Research Article

The Efficacy of Antioxidative Stress Therapy on Oxidative Stress Levels in Rheumatoid Arthritis: A Systematic Review and Metaanalysis of Randomized Controlled Trials

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Objective. To explore the efficacy of antioxidative stress therapy on oxidative stress levels in rheumatoid arthritis (RA) by a systematic review and meta-analysis of randomized controlled trials. Methods. Chinese and English databases such as PubMed, Embase, China National Knowledge Infrastructure (CNKI), and China Biomedical Literature were searched, mainly searching for clinical randomized controlled trials of antioxidant therapy for rheumatoid arthritis. The search time is from the establishment of the database to July 2021. Two researchers independently carried out literature search, screening, and data extraction. The bias risk tool provided by the Cochrane Collaboration was used to evaluate the bias risk of all the included literature, and the RevMan 5.3 software was used for meta-analysis. Results. A total of 24 RCTs (28 records) and 1277 participants were included. The time span of randomized controlled trials (RCTs) is from 1986 to 2020. These RCTs involve 14 types of antioxidants or antioxidant therapies, and these therapies have varying degrees of improvement on oxidative stress in RA patients. The summary results showed that the MDA in the experiment group is lower (SMD -0.82, 95% CI -1.35 to -0.28, P = 0.003). The difference of TAC, SOD, NO, GPx, CAT, and GSH between two groups was of no statistical significance (TAC (SMD 0.27, 95% CI -0.21 to 0.75, P = 0.27), SOD (SMD 0.12, 95% CI -0.16 to 0.40, P = 0.41), NO (SMD -2.03, 95% CI -4.22 to 0.16, *P* = 0.07), GPx (SMD 0.24, 95% CI -0.07 to 0.54, *P* = 0.13), CAT (SMD 2.95, 95% CI -2.6 to 8.51, *P* = 0.30), and GSH (SMD 2.46, 95% CI -0.06 to 4.98, P = 0.06)). For adverse events, the summary results showed that the difference was of no statistical significance (RR 1.16, 95% CI 0.79 to 1.71, P = 0.45). In addition, antioxidant therapy has also shown improvement in clinical efficacy indexes (number of tender joints, number of swollen joints, DAS28, VAS, and HAQ) and inflammation indexes (ESR, CRP, TNF-a, and IL6) for RA patients. Conclusion. The existing evidence shows potential benefits, mainly in reducing MDA and increasing TAC and GSH in some subgroups. However, more large samples and higher quality RCTs are needed to provide high-quality evidence, so as to provide more clinical reference information for the antioxidant treatment of RA.

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease of unknown etiology [1]. In the United States, RA affects more than 1.3 million adults, accounting for 0.6%– 1% of the population [1, 2]. Epidemiological research shows that the prevalence of rheumatoid arthritis in China is 0.2%~0.36%, which has increased from 5.8 million cases in 2015 to 5.9 million cases in 2019, and the 3-year disability rate has reached 70%; it has become a serious public health problem [3, 4]. The clinical manifestation of RA is mainly a chronic inflammatory (nonsuppurative inflammation)

disease of peripheral multiple joints. It may be accompanied by extra-articular systemic damage (causing subcutaneous nodules, pericarditis, myocarditis, pulmonary fibrosis, pleurisy, splenomegaly, renal amyloidosis, peripheral neuritis, arteritis, etc.) [5]. The pathological features of RA are mainly manifested as synovitis of the joints (which can later spread to articular cartilage, bone tissue, joint ligaments, and tendons), followed by extensive inflammation of connective tissues such as serosa, heart, lung, and eyes [5, 6]. When the disease involves cartilage and bone, joint deformities may occur, that is, synovial inflammation, exudation, cell proliferation, granuloma formation, cartilage and bone tissue destruction, and finally joint stiffness and dysfunction [6]. The cartilage destruction of joints is related to the abnormal expression of cytokines, and the imbalance between protective cytokines and destructive cytokines is the basis of RA pathology [7]. In addition, inflammatory chemokines and immune-inflammatory cells jointly promote the exacerbation of the pathological process of RA [8].

Current research shows that in addition to inflammation [9], oxidative stress products also play an important role in the pathogenesis and pathological progress of RA [10]. Oxidative stress can produce too many free radicals, which will cause the oxidation of many molecules in the body. Excessive free radicals in the body of RA patients increase the level of the oxidation marker malondialdehyde (MDA), and the antioxidant enzyme superoxide dismutase (SOD) system is disturbed, which leads to the weakening of the body's antioxidant capacity and aggravating bone destruction [11–14]. In addition, oxidative stress is closely related to the energy metabolism of synovial tissue in RA patients [15]. Therefore, research on oxidative stress, SOD antioxidation, and regulation relationship in patients with RA can reveal the pathological mechanism of RA and find new anti-RA drugs. At present, many randomized controlled trials (RCTs) of antioxidants [16-20] in the treatment of RA patients have been published. However, the results and interventions of these RCTs are diverse, and the quality of the evidence provided varies, which cannot provide clinical doctors with evidence to formulate treatment measures against oxidative stress. Therefore, it is urgent to conduct a comprehensive and indepth systematic review and meta-analysis of these RCTs for the treatment of RA against oxidative stress. Therefore, this study will conduct a comprehensive systematic review and meta-analysis of RCTs for the treatment of RA against oxidative stress for the first time, in order to provide clinicians with high-quality evidence and promote the clinical practice of antioxidant treatment of RA in the future and to further improve the adjuvant therapy for RA patients.

2. Why Is This Systematic Review Important?

Oxidative stress plays a central role in the pathogenesis of RA. At present, evidence of clinical randomized controlled trials surrounding oxidative stress interventions has been reported one after another. However, the results and interventions of these RCTs are diverse, and the quality of the evidence provided is not uniform, and the levels are not uniform, which cannot provide clinical doctors and patients

with evidence and treatment measures for the pathological mechanism of oxidative stress. Therefore, it is urgent to conduct a comprehensive and in-depth systematic review and meta-analysis of these RCTs for antioxidative stress treatment, in order to provide clinicians with high-quality evidence in the future, promote the clinical practice of RA treatment, and further improve the adjuvant treatment measures of RA.

3. Materials and Methods

3.1. Protocol. This systematic review and meta-analysis was conducted strictly in accordance with the protocol registered in PROSPERO (CRD42021256587) and PRISMA guidelines (see Supplementary Materials (available here)) [21].

3.2. Literature Search Strategy. English databases and Chinese databases were searched with the retrieval time up to July 2021. English databases include PubMed, Embase, MEDLINE Complete, Web of Science, and Cochrane Library. Chinese databases include Wanfang Database on Academic Institutions in China, China National Knowledge Infrastructure (CNKI), VIP Database for Chinese Technical Periodicals, and China Biology Medicine (CBM). This study also searched the Cochrane Library and ClinicalTrials.gov. The search strategy of PubMed and Embase is shown in Table S1 as an example.

3.3. Inclusion and Exclusion Criteria

3.3.1. Participants. Participants are RA patients. The diagnosis of RA conforms to the RA diagnostic criteria in the 2010 Rheumatoid Arthritis Diagnostic and Treatment Guidelines of the Chinese Medical Association Rheumatology Branch or the standard RA diagnostic criteria proposed by the American Academy of Rheumatology in 1987/European Rheumatism League in 2017 or other recognized diagnostic criteria for RA.

3.3.2. Intervention. The treatment of the experimental group is antioxidative stress therapy with no limitations to forms, preparations, and so on; the therapy could be combined with conventional therapy or the therapy in the control group. The treatment of the control group was conventional therapy or placebo or other nonantioxidative stress therapies.

3.3.3. Outcomes. The outcomes were clinical efficacy indexes, inflammation indexes, adverse events, and oxidative stressrelated indicators. Clinical efficacy indexes include the number of tender joints, number of swollen joints, 28-joint disease activity score (DAS28), Health Assessment Questionnaire (HAQ), and Visual Analog Scale (VAS); inflammation indexes include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tumor necrosis factor-(TNF-) α , and Interleukin- (IL-) 6; oxidative stress-related indicators include malondialdehyde (MDA), glutathione (GSH), Catalase (CAT), glutathione peroxidase (GPx), nitric oxide (NO), superoxide dismutase (SOD), and total antioxidant capacity (TAC).

3.3.4. Study Design. The study design includes randomized controlled trials (RCTs), with no limitations to publication time, language, quality, and publication status.

3.3.5. Exclusion Criteria. Exclusion criteria include non-RCT, review, cohort study, and patients with other rheumatism (such as systemic lupus erythematosus and Sjogren's syndrome).

3.4. Literature Screening and Risk of Bias Assessment. The two researchers jointly formulate a literature search strategy, independently collect literature, read literature titles and abstracts, and conduct preliminary screening. Then, the two researchers read the full text of the selected literature and finally determined the literature that met the inclusion criteria. The Cochrane Risk Bias Assessment Form is used to systematically evaluate the quality of the included literature. If opinions are inconsistent, they are resolved through discussion. The content of the risk assessment of bias includes [22] (1) random allocation method, (2) allocation plan hiding, (3) blind method, (4) completeness of result data, (5) selective reporting of research results, and (6) other sources of bias.

3.5. Data Extraction. The two researchers independently extracted data from the included literature, filled in the data extraction form, and cross-checked. The extracted content includes general information of the literature (such as author, sample size, patient's age, intervention time, and frequency) and related efficacy evaluation indicators [23].

3.6. Statistical Analysis. The Review Manager 5.3 software was used for statistical analysis. Subgroup analysis was carried out according to the intervention measures of RCTs. A heterogeneity test was performed on the included literature. If $I^2 > 50\%$ and P < 0.1, it is considered that there is a large heterogeneity, and the source of the heterogeneity is analyzed. If $I^2 < 50\%$ and P > 0.1, the heterogeneity is considered low (i.e., RCTs are homogeneous). The random effect model was used for analysis. For continuous variables, if the indicator units or measurement methods were different, or the value differs by more than 10 times, standardized mean difference (SMD) and 95% confidence interval (CI) would be used as the effect size indicator; for indicators with the same unit, weighted mean difference (WMD) and 95% confidence interval (CI) were used as the effect size indicator. For dichotomous variables, the risk ratio (RR) and 95% CI were used as the effect size indicator [23]. The publication bias was detected by STATA 15 with the Egger method (continuous variable) for outcomes with more than 5 RCTs. P > 0.1 is considered to have no publication bias.

