HHS Public Access

Author manuscript

Neurol Sci. Author manuscript; available in PMC 2021 October 01.

Published in final edited form as:

Neurol Sci. 2020 October ; 41(10): 2747–2754. doi:10.1007/s10072-020-04427-0.

Effects of saffron (Crocus Sativus L) on cognitive function. A systematic review of RCTs.

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Introduction

Optimal cognitive function is of great importance for the lives of people with or without clinical cognitive impairment. Alzheimer's disease (AD), is the most common cause of dementia and was first described more than 100 years ago (1). Today, AD burden is substantial with a prevalence of 40.2 cases per 1000 individuals over 60 years old (2). Mild cognitive impairment (MCI), especially its amnestic form, is often a transitory clinical entity that corresponds to the prodromal phase of AD (3). Despite decades of intense efforts and despite targeting multiple presumed pathogenic processes, no disease modifying treatment has been identified for MCI or AD (4). The only four currently approved medications are either acetylcholinesterase inhibitors enhancing cholinergic transmission (donepezil, rivastigmine, galantamine) or NMDA antagonist (memantine) and their effects are merely symptomatic. In this context, numerous natural products such as herbs, vitamins, antioxidants or naturally occurring compounds found in foods have been examined for their possible therapeutic use in MCI/AD (5-7) and, occasionally, for cognitive enhancement in healthy individuals (7-9).

The dried stigma of the plant Crocus Sativus L. is called saffron and is used in medicine, cosmetics and coloring industries (10). In animal studies, saffron was efficacious against various symptoms and disease processes including anxiety, insomnia, hyperglycemia, atherosclerosis, Parkinson's disease, cancer and morphine withdrawal syndrome (11). In addition, human studies have suggested that saffron may have therapeutic effects in depression and AD, with a relatively favorable safety profile (11). In the present systematic review, we aim to elucidate the evidence for effects of oral saffron intake on cognitive function in cognitively impaired and non-impaired individuals (Table 1).

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Ethical issues

On behalf of all authors, the corresponding author states that there is no conflict of interest. Also, there was no need for informed consent before conducting the present study, since it was a systematic review of literature. The present study was supported in part by the Intramural Program of the National Institute on Aging, National Institutes of Health.

Methods

For the conduction of the present systematic review, we adopted the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (12).

Eligibility criteria

In order to be included in the systematic review, a study had to follow the next eligibility criteria: (a) designed as randomized controlled trial (RCT) or cross-over RCT; (b) published in any language up to 11/12/2018.; (c) included humans only; (d) subjects were given saffron orally and compared to either placebo or any approved anti-AD drug (with no limitation in the dosing scheme or duration of intervention) or nothing; and (e) cognitive performance was evaluated through objective standardized tests before and after the intervention.

Information sources

We searched for relevant published studies, according to our eligibility criteria, in the next electronic databases: Medline, Science Direct and Cochrane Central Register of Controlled Trials.

Search

The following search query was followed for the identification of studies: “(saffron OR Crocus Sativus) AND (Alzheimer OR dementia OR cognitive OR cognition OR memory)”

Study selection

Eligible studies were identified by two reviewers (CV, NC), who searched independently based in the inclusion criteria. Any conflicts between the results of reviewers were solved with consensus and the addition of a third reviewer (KK).

Data collection process and data items

Two reviewers extracted data independently (CV, NC). Any conflicts between the results were solved with consensus and the addition of a third reviewer (KK). Collected data items included: title, first author, year of publication, ID, journal, country of origin, study type, study duration, number of patients assigned to saffron and placebo/drug of comparison, dosage of saffron/placebo/drug of comparison, baseline participants’ characteristics (gender, age, education), cognitive tests performed and their scores and finally, side effects.

Risk of bias in individual studies

Two reviewers assessed the risk of bias (ROB) independently (KK, PGM) by using the Cochrane Collaboration’s tool for assessing ROB (13). The following possible domains of ROB were evaluated: random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). A study was characterized as “low risk”, only if all domains of possible ROB were “low risk”. If at least one domain was “unclear risk”, the

study was deemed as “unclear risk”. If at least one domain was “high risk”, the study was deemed as “high risk”.

Results

Search results

The search yielded 200 possibly eligible studies. After duplications were removed and after screening of title and abstract, seven articles remained for full text assessment (figure 1). Of these, two articles were excluded for specific reasons (figure 1). Thus, five articles were finally included in qualitative synthesis (figure 1).

