Journal of Affective Disorders 323 (2023) 264–279

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review article

Protective role of antioxidant supplementation for depression and anxiety: A meta-analysis of randomized clinical trials

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ARTICLE INFO

Keywords:
Antioxidant supplementation
Depression
Anxiety
Randomized intervention trials
Meta-analysis

ABSTRACT

Background: New research supports an integrated approach to treating depression, and lifestyle modifications should be a regular component of both preventative and treatment programs. Therefore, in order to investigate the relationship between various antioxidant supplements and depressive status, we carried out a meta-analysis of randomized controlled trials (RCT).

Methods: We thoroughly searched PubMed, Medline, Scopus, and Web of Science databases to screen publications focusing on the effects of antioxidant supplements on depression status. The meta-analysis mainly compared depression scores between groups that received antioxidant supplements and controls. We also pooled studies reporting changes in anxiety status as a secondary outcome.

Results: 52 studies with 4049 participants were eventually identified. The meta-analysis found that the positive effect of antioxidant supplementation, such as magnesium (SMD = 0.16, $p = 0.03$), zinc (SMD = 0.59, $p = 0.01$), selenium (SMD = 0.33, $p = 0.009$), CoQ10 (SMD = 0.97, $p = 0.05$), tea and coffee (SMD = 1.15, $p = 0.001$) and crocin (MD = 6.04, $p < 0.00001$), on depressive status were all significant. And antioxidant supplementation also showed significant improvement in anxiety (SMD = 0.40, $p < 0.00001$). Subgroup analysis by scale types and countries were performed, and antioxidant supplementation's positive effects on depressive and anxiety states remained significant.

Limitations: This study did not limit the characteristics of the included population, and the diversity of scales also contributed to the heterogeneity.

Conclusion: Intake of antioxidant supplements is associated with improved depression and anxiety states, further affirms the therapeutic potential of antioxidant supplements as adjunctive therapy to conventional antidepressants.

1. Introduction

Depression is a mental disorder characterized by persistent sadness, retardation of thinking, decreased volitional activity, and cognitive impairment. In 2008, WHO ranked major depressive disorder the third cause of burden of disease worldwide and projected that the disease will rank first by 2030. Globally, the 12-month prevalence of major depressive disorder is approximately 6 % (Malhi and Mann, 2018). And depression is a risk factor for suicidal ideation and death (Ribeiro et al., 2018). The proportion of major depressive disorder recovered decreased significantly with the course of the disease, and the likelihood of relapse was high, with an increased risk in each episode (Verduijn et al., 2017). A recent systematic review in the *Lancet* reported that the COVID-19 epidemic increased by about 53 million depression patients in 2020, increasing by about 27.6 %. The prevalence of anxiety disorders increased by about 76 million (2021).

The clinical symptoms of depression range from mild to severe. Mild depression in the early stage is characterized by significant and

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https://doi.org/10.1016/j.jad.2022.11.072
Received 2 June 2022; Received in revised form 5 November 2022; Accepted 20 November 2022
Available online 25 November 2022

persistent low mood and pessimism, while depression without active treatment could lead to stubborn insomnia, headache, memory loss, nausea, palpitations, chest tightness, sweating, and other physical symptoms (Park and Zarate, 2019). Therefore, identifying specific interventions that improve depressive status is critical for public health policy. A lifestyle factor-focused approach represents a cost-effective and practical strategy, and there is now compelling evidence that a range of lifestyle factors are involved in the pathogenesis of depression. Many of these factors can be modified, but they are rarely considered in contemporary depression treatment, where pharmacological and psychological interventions remain first-line treatments (Sarris et al., 2014).

Nutrition is a modifiable lifestyle factor. Current evidence suggests that adherence to healthy eating patterns, intake of specific nutrients, or consumption of specific foods can help prevent and treat depression and anxiety (Kris-Etherton et al., 2021). For example, a meta-analysis of 48 studies involving 2788 subjects showed that higher flavonoid intake might improve symptoms of depression (Ali et al., 2021). Since nutritional psychiatry's emergence, it has identified many mechanisms involved in psychiatric disorders, including inflammation, epigenetics, mitochondrial dysfunction, gut microbiota, and oxidative stress (Marx et al., 2021). Studies have shown that the "oxidative-antioxidant" function of the body in patients with depression is dysfunctional, mainly manifested in the increased concentration of oxygen free radicals and the abnormal activity of some antioxidant enzymes. Suppose copper-zinc superoxide dismutase (CuZn SOD), glutathione peroxidase (GPX), and catalase (CAT) cannot effectively eliminate the oxygen free radicals produced by cell metabolism. In that case, the concentration of oxygen free radicals will increase, leading to abnormal structure and function of neurons, which might be one of the pathogenesis of depression. Studies have also shown that oxidative stress products are important parameters for measuring and predicting depressive status and determining the effectiveness of administered antidepressants (Vaváková et al., 2015).

Results from a series of observational and interventional studies in human have shown that multiple antioxidant supplements significantly affect depressive status (Das et al., 2021; Milajerdi et al., 2019). However, current randomized controlled trials (RCTs) are small sample studies focused on one or two specific antioxidants with inconsistent findings. The purpose of this study was to, first, analyze the effects of different types of antioxidant supplements on depression and anxiety, and second, to explore the direction of effects of this category of supplements on depression and anxiety by including as many antioxidant supplements as possible, and to quantify this effect. We also performed detailed subgroup analyses according to study country and type of depression and anxiety status assessment scales to minimize heterogeneity.

2. Method

2.1. Search strategy

Two researchers comprehensively searched PubMed, Medline, Scopus, and Web of Science databases for eligible randomized clinical trials (RCTs) on February 13–14, 2022, to identify articles published before January 2022 investigating the effects of antioxidant supplements on depressive states, and reviewed the references to supplement the missing. We used Boolean operators "AND" and "OR" to combine the following free text terms and MESH terms: ("proanthocyanidin" OR "OPC") OR ("grapeseed" OR "grape" OR "resveratrol") OR ("α-carotene" OR "alpha-carotene" OR "beta-carotene" OR "beta-carotene" OR "beta-cryptoxanthin" OR "beta-cryptoxanthin" OR "lutein" OR "zeaxanthin" OR "lycopene" OR "astaxanthin" OR "carotenoids") OR "Rhodiola" OR ("coenzyme Q10" OR "CoQ10") OR ("magnesium" OR "zinc" OR "selenium") OR ("catechin" OR "tea" OR "tea polyphenols" OR "coffee" OR "caffeine") AND ("depression" OR "depressed state" OR "depressive state") AND ("randomized controlled trial" OR "RCT" OR "prospective" OR "controlled clinical trial" OR "prospective clinical trial" OR "randomized clinical trial"). This study was designed and conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) without registration (Moher et al., 2015).

2.2. Eligibility criteria

After an initial search of studies using combinations of depression with different antioxidant supplements, retrieved papers were assessed for relevance by reviewing the titles and abstracts. The inclusion criteria were as follows: (1) original research article in English; (2) RCTs comparing antioxidant intervention and a control group in human; (3) studies that reported depression scores before and after the intervention. Exclusion criteria: (1) systematic review, meta-analysis, animal experiments, case reports, comments, or letters; (2) lack of outcome measures (depressive score); (3) self-reported depression; (4) repeated published results; (5) data cannot be extracted or calculated, and the authors cannot be contacted.

2.3. Quality evaluation and data extraction

Endnote 20 was used to deduplicate articles retrieved from different databases. The titles and abstracts of all the articles were screened by two researchers independently, followed by full-text browsing. When there was disagreement about a study's eligibility, a third researcher would make the inclusion decision. Two researchers independently scored the studies' quality according to the Jadad scale, and the risk of bias was assessed as "low", "high" or "unclear" in the following items: (1) Random sequence generation; (2) Allocation concealment (selection bias); (3) Blinding of participants and personnel (performance bias); (4) Blinding of outcome assessment (detection bias); (5) Incomplete outcome data (attrition bias); (6) Selective reporting (reporting bias). The original data were extracted according to the PICO principle (Patients, Intervention, Comparison, Outcomes) (Eriksen and Frandsen, 2018): Article's basic information, including the first author, publication year, country, participant characteristics (group, gender, age), study design, and intervention (type of the antioxidant supplements and dose); Valid data of meta-analysis, including duration of the intervention, scales used to measure depression or anxiety states, the depression scores and anxiety scores after the intervention.

2.4. Statistical analysis

The meta-analysis was performed using Revman 5.3 and Stata 12.0. Given the heterogeneity across interventions, participants, and assessment of outcomes, the depression and anxiety scores were expressed as mean difference (MD) (meta-analysis of the same scale) or standardized mean difference (SMD) (meta-analysis of different scales), and their 95 % confidence intervals (CI). The MD and SMD were defined as the (standardized) mean difference from the baseline to the completion of the RCT experiment. In addition to grouping different types of antioxidant supplements, we also conducted subgroup analysis for different scales and studies in different countries to achieve the role of sensitivity analysis. Heterogeneity was evaluated by Cochran's Q statistic and the I^2 statistic. Fixed-effects models were used for meta with no or low heterogeneity ($I^2 < 50\%, p > 0.1$), and random-effects models were used for meta with moderate or high heterogeneity ($I^2 \geq 50\ \%, p \leq 0.1$) (Higgins and Thompson, 2002). Sensitivity analysis was carried out by excluding low-quality studies and combining effect sizes. The publication bias was evaluated by the visual inspection of funnel plots and Egger's test using Stata software (Egger et al., 1997). Subgroup analyses were conducted based on the antioxidant type. A *p-value* < 0.05 (two-tailed) was considered statistically significant.