4. Results

4.1. Results of the Search. The total records identified through database searching and other sources were 1984. According to the search strategy, a total of 29 articles were obtained through preliminary search. By eliminating duplicate documents and carefully reading the title and abstract, a total of 1955 articles were excluded. After carefully reading

the full text and comparing the selection criteria, 28 records were screened out and finally included (Figure 1).

4.2. Description of Included Trials. Among the 28 records, 2 records [19, 20] belong to Abdollahzad et al. 2015, 2 records [24, 25] belong to Javadi et al. 2017 [24, 25], 2 records [26, 27] belong to Moosavian et al. 2020, and 2 records [28, 29] belong to Mirtaheri et al. 2015; therefore, a total of 24 RCTs and 1277 participants (most of them are female) were included. The time span of RCTs is from 1986 to 2020. Among those RCTs, 3 RCTs utilized N-acetylcysteine [16-18]; 2 RCTs utilized CoQ10 [19, 20, 30, 31]; 2 RCTs utilized probiotic [31, 32]; Ghavipour et al. 2016 utilized pomegranate extract [33]; 2 RCTs utilized quercetin [24, 25, 34]; Khojah et al. 2018 utilized resveratrol [35]; Moosavian et al. 2020 utilized garlic tablets [26, 27]; Aryaeian et al. 2009 [36] utilized conjugated linoleic acids, conjugated linoleic acids plus vitamin E, and vitamin E; 3 RCTs utilized vitamin E [36-38]; 4 RCTs utilized selenium [39-42]; Karagülle et al. 2017 utilized spa therapy [43]; Jaswal et al. 2003 utilized vitamins A, E, and C combination [44]; León Fernández et al. 2016 utilized ozone [45]; Ishibashi et al. 2014 utilized H₂-saline [46]; and 2 RCTs utilized alpha-lipoic acid [28, 29, 34]. Among those RCTs, 7 RCTs were registered clinical trials. Two RCTs were from Belgium; 2 RCTs were from China; 2 RCTs were from Germany; 8 RCTs were from Iran; Bae et al. 2009 was from Korea; Khojah et al. 2018 was from Egypt; Edmonds et al. 1997 was from the UK; Tarp et al. 1986 was from Denmark; Karagülle et al. 2017 was from Turkey; Jaswal et al. 2003 was from India; León Fernández et al. 2016 was from Cuba; and Ishibashi et al. 2014 was from Japan. Bae et al. 2009 [34] contains two intervention methods, so they were divided into Bae et al. 2009a and Bae et al. 2009b. Aryaeian et al. 2009 [36] has 3 intervention methods, so they were divided into Aryaeian et al. 2009a, Aryaeian et al. 2009b, and Aryaeian et al. 2009c. The details of study characteristics are presented in Table 1.

4.3. *Risk of Bias Assessment*. The RCTs were assessed by "risk of bias" assessment tools. The summary and graph of risk of bias are shown in Figures 2 and 3.

4.3.1. Random Sequence Generation and Allocation Concealment. Thirteen (13) RCTs describe random sequence generation methods [16, 17, 19, 20, 24–33, 36, 43, 45] and were rated as low risk of bias. The other RCTs do not describe random sequence generation methods and were rated as unclear risk of bias. Fourteen RCTs [18–20, 34–42, 44–46] did not describe allocation concealment methods and were assessed as unclear risk of bias.

4.3.2. Blinding, Incomplete Outcome Data, and Selective Reporting. Only 6 RCTs [16, 17, 26, 27, 31–33] describe the implementation process of the blind method and were rated as low risk of bias. Four RCTs [18, 24, 25, 44, 46] did not describe the implementation process of blinding, and the indicators of this study are biochemical indicators (such as MDA); they are assessed as low risk of bias. Twelve (12) RCTs [20, 28, 29, 34, 36–43, 45] claimed to use blinding but did not describe the implementation process of blinding

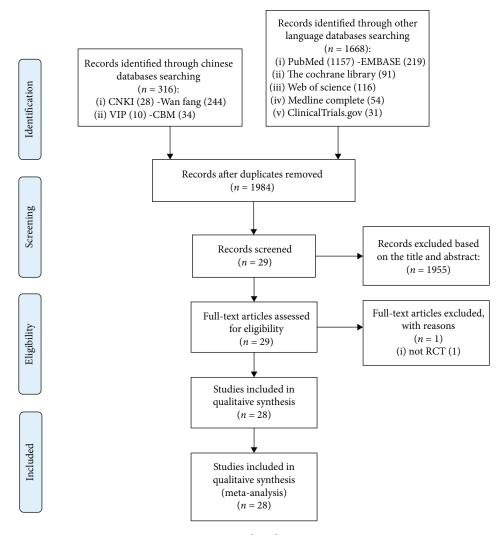


FIGURE 1: Flow diagram.

and included subjective indicators (such as DAS28 and VAS), so they were assessed as unclear risk of bias. Two RCTs [30, 35] did not utilize blinding, and the indicators of this study are subjective indicators (such as VAS and DAS28); they are assessed as high risk of bias. Six RCTs [16, 17, 28, 29, 31, 33, 34] have missing data, and the number of missing is unbalanced, but no appropriate statistical treatment method is specified, and the risk of bias is estimated to be unclear.

4.4. Other Potential Bias. Other sources of bias were not observed in 24 RCTs; therefore, the risks of other bias of the RCTs were low.

4.5. Outcomes

(1) Oxidative Stress Index and Adverse Events. A total of 11 RCTs reported MDA; the summary results showed that the MDA in the experiment group is lower (SMD -0.82, 95% CI -1.35 to -0.27, P = 0.003; random effect model) (Figure 4). Eight RCTs reported TAC; the summary results showed that

the difference was of no statistical significance (SMD 0.27, 95% CI -0.21 to 0.75, *P* = 0.27; random effect model) (Figure 5). Four RCTs reported SOD; the summary results showed that the difference was of no statistical significance (SMD 0.12, 95% CI -0.16 to 0.40, P = 0.41; random effect model) (Figure 6). Three RCTs reported NO; the summary results showed that the difference was of no statistical significance (SMD -2.03, 95% CI -4.22 to 0.16, P = 0.07; random effect model) (Figure 7). Three RCTs reported GPx; the summary results showed that the difference was of no statistical significance (SMD 0.24, 95% CI -0.07 to 0.54, P = 0.13; random effect model) (Figure 8). Two RCTs reported CAT; the summary results showed that the difference was of no statistical significance (SMD 2.95, 95% CI -2.6 to 8.51, P = 0.30; random effect model) (Figure 9). Three RCTs reported GSH; the summary results showed that the difference was of no statistical significance (SMD 2.46, 95% CI -0.06 to 4.98, P = 0.06; random effect model) (Figure 10). Five RCTs reported adverse events; Abdollahzad et al. 2015