Studies ’ and patients ’ characteristics

The five included studies were all designed as randomized controlled trials (RCTs) and had a total of 325 participants. In four studies subjects had a diagnosis of AD or MCI and in one study subjects were not cognitively impaired (table 1). Saffron intake was compared either with placebo or another drug for AD or nothing (table 1). Various cognitive batteries were applied for cognitive assessment (table 1). Details about the characteristics of the studies and their participants are depicted in tables 2 and 3, respectively.

Risk of bias

Three studies were deemed as “unclear” for ROB, one study as “low” for ROB and one study as “high” for ROB. Details about the ROB assessment are shown in figures 2 and 3.

Results of individual studies

Safety—Four out of five studies reported adverse events (14-17). Compared to another drug or placebo, saffron administration showed no significant difference in adverse events like nausea, dizziness, mouth dryness, fatigue, hypomania, agitation and confusion (14-17). Of note, in a study that compared saffron to donepezil, donepezil group had significantly higher incidence of vomiting (15).

Cognitive performance assessment—Scores on ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale) were assessed in two studies (14, 15). Score change was similar when saffron was compared to donepezil in the first study and better for saffron when it was compared to placebo, in the second study (14, 15). Mini Mental State Examination (MMSE) was assessed in three studies (16-18). In the first study, MMSE score change was significantly higher in the saffron group when compared to the no treatment group (18). Score change did not differ in the second study in which saffron was compared to memantine (16). No differences in MMSE score change was identified in the third study, which was the only study that enrolled non-demented participants and saffron was compared to placebo (17). More details about cognitive outcomes regarding the above and additional tests are shown in table 4.

Assessment of functional status—Scores on Clinical Dementia Rating scale-sum of boxes (CDR-SB) were assessed in two studies (14, 15). Results showed equal efficacy of saffron with donepezil and superiority of saffron against placebo (14, 15). Other functional

assessment scales used were FAST (Functional Assessment Staging) and FRSSD (Functional Rating Scale of Symptoms of Dementia) (16, 18). In one study in which saffron was compared to memantine, FAST score changes did not differ significantly (16). In another study, saffron resulted in no significant change on FRSSD score (18). Details about functional status assessments are found in table 4.

Discussion

In this systematic review of RCTs, we found evidence that oral intake of saffron by patients with AD, may have similar efficacy with common anti-AD drugs (such as donepezil and memantine) on cognitive function and functional status. Furthermore, saffron was superior to placebo. Additionally, saffron was shown to be safe, since the saffron group had no more side effects than the comparison group (either anti-AD drug or placebo). However, we emphasize that despite results may be deemed encouraging, they should not be overinterpreted. The degree of uncertainty regarding these conclusions is high since several studies upon which we based our conclusions, were of unknown risk of bias and one was of high risk of bias.

All the currently approved treatments for AD (cholinesterase inhibitors and NMDA receptor antagonist memantine) are merely symptomatic and do not modify the course of the disease. Disappointingly, numerous other agents, whether repurposed drugs (such as statins, NSAIDs, omega-3 fatty acids) (19-21) or novel compounds have failed as disease modifying agents in clinical trials urging the field to re-examine its underlying assumptions about disease pathophysiology (4). Several herbal therapies have already shown both efficacy and safety against mental diseases like major depression, premenstrual syndrome, anxiety, sleep disorders and may potentially be effective against cognitive impairment (22, 23). Ingestion of certain vegetables, fruits and spices which contain hormetic phytochemicals such as capsaicin, curcumin, resveratrol and sulforaphane, results in expression of cytoprotective proteins (growth factors, mitochondrial proteins, antioxidant enzymes and protein chaperones) that reduce neurodegenerative damage and thus could possibly have therapeutic action (24-26).

