusion criteria contained participants diagnosed with AD-type dementia, regardless of gender, race, age, and severity of the disease, receiving saffron, as the main therapeutic agent or supplementation, compared to a control group. To be included in the systematic review, a study had to follow the next eligibility criteria: (a) published in the English language up to 5/1/2023; (b) included human participants; (c) subjects were given saffron extract and compared to either placebo or any approved anti-AD drug or no intervention. The studies with any of the following criteria have been excluded from this review: (a) case reports, (b) review articles, (c) conference abstracts, (d) letters, (e) comments, (f) non-English articles, (g) book chapters, and (h) animal studies.

Search strategy

In this study, we electronically searched the databases PubMed, Embase, Scopus, and Web of Science, based on the following keywords on May 1st, 2023: "saffron, Alzheimer's disease, dementia, treatment". The strategy designed by the trained authors (A.N. and R-M-H.). In addition, the reference lists of the relevant articles were inspected to identify potential studies that met the selection criteria.

Study selection and data collection

After removing the duplicate studies with EndNote reference manager software, the final library was imported into Rayyan [42], and studies that met the eligibility criteria of this systematic review were selected by assessing the title/abstract (A.J. and N.D.) and full text (A.N. and R.M-H.), by two independent authors. Any disagreements were resolved by another author's opinion (M.T. or S.S.).

Data collection

Two authors independently extracted the data on demographics, interventions, and outcomes separately (A.Nr. and H.S.). Any disputes were addressed through consensus or by another author's opinion (M.T. or S.S.). For each included study, the following data were collected: the authors' name, country, year of publication, and patient's demographic characteristics.

Assessment of quality and certainty of the evidence

Two reviewers (A.N. and H.Sh.) assessed the quality of each included study by the Cochrane Risk of Bias tool version 2.0 (RoB 2.0) and the final results are visualized with the robvis tool [43]. The certainty of the evidence was rated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. According to the GRADE structure, the evaluation of efficacy and safety result measures was categorized into four evidence-quality grades, namely high, medium, low, and very low. These grades were further classified as either 'strong recommendation' or 'weak recommendation.' The quality grading of a study is influenced by five factors: risk of bias, inaccuracies, inconsistencies, other biases, and indirectness [44]. Any disagreements were reviewed by a third author (M.T. or S.S.) if it was needed.

Results

Study inclusion

565 studies were identified in the initial comprehensive search, with 259 remaining for the title/abstract review following the de-duplication procedure. Of those, 254 were excluded for not meeting the inclusion criteria. The remaining 5 articles were assessed for eligibility, but only 4 met the criteria. During the full-text review, one study was excluded because it did not clearly state the diagnosis of AD [45]. The details of the screening process are presented in Fig. 1.

Characteristics of included studies

All the selected articles were double-blind randomized clinical trial studies conducted in Iran and published between 2009 and 2022. The sample sizes ranged from 46 to 68. All the trials utilized a standard saffron extract of 30 mg per day with two [35, 36] using 15 mg for the first 4 weeks. Two studies focused on the efficacy of saffron compared to placebo as the main treatment [35] and supplementation [46], while one study compared the efficacy of saffron to Donepezil [36]; and one compared saffron to Memantine [38]. Two studies [35, 36] used the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) and Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) to measure efficacy. One study [46] measured serum inflammatory markers (TNF-α, IL-6, IL-1β) and oxidative stress markers such as glutathione peroxidase (GPx), superoxide dismutase (SOD), malondialdehyde (MDA), and total antioxidant capacity (TAC) along with the mini-mental state examination (MMSE) score. Another study [38] used the Severe Cognitive Impairment Rating Scale (SCIRS) and Functional Assessment Staging (FAST), for efficacy measurements. More details of the characteristics of the included studies are presented in Table 1.

Risk-of-bias assessment

The details of the results of the RoB assessment are presented in supplementary material 1, and Fig. 2 is a summary of the findings. The most common possible source of bias in the included studies was the lack of intention-to-treat (ITT) analysis which did not seem to significantly influence the overall conclusions of the studies. Randomization was concluded using computer-based methods in three studies [35, 36, 38], and the rest mentioned the table of random numbers as the method of randomization [46].