			Sample size	e size	To be a second se				· · · · · ·	~	V			CBB (11)			4	000101	
	Trial registration number	Country	e	s/male)	intervention		Relevant	Mean ag	Mean age (years)	Disease duration (years)	tion (years)	case se		Baseline CKP (mg/L)	Baseline	Baseline ESK (mm/h)	Basell	baseline DAS28	Duration
			group	group	Trial group	Control group	outcomes	Trial group	group	Trial group	group	Irtal Co group gr	Control Trial group group	up group	Trial group	group	group	group	
Hashemi et al. 2019 [16]	IRCT2015071722965N2	Iran	23 (20/ 3)	(0 (0	N-acetyleyteine 600 mg Bid-conventional treatment (ranish) mcharceata, salikalasine, hydrosychiosoytada, predinisolasi e alciun D, folic acid, nonsteroidal anti-inflummatory drugo)	Placebo+convertional treatment (mainly methorexate, suffasalazine, hydroxychloroquine, prednisolone, calcium D, folic acid, nonsteroldal anti- inflammatory drugs)	CRP, ESR, TNF- a, IL6, MDA, TAC, NO	53.91±13.90	5.91±1.30 50.68±11.15 10.52±7.19	10.52±7.19	10.05 ± 7.56	Moderate: Moc 13 patients: pat severe: 10 sew patients pat	Moderate: 10 8.57±0.99 patients 9 patients	.99 7.89 ± I.I.I	26.91 ± 4.29	9 26.26 ±6.77	-	I	12 weeks
Batooei et al. 2018 [17]	Cannot be found	Iran	27 (22/ 5)	24 (23/ 1)	N-acctyloyst dine 600 mg Bid+conventional treatment (mainly methorscatts aufliashizine, hydrosychbroquine, calcium D, folic æid)	Placebo+conventional treatment (mainly methorexate, sulfasalazine, hydroxychloroquine, calcium D, folic acid)	DAS28, ESR, number of tender joints, number of swollen joints, HAQ, VAS, adverse events	53.2±12.5	51.6 ± 11.3	10±7.0	9.8±8.2	Moderate: Moc 16 : patients: pat severe: 11 seve patients pat	Moderate: 13 patients: 31.4±19.6 severe: 11 patients	9.6 29.2 ± 19.3	I	I	5.1±1.2	5.3 ± 1.1	12 weeks
Yin et al. 2017 [18]	I	China	48 (42/6)	(9/2)	N-acetylcysteine 600 mg+conventional treatment (mainly sulfasalazine, methotrexate)	Conventional treatment (mainly sulfasalazine, methotrexate)	None	36-	36-75	I	I	I	I	I	I	I	I	I	12 weeks
Abdollahzad et al. 2015 [19, 20]	IRCT20131 1014 105N1 6	Iran	22 (19/ 3)	22 (20/ 2)	CoO10 100 mg-conventional treatment (mainly methorecastic alfacabatine, hydroxychbroquine, prednisolono)	Placebo (wheat starch)+conventional treatment (maniny methorexate, sulfasalazine, hydroxychloroquine, prednisolone)	DAS28, number of tender joints, number of swollen joints, TNF-a, IL6, VAS, ESR, MDA, TAC, adverse events	48.77±11.58	48.77±11.58 50.41±11.28	6.91 ±5.87	6.94 ± 6.50	All patients are moderate and severe	lerate	I	39.64 ± 25.5	39.64±25.53 40.27±25.75	5 5.01±1.21	4.88 ± 0.96	8 weeks
Zhu et al. 2020 [30]	I	China	45 (35/ 10)	45 (37/ 8)	CoQ1010 mg Tki+conventional treatment (mainly methotreaste, low-dose prednisone)	Placebo (wheat starch)+ conventional treatment (mainly methotrexate, low- dose prednisone)	CRP, ESR, TNF- a, 116, MDA, TAC	48.15±11.68	47.36 ±12.11	5.2 (1.9, 8.6)*	5.1 (2.2, 8.1)*	I			57.42±18.46 42.21±16.11	1 41.26 ± 15.26	- 92	I	12 weeks
Vaghef- Mehrabany et al. 2016 [31]	IRCT201207024105N10	Iran	22 (22/ 0)	24 (24/ 0)	Probiotic (Lactobacillus casei 01)+cenventional treatment (minity methotreate: hydroxychloroquine prednisolne)	Placebo+convertional treatment (mainly methotrexate, hydroxychloroquine, prednisolone)	MDA, SOD, GPx, CAT, TAC	41.14±12.65	44.29±9.77	4.75 (3.0, 9.0)*	5.25 (3.75, 10.0)*	All patients are inactive to moderate (DAS28 < 5.1)	ctive	I	I	I		<5.1	8 weeks
amani et al 2017 [32]	Zammi et al. 2017 [32]	Iran	27 (22/ 5)	27 (24) 3)	Synbiotic capsule (Lactobacillus acidophilus, Lactobacillus casei, and Bridobacterium bridum (2 × 10° colony-formingunits/g each)+800 ng indin)	Placebo (starch only)	CRP, DAS28, VAS, NO, TAC, GSH, MDA	49.3 ±11.0	49.5 ± 12.9	7.7 ±6.1	7.5 ± 6.4	All patients are moderate and severe	lerate 6.03 ± 4.84 [®]	84" 5.64±5.14"	I	I	4.2 ± 0.7	3.5 ± 0.8	8 weeks
Ghavipour et al. 2016 [33]	IRCT201202183236N2	Iran	30 (20/	30 (20/ 10)	Pomogranate extract (contained 40% ellagic acids) more oblagases acids) method esharges the correct medication (mainly methodresate, hydroxychlorequine, sufficializzine, and prednisolone)	Placebo with no changes to current medication (mainly methotrexate, hydroxychloroquine, sulfasalazine, and prednisolone)	DAS28, HAQ, ESR, CRP, number of tender joints, number of swollen joints, MDA, GPX	48.4±11.4	49.1 ± 12.2	10.9±5.8	12.3 ±5.8	Active RA	29.0±15.6	5.6 30. <i>6</i> ±19.6	8.0±4.2	6.6±4.5	4.9 ± 0.8	4.7 ±1.1	8 weeks
	Javadi et al. 2017 [24, 2.5]	Iran	20 (20/ 0)	20 (20/ 0)	Queretin 500 ng-conventional treatment (multi) methotrasia, hydrosystahoroguna, suffasitizna, cyclosporine, predniobna, NSADD3	Placebo+conventional treatment (mainly methotreate, hydroxychloroquine, sulfasalazine, cyclogorine, prednisolone, NSAIDs)	DAS28, HAQ, ESR, CRP, TNF- a, number of tender joints, number of swollen joints, VAS, MDA, TAC	46.55 ±9.94	48.00 ± 8.39	5.17±3.83	4.87 ± 3.03	Mild to moderate disease activity	isease 2.89 ± 2.95*	95" 3.28 ± 2.32"	r 19.00 ± 8.62	2 21.10±12.38	38 3.22±0.93	3.13±1.1	8 weeks
Bae et al. 2009 [34]	I	Korea	20 (19/1)		Querectin +vitarnin C (166 mg 133 mg/ capsule) +conventional treatment (mainly hydroxychborequine, sulfasalazine, methoresate with foldre, bucillamine, NSMD, low-dose ateroid)	Placebo+conventional treatment (mainly hydroxychloroquine, sulfasalazine, methotrexate with folate, bucillamine, NSAID, low-dose steroid)	CRP, TNF-6, IL6	52.1±10.3	.10.3	10.2 ± 5.9	F 5.9	N of known	0.85 (0.28, 4.00)*	28, 1.05 (0.22, 6.44)*	I	I	I	I	4 weeks

TABLE 1: The characteristics of the included studies.

Outmative Bary True Currentian From the part of the part			Sam	Sample size	Intervention		a strengt	Mean age (years)	(years)	Disease duration (years)	tion (years)	Disease severity	rity	Baseline CRP (mg/L)	(mg/l)	Baseline ESR (mm/h)	SR (mm/h)	Baselin	Baseline DAS28	
	Trial registration number Co	untry	Г ыз		Trial group	Control group	outcomes	Trial group	Control group	Trial group	Control group			rial group	Control group	Trial group	Control group	Trial	Control group	Duration
111 <th1< td=""><td>Khojah et al. 2018 [35]</td><td>Egypt</td><td>50 (36/ 14)</td><td></td><td>Reverted 1000 mg+conventional treatment</td><td>Placebo+conventional treatment</td><td>Number of tender joints, number of swollen joints, DAS28, CRP, ESR, TNF-4, IL6</td><td>46.5±12.3</td><td>44.2 ± 16.4</td><td>9.4 ±5.8</td><td>9.8±5.5</td><td>Not know</td><td></td><td>2.7±0.7</td><td>2.9 ± 0.8</td><td>39.4±11.5</td><td>43.8 ± 14.8</td><td>4.62 ± 0.99</td><td></td><td></td></th1<>	Khojah et al. 2018 [35]	Egypt	50 (36/ 14)		Reverted 1000 mg+conventional treatment	Placebo+conventional treatment	Number of tender joints, number of swollen joints, DAS28, CRP, ESR, TNF-4, IL6	46.5±12.3	44.2 ± 16.4	9.4 ±5.8	9.8±5.5	Not know		2.7±0.7	2.9 ± 0.8	39.4±11.5	43.8 ± 14.8	4.62 ± 0.99		
In the interval of the i	Mooavian e al. 2020 IRCT20141108019853N6 [26.27]	Iran	31 (31/ 0)		Gardic tablets 500 mg (equivalent to 2500 mg of fresh gardic and corntaining 2.5 mg allein) Bid with no changes to current madication (mainly predinisolone, methotreeate, sulfasalazine)	Placebo with no changes to current medication (mainly prednisolone, methotrexate, sulfasalazine)	HAQ, VAS, CRP, ESR, TNF- <i>a</i> , number of tender joints, number of swollen joints, MDA, TAC		51.39 ±10.38	6.58 ±7.75	6.61 ± 8.11	All patients are r and sever		44 ± 13.76 1	3.57 ± 14.04	23.63 ± 13.82		4.61 ± 0.92		
111	Aryaeian et al. 2009 [36]	Iran	22 (19/ 3)		Conjugated linoleic add 2 g with no changes to current medkation (mainly hydroxychloroquine, choloroquine and methotrexate, lower amounts of NSAIDs)			46.23 ± 13.07	47.95 ± 11.14		8.88 ± 8.65					26.81 ± 15.50		4.63 ± 1.26		
10 100 000 <td>Aryacian et al. 2009 [36]</td> <td>Iran</td> <td>22 (17/ 5)</td> <td></td> <td>Conjugated Inoldc adds 2 gyvitamin E 400 mg with no changes to carrent medication (mainty hydrarychorquine, choloroquine and methorrecate, lower amounts of NSAID5)</td> <td>Placebo with no changes to current medication (mainly hydroxychloroquine, choloroquine and methotrecate, lower monomic of NALIPA)</td> <td>VAS, ESR, CRP, DAS28, number of tender joints, number of swollen joints</td> <td>43.77 ± 12.75</td> <td>47.95 ± 11.14</td> <td></td> <td>8.88±8.65</td> <td></td> <td></td> <td></td> <td></td> <td>28.45 ± 17.26</td> <td></td> <td>4.59 ± 1.11</td> <td>4.35 ± 0.95</td> <td>12 weeks</td>	Aryacian et al. 2009 [36]	Iran	22 (17/ 5)		Conjugated Inoldc adds 2 gyvitamin E 400 mg with no changes to carrent medication (mainty hydrarychorquine, choloroquine and methorrecate, lower amounts of NSAID5)	Placebo with no changes to current medication (mainly hydroxychloroquine, choloroquine and methotrecate, lower monomic of NALIPA)	VAS, ESR, CRP, DAS28, number of tender joints, number of swollen joints	43.77 ± 12.75	47.95 ± 11.14		8.88±8.65					28.45 ± 17.26		4.59 ± 1.11	4.35 ± 0.95	12 weeks
10 10 10 1010 10 1010 10 1010 <b< td=""><td>Aryaeian et al. 2009 [36]</td><td>Iran</td><td>21 (17/ 4)</td><td></td><td>Vitamin E 400 mg with no dranges to current medication (mainjy hydroxychoroquine, choloroquine and methorocaste, lower amounts of NSAID5)</td><td>(GATIVON) IO STIMOTIE</td><td></td><td></td><td>47.95 ±11.14</td><td></td><td>8.88 ± 8.65</td><td></td><td></td><td></td><td></td><td>40.43 ± 26.22</td><td></td><td>4.52 ± 1.08</td><td>4.35 ± 0.95</td><td></td></b<>	Aryaeian et al. 2009 [36]	Iran	21 (17/ 4)		Vitamin E 400 mg with no dranges to current medication (mainjy hydroxychoroquine, choloroquine and methorocaste, lower amounts of NSAID5)	(GATIVON) IO STIMOTIE			47.95 ±11.14		8.88 ± 8.65					40.43 ± 26.22		4.52 ± 1.08	4.35 ± 0.95	
4 0 m (1)4 0 m (1)4 0 m (1)4 0 m (1)4 0 m (1)6 0 m 	Edmonds et al. 1997 [37]	The UK			Varaini E 600 ng Bid vith to chungs to current recktation (nauhy NSAID, methrecast, sklanopyrin, azhinoprine D- pentollarnin, Myocicito, saliasalario, orticontroldo)	Placebo with no changes to current medication (mainly NSAID, methotreaute, Salazopyrin, azathoprine, D-pendilamine, Myocristi, adfiasalazie, corticosteroids)	Adverse events	24-75	32-66	I	I	Not know	=	I	I	I	I	I	I	12 weeks
301 3	Wittenborg et al. 1998 [38]	Germany			Vitamin E 400 mg Tid with no changes to basic treatment and physical therapy, other NSAIDs are not allowed during treatment	Didofenac-sodium 50 mg Tid with no changes to basic treatment and physical therapy; other NSAIDs are not allowed during treatment	VAS, adverse events	61 ± 9	58±9	10±9	11±11	Not know	=	I	I	I	I	I	I	3 weeks
8 (80)7 (70)Selation 20 (a)MethodsVAS E88 (11) -1 -1 Nek holor -23 ± 15 30 ± 17 -1 <	Tarp et al. 1986 [39]	Denmark			Selanium 256 µg with no changes to current medication (mainly gold 2 D-penicillamine, antimalarials, and NSAIDS)	Placebo with no changes to current medication (mainly gold, 2 D-penicillamine, antimalarials, and NSAIDs)	Number of swollen joints, ESR	$54, 3 \pm 12, 4$	54.6 ± 12.7	16.4 ± 10.1	10.5 ± 8.0	Not know	E	I	I	47 ± 35	39 ± 26	I	I	24 weeks
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Peretz et al. 1992 [40]	Belgium			Selenium 200 µg	Placebo	VAS, ESR	€1 ±	11	Ι	I	Not know	a.	I	I	23 ± 15	30 ± 17	I	Ι	24 weeks
	Paretz et al. 2001 [41]	Belgium			Selenium 200 <i>pg</i> with stable dose of corticosteroids and of disease-modifying drugs (such as NSAIDs and low-dose glucocorticosteroids)	Placebo with stable dose of corticosteroids and of disease-modifying drugs (such as NSAIDs and how- dose glucocorticosteroids)	Number of swollen joints, CRP, ESR, VAS	61±13	60 ±13	I	I	All patients are <i>r</i>	noderate	28 ± 17	28±17	34±16	29±12	I	I	12 weeks
15 (13) 21 222 mentorizadan ding treatment (multy protosytosytosytosytosytosytosytosytosytos	Heinle et al. 1997 [42]	Germany			Selenium 200 µg	Placebo with no changes to basic treatment and the cortisone or NSAIDs were adjusted as needed	Number of tender joints, number of swollen joints, CRP	58.2±12.78	57.2±13.27	12.69 ± 8.3	12.03 ± 7.8	N of know		23.4±18	17.1 ± 28	I	I	I	Ι	12 weeks
	Kangüle et al. 2017 [43]	Turkey			Spa therpy+standard drug, treatment (mainly methororeast any hydroxyblioropation technomide or ratioalatance glucocriticids and NSAIDs)	Standard drug treatment (mainly methotrexate, hydroxychtoroquine, hydroxychtoroquine, atlfasalazine glucocorticoits and NSAIDs)	VAS, HAQ, DAS28, MDA, number of tender joints, number of swollen joints, SOD, adverse events	53.3±11.1	52.3 ±12.3	12.3 ± 12.9	13.4±12.0	Not know	-	T	T	38.5 ± 18.0	38.5±18.0	6.5 ± 0.9	5.9±1.6	12 weeks