Saffron is a product of Crocus L. Sativus, which is a perennial bulb widely cultivated in Iran, India and Mediterranean countries (mostly Greece) (11). It has been used since ancient years for medicinal and cosmetic purposes (11). There is evidence from animal studies that saffron has antidiabetic, anti-inflammatory, anti- atherosclerotic, antitumor, immunomodulatory and antioxidant effects (11, 27, 28). In addition, saffron has four potential pathophysiologic actions that may partially explain why it could be effective in AD. First, it may inhibit glutamate excitotoxicity and neuronal death through NMDA receptor antagonism similar to memantine (29). Second, it has a relative inhibitory effect on acetylo-cholinesterase in the same way as homonymous AD drugs do (30). Third, there is some evidence that it may inhibit deposition of beta-amyloid fibrils, which is one of the pathological hallmarks of AD (31). Fourth, it has antioxidant properties which may further establish saffron's beneficial effects against oxidative stress that is known to occur in the AD brain (31, 32). The described mechanisms lend some external validity and biological plausibility to the RCT findings. Moreover, the magnitude of saffron's effect in AD may not be negligible. In two

studies, saffron had same efficacy as donepezil and memantine, perhaps, because saffron shares similar mechanisms of actions with these drugs (15, 16).

Three studies compared saffron to placebo and results were conflicting (14, 17, 18). In the first study, saffron was found to be superior to placebo, which supports its claim as an anti-AD treatment (14). In two other studies (second, third), saffron showed no benefit against placebo except for one cognitive task (17, 18). Unfortunately, the second study was of low methodological quality (high ROB study) and therefore could not be used as a basis to confirm the null hypothesis (18). In the third study, participants were non-demented; therefore, the failure of saffron to improve their cognitive scores could have been due to a ceiling effect (17).

Depression is common among MCI/AD patients, affecting half of all patients (33, 34). It results in higher morbidity and mortality among patients and a higher occurrence of depression among caregivers (35). Rivastigmine has shown some promising effects on depressive symptoms of AD patients, but further studies are needed to confirm that (36, 37). Regarding the use of anti-depressants for depression in AD, the evidence is not supportive; their efficacy is uncertain and there is a potential of side effects (38, 39). Therefore, natural compounds could be potentially useful in the treatment of AD depression (35). Saffron, has anti-depressive properties and has been shown to be superior to placebo and equal to an SSRI and a TCA in various RCTs (40-42). However, SSRIs may cause serotonin syndrome, agitation, insomnia, sexual dysfunction, dizziness and other symptoms, while TCAs are responsible for anticholinergic effects (therefore, they are generally avoided in AD) and cardiac arrhythmias (35). Saffron is associated with no known side effects and as such, it could be a better choice for depression in AD patients. The combination of putative cognitive-enhancing and anti-depressive effects of saffron make it a reasonable treatment option for AD patients.

Limitations and strengths

The finding that a natural compound (saffron) is likely as efficacious as common drugs against AD is promising. However, our results should be interpreted with caution for several reasons. First, this systematic review included only five studies, and, of those five, three were deemed as of unknown ROB while one as of high ROB. In addition, a meta-analysis was not feasible mainly because i) the comparison group was different in each study (in some studies the comparator was placebo, while in other studies it was donepezil or memantine or was not described adequately) ii) the cognitive scales varied greatly from study to study. Finally, four of five studies took place in Iran, a fact that results in non-generalizable conclusions.

Conclusion

In the present systematic review, we examined the effects of oral saffron intake on cognitive function. Saffron showed similar efficacy in improving cognitive scores as common anti-AD drugs. The incidence of side effects was similar in the saffron and comparison groups. However, these findings should be interpreted cautiously since there was potential risk of bias in many of the included studies. On the other hand, saffron has been reported to have

additional anti-depressive properties, which are of interest given the increased incidence of depression in AD. Taken together, these findings and background evidence should motivate future RCTs to explore the potential properties of this herb as an alternative or adjunct treatment for MCI/AD. Such trials would require larger sample sizes and inclusion of a sufficient number of patients with high-probability AD.