Results of individual studies

A study conducted by S. Akhondzadeh and colleagues [35] aimed to determine the effectiveness of saffron in treating mild-to-moderate AD. Forty-six patients, aged 55 or older with baseline MMSE scores of 15–26, were randomized and assigned to either saffron or placebo groups. This study found that Saffron is safe and effective in mild-to-moderate AD, as it can improve ADAS-cog and CDR-SB. Akhondzadeh and colleagues [36] in another study assessed the efficacy of saffron in the treatment of mild-to-moderate AD and compared its efficacy to Donepezil. They included 54 participants with MMSE scores between 15 and 26 and visually equal capsules of saffron and donepezil were given for the first 4 weeks, after which the dose was raised to two capsules per day for the remainder of the trial. The conclusion of this study was the similarity of the effectiveness of saffron to donepezil in the treatment of mild-to-moderate AD after 22 weeks, due to its effective improvements in ADAS-cog

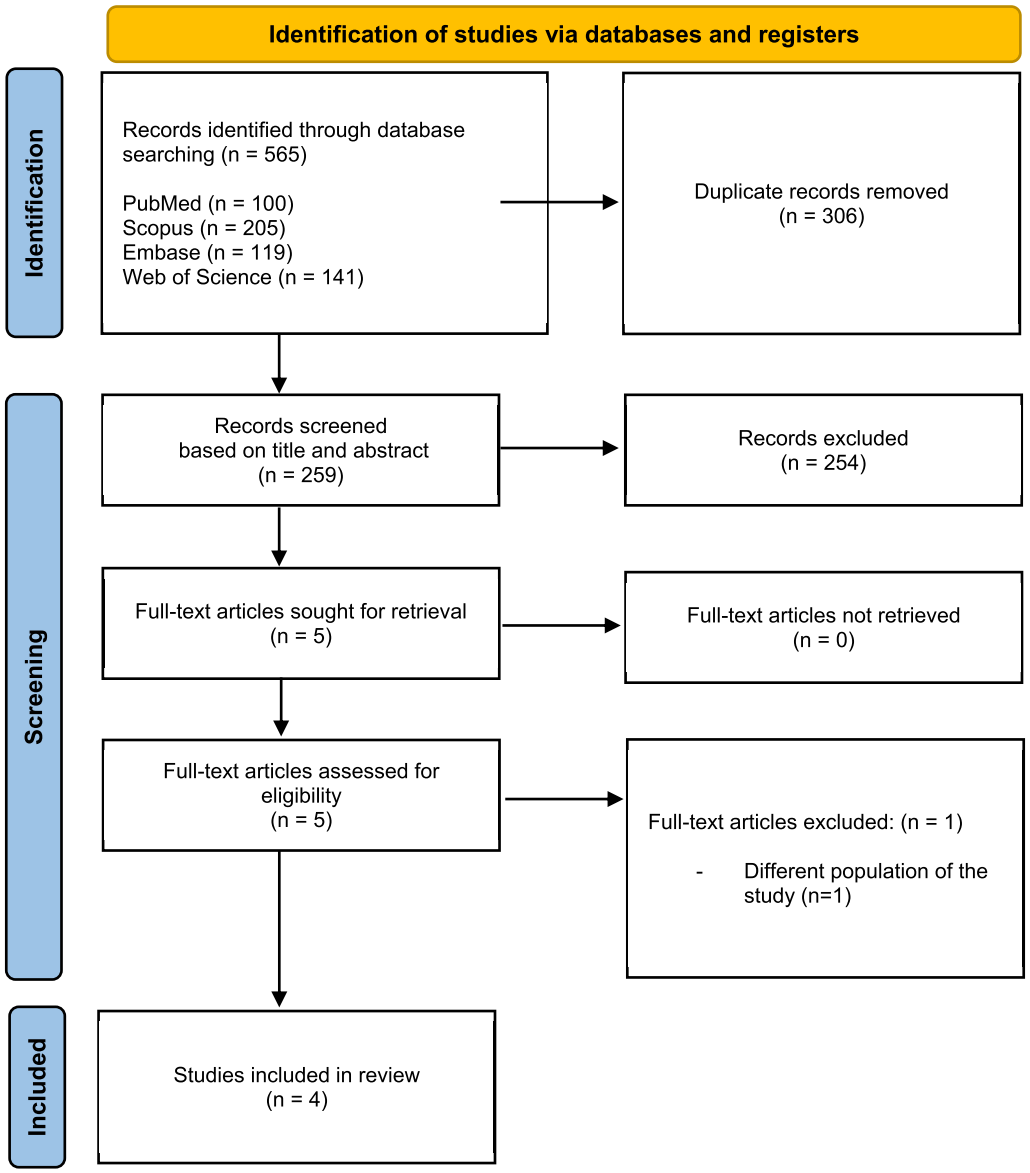

Fig. 1 The PRISMA 2020 flow diagram

and CDR-SB, as seen equally in donepezil. There was a similarity in the frequency of adverse events between the two groups, except for a higher incidence of vomiting with donepezil.

Rasi Marzabadi and colleagues [46] investigated the effects of saffron on cognitive outcomes and circulatory markers in patients with mild-to-moderate AD. Both the intervention and control groups received 10 mg of donepezil per day as a baseline treatment and were given 15 mg of Saffrotin® and placebo twice daily for 12 weeks, respectively. In the end, 54 participants (27 in each group) were analyzed, and the difference in final MMSE scores between the two groups was not significant; however, there was a remarkable decrease in IL-1β and MDA levels and an increase in TAC in the serum in the saffron group, as opposed to the placebo.

Farokhnia and colleagues [38] assessed the efficacy of saffron in daily functional living and cognitive functions, in comparison to memantine. 68 participants with moderate to severe AD were given either Saffrotin® or memantine for 12 months and 60 participants ended the trial. The primary outcome of the study was an improvement in MMSE, SCIRS scores, FAST scale, and adverse events at 12 months, which was statistically comparable between the groups.