TABLE 1: Continued.

6

								TABLE 1. COMMING	nimion											
				Sample size (female/male)	·le size */male)	Intervention		Relevant	Mean age (years)	(years)	Disease dur	Disease duration (years)	Disease severity	Baseline (Baseline CRP (mg/L)	Baseline ESR (mm/h)	SR (mm/h)	Baseline DAS28	DAS28	
Subgroup	Study	I rial registration number Country	Country	Trial group	Trial Control group group	Trial group	Control group	outcomes	Trial group	Control group	Trial group	Control group	Trial Control group group	Trial group	Control group	Trial group	Control group	Trial group	Control group	Duration
Vitamins A, E, and C	Jaswal et al. 2003 [44]	I	India	20 (not known)	20 (not 20 (not known) known)	Vitamins A, E, and C+conventional treatment	Conventional treatment	MDA, GSH	I		I	I	Not known	I	I	I	I	L	I	12 weeks
Ozone	León Fernández et al. 2016 [45]	I	Cuba	30 (28/ 2)		 (27) Ozone+methotroxate 12.5 mg+fbuprophen 400 mg+folic acid 5 mg 	Methotrexate 12.5 mg +1buprophen 400 mg+folic acid 5 mg	DAS28, HAQ, CRP, ESR, MDA, NO, GSH, SOD, CAT	57±7	53±7	11±3	7±2	All patients are moderate	16±4	21 ±7	36±6	40 ± 6	6.4 ± 0.2	5.6 ± 0.3	3 weeks
H ₂ -saline	Ishibashi et al. 2014 [46]	I	Japan	12 (10/ 2)	12 (10/ 2)	H ₂ -saline 500 ml	Placebo	DAS28, CRP, 'TNF-a; IL6	62.4 ± 18.4	68.2 ± 12.6	Mean: 4.25	Mean: 4.92	Not known	14.7 ± 17	13 ± 20	I	I	5.10 ± 0.96	5.10±0.96 5.18±1.16 4 weeks	4 weeks
Alpha-Ipoic acid	Mirtaheri et al. 2015 [28, 29]	IRCT201205263140N5	Iran	33 (33/ 0)	32 (3 <i>2</i> / 0)	Alpha. Ippet and 1200 mg with no changes to current medication (manky preducionan methorica eta hydrosychkoroquine aufisalazine, calcum and vitamin D, folic alfasalazine, calcum and vitamin D, folic	Placebo (maltodestrin) with no danges to current medication (multy predisolone, methorecate, hydrosychloroquine, sulfasalazine, cakium and vitamin D, folic acid)	SOD, TAC, GPs, TNF-a, IL6, CRP	36.09 ±8.77	38.28±8.63	38.28±8.63 7.26±4.9 6.78±4.72	6.78 ± 4.72	All putients are inactive to moderate (DA328 < 5.1)	3 (1.1, 10.1)* *	3.5 (0.9, 9.5)**	I	I	2.1 ± 0.76	21±0.76 214±0.72 8 weeks	8 weeks
2	Bae et al. 2009 [34]	I	Korea	20 (19/1)	(1/61	e-Lipoic acid (300 my/capsule)+conventional treatment (mainh hydroxychloroquine, suffisaliaria: muchorceate with folate, bucillamine, NSAID, low-dose steroid)	Placebo+conventional treatment (mainly hydroxychloroquine, sulfasalazine, methotrexate with folate, bucillamine,	CRP, TNF-a, IL6	52.1±10.3	10.3	10.2	10.2 ± 5.9	N ot known	0.84 (0.14, 4.28)*	1.05 (0.22, 6.44)*	I	T	I	T	4 weeks

NSAID, low-dose steroid)

TABLE 1: Continued.

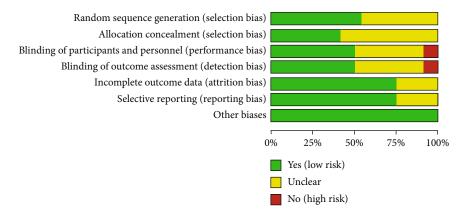


FIGURE 2: Risk of bias graph.

showed that no obvious adverse events were seen in the two groups. The summary results showed that the difference was of no statistical significance (RR 1.16, 95% CI 0.79 to 1.71, P = 0.45; random effect model).

- (2) Clinical Efficacy Indexes. Nine RCTs reported the number of swollen joints; the summary results showed that the number of swollen joints in the experiment group is lower (WMD -1.15, 95% CI -1.82 to -0.47, P = 0.0008; random effect model) (Figure 12). Seven RCTs reported the number of tender joints; the summary results showed that the number of tender joints in the experiments group is lower (WMD -2.50, 95% CI -3.12 to -1.89, P < 0.00001; random effect model) (Figure 13). Eleven RCTs reported the DAS28; the summary results showed that the DAS28 in the experiment group is lower (WMD -1.02, 95% CI -1.37 to -0.68, *P* < 0.00001; random effect model) (Figure 14). Nine RCTs reported the VAS; the summary results showed that the VAS in the experiment group is lower (SMD -0.66, 95% CI -1.02 to -0.31, P = 0.0003; random effect model) (Figure 15). Nine RCTs reported the HAQ; the summary results showed that the HAQ in the experiment group is lower (SMD -0.74, 95% CI -0.97 to -0.50, P < 0.00001; random effect model) (Figure 16).
- (3) Inflammation Indexes. Thirteen RCTs reported the ESR; the summary results showed that the ESR in the experiment group is lower (WMD -7.89, 95% CI -12.21 to -3.58, *P* = 0.0003; random effect model) (Figure 17). Eleven RCTs reported the CRP; the summary results showed that the CRP in the experiments group is lower (WMD -1.06, 95% CI -1.83 to -0.29, P = 0.007; random effect model) (Figure 18). Six RCTs reported the TNF- α ; the summary results showed that the TNF- α in the experiment group is lower (SMD -0.49, 95% CI -0.89 to -0.09, P = 0.02; random effect model) (Figure 19). Four RCTs reported IL6; the summary results showed that the difference was of no statistical significance (SMD -0.32, 95% CI -1.28 to 0.63, *P* = 0.51; random effect model) (Figure 20).

4.5.1. *N*-acetylcysteine. Three RCTs utilized to N-acetylcysteine treat RA. Hashemi et al. 2019 assessed the CRP, ESR, TNF- α , IL6, MDA, TAC, and NO. Batooei et al. 2018 assessed the DAS28, ESR, number of tender joints, number of swollen joints, HAQ, VAS, and adverse events. Yin et al. 2017 did not report any outcomes related to oxidative stress. The summary results of ESR showed that there was no statistically significant difference between the two groups after N-acetylcysteine intervention (WMD -0.87, 95% CI -2.85 to 1.12, P = 0.39) (Figure 17).