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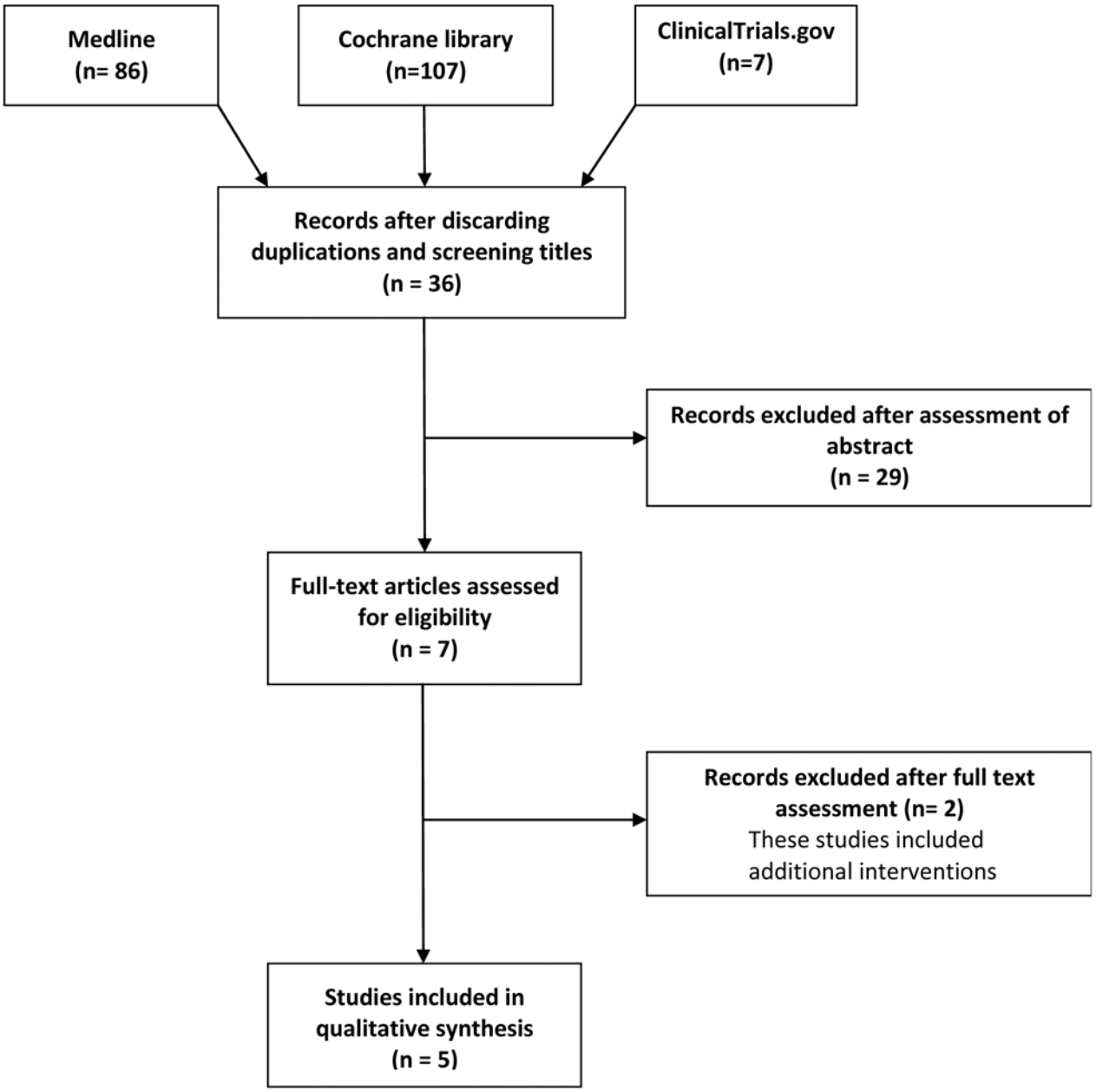