Table 1 The characteristics and findings of the included study

Study	Setting	Study design	Study duration	Sample size (saffron/control)	Participants	Age (saffron/control)	Male ratio (saffron/control)	Intervention groups	Control	Parameter	Saffron	Control	Conclusion of the study
(Rasi Marzabadi and colleagues, 2022) [46]	Tabriz, Iran	Double-blind placebo-control parallel RCT	12 weeks	54 (27/27)	Mild-to-moderate AD (MMSE: 11–24)	(76.70 ± 6.10/75.33 ± 5.06)	(22.2%/25.9%)	Donepezil 10 mg + saffrotin 15 mg/BID	Donepezil 10 mg + placebo	MMSE	Before: 19.00 ± 4.27 After: 20.22 ± 4.39	Before: 18.33 ± 4.36 After: 19.85 ± 5.25	No additional effects of saffron supplementation on global cognitive outcomes; saffron significantly decreases inflammation and oxidative stress and increases antioxidant capacity
										TNF-α	Before: 8.70 ± 6.63 After: 9.62 ± 7.71	Before: 10.64 ± 9.06 After: 10.41 ± 8.47	
										IL-6	Before: 15.38 ± 7.38 After: 11.89 ± 10.20	Before: 17.42 ± 9.83 After: 13.90 ± 11.60	
										IL-1β	Before: 3.84 ± 2.14 After: 3.03 ± 1.42	Before: 4.62 ± 2.69 After: 4.07 ± 3.28	
										GPx	Before: 40.43 ± 16.91 After: 52.44 ± 11.56	Before: 46.75 ± 18.49 After: 55.74 ± 14.04	
										SOD	Before: 1111.07 ± 156.99 After: 1235.47 ± 235.71	Before: 1104.70 ± 97.52 After: 1247.22 ± 237.87	
										MDA	Before: 1.59 ± 0.47 After: 1.44 ± 0.51	Before: 1.56 ± 0.37 After: 1.45 ± 0.38	
										TAC	Before: 1.52 ± 0.39 After: 1.70 ± 0.47	Before: 1.28 ± 0.53 After: 1.39 ± 0.54	
(Akhondzadeh, Sabet and colleagues, 2010) [35]	Tehran, Iran	double-blind placebo-control parallel RCT	22 weeks	42 (22/20)	mild-to-moderate AD (MMSE: 15–26)	(72.65 ± 3.89/73.13 ± 4.70)	(56.5%/52.1%)	Saffron 15 mg/BID	Placebo	ADAS-cog	Changes at week 16 from baseline: -3.69 ± 1.69	Changes at week 16 from baseline: 4.08 ± 1.34	Saffron is both safe and effective in mild-to-moderate AD
										CDR-SB	Changes at week 16 from baseline: -0.67 ± 0.24	Changes at week 16 from baseline: 0.63 ± 0.45	
										Dizziness	2 (8.69%)	3 (13.04%)	
										Dry mouth	3 (13.04%)	1 (4.34%)	
										Fatigue	1 (4.34%)	2 (8.69%)	
										Hypomania	2 (8.69%)	0 (0.0%)	
										Nausea	2 (8.69%)	1 (4.34%)	