3. Results

3.1. Search results and basic information of the original literature

The process of literature screening is summarized in Fig. 1. According to the eligibility criteria, this meta-analysis finally included 52 studies. Table 1 summarizes the characteristics and study ID. of the studies. There were 22 studies (42.3 %) on antioxidant minerals: nine studies (17.3 %) for zinc (study ID. 1–9), eight studies (15.4 %) for magnesium (study ID.10–17), four studies (7.7 %) for selenium (study ID. 29–32), five studies (9.6 %) on CoQ10 (study ID.18–22), six studies (11.5 %) on tea and coffee (study ID.23–28), three studies (5.8 %) on Rhodax (study ID.37–39), four studies (7.7 %) on crocin (study ID.33–36), two studies (3.8 %) on resveratrol (study ID.40–41), two studies (3.8 %) on carotenoids (study ID.42–43) and one study (1.9 %) on anthocyanins (study ID.44), and eight studies (15.4 %) on antioxidant supplements combinations (study ID.45–62).

A total of 4049 participants were enrolled, of whom 2004 were treated with antioxidant supplements, and 2045 were treated with a placebo or nothing. The median treatment duration was 11 (8, 12) weeks. The longest duration was two years (study ID.47), the shortest duration was two weeks (study ID.24, 26, and 51). 11 studies were conducted only in males (study ID.41, 43, 45) or females (study ID.2, 8, 20, 26, 31, 32, 36, 44, 46, 52). All trials assessed the depressive status of the subjects, and 21 studies (40.4 %) reported the anxiety status (study ID.2, 5, 8, 12, 18, 24, 29–31, 33–36, 41–43, 45, 46, 48, 51, 52). Multiple depression scales, such as Beck Depression Inventory (BDI), The Edinburgh Postnatal Depression Scale (EPDS), Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HDRS), center for epidemiologic studies-depression (CES-D), Hospital Anxiety and Depression Scale (HADS) were applied in the studies.

3.2. Risk of bias

Almost all studies were randomized (94.2 %, $n = 49$), while some failed to detail the process of generating random sequences. Nearly half of the studies described allocation concealment (44.2 %, $n = 23$). Double-blind setups were lacking or ambiguous in ten studies (19.2 %), and seven studies (13.5 %) did not demonstrate blinding of outcome assessments. Thirteen studies (25 %) were considered attrition biased because the reasons for withdrawal were not explained. The risk of bias in individual studies is exhibited in Fig. 2. In addition, the Jada scale was used to determine the quality of evidence. We considered the evidence to be of moderate to high quality except for (Bambling et al., 2017) (Table 1). It is worth mentioning that, participants in six studies (study ID: 3, 4, 11, 16, 21, 28) received antidepressant therapy in addition to antioxidant supplementation, and controls received the same dose of antidepressant therapy, ensuring that the difference between groups was only in antioxidant supplementation.

3.3. Meta-analysis of the effect of the antioxidant supplement on depression status

Fig. 3 displayed a forest plot with the summary effect of different antioxidant supplement interventions on depression states. Overall, 52 studies reported the depression states, involving 2004 and 2045 subjects

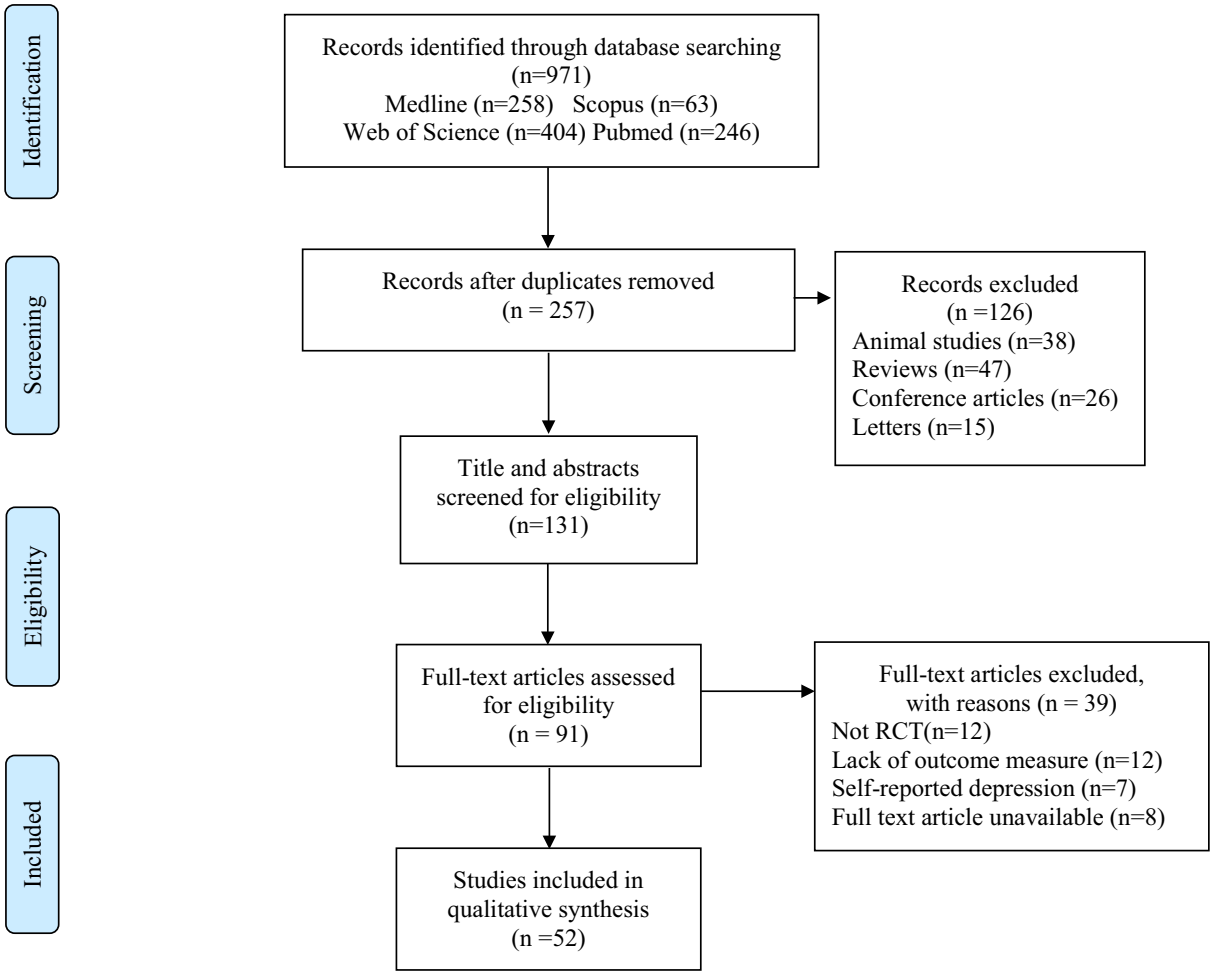

Fig. 1. Inclusion procession.

Table 1
Overview of studies investigating the relationship between antioxidant supplements and depression states.

ID.	Study	Location	Population characterize				Intervention	Duration	Scale	Jada score
			Group	Number	Male/female (case, control)	Age (case, control)				
1	(DiGirolamo et al., 2010)	Guatemala	Treated Control	331 343	163/168 174/169	8.9 ± 1.2 9.0 ± 1.2	10 mg ZnO/day for 5 d/week	6 months	CDI	5
2	(Fard et al., 2017)	Iran	Treated Control	31 33	0/31 0/33	27.6 ± 5.1 29.4 ± 5.4	27 mg zinc sulfate/day	6 weeks	EPDS	4
3	(Nowak et al., 2003)	Poland	Treated Control	6 8	4/2 2/6	42.2 ± 13.7 43.4 ± 8.5	25 mg of Zn^{2+}/day	12 weeks	BDI	4
4	(van der Burg et al., 2020)	Australia	Treated Control	47 49	15/32 9/40	41.6 ± 12.6 45.8 ± 12.1	30 mg zinc picolinate/day	8 weeks	MADRS	5
5	(Katz et al., 1987)	America	Treated Control	6 7	–	–	15 mg zinc/day	6 months	sSDS	4
6	(Heckmann et al., 2005)	German	Treated Control	24 26	5/21 2/22	61.1 ± 10.6 61.0 ± 8.9	140 mg zinc gluconate/day	3 months	BDI	5
7	(Salari et al., 2015)	Iran	Treated Control	21 22	8/13 5/17	33.9 ± 10.21 37.22 ± 5.8	50 mg zinc element/day	12 weeks	BDI	6
8	(Sawada and Yokoi, 2010)	Japan	Treated Control	15 15	0/15 0/15	19.3 ± 0.6 19.5 ± 1.2	7 mg Zn/day	10 weeks	CES-D	6
9	(Solati et al., 2015)	Iran	Treated Control	22 24	8/14 7/17	29.77 ± 4.21 31.29 ± 3.81	30 mg zinc/day	12 weeks	BDI II	6
10	(Rajizadeh et al., 2017)	Iran	Treated Control	26 30	7/20 7/19	32.20 ± 9.54 32.07 ± 7.69	250 mg MgO/day	8 weeks	BDI	6
11	(Ryszewska-Pokraśniewicz et al., 2018)	Poland	Treated Control	17 20	6/11 10/10	48.1 ± 15.5 49.7 ± 12.3	40 mg magnesium effervescent tablets or powder containing 40 mg of magnesium/day.	8 weeks	HDRS	5
12	(Tarleton et al., 2017)	America	Treated Control	55 57	22/33 22/35	55.2 ± 12.3 50.1 ± 13.0	Four 500 mg tablets of magnesium chloride/day	6 weeks	PHQ-9	7
13	(Fard et al., 2017)	Iran	Treated Control	31 33	0/31 0/33	26.4 ± 4.8 27.6 ± 5.1	320 mg magnesium sulfate/day for eight weeks	8 weeks	EPDS	4
14	(Barragan-Rodriguez et al., 2008)	Mexico	Treated Control	12 9	–	69 ± 5.9 66.4 ± 6.1	2.5 g $MgCl_2$/day	12 weeks	GDS	5
15	(Afsharfar et al., 2021)	Iran	Treated Control	23 23	–	54.5 ± 7.3 52.8 ± 8	500 mg magnesium/day	8 weeks	BDI	6
16	(Bambling et al., 2017)	Australia	Treated Control	12 12	4/8 4/8	49.9 ± 10.9	Combination of lyophilized probiotics and magnesium orotate 1600 mg/two days	8 weeks	BDI	3
17	(Bhudia et al., 2006)	America	Treated Control	174 176	133/41 137/39	64 ± 12 64 ± 13	780 mg (32 mmol) of $MgSO_4$ in 100 mL of normal saline intravenously	3 months	BDI-II	4
18	(Maguire et al., 2021)	Ireland	Treated Control	32 40	51 21	48.56 ± 10.84 47.63 ± 10.11	300 mg CoQ10/day	6 months	BDI	6
19	(Alcocer-Gomez et al., 2014)	Spain	Treated Control	10 10	–	–	300 mg CoQ10/day	40 days	BDI	5
20	(Lesser et al., 2013)	America	Treated Control	122 114	0/122 0/114	52 (31–85) 50 (28–72)	300 mg CoQ10/day	24 weeks	CES-D	5
21	(Jahangard et al., 2019)	Iran	Treated	36	8/28	37.47 ± 10.69	100 mg CoQ10/day	8 weeks	MADRS	5