Fig. 1.
flow diagram of studies selection

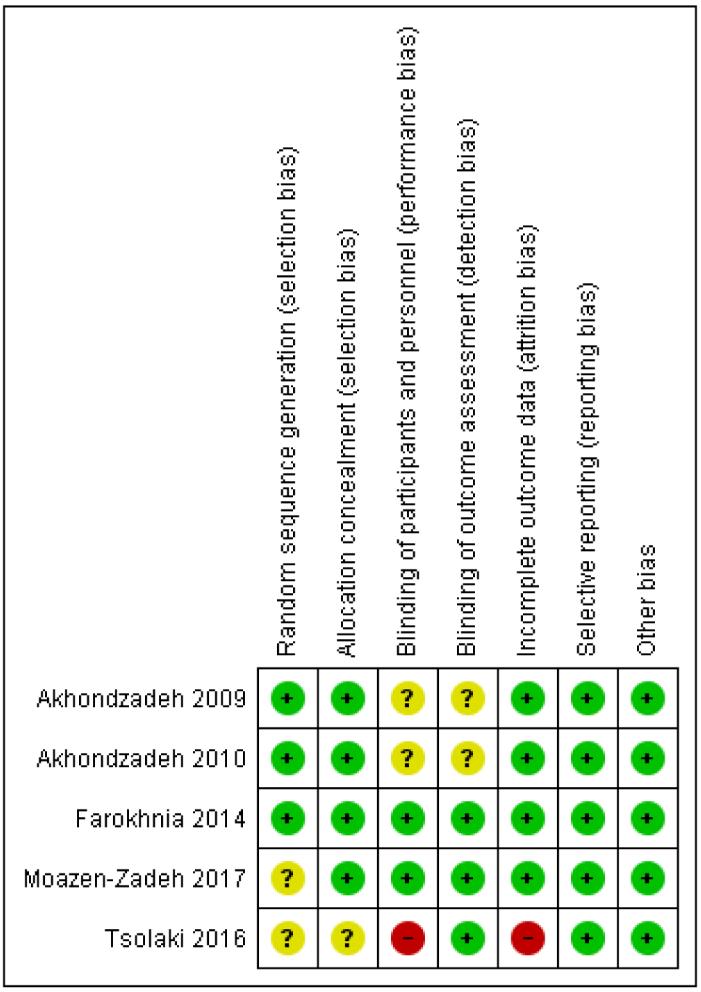

Fig. 2.

Risk of bias graph authors' judgements about each risk of bias item, presented as percentage across all included studies

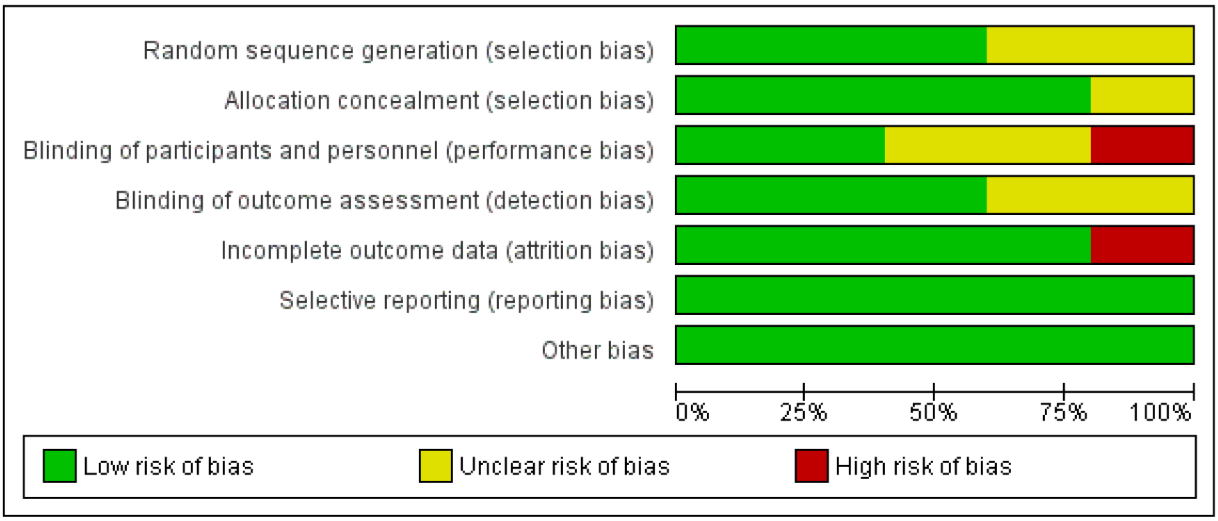

Fig. 3.
Risk of bias summary

Table 1.

PICOS presentation

Participants	Healthy or Mild Cognitive Impairment/Alzheimer's Disease (MCI/AD) patients
Interventions	Oral saffron (Crocus L. Sativus) administration
Comparator	Placebo or any approved anti-AD drug or nothing
Outcome	Cognitive performance on standardized tests before/after the intervention
Study Design	Randomized controlled trials (RCTs) or cross-over RCTs

Table 2.