Table 1 (continued)

Study	Setting	Study design	Study duration	Sample size (saffron/control)	Participants	Age (saffron/control)	Male ratio (saffron/control)	Intervention groups	Control	Parameter	Saffron	Control	Conclusion of the study
(Akhondzadeh, Shafiee Sabet, and colleagues, 2010) [36]	Tehran, Iran	double-blind placebo-control parallel RCT	22 weeks	54 (27/27)	mild-to-moderate AD (MMSE: 15–26)	(72.70 ± 6.20/73.85 ± 4.63)	(51.8%/55.5%)	Saffron 15 mg (once daily first 4 weeks, then BID for the rest)	Donepezil 5 mg (once daily for the first 4 weeks, then BID for the rest)	ADAS-cog	Changes at week 16 from baseline: − 3.96 ± 3.50	Changes at week 16 from baseline: − 3.77 ± 3.80	Saffron was found to be effective similar to donepezil in the treatment of mild-to-moderate AD
										CDR-SB	Changes at week 16 from baseline: − 0.77 ± 0.97	Changes at week 16 from baseline: − 0.83 ± 0.95	
										Vomiting	1 (3.70%)	7 (25.92%)	
										Dizziness	2 (7.40%)	5 (18.51%)	
										Dry mouth	5 (18.51%)	3 (11.11%)	
										Fatigue	1 (3.70%)	4 (14.81%)	
										Hypomania	1 (3.70%)	0 (0.0%)	
										Nausea	2 (7.40%)	6 (22.22%)	
(Farokhnia and colleagues, 2014) [38]	Tehran, Iran	Double-blind placebo-control parallel RCT	12 months	60 (30/30)	Moderate to severe AD (MMSE score of 8–14)	(77.73 ± 8.05/77.47 ± 7.99)	(61.7%/52.9%)	Saffrotin® 15 mg (once daily for the first month, BID for the rest)	Memantine (Ebixa®, 10 mg, once daily for the first month, then twice daily for the rest)	SCIRS	Before: 20.76 ± 1.59	Before: 20.47 ± 1.69	Administration of saffron showed to be comparable with memantine in reducing cognitive decline in AD
											Change: 1.88 ± 1.14	Change: 1.61 ± 1.34	
										FAST	Before: 2.97 ± 0.96	Before: 3.05 ± 1.01	
											Change: 0.94 ± 0.73	Change: 0.97 ± 0.83	
										MMSE	Before: 11.23 ± 1.92	Before: 11.11 ± 1.53	
											Change: 1.29 ± 1.36	Change: 1.67 ± 1.57	
										Nausea and vomiting	8 (26.66%)	6 (20.0%)	
										Dry mouth	4 (13.33%)	44 (13.33%)	
										Fatigue	4 (13.33%)	5 (16.66%)	
										Dizziness	4 (13.33%)	6 (20.0%)	
										Confusion	1 (3.33%)	1 (3.33%)	
										Agitation	`	2 (6.66%)	
										Sedation	1 (3.33%)	3 (10.0%)	

AD: Alzheimer's disease; MMSE: Mini-Mental State Examination; RCT: randomized controlled trial; TNF: tumor necrosis factor; IL: interleukin; GPx: glutathione peroxidase; SOD: superoxide dismutase; MDA: malondialdehyde; TAC: total antioxidant capacity; SCIRS: severe cognitive impairment rating scale; FAST: functional assessment staging; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB: Clinical Dementia Rating Scale-Sums of Boxes; TNF-α: tumor necrosis factor alpha; IL-6: interleukin 6; IL-1β: interleukin 1 beta; GPx: glutathione peroxidase; SOD: superoxide dismutase; MDA: malondialdehyde; TAC: total antioxidant capacity