Hashemi et al. 2019 showed that the MDA and NO in the experiment group were lower (MDA (SMD -0.75, 95% CI -1.38 to -0.12, P = 0.02); NO (SMD -0.65, 95% CI -1.27 to -0.02, P = 0.04)) (Figures 4 and 7), while the IL6 in the experimental group was higher (SMD -0.05, 95% CI -0.66 to 0.56, P = 0.01) (Figure 20). The TAC, CRP, and TNF- α in Hashemi et al. 2019 between two groups were of no statistical significance (TAC (SMD -0.05, 95% CI -0.66 to 0.56, P = 0.87), CRP (WMD -0.20, 95% CI -0.91 to 0.51, P =0.58), and TNF- α (SMD -0.28, 95% CI -0.89 to 0.33, P =0.37)) (Figures 5, 18, and 19).

Batooei et al. showed that the adverse events, number of tender joints, number of swollen joints, and DAS28 between two groups were of no statistical significance (adverse events (RR 1.33, 95% CI 0.24 to 7.32, P = 0.74), number of swollen joints (WMD -0.80, 95% CI -3.67 to 2.07, P = 0.59), number of tender joints (WMD -0.70, 95% CI -4.35 to 2.95, P = 0.71), and DAS28 (WMD -0.35, 95% CI -1.10 to 0.40, P = 0.36)) (Figures 11–16). The HAQ and VAS in Batooei et al. were lower (VAS (SMD -1.15, 95% CI -1.75 to -0.55, P = 0.0002); HAQ (SMD -0.85, 95% CI -1.42 to -0.27, P = 0.004)) (Figures 18 and 19).

Abdollahzad et al. 2015 reported the effect of Nacetylcysteine combined with pulmonary rehabilitation exercise treatment on lung function in patients with RArelated interstitial lung disease; they found that Nacetylcysteine combined with pulmonary rehabilitation exercise therapy has a significant effect.

4.5.2. Coenzyme Q10. Three RCTs utilized coenzyme Q10 to treat RA. Abdollahzad et al. 2015 assessed the MDA, TAC, DAS28, number of tender joints, number of swollen joints, ESR, TNF- α , IL6, VAS, and adverse events. Zhu et al. 2020

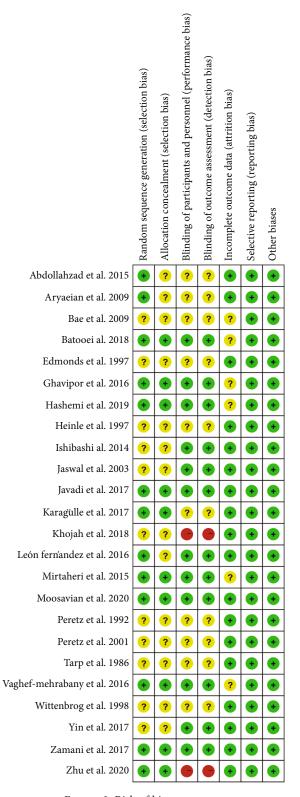


FIGURE 3: Risk of bias summary.

assessed the MDA, TAC, CRP, ESR, TNF- α , and IL6. The summary results in the CoQ10 subgroup showed that the MDA and ESR in CoQ10 groups were lower (MDA (SMD -0.71, 95% CI -1.06 to -0.36, *P* < 0.0001); ESR (WMD -14.27, 95% CI -19.41 to -9.13, *P* < 0.00001)) (Figures 4

and 17), while the difference of TAC between two groups was of no statistical significance (SMD -0.19, 95% CI -0.53 to 0.15, P = 0.43) (Figure 5). For TNF- α and IL6, the data representation of Abdollahzad et al. 2015 is median (interquartile range); hence, it cannot be merged with Zhu et al. 2020. However, both groups showed that after CoQ10 intervention, compared with the control group, the TNF- α in the experimental group decreased (P < 0.05). Mean-while, Zhu et al. 2020 showed that compared with the control group, the IL6 in the experimental group decreased (P < 0.01) (Figure 20), while Abdollahzad et al. 2015 showed that there was no statistical difference between the two groups (P > 0.05).

Abdollahzad et al. 2015 showed that the DAS28 and VAS in experiments group were lower (DAS28 (WMD -1.70, 95% CI -2.34 to -1.06, P < 0.00001); VAS (SMD -2.29, 95% CI -3.06 to -1.51, P < 0.00001)) (Figures 14 and 15). It also showed that no obvious adverse events were seen in the two groups. Zhu et al. 2020 showed that the CRP in the experiment group was lower (WMD -3.92, 95% CI -6.51 to 1.33, P = 0.003). The data representation of the number of swollen joints and number of tender joints in Abdollahzad et al. 2015 is median (interquartile range), and the results showed that compared with the control group, the number of swollen joints and number of tender joints in the experimental group decreased.

4.5.3. Probiotics. Two RCTs utilized probiotics to treat RA. Vaghef-Mehrabany et al. 2016 assessed the MDA, SOD, GPx, CAT, and TAC. Zamani et al. 2017 assessed the TAC, GSH, MDA, CRP, DAS28, and VAS. The summary results in the probiotic subgroup showed that the MDA in the probiotic groups was lower (SMD -0.71, 95% CI -1.06 to -0.36, P < 0.001) (Figure 4), while the difference of TAC between two groups was of no statistical significance (SMD -0.19, 95% CI -0.53 to 0.15, P = 0.27) (Figure 5).

Vaghef-Mehrabany et al. 2016 showed that the difference of SOD, GPx, and CAT between two groups was of no statistical significance (SOD (SMD -0.10, 95% CI -0.68 to 0.48, P = 0.73), GPx (SMD -0.00, 95% CI -0.58 to 0.57, P = 0.99), and CAT (SMD -0.14, 95% CI -0.43 to 0.72, P = 0.62)) (Figures 6, 8, and 9).

Zamani et al. 2017 showed that the difference of GSH and VAS between two groups was of no statistical significance (GSH (SMD 0.29, 95% CI -0.20 to 0.78, P = 0.25); VAS (SMD -0.40, 95% CI -0.94 to 0.14, P = 0.15)) (Figures 10 and 15). It also showed that after probiotic intervention, compared with the control group, the DAS28 and CRP in the experimental group decreased (DAS28 (WMD -0.60, 95% CI -1.09 to -0.11, P = 0.02); CRP (WMD -3.86, 95% CI -6.63 to -1.09, P = 0.006)) (Figures 14 and 18).

4.5.4. Pomegranate Extract. Only one RCT utilized pomegranate extract to treat RA. Ghavipour et al. 2016 assessed the DAS28, HAQ, ESR, CRP, number of tender joints, number of swollen joints, MDA, and GPx. The summary results in the pomegranate extract subgroup showed that the MDA in the pomegranate extract groups was higher (SMD 0.56, 95% CI 0.02 to 1.10, P = 0.04) (Figure 4), while the difference

Study or subgroup	Ex Mean	cperime SD	ntal Total	Mean	Contro SD	l Total	Weight	Std. Mean Difference IV, Random, 95% C		Difference om, 95% CI	Risk of Bias A B C D E F G
$\begin{array}{l} 1.2.1 \ \mathrm{N-acetylcysteine} \\ \mathrm{Hashemi} \ \mathrm{el} \ \mathrm{al}. \ 2019 \\ \mathrm{Subtorial} \ (95\% \ \mathrm{CI}) \\ \mathrm{Heterogenity:} \ \mathrm{Not} \ \mathrm{applicable} \\ \mathrm{Test} \ \mathrm{for} \ \mathrm{overall} \ \mathrm{effct:} \ Z = 2.34 \ \mathrm{(} \end{array}$	462.71 P = 0.02)		23 23	524.76	90.48	19 19	9.1% 9.1%	-0.75 [-1.38, -0.12 -0.75 [-1.38, -0.12			• • • • • • •
1.2.2 CoQ10 Abdollahzad et al. 2015 Zhu et al. 2020 Subtotal (95% CI)	2.13 2.75	1.44 0.76	22 45 67	3.16 3.38	1.71 0.9	22 45 67	9.2% 9.7% 18.9%	-0.64 [-1.25, -0.03 -0.75 [-1.18, -0.32 -0.71 [-1.06, -0.36	2]		€ ? ? ? 8 € € € 8 € 6 € € €
Heterogenity: $Tau^2 = 0.00$; Chi ² Test for overall effect: $Z = 4.00$	= 0.08, d (P < 0.00)	df = 1 (p)	= 0.77); $I^2 = 0$ %	6						
1.2.3 probiotic Vaghef-Mehrabany et al. 2016 Zamina et al. 2017 Subtotal (95% CI) Heterogenity: Tau ² = 0.00; Chi ²			22 27 49 = 0.91	2.2 2.2); I ² = 0%	1.57 0.4	24 27 51	9.3% 9.4% 18.7%	-0.43 [-1.02, -0.15 -0.3 [-0.93, -0.15] -0.41 [-0.80, -0.01]			•••••••••••
Test for overall effect: Z = 2.01 1.2.4 Pomogranate extract Ghavipour et al. 2016 Subtotal (95% CI) Heterogenity: Not applicable Test for overall effect: Z = 2.03	4.78	0.97	30 30	3.6	1.07	25 25	9.4% 9.4%	0.56 [0.02, -1.10] 0.56 [0.02, -1.10]		- ◆	••••
1.2.5 Quercetin Javadi et al. 2017 Subtotal (95% CI) Heterogenity: Not applicable Test for overall effect: Z = 2.67	3.98 (<i>P</i> = 0.00	0.1	20 20	5.25	1.98	20 20	9.0% 9.0%	-0.89 [-1.54, -0.24 -0.89 [-1.54, -0.24	· 🔺		••••••
1.2.6 Garlic tablets Moosavian et al. 2020 Subtotal (95% CI) Heterogenity: Not applicable Test for overall effect: $Z = 2.37$	2.73 (<i>P</i> = 0.02	1.27	31 31	3.68	1.73	31 31	9.5% 9.5%	-0.62 [-1.13, -0.11 -0.62 [-1.13, -0.11			•••••
1.2.7 Spa therapy Karagulle et al. 2017 Subtotal (95% CI) Heterogenity: Not applicable Test for overall effect: $Z = 1.31$	3.82 (P = 0.19	5.12 9)	15 15	2.06	2.76	22 22	9.0% 9.0%	0.44 [-0.22, -1.11] 0.44 [-0.22, -1.11]		▲	●●๋๋๋๋๋๋๋€€
1.2.11 Vitamins A, E and C Jaswal et al. 2003 Subtotal (95% CI) Heterogenity: Not applicable Test for overall effect: $Z = 6.85$	5.63 (P < 0.00	1.09 0001)	20 20	10.97	1.7	20 20	7.5% 7.5%	-3.67 [-4.71, -2.62 -3.67 [-4.71, -2.62			€●●●●●
1.2.12 Ozone Leon Fernandez et al. 2016 Subtotal (95% CI) Heterogenity: Not applicable Test for overall effect: $Z = 7.09$	5 (P < 0.00	2	30 30	10	2	30 30	8.9% 8.9%	-2.47 [-3.15, -1.79 -2.47 [-3.15, -1.79			~? ** ** *
Total (95% CI) Hetreogrnity: Tau ² = 0.74; Chi ² Test for overall effect: $Z = 2.95$ Test for subgroup differences: C						285 .2%	100.0%	-8.82 [-1.36, -0.27	- T	0 5 10	
Risk of bias legend (A) Random sequence generati (B) Allocation concealmeant (s) (C) Blinding of participants an (D) Blinding of outcome assess (E) Incomplete outcome data ((F) Selective reporting (reporting (G) Others biases	eletion b d personi ment (de attrition	ias) nel (per etection	forma	nce bias)					Favours (experimente	l) Favours (control)	