(*continued on next page*)

Table 1 (*continued*)

ID.	Study	Location	Population characterize				Intervention	Duration	Scale	Jada score
			Group	Number	Male/female (case, control)	Age (case, control)				
			Control	33	3/30	39.52 ± 10.82				
22	(Sanoobar et al., 2016)	Iran	Treated	24	2/22	33.1 ± 7.6	500 mg CoQ10/day	12 weeks	BDI	5
			Control	24	2/22	30.9 ± 7.7				
23	(Manshadi Seyed Ali et al., 2021)	Iran	Treated	25	17/8	<30: 5 30–40: 11 >40: 9	400 mg green tea extract capsules/day	12 weeks	Hamilton mean score	5
			Control	25	15/10	<30: 7 30–40: 14 >40: 4				
24	(Bazrafshan et al., 2020)	Iran	Treated	30	10/20	66.63 ± 5.54	4 g lavender teabag/day	2 weeks	BDI, BAI	5
			Control	30	10/20	67.77 ± 6.02				
25	(Zhang et al., 2013)	China	Treated	24	10/12	26.79 ± 4.48	400 mg green tea or cellulose/day	5 weeks	MADRS	5
			Control	22	11/13	24.55 ± 4.47				
26	(Chang and Chen, 2016)	China	Treated	35	0/35	24–43 ± 33.20	2 g chamomile tea/day	2 weeks	EPDS	5
			Control	38	0/38	25–40 ± 32.68				
27	(Baek et al., 2018)	China	Treated	20	8/12	39.9 ± 2.6	1200 mg Astragali Radix + 900 mg Angelicae gigantis + 900 mg Zizyphi Fructus/day	8 weeks	BDI	5
			Control	20	10/10	39.3 ± 2.9				
28	(Liu et al., 2017)	China	Treated	30	61/0	42.57 ± 7.15	120 mg caffeine/day	4 weeks	MADRS	4
			Control	31		41.15 ± 5.72				
29	(Raygan et al., 2019)	Iran	Treated	27	10/17	62.4 ± 13.1	200 μg selenium/day	12 weeks	BDI	5
			Control	27	11/16	64.8 ± 8.3				
30	(Shor-Posner et al., 2003)	America	Treated	28	11/17	39.7 ± 6.4	200 μg selenium/day	12 months	BDI.	5
			Control	35	21/14	40.4 ± 6.5				
31	(Jamilian et al., 2018)	Iran	Treated	30	0/30	25.6 ± 3.8	200 μg selenium/day	12 weeks	BDI	5
			Control	30	0/30	26.0 ± 5.3				
32	(Mokhber et al., 2011)	Iran	Treated	44	0/44	21.64 ± 2.45	100 μg of selenium/day	8 weeks	EPDS	5
			Control	41	0/41	21.59 ± 3.40				
33	(Ghaderi et al., 2019)	Iran	Treated	26	–	44.5 ± 9.4	15 mg crocin/day	8 weeks	BDI	7
			Control	27		45.6 ± 9.9				
34	(Khalatbari-Mohseni et al., 2019)	Iran	Treated	25	–	40.1 ± 9.3	30 mg crocin/day	8 weeks	BDI	6
			Control	25		41.4 ± 8.8				
35	(Talaei et al., 2015)	Iran	Treated	20	2/18	35.9 ± 7.10	30 mg crocin/day	4 weeks	BDI	5
			Control	20	4/16	36.5 ± 7.67				
36	(Salek et al., 2021)	Iran	Treated	36	0/36	>40 y 25 (69.4 %)	30 mg crocin/day	4 months	BDI	6
			Control	36	0/36	>40 y 25 (69.4)				
37	(Olsson et al., 2009)	Sweden	Treated	30	3/27	41.0 ± 7.9	576 mg SHR-5 extract/day	28 days	MADRS	5
			Control	30	3/27	42.1 ± 8.5				

(*continued on next page*)

Table 1 (*continued*)

ID.	Study	Location	Population characterize				Intervention	Duration	Scale	Jada score
			Group	Number	Male/female (case, control)	Age (case, control)				
38	(Mao et al., 2015)	America	Treated	20	12/8	46.9 ± 16.9	340 mg SHR-5 powdered extract/day	12 weeks	BDI	6
			Control	18	10/8	46.7 ± 15.2				
39	(Darbinyan et al., 2007)	Sweden	Treated	29	12/17	44.6 ± 25.49	680 mg SHR-5/day	6 weeks	BDI	5
			Control	30	15/15	42.8 ± 12.87				
40	(Malaguarnera et al., 2018a)	Italy	Treated	35	25/10	39–60	19.8 mg resveratrol/day	90 days	HADS	6
			Control	35	23/12	35–60				
41	(van Die et al., 2017)	Australia	Treated	9	9/0	69 ± 6.4	120 mg resveratrol/day	12 weeks	HADS	5
			Control	11	11/0	75 ± 8.3	400 mg turmeric/day 100 mg catechins/day 8 g broccoli/day			
42	(Stringham et al., 2018)	Georgia	Treated	25	–	–	27 mg macular carotenoids/day	12 months	BDI	5
			Control	10						
43	(Nouri et al., 2020)	Iran	Treated	19	19/0	31.89 ± 2.51	25 mg lycopene/day	12 weeks	DASS-21	6
			Control	19	19/0	32.15 ± 2.16				
44	(Terauchi et al., 2014)	Japan	Treated	29	0/29	49.8 ± 4.7	200 mg proanthocyanidin/day	12 months	HADS	5
			Control	30	0/30	49.8 ± 5.2				
45	(Harris et al., 2011)	Australia	Treated	25	25/0	62.1 ± 3.8	Swisse men's ultivite	8 weeks	POMS	6
			Control	25	25/0	62.9 ± 7.0				
46	(Belcaro et al., 2010)	Italy	Treated	33	0/33	43 ± 3.50	800 mg calcium carbonate/lactate; 0.27 mg astaxantin/day; 1 mg lycopene/day; 0.23 mg Vit D3/day; 33 mg bioflavonoids/day	8 months	MSSQ	5
			Control	32	0/32	42 ± 3.2				
47	(Leng et al., 1998)	America	Treated	29	–	–	One capsule of antioxidant	2 years	HADS	5
			Control	39						
48	(Malaguarnera et al., 2016)	Italy	Treated	31	18/13	–	94 mg Silybin/day; 30 mg vitamin E/day; 194 mg phospholipids/day in pills for 12 months.	12 months	BDI.	5
			Control	31	17/14					
49	(Gosney et al., 2008)	America	Treated	26	–	–	Vitamin A: 2666 IU, Vitamin D3: 400 IU, Vitamin E: 60 mg, Vitamin B1: 1.2 mg, Vitamin B2: 1.4 mg, Vitamin B6: 3.0 mg, Nicotinamide: 14 mg, Folic acid: 0.6 mg, Vitamin B12: 200 g, Biotin: 30 g Calcium pantothenate: 5 mg, Vitamin C: 120 mg, Iron: 12 mg, Zinc: 14 mg, Copper: 2 mg, Iodine: 150 g, Manganese: 1 mg, Chromium: 50 g, Selenium: 60 g, Molybdenum: 100 g, Calcium: 240 mg, Magnesium: 100 mg	8 weeks	MADRS	6
			Control	33						
50	(Gariballa and Forster, 2007)	The United Arab Emirates	Treated	106	69/37	75.9 ± 6.0	Oral nutritional supplement (400 mL/d)	6 weeks	GDS.	5
			Control	119	73/46	75.3 ± 5.9				
51	(Conner et al., 2017)	Australia	Treated	57	–	19.43 ± 1.45	Fruit and vegetable consumption (3.7 servings/day)	2 weeks	CES-D	4
			Control	59						
52	(Hamedifard et al., 2020)	Iran	Treated	27	0/27	61.7 ± 9.4	250 mg magnesium oxide + 150 mg zinc sulfate/day	12 weeks	BDI	5
			Control	28	0/28	62.6 ± 10.8				

Studies were ordered by types of supplements and publish year. All the studies were randomized controlled trials (RCTs).
Abbreviations: BDI, Beck Depression Inventory; CDI, the Children's Depression Inventory; EPDS, The Edinburgh Postnatal Depression Scale; STAI, the Spielberger State-Trait Anxiety Inventory; MADRS, Montgomery-Asberg Depression Rating Scale; SDS, Zung Self-Rating Depression Scale; POMS, The Profile of Moods State; HDRS, Hamilton Depression Rating Scale; PHQ-9, Patient Health Questionnaire-9; GDS, the geriatric depression scale; CES-D, centre for epidemiologic studies-depression; BAI, Berger Anxiety Inventory; HDRS-17, the Chinese version of 17-item Hamilton Depression Rating Scale; HADS, Hospital Anxiety and Depression Scale; DASS, The Depression Anxiety Stress Scale; SHR-5, *Rhodiola rosea*; DASS-21, 21-item questionnaire; MSSQ, The Menopause Symptoms Questionnaire.

in the treated and control groups. Our meta-analysis showed a statistically significant improvement in depressive status after taking antioxidant supplements (SMD = 0.60; 95 % CI: 0.40, 0.81, $p < 0.00001$).