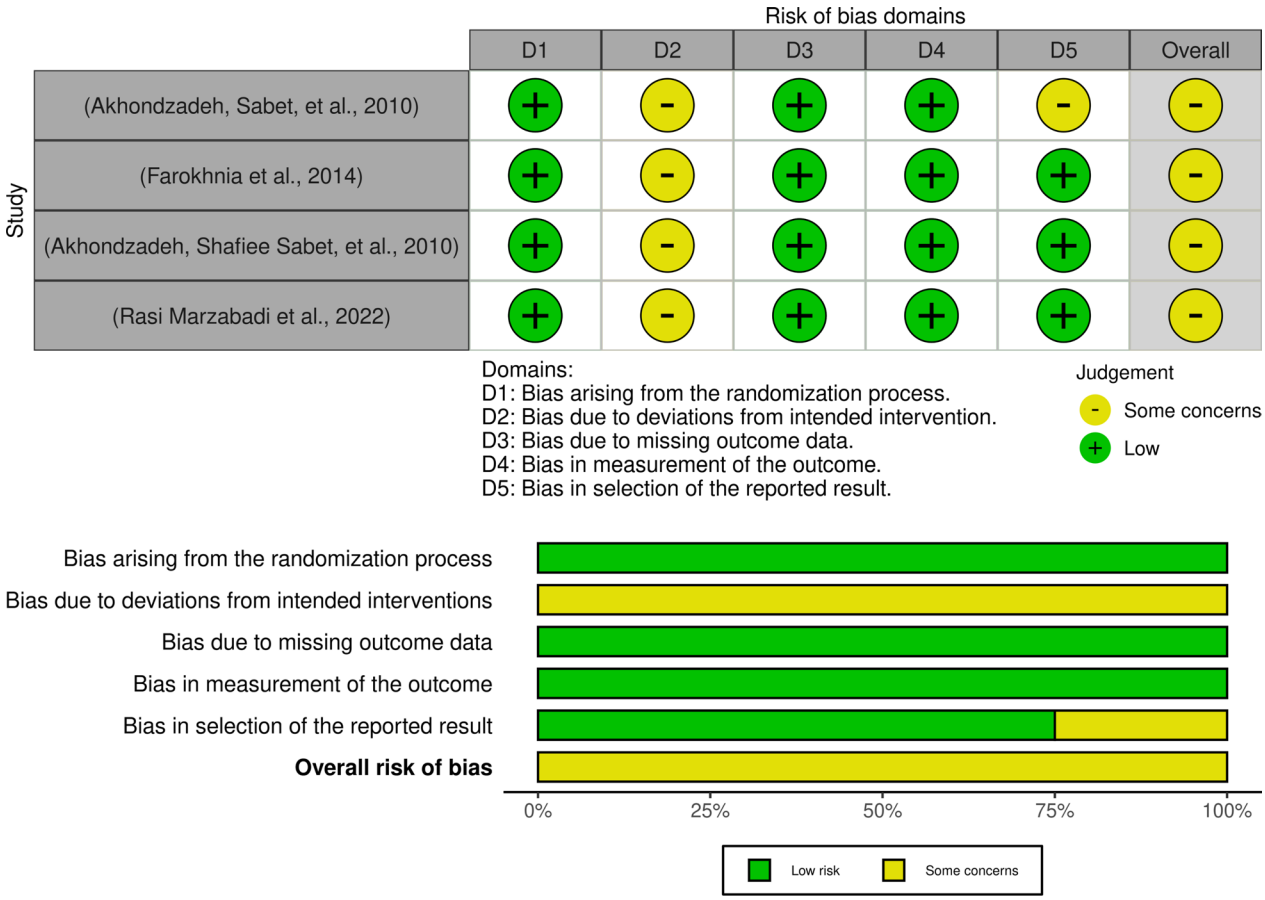

Fig. 2 Results of risk-of-bias assessments based on the second version of the Cochrane risk-of-bias assessment tool (RoB2)

Results of meta-synthesis

The effect of saffron on cognitive function

A study conducted by Akhondzadeh and colleagues [35] in 2010 discovered that saffron significantly improved ADAS-cog and CDR-SB scores over 16 weeks when compared to a placebo. Another study by Akhondzadeh and colleagues [36] revealed that when compared to donepezil, saffron also improved ADAS-cog and CDR-SB scores at 22 weeks, with both groups showing statistically comparable changes. Farokhnia and colleagues [38] conducted a study that found the saffron treatment to cause an improvement in SCIRS and MMSE scores at 48 weeks when compared to memantine, with both groups showing statistically comparable changes. However, the study conducted by Rasi Marzabadi and colleagues [46] found no significant difference in MMSE scores between the saffron, as a supplementation, and placebo groups in patients treated with donepezil after 12 weeks.