FIGURE 4: MDA.

of GPx, HAQ, and CRP between two groups was of no statistical significance (GPx (SMD 0.54, 95% CI 0.00 to 1.08, P = 0.05), HAQ (SMD -0.52, 95% CI -1.06 to 0.02, P = 0.06), and CRP (WMD 0.20, 95% CI -2.19 to 2.59, P = 0.87)) (Figures 8, 16, and 18). It also showed that the number of swollen joints, number of tender joints, DAS28, and ESR were lower (number of swollen joints (WMD -1.38, 95% CI -3.67 to -0.01, P = 0.05), number of tender joints (WMD -4.20, 95% CI -6.82 to -1.58, P = 0.002), DAS28 (WMD -0.80, 95% CI -1.41 to -0.19, P = 0.010), and ESR (WMD -9.40, 95% CI -17.73 to -1.07, P = 0.003)) (Figures 12–14 and 17).

4.5.5. *Quercetin*. Two RCTs utilized quercetin to treat RA. Javadi et al. 2017 assessed the DAS28, HAQ, ESR, CRP, TNF- α , number of tender joints, number of swollen joints, VAS, MDA, and TAC. Bae et al. 2009 reported CRP, TNF- α , and IL6.

Javadi et al. 2017 showed that MDA, VAS, and HAQ in the quercetin groups were lower (MDA (SMD -0.89, 95% CI -1.54 to -0.24, P = 0.008), VAS (SMD -0.83, 95% CI -1.48 to -0.18, P = 0.01), and HAQ (SMD -0. 92, 95% CI -1.58 to -0.27, P = 0.006)) (Figures 4, 15, and 16), while the difference of TAC, DAS28, ESR, and CRP between two groups was of no statistical significance (TAC (SMD -0.25, 95% CI -0.87

Study or Subgroup		xperien			Contro		Weight	Std. Mean Difference		n Difference	Risk of Bias
	Mean	SD	Iotal	Mean	SD	Total		IV, Random, 95% CI	IV, Rand	om, 95% CI	ABCDEFG
1.3.1 N-acetyalcystenie Hashemi et al. 2019 Subtotal (95% CI) Heterogenity: Not applicable	471.19	151.9	23 23	477.95	97.73	19 19	12.1% 12.1%	-0.05 [-0.66, 0.56] -0.05 [-0.66, 0.56]		∔	••••
Test for overall effect: $Z = 0.16$ ((P = 0.87))									
1.3.2 CoQ10											
Abdollahzad et al.2015	0.96	0.58	22	0.93	0.47	22	12.3%	0.00 [-0.59, 0.56]		<u>†</u>	
Zhu et al.2020	0.85	0.27	45	0.93	0.28	45	13.5%	-0.29 [-0.70, 0.13]		1	
Subtotal (95% CI) Hetrogenity: Tau ² = 0.00; Chi ² :	-061 df	- 1 (n -	67 - 0 43)-	$I^2 = 0\%$		67	25.8%	-0.19 [-0.53, 0.15]		•	
Test for overall effect: $Z = 1.11$			0.10),	1 0/0							
2.2.D. 11.01											
1.3.3 Probiotic Vaghef-Mehrabany et al. 2016	1.21	0.14	22	1.15	0.16	24	12.3%			-	
Zamani et al. 2017	835.6	123.5	27		128.4	27	12.7%	0.39 [-0.19, 0.98]		ŧ	
Subtotal (95% CI)			49			51	25.0%	-0.01 [-0.54, 0.53] 0.17 [-0.22, 0.57]		•	
Hetrogenity: $Tau^2 = 0.00$; $Chi^2 =$ Test for overall effect: $Z = 0.86$			= 0.32);	$I^2 = 0\%$				0.17 [0.22, 0.07]			
lest for overall effect. $Z = 0.80$	(F = 0.39)									
.3.5 Quercetin											
avadi et al. 2017	0.32	0.08	20	0.34	0.08	20	12.0%	-0.25 [-0.87, 0.38]		1	
Subtotal (95% CI) Heterogenity: Not applicable			20			20	12.0%	-0.25 [-0.87, 0.38]		Y	
Test for overall effect: $Z = 0.77$	(P = 0.44))									
	(,									
1.3.7 Garlic tablets Moosavian et al. 2020	224.6									-	
Subtotal (95% CI)	334.6	13.72	31 31	305	15.32	31 31	12.1% 12.1%	2.01 [1.39, 2.63] 2.01 [1.39, 2.63]		•	
Heterogenity: Not applicable						51		2.01 [1.59, 2.05]			
Test for overall effect: $Z = 6.38$	(P < 0.00)	001)									
1.3.13 Alpha-lipoic acid											
Mirtaheri et al. 2015	1.08	0.16	33	1	0.2	32	13.0%	0.44 [-0.06, 0,93]		-	
Subtotal (95% CI)			33			32	13.0%	0.44 [-0.06, 0,93]		•	
Heterogenity: Not applicable	(D 0.00										
Test for overall effect: $Z = 1.74$	(P = 0.08))									
fotal (95% CI)			223			220	100.0%	0.27 [-0.25, 0.75]		•	
letrogenity: Tau ² = 0.40; Chi ² =			< 0.000	$(001); I^2 =$	88.0%						_
Test for overall effect: $Z = 1.10$ Test for sugroup differences: Cl			5 (n < 0	00001).	I ² - 88	0%			-10 -5	0 5 10	
Risk of bias legend	11 - 41.0)4, ui – .) (p < 0	.00001),	1 = 00.	070			Favours (control)	Favours (experimen	(lat
A) Random sequence generati	on (select	ton bias))						ravours (control)	ravours (experimen	iici)
 B) Allocaction concealmeant (
C) Blinding of participants and				e bias)							
 D) Blinding of outcome assem E) Incomplete outcome data (a) 			as)								
F) Selective reporting (reporti		143)									
(G) Others biases	0										

FIGURE 5: TAC.

to 0.38, P = 0.44), DAS28 (WMD -0.46, 95% CI -1.17 to 0.25, P = 0.20), ESR (WMD -5.10, 95% CI -13.86 to 3.66, P = 0.25), and CRP (WMD -0.51, 95% CI -1.98 to 0.96, P = 0.50)) (Figures 5, 14, 17, and 18). The data representation of the TNF- α , number of tender joints, and number of swollen joints in Javadi et al. 2017 is median (interquartile range), and the results showed that compared with the control group, the TNF- α in the experimental group decreased (P < 0.05); meanwhile, the difference of the number of tender joints and number of swollen joints between the experimental group and the placebo group was of no statistical significance (P > 0.05).

Bae et al. 2009 showed that the difference of TNF- α and IL6 between two groups was of no statistical significance (TNF- α (SMD -0.07, 95% CI -1.26 to 1.12, P = 0.91); IL6 (SMD -0.09, 95% CI -1.27 to 1.10, P = 0.89)) (Figures 19 and 20). The data representation of the CRP is median (interquartile range), and the results showed that the difference of CRP between the experimental group and the placebo group was of no statistical significance (P > 0.05).

4.5.6. Resveratrol. Only one RCT utilized resveratrol to treat RA, and it reported number of tender joints, number of

swollen joints, DAS28, CRP, ESR, TNF- α , and IL6. The RCT evaluated 100 patients with RA. The control group used traditional RA therapy, while the test group was treated with 1 g resveratrol on the basis of traditional therapy. The treatment lasted 3 months. The study showed that the number of swollen and tender joints and the DAS28 in the resveratrol group were significantly reduced (P < 0.05) (Figures 12–14), and CRP, ESR, TNF- α , and IL6 were also reduced (P < 0.05) (Figures 17–20).

4.5.7. *Garlic Tablets*. Only one RCT utilized garlic tablets to treat RA. Moosavian et al. 2020 assessed the HAQ, VAS, CRP, ESR, TNF- α , number of tender joints, number of swollen joints, MDA, and TAC. The summary results showed that the MDA in the experiment groups was lower (SMD -0.62, 95% CI -1.13 to -0.11, *P* = 0.008) (Figure 4), while the TAC in the experiment groups was higher (SMD 2.01, 95% CI 1.39 to 2.63, *P* < 0.00001) (Figure 5). It also showed that the difference of number of tender and swollen joints, ESR, and CRP between two groups was of no statistical significance (*P* > 0.05) (Figures 12, 13, 17, and 18), while the HAQ, VAS, and TNF- α in the experimental group were lower (*P* < 0.05) (Figures 15, 16, and 19).