3.4. Subgroup analysis of the effect of different kinds of antioxidant supplements

We performed a subgroup meta-analysis of groups with at least four studies according to the type of antioxidant supplementation. First, we

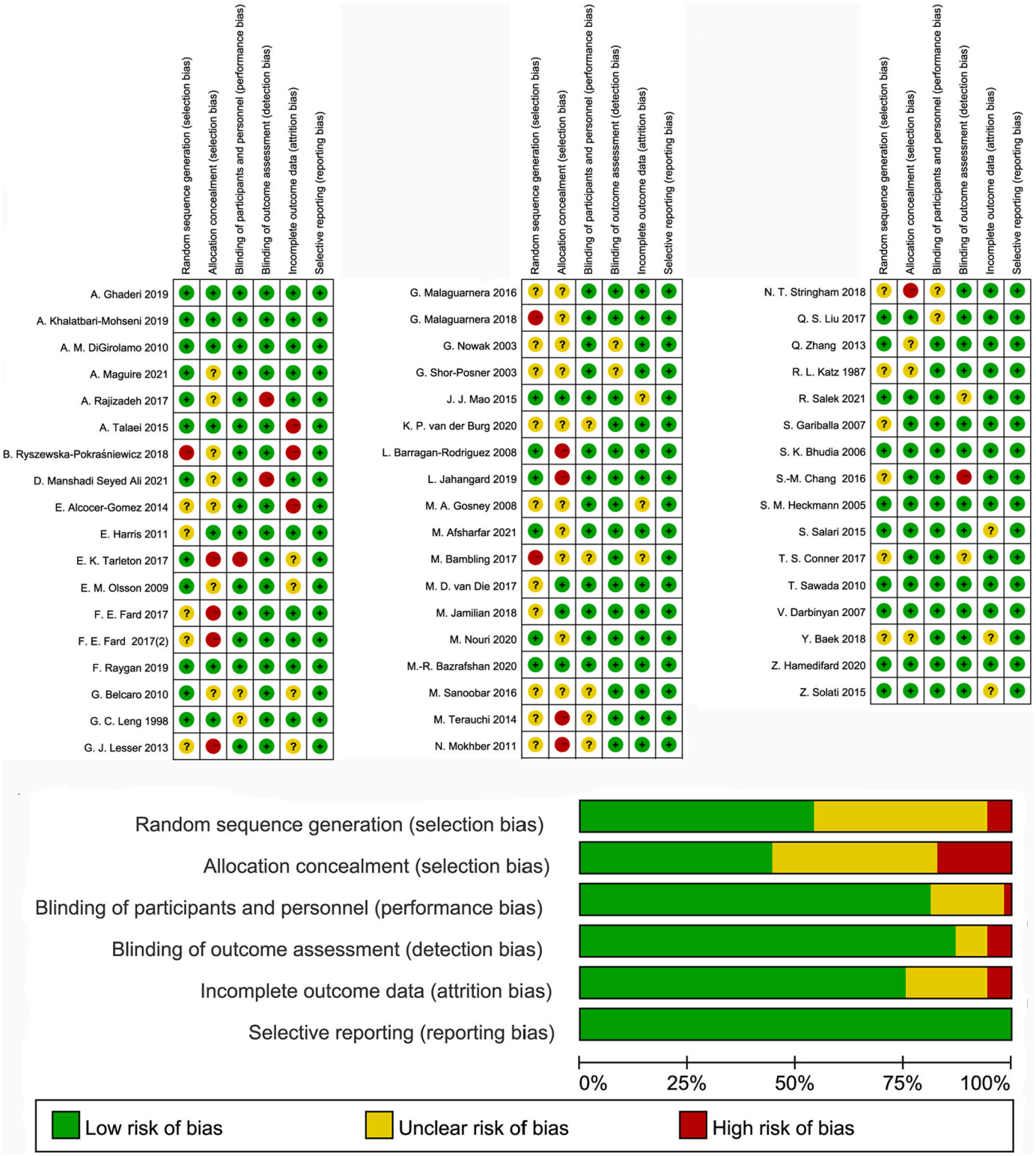

Fig. 2. Risk of bias assessment for the included randomized controlled trials.

conducted a meta-analysis in nine RCTs that reported depression scores before and after zinc supplementation. There were 515 and 516 participants included in the zinc and control groups, respectively (study ID.1–9). The results showed that zinc supplementation could significantly improve depression status (SMD = 0.59; 95 % CI: 0.13, 1.05, p = 0.01) (Fig. 4A). Second, eight RCTs reported the effect of magnesium supplementation was integrated, including 347 subjects in the magnesium group and 351 subjects in the control group (study ID.10–17). Significant improvement was found in depressive status after taking magnesium supplements (SMD = 0.16; 95 % CI: 0.01, 0.31, p = 0.03) (Fig. 4B). Third, four RCTs that compared depression scores before and after selenium supplementation were summarized, involving 129 and 133 subjects in the selenium and control groups (study ID.29–32). The group taking selenium supplements was associated with

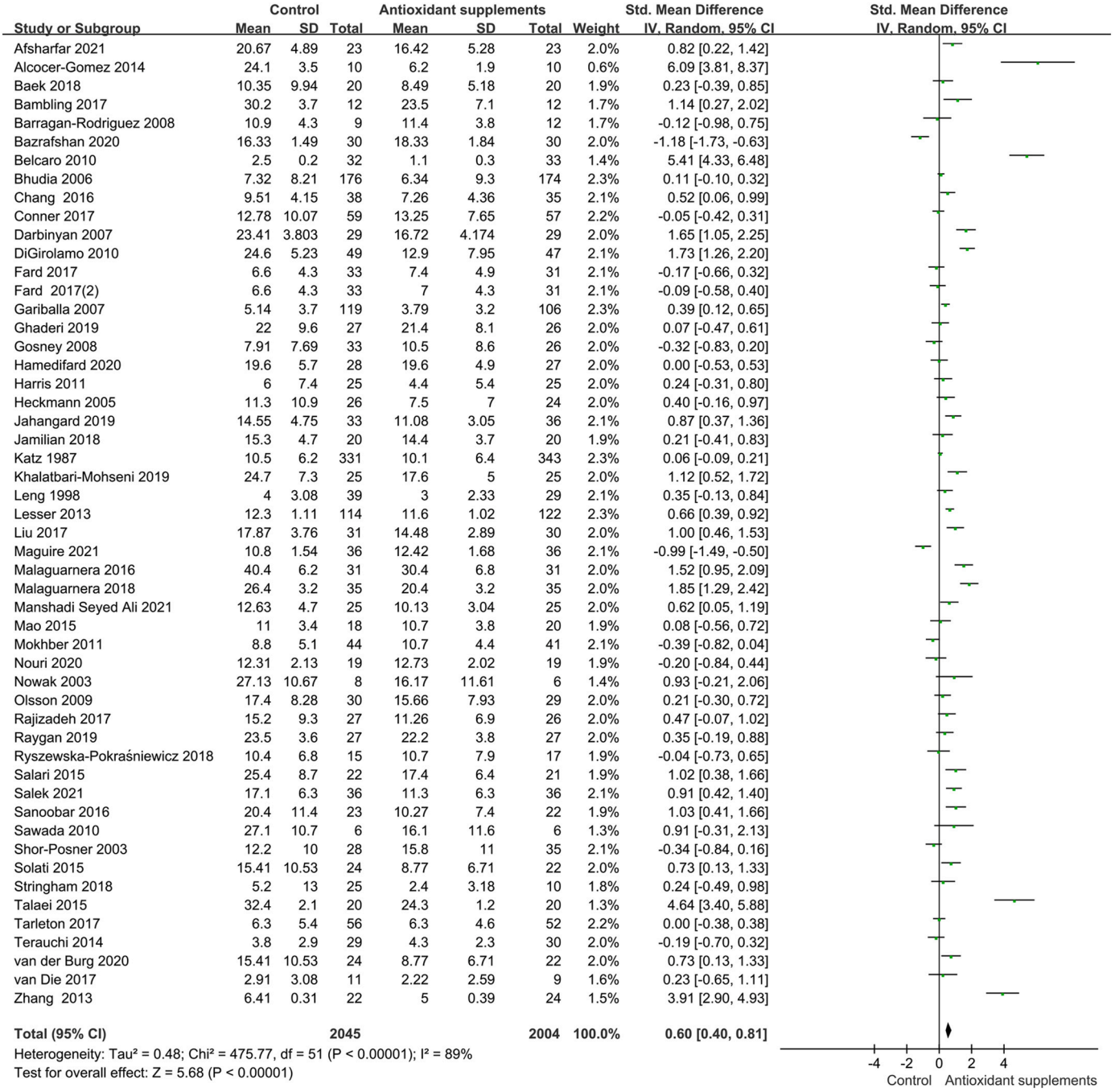

Fig. 3. Forest plot with the summary effect of different kinds of antioxidant supplement intervention on depression states.

significantly lower depression scores than the control group. (SMD = 0.33; 95 % CI: 0.08, 0.57, $p = 0.009$) (Fig. 5A). Fourth, we recruited five RCTs that reported CoQ10, involving a total of 442 subjects (study ID.18–22), and the results indicated that CoQ10 had a significant improvement in depressive status (SMD = 0.97; 95 % CI: 0.01, 1.93, $p = 0.05$) (Fig. 5B). Fifth, the meta-analysis of six randomized controlled trials (study ID.23–28) involving 330 participants showed a significant effect of tea and coffee consumption on improving depressive status (SMD = 1.15; 95 % CI: 0.45, 1.86, $p = 0.001$) (Fig. 6A). Sixth, the meta-analysis of s four RCTs (study ID.33–36) involving 215 subjects concluded that crocin supplementation could significantly reduce depression scores (MD = 6.04; 95 % CI: 3.43, 8.65, $p < 0.00001$) (Fig. 6B).