Adverse events

All the studies reported information on the number of people who dropped out of the trial. Three studies [35, 36, 38] measured the frequency of adverse events. However, Rasi Marzabadi and colleagues [46] declared no adverse events. In one particular study [35] that compared saffron to placebo, one participant in the control group died due to myocardial infarction. Both the saffron and control groups experienced minor side effects such as dizziness, dry mouth, fatigue, and nausea, with no significant differences found between the two groups. Two studies [36, 38] comparing saffron to conventional medicines reported mild side effects such as nausea, fatigue, and dry mouth, However, there were

no statistically significant differences found between the two groups in either study.

Certainty of evidence

All the studies were RCTs with some concerns regarding the RoB; however, the details of sample size calculations are only reported in two studies [38, 46]. All the evidence are graded as 'Moderate certainty' based on the GRADE approach.

Summary of findings

Limited available evidence suggested that saffron may be associated with cognitive improvements in patients with AD and there are no considerable side effects; however, supplementation with saffron does not add beneficial cognitive effects to the approved AD drugs.

Discussion

This research indicates that saffron enhances cognitive abilities in individuals with AD with appropriate tolerability; however, a definitive conclusion cannot be drawn at this time due to the scarcity of clinical trials and varying control groups and outcome assessment scales. The administration of saffron treatments resulted in a noteworthy enhancement in clinical outcomes compared to the placebo group, as determined by ADAS-cog and CDR-SB assessments. The observed alterations in ADAS-cog exhibit a considerable change, given the widely accepted notion that a minimum of four units of change in ADAS-cog is necessary to indicate a clinically significant enhancement [47]. Based on the RCTs, saffron was found to have comparable efficacy with approved AD drugs, which is actually superior to placebo; however, supplementation with saffron does not add beneficial effects in this regard.

Considering the swiftly increasing global rate of AD, only a limited number of symptomatic treatments were accessible for its management [3, 48]. Memory loss is typically the initial presenting symptom and the symptoms develop over time. Behavioral and psychiatric problems are prevalent, causing considerable anguish to caregivers and elevating mortality rates in patients [49]. Nonetheless, there are no authorized therapies for these symptoms [50]. Dementia is a complicated condition, necessitating supplementary therapy approaches to assist patients in coping with the disease's progression [51, 52]. Amyloid beta aggregation in the brain is believed to initiate AD, and over the past 2 decades, attempts have been made to create medications that influence the formation or reduce Aβ accumulation; however, these interventions have consistently failed to demonstrate beneficial effects on cognitive function in previous clinical trials [52, 53]. Cognitive results not only failed to improve but also, in many patients, symptoms worsened, despite therapy lowering brain Aβ levels.

The level of antioxidant, anti-inflammatory, and oxidative stress markers in serum is found to be correlated with the severity of cognitive impairment in AD [54]. Cognitive improvements do not always accompany saffron use in AD patients. Rasi Marzabadi and colleagues reported that saffron consumption did not affect the cognitive function of patients treated with donepezil, based on MMSE [39]. However, the intervention group had improvements in IL-1β, MDA, and TAC profile [46], while Akhondzadeh and colleagues, in two separate clinical trials in 2010 with 22 weeks and 16 weeks of observations, found that saffron is effective and safe in patients with mild-to-moderate AD [35, 36].