Study or subgroup	Ex	perime	ntal		Control	l	Weight	Std. mean difference	e Std. mean difference	Risk of bias
Study of subgroup	Mean	SD	Total	Mean	SD	Total	weight	IV, Random, 95% C	I IV, Random, 95% CI	ABCDEFG
1.1.1 Probiotic										
Vaghef-Mehrabany et al. 2016 Subtotal (95% CI)	1, 090.35	198.92	22 22	1, 111.16	206.44	24 24	22.5% 22.5%	-0.10 [-0.68, 0.48] -0.10 [-0.68, 0.48]	•	•••• •••
Heterogenity: Not applicable Test for overall effect: $Z = 0.34$	(<i>P</i> = 0.73)									
1.1.3 Spa therapy										
Karagulle et al. 2017 Subtotal (95% CI)	37.37	7.3	15 15	35.45	6.11	22 22	17.5% 17.5%	$\begin{array}{c} 0.28 \\ 0.28 \\ -0.38, 0.94 \end{array}]$		╋╋┇┇╋╋╉
Heterogenity: Not applicable Test for overall effect: $Z = 0.84$	(<i>P</i> = 0.40)									
1.1.11 Ozone Leon Fernadez et al. 2016 Subtotal (95% CI)	22	8	30 30	18	10	30 30	28.5% 28.5%	0.44 [-0.08, 0.95] 0.44 [-0.08, 0.95]	•	₽ ? ₽₽₽₽€
Heterogenity: Not applicable Test for overall effect: $Z = 1.67$	(<i>P</i> = 0.10)									
1.1.13 Alpha-lipoic acid Mirtaheri et al. 2015 Subtotal (95% CI) Heterogenity: Not applicable Test for overall effect: Z = 1.44	218 (<i>P</i> = 0.66)	58.5	33 33	225	69	32 32	31.5% 31.5%	-0.11 [-0.59, 0.38] -0.11 [-0.59, 0.38]	÷	••••
Total (95% CI) Hetrogenity: Tau ² = 0.00; df = 3 Test for overall effect: $Z = 0.82$			100 %			108	100.0%	0.12 [-0.16, 0.40]	-4 -2 0 2 4	
Test for subgroup differences: (Risk of bias legend	Chi ² = 3.10), df = 3	(<i>p</i> = 0.	38), $I^2 = 3$.3%				Favours (control) Favours (experimental))
(A) Random sequence generat			s)							
B) Alloction concealmeant (sC) Blinding of participants anD) Blinding of outcome assess	d personn smeant (de	el (perfo tection		e bias)						
 (E) Incomplete outcome data ((F) Selective reporting (reporti (G) Other biases 		ias)								

FIGURE 6: SOD.

Study or subgroup	Ex	perime			Contro	ol	Weight	Std. mean difference	Std. mean difference	Risk of bias
Study of subgroup	Mean	SD	Total	Mean	SD	Total	weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
1.4.1 N-acetylcysteine										
Hashemi et al. 2019	3.6	0.9	23	4.23	1.01	19	33.8%	-0.65 [-1.27, -0.02]		$\oplus \oplus \oplus \oplus \oplus \bigcirc \bigcirc \oplus \oplus \bigcirc \bigcirc$
Subtotal (95% CI)			23			19	33.8%	-0.65 [-1.27, -0.02]	▼	
Heterogeneity: Not applicable		>								
Test for overall effect: $Z = 2.0$	4 (P = 0.	04)								
1.4.3 Probiotic										
Zamani et al. 2017	38.6	4.5	27	42	7	27	34.0%	-0.57 [-1.11, -0.02]		$\bullet \bullet $
Subtotal (95% CI)			27			27	34.0%	-0.57 [-1.11, -0.02]	•	
Heterogeneity: Not applicable										
Test for overall effect: $Z = 2.0$	5(P=0.	· ·								
1.4.13 Ozone		3								
León fernández et al. 2016	39	3	30	52	2	30	32.2%	-5.03 [-6.09, -3.97]	•	
Subtoal (95% CI)	39	5	30	32	2	30	32.2%	-5.03 [-6.09, -3.97]		
Heterogeneity: Not applicable	•									
Test for overall effect: $Z = 9.3$		00001)								
Total (95% CI)			80			76	100.0%	-2.03 [-4.22, 0.16]	•	
Heterogineity: Tau ² = 3.60; C	hi² = 58.3	32, df =	2(P < 0)	0.00001), $I^2 =$	97%				
Test for overall effect: $Z = 1.8$									-10 -5 0 5 10	
Test for subgroup differences	: Chi ² = 5	58.32, d	f = 2 (P	< 0.000	01), I ²	= 96.69	6		Favours (experimental) Favours (control)	
Risk of bias legend									· · · · · ·	
(A) Random sequence genera			bias)							
(B) Allocation concealment (
(C) Blinding of participants a			performa	ance bia	s)					
(D) Blinding of outcome data (E) In complete systems data										
(E) Incomplete outcome data	·									
(F) Selective reporting (repor (G) Other biases	ting bias)								

Figure 7: NO.

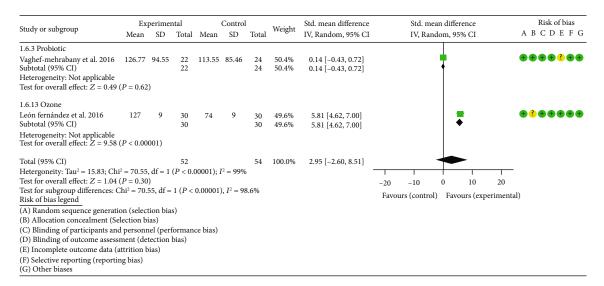
4.5.8. Vitamin E and Conjugated Linoleic Acids. Three RCTs utilized vitamin E to treat RA. Edmonds et al. 1997 reported adverse events; Wittenborg et al. 1998 reported VAS and adverse events; Aryaeian et al. 2009 reported VAS, ESR, CRP, DAS28, number of tender joints, and number of swollen joints. The summary results showed that the difference of adverse events and VAS between two groups was of no statistical significance (adverse events (RR 1.10, 95% CI 0.74 to

1.65, P = 0.64; VAS (SMD -0.02, 95% CI -0.04 to 0.36, P = 0.93)) (Figures 11 and 15).

Aryaeian et al. 2009 uses vitamin E alone and in combination with conjugated linoleic acids to intervene in RA patients. It showed that when conjugated linoleic acids were used alone, number of tender joints, number of swollen joints, and DAS28 were improved (P < 0.05) (Figures 12– 14), but VAS, ESR, and CRP were not significantly improved

Ci. 1	Ex	perime	ntal		Contro	ol	147.1.1.4	Std. mean difference	Std. mean difference	Risk of bias
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFO
1.5.3 Probiotic										
Vaghef-mehrabany et al. 2016 Subtotal (95% CI)	37.23	3.24	22 22	37.25	4.75	24 24	28.1% 28.1%	-0.00 [-0.58, 0.57] -0.00 [-0.58, 0.57]	*	
Heterogeneity: Not applicable										
Test for overall effect: $Z = 0.02$	P = 0.	99)								
1.5.4 Pomegranate extract										
Ghavipour et al. 2016	165.7	30.12	30	151.1	21.3	25	32.2%	0.54 [0.00, 1.08]	T	$\oplus \oplus \oplus \oplus \oplus \bigcirc \bigcirc \oplus \oplus$
Subtotal (95% CI)			30			25	32.2%	0.54 [0.00, 1.08]	•	
Heterogeneity: Not applicable Test for overall effect: $Z = 1.97$		05)								
1.5.13 Alpha-lipoic acid										
Mirtaheri et al. 2015	6,062	965	33	5,926	688	32	39.7%	0.16 [-0.33, 0.65]		
Subtotal (95% CI)	0,002	705	33	5,720	000	32	39.7%	0.16 [-0.33, 0.65]	*	
Heterogeneity: Not applicable										
Test for overall effect: $Z = 0.64$	P = 0.	05)								
Total (95% CI)			85			81	100.0%	0.24 [-0.07, 0.54]	•	
Hetergoneity: Tau ² = 0.00; Chi			(P = 0.3)	37); $I^2 =$	0%					
Test for overall effect: $Z = 1.51$	·								-4 -2 0 2 4	
Test for subgroup differences: Risk of bias legend	Chi ² = 2	2.00, df =	= 2 (P =	= 0.37),	$I^2 = 0\%$	ó			Favours (control) Favours (experimental)
(A) Random sequence generat			ias)							
(B) Allocation concealment (S										
 (C) Blinding of participants ar (D) Blinding of outcome asses 				ance Dia	is)					
 (E) Incomplete outcome data (
(F) Selective reporting (report (G) Other biases	·									

FIGURE 8: GPx.





(P > 0.05) (Figures 15, 17, and 18). When conjugated linoleic acids were combined with vitamin E, number of swollen joints, VAS, and DAS28 were improved (P < 0.05) (Figures 13–15), but number of tender joints, ESR, and CRP were not significantly improved (P > 0.05) (Figures 13, 17, and 18).

4.5.9. Selenium. Four RCTs utilized selenium to treat RA. Tarp et al. 1986 reported the number of swollen joints and ESR; Peretz et al. 1992 reported VAS and ESR; Peretz et al. 2001 reported number of swollen joints, CRP, ESR, and VAS; Heinle et al. 1997 reported number of tender joints, number of swollen joints, and CRP. The summary results showed that the difference of number of swollen joints,

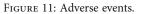
ESR, and CRP between the two groups was of no statistical significance (number of swollen joints (WMD 0.04, 95% CI -1.43 to 1.51, P = 0.96), ESR (WMD -6.69, 95% CI -14.50 to 1.11, P = 0.09), and CRP (WMD -8.84, 95% CI -17.84 to 0.16, P = 0.05)) (Figures 12, 17, and 18). The data representation of the VAS in Peretz et al. 1992 is median (interquartile range), and the results showed that compared with the control group, the VAS in the experimental group decreased (P < 0.05). However, the difference of VAS in Peretz et al. 2001 between two groups was of no statistical significance (P > 0.05) (Figure 15). Heinle et al. 1997 also showed that the difference of number of tender joints between two groups was of no statistical significance (P > 0.05) (Figure 13).