In addition, subjects in eight studies were supplemented not with a single antioxidant but with a complex of antioxidants (study ID.45–62). We also performed a meta-analysis of these eight studies involving 334 and 366 subjects in the treatment and control groups. The results showed that multiple antioxidant co-supplementation also significantly improved depressive status (SMD = 0.85; 95 % CI: 0.19, 1.51, $p = 0.01$) (Fig. 6C). See all the data summarization in Table 2.

3.5. Meta-analysis of the effect of antioxidant supplement on anxiety status

Among the 52 publications, 21 studies (21.4 %) reported anxiety status as a secondary outcome, involving 628 and 593 subjects in the treated and control groups. The meta result showed a statistically significant improvement in anxiety after taking antioxidant supplements

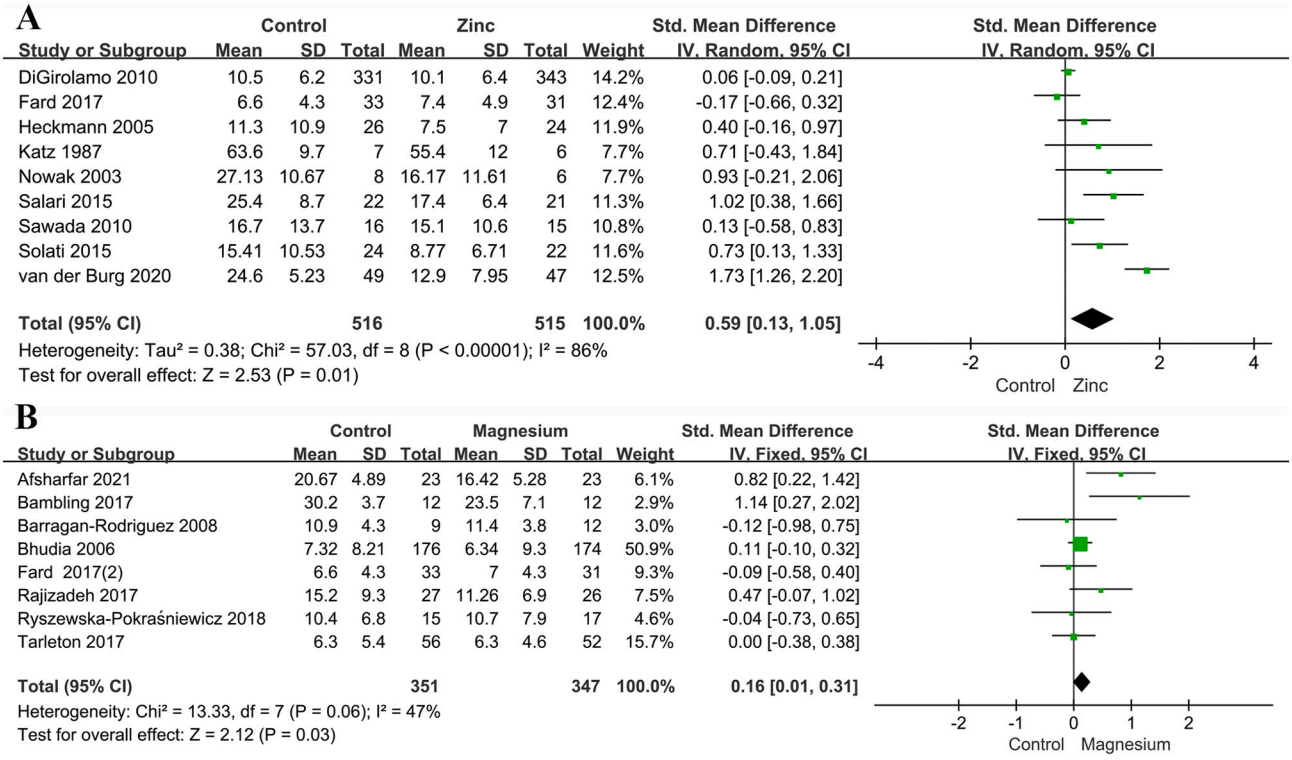

Fig. 4. Forest plot of summary effects of (A) zinc and (B) magnesium supplementation interventions on depressive states.

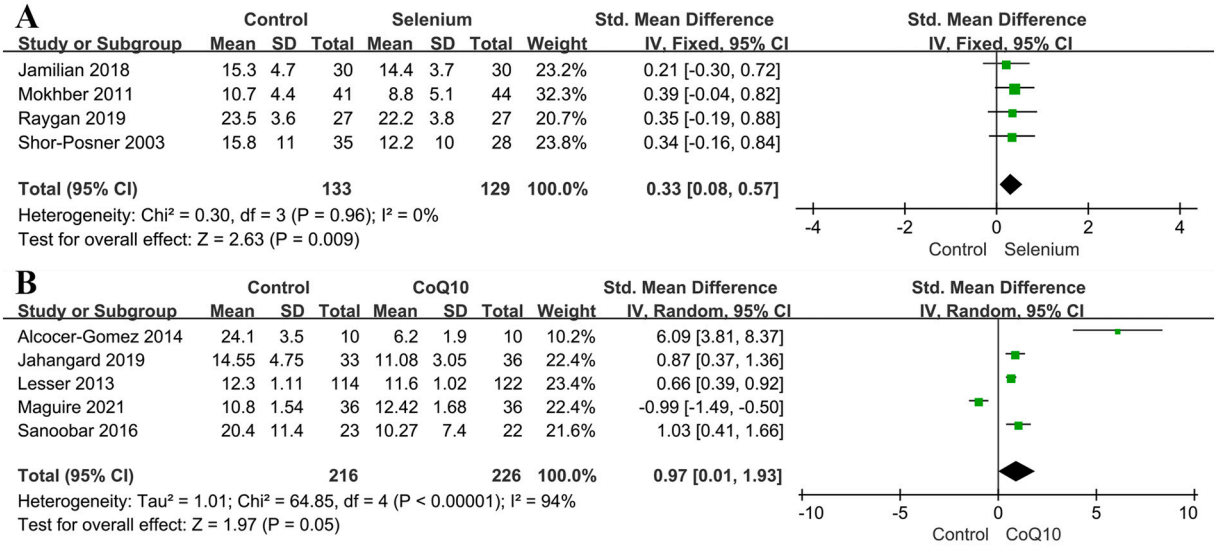

Fig. 5. Forest plot of summary effects of (A) selenium and (B) CoQ10 supplementation interventions on depressive states.

(SMD = 0.40, 95 % CI = 0.28–0.51, $p < 0.00001$). See the forest plot in Fig. 7.

3.6. Subgroup analysis of the effect of antioxidant supplements in different countries

Of the 52 RCTs, 19 studies (36.5 %) were from Iran, five (9.6 %) from Australia, eight (15.4 %) from the United States, four (7.7 %) from China, three (5.8 %) from Italy, two (3.8 %) from Sweden, two (3.8 %) from Japan, and two (3.8 %) from Poland. There is also one (1.9 %) study each from Guatemala, German, Mexico, Ireland, Spain, Georgia, and United Arab Emirates. We conducted a subgroup analysis for countries with three or more studies. The results showed that antioxidant supplementation significantly improved depression (SMD = 0.49, 95 % CI = 0.14–0.83, $p = 0.0006$) and anxiety states (SMD = 0.51, 95 % CI = 0.10–0.92, $p = 0.01$) in the Iranian study population. It also improved depression states in Chinese (SMD = 1.33, 95 % CI = 0.20–2.46, $p = 0.02$) and Italian (SMD = 2.86, 95 % CI = 10.05–4.66, $p = 0.002$) study populations significantly (See forest plot in Figs. S1–S2).