The dose of saffron was the same in all trials. All trials used 30 mg hydro-alcoholic extract daily or 15 mg twice a day. The AD clinical trials utilized saffron extracts that were standardized through safranal and crocin, two of the most biologically active components of saffron. In all clinical trials conducted on AD, it was observed that each capsule comprised crocin and safranal in the quantities of 1.65–1.75 mg and 0.13–0.15 mg, respectively. Based on prior research, it has been established that the toxic threshold for saffron powder is above 5 g/day. Thus, the dosage employed in the included studies is deemed to be within safe limits [55, 56]. Saffron's safety profile appeared favorable. In the saffron-treated groups, no significant adverse effects were reported. Mild general adverse effects, including nausea, vomiting, hypomania, fatigue, and vertigo, were observed; nevertheless, the findings indicate that the prevalence of adverse effects was not statistically significant between the placebo and saffron groups in none of the included studies.

Although the exact pathophysiologic pathway is unknown, there are numerous in vivo and in vitro studies confirming that saffron consumption can have antidiabetic, anti-inflammatory, anti-atherosclerotic, and antioxidant effects [32–34]. There are three potential pathophysiologic pathways defined that saffron consumption can affect the cognitive function in AD consisting: inhibition of glutamate excitotoxicity and neuronal death as done by memantine [57], inhibition of amyloid-beta deposition [58], and inhibition of acetyl-cholinesterase activity [59]. These potential mechanisms of action elucidated serve to substantiate the external validity of the findings obtained through RCTs. Besides, this study highlights the positive impact of saffron consumption on inflammatory and antioxidant marker profiles in AD patients, potentially preventing the progression from cognitive impairment to AD [60]. This review confirmed

the findings of the previous systematic review study done by Ayati and colleagues [37], that saffron could have a key role in the improvement of cognitive functions in mild cognitive impairment and dementia. Despite the methodological limitations of the included studies and their heterogeneity, the findings suggest that saffron may reduce the AD symptoms and alleviate symptoms. In addition, saffron could be used as adjuvant therapies in clinical practice to enhance efficacy and mitigate the constraints of conventional medicine. Further studies and clinical trials in larger sample sizes are warranted to investigate the effect of saffron in combination with other drugs in AD patients.

Although there was no considerable RoB in the studies, all the included RCTs had some limitations, including a small sample size and a short duration of follow-up. Further RCTs are required in bigger sample sizes and long periods of follow-up. The inclusion of the studies published in English and the small number of included studies were the main limitations during the review process. In addition, all the included studies were conducted in Iran which limits the generalizability of the findings in other populations.

Conclusion

Saffron, as the main treatment, is found to be beneficial in improving cognitive functions in patients with AD which is comparable to approved drugs for AD, memantine, and donepezil, with acceptable safety issues. Adding saffron to the main treatments as supplementation may lead to improved inflammation and oxidative stress status; however, it does not add additional cognitive benefits. Although limited evidence did not support the routine administration of saffron extract in clinical practice, the outcomes of this study shed light on the need for future studies on this topic. Future research, particularly well-designed multicenter RCTs with larger sample sizes conducted outside of Iran, is essential to validate the efficacy of saffron on various outcomes, including cognitive functions, daily activities, safety, and side effects in patients with AD.

Abbreviations

AD	Alzheimer's disease
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RoB2	Cochrane risk of bias tool version 2.0
GRADE	Grading of recommendations, assessment, development, and evaluation
CDR-SB	Clinical dementia rating scale sum of boxes
ADAS-cog	Alzheimer's disease assessment scale–cognitive subscale
GPx	Glutathione peroxidase
SOD	Superoxide dismutase
MDA	Malondialdehyde
TAC	Total antioxidant capacity
MMSE	Mini-mental state examination
SCIRS	Severe cognitive impairment rating scale
FAST	Functional assessment staging
ITT	Intention-to-treat

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41983-025-00950-z.

Supplementary Material 1.

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Author contributions

Conceptualization: A.N., S.S., M.T.; methodology: A.N., R.M-H.; validation: A.N., S.S., M.T.; investigation: A.Nr., A.J., N.D., H.S., M.S., H.Sh.; writing—original draft: A.Nr., M.S., H.S., A.J.; writing—review and editing: A.N., S.S., M.T., R.M-H.; visualization: A.N., A.Nr.; supervision: A.N., S.S., M.T.; project administration: A.N., H.Sh.; funding acquisition: A.N., R.M-H.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary files.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Tabriz University of Medical Sciences (Ethics code: IR.TBZMED.VCR.REC.1402.151).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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