Characteristics of included studies

First author and year	Country	Study type	Treatment duration (weeks)	Patients with	Total n of patients in study	Daily saffron dose	Daily comparator dose	Cognitive tasks used
Akhondzade h, 2010 (14)	Iran	RCT	22	Mild/moderate AD	54	30 mg	10 mg (donepezil)	ADAS-Cog, CDRS-SB
Akhondzade h, 2010' (15)	Iran	RCT	16	Probable AD	46	30 mg	30 mg (placebo)	ADAS-Cog, CDRS-SB
Farokhnia, 2014 (16)	Iran	RCT	48	Moderate / severe AD	68	30 mg	20 mg (memantine)	SCIRS, MMSE FAST
Tsolaki, 2016 (18)	Greece	RCT	48	aMCI	102	N/R	N/R	MoCA, MMSE
Moazen-Zadeh, 2018 (17)	Iran	RCT	12	CABG	55	30 mg	30 mg (placebo)	WMS-R, MMSE

ADAS-Cog: AD assessment scale-cognitive subscale; CDRS-SB: Clinical Dementia Rating Scale- Sums of Boxes: SCIRS: Severe Cognitive Impairment Rating Scale; FAST: Functional Assessment Staging; CABG: Coronary Artery Bypass Surgery; WMS-R: Wechsler Memory Scale-Revised MMSE: Mini Mental State Examination; aMCI: amnestic Mild Cognitive Impairment; MoCA: Montreal Cognitive Assessment

Table 3.

Demographic characteristics of patients in each study

First author year	Gender (m/f)	Age (years)	Education (diploma/no diploma)* or (years)**
Akhondzadeh, 2010 (14)	14/13 (saffron) 15/12 (donepezil)	72.70±6.20 (saffron) 73.85±4.63 (donepezil)	11/16 (saffron)* 12/15 (donepezil)*
Akhondzadeh, 2010' (15)	13/10 (saffron) 12/11 (placebo)	72.65 ± 3.89 (saffron) 73.13 ± 4.70 (placebo)	11/12 (saffron)* 10/13 (placebo)*
Farokhnia, 2014 (16)	21/13 (saffron) 18/16 (memantine)	77.73 ± 8.05 (saffron) 77.47±7.99 (memantine)	5.88 ± 4.63 (saffron)** 5.91 ± 4.84 (memantine)**
Tsolaki, 2016 (18)	5/12 (saffron) 4/14 (control)	71.47 ± 6.73 (saffron) 69.72 ± 7.33 (control)	8.17 ± 4.91 (saffron)** 10.1 ± 4.00 (control)**
Moazen-Zadeh, 2018 (17)	20/2 (saffron) 21/2 (placebo)	58.14 ± 4.43 (saffron) 56.61 ± 5.60 (placebo)	18/4 (saffron)* 19/4 (placebo)*

Age is reported as mean ± SD in most studies; Education is reported as mean ± SD in Farokhnia and Tsolaki studies.

Table 4.

Cognitive and functional status outcomes

First author and year	Comparison	Cognitive task	Change of scores from baseline to endpoint
Akhondzadeh, 2010 (14)	Saffron vs donepezil	ADAS-Cog CDRS-SB	NS difference in score change between two groups (t = 0.18, df = 52, p = 0.85) NS difference in score change between two groups (t = 0.21, df = 52, p = 0.83)
Akhondzadeh, 2010' (15)	Saffron vs placebo	ADAS-Cog CDRS-SB	Significantly better score change in saffron group (t = 17.27, d.f = 44, p < 0.0001) Significantly better score change in saffron group (t = 12.06, d.f = 44, p < 0.0001)
Farokhnia, 2014 (16)	Saffron vs memantine	SCIRS MMSE FAST	NS difference in score change between two groups (t = 0.87, df = 66, p = 0.38) NS difference in score change between two groups (t = −1.07, df = 66, P = 0.28) NS difference in score change between two groups (t = −0.15, df = 66, p = 0.87)
Tsolaki, 2016 (18)	Saffron vs control	MoCA MMSE FRSSD	NS difference in score between two groups (p = 0.62) Sig. positive change in saffron group compared no treatment group (p =0.02) NS difference in score change between two groups (p = 0.67)
Moazen-Zadeh, 2018 (17)	Saffron vs placebo	WMS-R MMSE	NS difference in score change between two groups (t = −0.09, df = 43, p = 0.93) NS difference in score change between two groups (t= 0.39, df = 29.01, p = 0.69)

ADAS-Cog: AD assessment scale-cognitive subscale; CDRS-SB: Clinical Dementia Rating Scale- Sums of Boxes; SCIRS: Severe Cognitive Impairment Rating Scale; FAST: Functional Assessment Staging; WMS-R: Wechsler Memory Scale-Revised; MMSE: Mini Mental State Examination;;MoCA: Montreal Cognitive Assessment; NS: Non-significant; FRSSD: Functional Rating Scale of Symptoms of Dementia