3.7. Sensitivity analysis and publication bias

Due to the wide variety of current rating scales for depression and anxiety, the heterogeneity of this meta-analysis is unavoidable. While

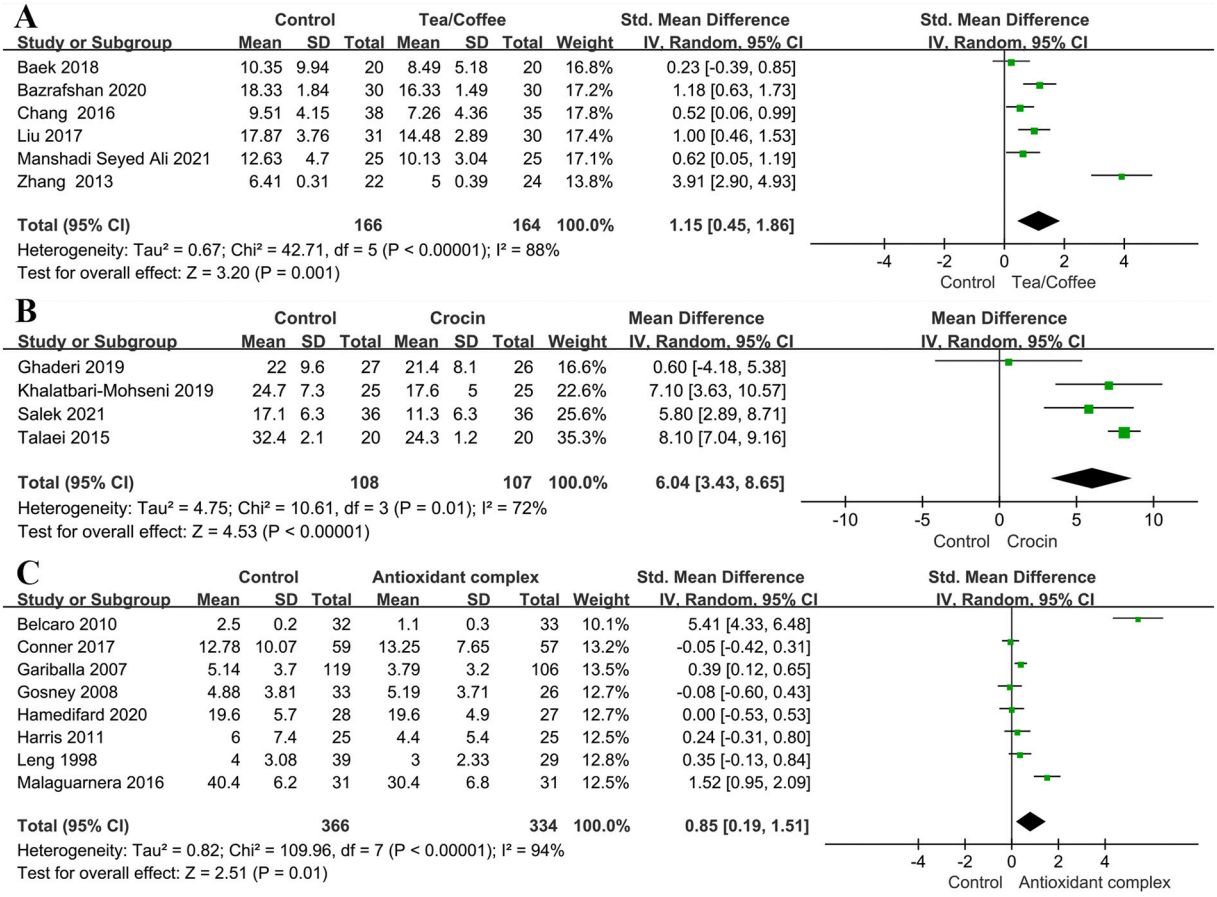

Fig. 6. Forest plot of summary effects of (A) tea or coffee and (B) crocin and (C) antioxidant complexes interventions on depressive states.

Table 2
Subgroup analysis of effect of different kinds of antioxidant supplement.

Grouped by supplements	No. of studies	Control (n)	Treated (n)	SMD (95 % CI)	Z	*p*
Magnesium	8	347	351	0.16 (0.01, 0.31)	2.53	0.01
Zinc	9	516	515	0.59 (0.13, 1.05)	2.42	0.02
Selenium	4	133	129	0.33 (0.08, 0.57)	2.63	0.009
CoQ10	5	216	226	0.97 (0.01, 1.93)[a]	1.97	0.05
Tea and coffee	6	166	164	1.15 (0.45, 1.86)	3.20	0.001
Crocin	4	107	108	6.04 (3.43, 8.65)	4.53	0.00001
Combinations	8	366	334	0.85 (0.19, 1.51)	2.51	0.01

[a] MD. (95 % CI).

selecting an appropriate model (fixed-effects model or random-effects model) according to the size of the heterogeneity, we also performed subgroup analyses according to the scale type. The most widely used were BDI and MARDS scales in the original literature. The heterogeneity decreased by 18 % after a subgroup analysis of studies using the MARDS scale. Sensitivity analysis did not change the conclusions drawn using the random-effects model prior to subgroup analysis. The positive effect of antioxidant supplementation on depression remained significant (MD = 2.32; 95 % CI: 0.77, 3.87, $p = 0.004$) (Fig. 8A). Likewise, there were 25 studies (48.1 %) in the BDI-scale subgroup. Although heterogeneity remained significant after grouping, the conclusion was consistent with no grouping under the random effects model (MD = 4.29; 95 % CI: 2.14, 6.44, $p < 0.00001$) (Fig. 8B).

In the meta-analysis of zinc supplementation on depressive status, the heterogeneity was 90 %, with four studies using the BDI scale. After subgroup analysis of these four studies, the heterogeneity reduced to 0, and the positive effect of zinc supplementation on depressive status remained significant under the fixed effect model (MD = 6.52; 95 % CI: 3.70, 9.26, $p < 0.0001$) (Fig. 9A). In the meta-analysis of magnesium supplementation on depressive status, the heterogeneity was 47 %, which decreased to 28 % after removing the study by Bambling et al. (rated as a low-quality study by Jada). However, in this case, the effect of magnesium supplementation on depressive status was no longer significant (MD = 0.13; 95 % CI: −0.02, 0.28, $p = 0.09$) (Fig. 9B).

In the sensitivity analysis with anxiety as an outcome, we found that heterogeneity was significantly reduced ($I^2 = 47$ %) after removing the studies by Talaei et al. and Belcaro et al. The positive effect status of antioxidant supplementation on depression remained significant under the fixed-effects model (MD = 0.27; 95 % CI: 0.15, 0.39, $p < 0.00001$). Additionally, visual inspection of funnel plots and Egger's test indicated no evidence of asymmetry and thus no firm evidence of publication bias (all $p > 0.05$). The funnel plots are exhibited in Fig. 10.

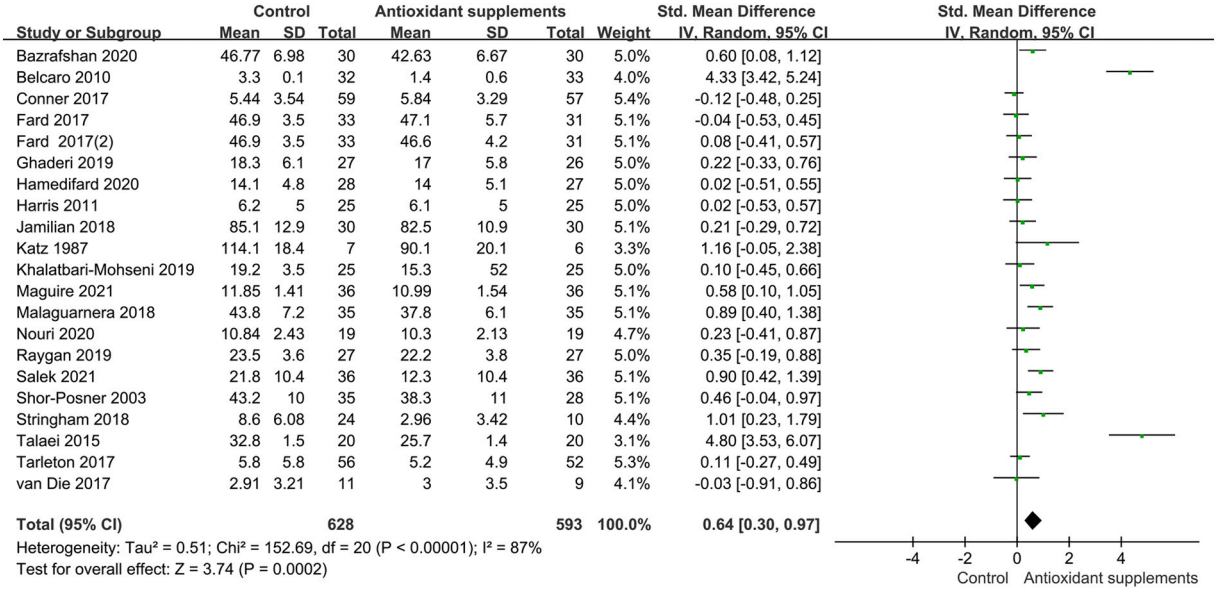

Fig. 7. Forest plot of summary effects of antioxidant supplements on anxiety states.

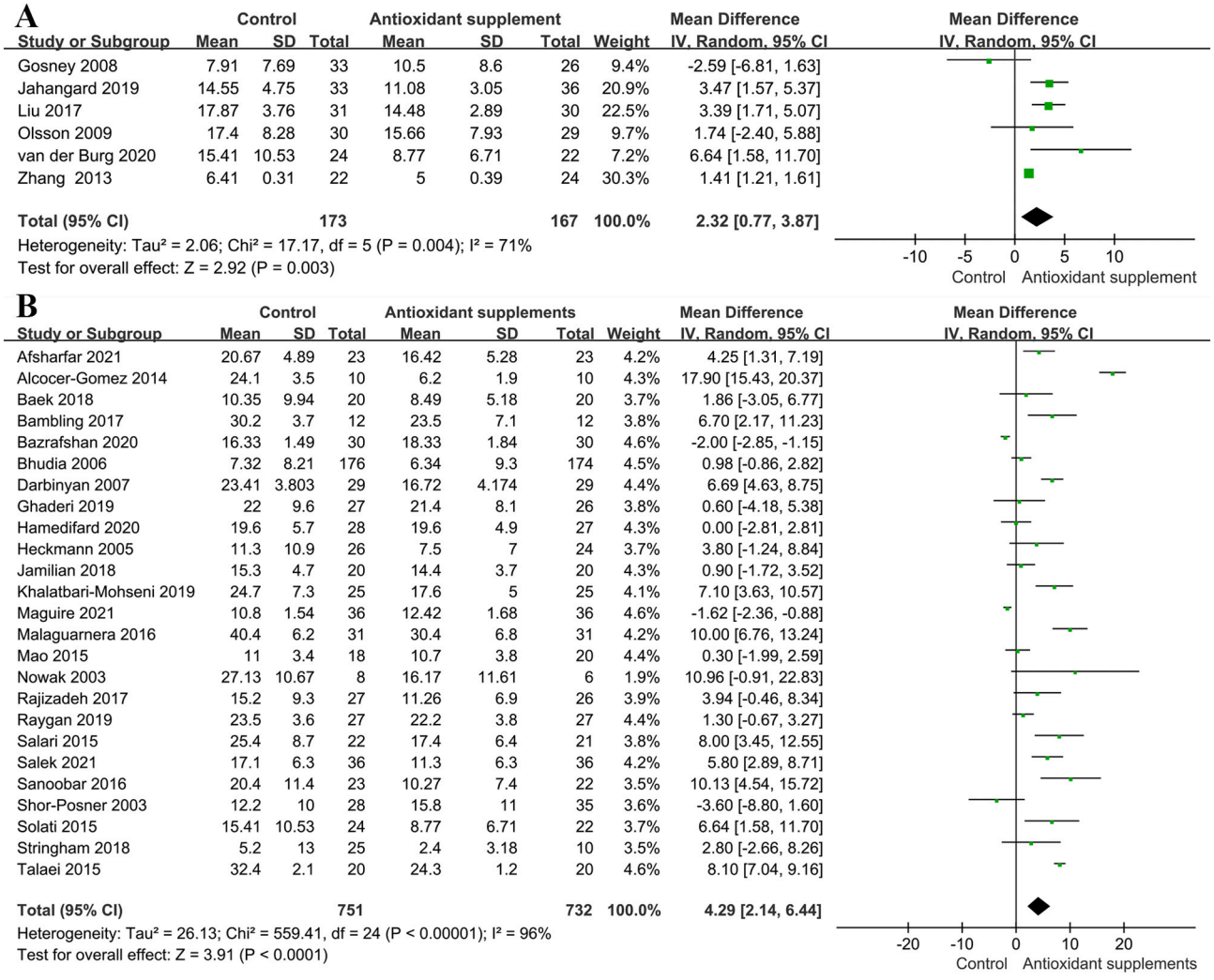

Fig. 8. Sensitivity analysis. (A) Forest plot using the MADRS scale to assess the summary effect of antioxidant supplementation on depressive status. (B) Forest plot using the BDI scale to assess the summary effect of antioxidant supplementation on depressive status.

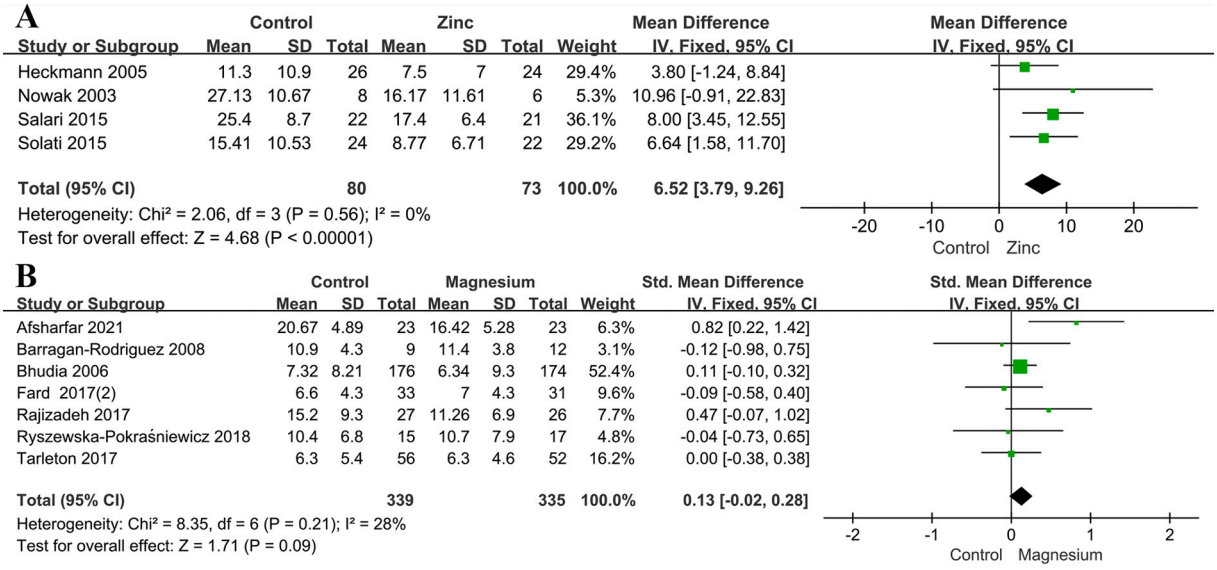

Fig. 9. Sensitivity analysis. (A) Forest plot using the BDI scale to assess the summary effect of zinc supplementation on depressive status. (B) Forest plot evaluating the summary effect of magnesium supplementation on depressive states after excluding the study by M. Bambling et al.

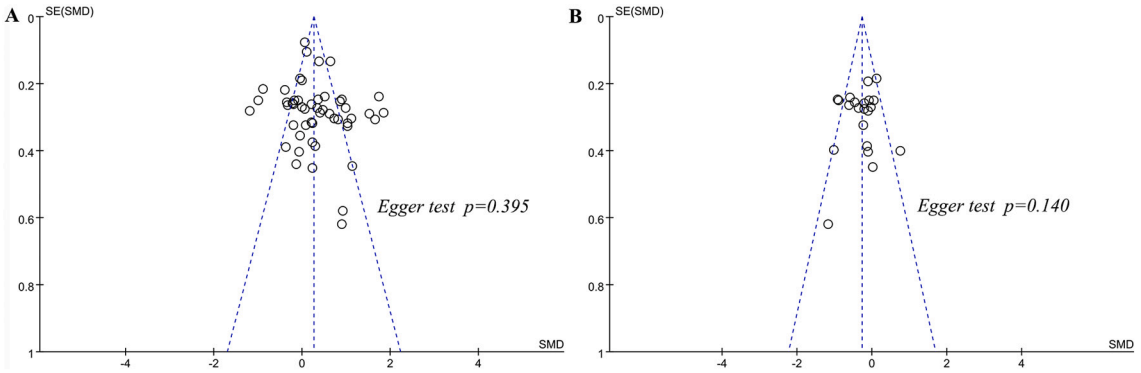

Fig. 10. Funnel plot with 95 % confidence interval (CI) to assess publication bias. (A) Funnel plot of studies investigating the effects of antioxidant supplements on depressive states. (B) Funnel plot of studies investigating the effects of antioxidant supplements on anxiety states.

4. Discussion

An imbalance between the oxidative and antioxidant systems in cells and tissues is known as oxidative stress, and it can harm biological macromolecules including lipids, proteins, and DNA (Rani et al., 2016). According to Cecerska-Heryć et al. (2022), persistent oxidative stress may have a role in the development of depression and other psychiatric illnesses. According to a meta-analysis of 115 studies, depressive patients showed reduced antioxidant markers and higher oxidative stress markers, such as malondialdehyde and 8-F2-isoprostaglandin, compared to healthy controls (Liu et al., 2015). A growing body of research supports the use of dietary changes as complementary therapies for psychiatric problems. Depriving or boosting the supply of food components with antioxidant capabilities might worsen or lessen oxidative stress.

4.1. Improvement of depressive states by minerals such as zinc, magnesium, and selenium

Our findings demonstrated that supplementing with zinc, magnesium, and selenium, three common minerals, could significantly improve depressive status. Zinc and magnesium are two essential trace elements that have a major impact on a variety of physiological and biochemical processes related to the development and operation of the brain and cellular metabolism (de Baaij et al., 2015; Wang et al., 2018). A zinc deficit may lead to disruption of the zinc balance in the brain, altering behavior, cognition, learning, psychological processes, and even increasing the risk of epileptic convulsions. (Nowak et al., 2005). Bernadeta Szewczyk et al. demonstrated the antidepressant potential of zinc in most experiments with rodents and depressive models and uncovered the etiological effects of zinc deficiency in triggering depression-like conditions, diminished neurogenesis and interneuronal viability or compromised capacity of memory and learning (Szewczyk et al., 2011). According to a cohort study from Australia, individuals with the highest zinc consumption were about 30–50 % less likely to suffer from depression than individuals with the lowest zinc consumption (Vashum et al., 2014). Previous studies have revealed that magnesium has a critical impact on nerve conduction as well as nerve-muscle transmission and also plays a protective function against over-excitation, which results in the death of neuronal cells, and is intimately linked with multiple neurological pathologies, such as Alzheimer's disease, Parkinson's disease, anxiety and depression (Kirkland et al., 2018). The cross-sectional findings from Sun et al. indicated a statistically significant negative correlation between magnesium consumption and depressive risk in females, while a linear relationship between magnesium ingestion and depressive risk was detected in dose-response

analysis (Sun et al., 2019).

Regarding selenium, a cross-sectional study from China found that higher intakes were linked to fewer depression symptoms (Gao et al., 2012). According to a study by D Benton et al., lower levels of dietary selenium were accompanied by greater rates of specific illnesses such as anxiety, depression and fatigue, while after five weeks of selenium therapy, the reported rates of these symptoms decreased (Benton and Cook, 1991). A study by Tatiana Lourençoni Ferreira de Almeida et al. revealed that in Brazil, higher selenium consumption among farmers was significantly correlated with a lower incidence of depression (Ferreira de Almeida et al., 2021). Through a nested case-control study, Julie A Pasco et al. identified that lower selenium ingestion was firmly tied to an elevated risk of major depression disorder (Pasco et al., 2012).

4.2. Improvement of depressive states by CoQ10

In this meta-analysis, coenzyme Q10 showed its potent antidepressant properties. CoQ10, as a lipid moiety, is a mobile carrier of electronic transmission chains and possesses antioxidant properties. CoQ10 may be used to treat other brain illnesses like depression and bipolar disorder as well as degenerative neurological diseases like Alzheimer's and Parkinson's disease (Pradhan et al., 2021). In an animal model of depression, CoQ10 was found to reduce behavioral impairment (Andalib et al., 2019).

4.3. Consumption of coffee and tea could improve depression states

Many original studies have pointed out that the consumption of coffee and tea is significantly associated with a reduced risk of depression in the population (Grosso et al., 2016; Hintikka et al., 2005; Wang et al., 2016). It is thought that some of the protective effects of coffee and tea on depression may stem from the effects of caffeine on the nervous system (Asil et al., 2021; Omagari et al., 2014). Caffeine stimulates the central nervous system and enhances dopaminergic neurotransmission, thereby reducing the risk of depression in people who drink coffee or tea (Lucas et al., 2011). In addition, coffee and tea have many antioxidants and phytochemicals, such as chlorogenic acid, pyrogallic acid, cucurbitacin, catechol, etc. These bioactive ingredients have been shown to increase dopamine release, thereby alleviating depression (Lucas et al., 2011; Walker et al., 2012).

4.4. The effects of plant extracts and Chinese herbs on depression states

The role of some plant extracts and Chinese herbal medicines in depression is constantly being discovered, such as saffron, Rhodiola, and resveratrol. Saffron is a spice derived from saffron crocus, and its supplements contain various antioxidants such as safranal, crocin, and crocetin. Current research suggests that crocin supplementation significantly improves depressive status, and our findings support this conclusion. Regarding the neurobiological mechanism of the antidepressant effect of saffron, it has been suggested that saffron significantly affects dopamine (Orio et al., 2020). The main symptom of depression lies in anhedonia associated with low dopamine levels, and saffron increases brain dopamine levels by affecting the brain's monoamine oxidase MAO-A and MAO-B (Khazdair et al., 2015). In addition, it has also been suggested that the antidepressant effect of saffron may be due to its serotonergic, antioxidant, anti-inflammatory, neuro-endocrine, and neuroprotective effects (Lopresti and Drummond, 2014). However, saffron, crocin, safranal and crocetin all showed some embryonic malformation in animal's models at high doses and there are insufficient clinical trials on the safety of saffron use in pregnant individuals. In addition to saffron, Rhodiola and resveratrol, a botanical antidepressant, significantly improve depressive status. The results of many clinical trials support this, but the underlying biological mechanisms are unclear (Darbinyan et al., 2007; Gao et al., 2020; Malaguarnera et al., 2018b).

4.5. Antioxidant supplements and anxiety

Moreover, our meta-analysis showed that the intake of antioxidant supplements significantly improved anxiety status. There is a wide variety of antioxidants and many studies on their relationship with anxiety disorders. Coffee and tea rich in polyphenols (Lin et al., 2021), macular carotenoids (Stringham et al., 2018), and selenium (Raygan et al., 2019), all have an alleviating effect on anxiety symptoms. The above studies indirectly prove from various perspectives that antioxidant supplements have a moderating effect on anxiety disorders. Some studies have shown that oxidative stress may trigger neuropsychological disorders and is one of the leading causes of depression and anxiety disorders (Ng et al., 2008). Antioxidants prevent the impairment of antioxidant defenses caused by oxidative stress. In addition, brain neurons are characterized by high metabolic demands and low levels of endogenous antioxidants and are more susceptible to damage from oxidative stress, resulting in a redox imbalance in the brain. Redox imbalance in the brain is strongly associated with increased inflammation, impaired neuronal plasticity and reduced neuronal signaling, which are risk factors for the development of anxiety and depression (Lehtinen and Bonni, 2006; Ng et al., 2008; Pereira et al., 2021).

4.6. Improvements from antioxidants were especially pronounced in people with higher depression scores

We also tried to perform a subgroup analysis of studies in different countries. The results showed that antioxidant supplementation significantly improved depressive status in Iranian, Chinese, and Italian study populations. Nevertheless, no significant improvement was found in the United States, Australia, Italy and other countries. Thus, we tried to find the underlying reasons. On the one hand, it might be due to fewer publications in other countries and insufficient sample size, and the significance is not reflected. On the other hand, the improvement brought about by antioxidants might be particularly pronounced in people with significant depression and higher depression scores. Studies have shown that Asian countries have fewer psychiatrists and more expensive treatments. In Iran, there is only one psychiatrist for every 45,000 people, unevenly distributed across the country. Ahmed Hajbi, head of the Mental Health Office of the Iranian Ministry of Health, said on October 11, 2020 that about 23 % of the Iranian population suffers from some kind of mental illness, of which about 66 %–75 % do not seek treatment from psychiatrists. A survey of 32,552 respondents showed that in China, only 0.5 % of patients with depressive disorders received adequate treatment because most patients with depressive disorders did not seek professional help (Lu et al., 2021).

4.7. Limitations and outlook

Summarily, most studies included in this meta-analysis were high-quality randomized controlled trials considered the “gold standard” for clinical research. We performed subgroup analyses by type of antioxidant supplement and depression scale, addressing some heterogeneity. Furthermore, no evidence of publication bias was found. Although this study further supports the therapeutic potential of antioxidant supplements as adjunctive therapy to conventional antidepressants, there are some limitations. 1) The review protocol of the current study was not registered and may have a slight deviation, but the study was designed and conducted in strict accordance with the PRISMA guidelines. 2) There are many types of antioxidant supplements, and the categories selected for this study were all derived from a literature search, which is not comprehensive enough. However, compared with independent studies, the conclusion of the meta-analysis including 52 RCTs has a certain credibility. 3) To aggregate more data, this study did not limit the characteristics of the included population. The subjects are from different groups: postmenopausal women, the elderly, patients with chronic diseases, etc. Subgroup analyses for different populations

are insufficient. When the amount of evidence for subgroups could be warranted, adding more granular groupings of participants would be ideal. 4) While integrating research on the effects of antioxidant supplements on depressive states, we found that many of the original studies included anxiety scores as a secondary outcome. Therefore, we summarize them as secondary results for the general researchers. For the positive effect of antioxidants on anxiety states, a more comprehensive search and subgroups should be established in future studies.

The mechanisms of action associated with diet and health outcomes are complex, multifaceted, and interacting, and are not limited to any single biological pathway. Daily dietary intake, in addition to antioxidant supplementation, may change important biological parameters linked to the onset of depression. For instance, taking probiotic supplements considerably lifts people with mild to moderate depressive symptoms' moods (Ng et al., 2018). The underlying mechanism might be, on the one hand, the probiotics increase the supply of the neurotransmitter tryptophan and BDNF (brain-derived neurotrophic factor) in gut microbiota metabolism, which in turn improves depression (Heidarzadeh-Rad et al., 2020; Kazemi et al., 2019). On the other hand, the gut microbiota balancing effect of probiotics promotes the absorption of dietary nutrients that positively affect the improvement of depression. Similarly, a high-fiber diet may lower inflammation by altering pH and intestinal permeability, and the resulting reduction in inflammatory compounds may alter neurotransmitter concentrations to reduce symptoms of depression (Swann et al., 2020). Therefore, it is not rigorous and scientific to explore the independent effects of certain supplements thoroughly without dietary factors. The original literature included in this study focused on the effects of antioxidant supplements on depression and anxiety scores and did not report subjects' dietary intake in detail, which is also the future improvement direction of this study.

Our study suggests that intake of antioxidant supplements and dietary supplements may be beneficial for the improvement of depression and anxiety. Although the result of combining individual studies of a range of different antioxidant supplements is a “preliminary data”, at this stage, there is no such data for reference, which could provide us some inspiration on living habits. The combination of multiple studies also reduces the statistical power, which makes the conclusion of this study need to be interpreted and applied more rigorously. Additional data from large clinical trials are needed to confirm the efficacy and safety of antioxidant supplements in improving depressive status. The expansion of nutritional psychiatry research promises to develop new targeted strategies and clinical guidelines for people with depression, addressing each need more individually.

5. Conclusion

According to this meta-analysis, there was a substantial favorable impact of antioxidant supplementation on depressed status, including magnesium, zinc, selenium, coenzyme Q10, tea and coffee, and crocin. Intake of antioxidant supplements is associated with reduced depression and anxiety states, further affirming the therapeutic potential of antioxidant supplements as adjunctive therapy to conventional antidepressants.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.11.072.

Funding

This work was supported by the National Natural Science Foundation of China [81673253].

CRediT authorship contribution statement

HW, GW, and QY designed the study; MJ, MX, and YY extracted the data from the study; MJ, HW, FX, and WL analyzed the data and drafted the manuscript; MZ, ZL, LD, and NJ gave the quality assessment of the original studies; XL, YL, GH, and XC participated amending the manuscript. All authors approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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