C4 d	Ex	perimei	ntal		Control		Weight	Std. mean difference	Std. mean difference	Risk of bias
Study or subgroup	Mean	SD	Total	Mean	SD	Total	weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFO
1.7.3 Probiotic										
Zamani et al.2017	696.9	151.7	27	643.8	208.5	27	34.0%	0.29 [-0.25, 0.82]	•	$\bullet \bullet $
Subtotal (95% CI)			27			27	34.0%	0.29 [-0.25, 0.82]	•	
Heterogeneity: Not applicabl	le									
Test for overall effect: $Z = 1.0$	05 (P = 0	0.29)								
1.7.12 Vitamins A, E and C										
Jaswal et al.2003	1.84	0.16	20	1.41	0.15	20	33.1%	2.72 [1.84, 3.60]		<mark>??+++++</mark>
Subtotal (95% CI)			20			20	33.1%	2.72 [1.84, 3.60]	•	
Heterogeneity: Not applicabl										
Test for overall effect: $Z = 6.0$	04 (P < 0	0.00001)								
1.7.13 Ozone										
Leon fernandez et al.2016	155	10	30	110	10	30	32.9%	4.44 [3.48, 5.41]		$\oplus \bigcirc \oplus \oplus$
Subtotal (95% CI)			30			30	32.9%	4.44 [3.48, 5.41]	•	
Heterogeneity: Not applicabl										
Test for overall effect: $Z = 9.0$	02 (P < 0	0.00001)								
Total (95% CI)			77			77	100.0%	2.46 [-0.06, 4.98]	◆	
Heterogeneity: Tau ² = 4.79; C	$Chi^2 = 62$	2.47, df =	= 2 (p <	0.0000	1); $I^2 = 9$	97%				_
Test for overall effect: $Z = 1.9$									-20 -10 0 10 20	
Test for subgroup differences	s: Chi² =	62.47, d	f = 2 (p	0.00	$001); I^2$	= 96.8%	Ď		Favours (experimental) Favours (control))
Risk of bias legend										
(A) Random sequence gener	ation (se	election	bias)							
(B) Allocation concealment			,							
(C) Blinding of participants :					as)					
(D) Blinding of outcome asso (E) Incomplete outcome data			on bias)						

(F) Selective reporting (reporting bias) (G) Other biases

FIGURE 10: GSH.

Study or subgroup	Ex Events	perime Total	ntal Events	Control Total	Weight	Risk ratio M-H, Random,95% CI	Risk ratio M-H, Random,95% CI	Risk of bias A B C D E F G
2.1.1 N-Acetylcysteine								
Batooei et al. 2018	3	27	2	24	5.2%	1.33 [0.24, 7.32]		$\oplus \oplus \oplus \oplus \oplus \oplus \oplus \oplus \oplus$
Subtotal (95% CI)		27		24	5.2%	1.33 [0.24, 7.32]		
Totalevents	3		2					
Heterogeneity: Not applica	ble							
Test for overall effects: $Z =$	0.33 (<i>p</i> = 0.7	74)						
2.1.9 Vitamin E								
Edmonds et al. 1997	5	20	7	22	15.9%	0.79 [0.30, 2.08]		
Wittenborg et al. 1998	22	42	19	43	77.1%	1.109 [0.74, 1.85]		<u>• • • • • • • •</u>
Subtotal (95% CI)		62		65	93.0%	1.10 [0.74, 1.65]	\bullet	
Totalevents	27		26					
Heterogeneity: Tau ² = 0.00 , Test for overall effects: $Z =$			<i>p</i> = 0.45): $I^2 = 0\%$	5			
2.1.11 Spa therapy								
Karagulle et al. 2017	3	15	0	22	1.8%	10.06 [0.56, 181.72]		
Subtotal (95% CI)		15		22	1.8%	10.06 [0.56, 181.72]		
Totalevents	3		0					
Heterogeneity: Not applica Test for overall effects: $Z =$		2)						
Total (95% CI)		104		111	100.0%	1.16 [0.79, 1.71]		
Totalevents	33	104	28	111	100.070	1.10 [0.79, 1.71]	ľ	
Heterogeneity: $Tau^2 = 0.00$ Test for overall effects: $Z =$; Chi ² = 2.88,): $I^2 = 0\%$	6	0.001	0.1 1 10	1000
Test for subgroupdifference	-1		(p = 0.33)	3): $I^2 = 10^{-3}$	0.0%			
Risk of bias legend						Favou	rs (experimental) Favours (cor	itrol)
(A) Random sequence gen (B) Allocation concealmen (c) Blinding of participants (D) Blinding of outcome as (E) Incomplete outcome da (F) Selective reporting (rep (G) Other biases	t (selection b s and personr ssessment (de ata (attrition	vias) nel (perf etection	formance	e bias)				



4.5.10. Spa Therapy. Only one RCT utilized spa therapy to treat RA. Karagülle et al. 2017 assessed the VAS, HAQ, DAS28, number of tender joints, number of swollen joints, MDA, SOD, and adverse events. The summary results showed that the difference of MDA, SOD, and adverse events between two groups was of no statistical significance (MDA (SMD 0.44, 95% CI -0.22 to 1.11, P = 0.19), SOD (SMD 0.28, 95% CI -0.08 to 0.95, P = 0.10), and adverse

Study or subgroup	Exj Mean	perime SD		Mean	Contro SD	l Total	Weight	Mean difference IV, Random, 95% (fference m, 95% CI	Risk of bias A B C D E F G
2.2.1 N-acetylcystein Batooei et al. 2018 Subtotal (95% CI) Heterogeneity: Not a Test for overall effect	6.3 pplicable		27 27 0.59)	7.1	5.5	24 24	4.9% 4.9%	-0.80 [-3.67, 2.07 -0.80 [-3.67, 2.07		-	•••••
2.24 Pomergranate e Ghavipour et al. 2010 Subtotal (95% CI) Heterogeneity: Not a Test for overall effect	6 3.1 applicable		30 30 0.05)	4.48	3.06	25 25		-1.38 [-2.75, -0.0] -1.38 [-2.75, -0.0]			⊕⊕⊕⊕€€
2.26 Resveratrol Khojah et al. 2018 Subtotal (95% CI) Hetrogeneity: Not ap Test for overall effect		1.1 08 (P <	50 50 0.000	4.1 01)	1.5	50 50		-1.60 [-2.12, -1.08 -1.60 [-2.12, -1.08			? ?●●●●
2.2.7 Garlic tablets Moosavian et al. 202 Subtotal (95% CI) Heterogeneity: Not a Test for overall effect	pplicable		31 31 0.29)	1.71	2.34	31 31	23.3% 23.3%	-0.52 [-1.48, 0.44 -0.52 [-1.48, 0.44		I	••••
2.2.8 Conjugated line Aryaeian et al. 2009a Subtotal (95% CI) Heterogeneity: Not a Test for overall effect	ı −6.63 applicable	7.74 e	22	-1.05	7.74	7 7	1.0% 1.0%	-5.58 [-12.16, 1.00 -5.58 [-12.16, 1.00		-	⊕ € € € ⊕ ⊕ ⊕
2.2.9 Conjugated line Aryaeian et al. 2009b Subtotal (95% CI) Heterogeneity: Not a Test for overall effect	9 –4.55 opplicable	5.39 e	22 22	-1.05	7.74	8 8	1.3% 1.3%	-3.50 [-9.32, 2.32 -3.50 [-9.32, 2.32		-	⊕ € € € ⊕ ⊕ ⊕
2.2.10 Vitamin E Aryaeian et al. 2009c Subtotal (95% CI) Heterogeneity: Not a Test for overall effect	pplicable	e	21	-1.05	7.74	7 7	0.9% 0.9%	-1.57 [-8.71, 5.57 -1.57 [-8.71, 5.57		_ ►	⊕ € € € ⊕ ⊕ ⊕
2.2.11 Selenium Tarp et al. 1986 Peretz et al. 2001 Heinle et al. 1997 Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect	= 0.00; C			7.4 10 23.8 f = 2 (F	2.8 7 15.2 P = 0.77	20 27 35 82 $I^2 =$	11.5% 3.9% 0.9% 16.3% 0%	0.30 [-1.40, 2.00] -1.00 [-4.23, 2.23 0.57 [-6.34, 7.48] 0.04 [-1.43, 1.51]]	-	00000000000000000000000000000000000000
2.2.12 Spa therapy Karagulle et al. 2017 Subtotal (95% CI) Heterogeneity: Not a Test for overall effect			15	14.64	11.47	22 22		-6.64 [-12.11, -1.1 -6.64 [-12.11, -1.1			€€??⊕₽₽
Total (95% CI) Heterogeneity: Tau ² Test for overall effect Test for overall effect Risk of bias legend (A) Random sequenc (B) Allocation conce (C) Blinding of parti (D) Blinding of outco (E) Incomplete outco (F) Selective reportin (G) Other biases	Z = 3.3 :: Chi ² = ce genera alment (cipants a ome asse ome data	P = 12.99, ation (selection and peressmen (attrit	0.000 df = 8 selection on bia rsonne t (dete ion bia	($P = 0$) ($P = 0$) on bias s) el (perfection t	.11), <i>I</i> ²) ormano	.20); I ⁴ = 38.4	² = 26%	–1.15 [–1.82, –0.48 Fa	3] -20-10 (avours (experimental)		

FIGURE 12: Number of swollen joints.

events (RR 1.16, 95% CI 0.79 to 1.71, P = 0.45)) (Figures 4, 5, and 11). It also showed the number of swollen joints (P < 0.05) (Figure 12), while the difference of number of tender joints, DAS28, VAS, and HAQ between two groups was of no statistical significance (P > 0.05) (Figures 13–16).

4.5.11. Vitamins A, E, and C Combination. Only one RCT utilized vitamins A, E, and C combination to treat RA. Jas-wal et al. 2003 assessed the MDA and GSH. The summary

results showed that the MDA in the experiment group was lower (SMD -3.67, 95% CI -4.71 to -2.62, P < 0.00001) (Figure 4), while the GSH in the experiment group was higher (SMD 2.72, 95% CI 1.84 to 3.60, P < 0.00001) (Figure 10).

4.5.12. Ozone. Only one RCT utilized ozone to treat RA. León Fernández et al. 2016 assessed the DAS28, HAQ, CRP, ESR, MDA, NO, GSH, SOD, and CAT. The summary

	Exp	erime	ental	(Contro	ol	147 * 1 4	Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mear	n SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	A B C D E F G
2.1.1 N-acetylcysteine Batooei et al. 2018 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect:	6.9 pplicabl		27 27 = 0.71)	7.6	7.5	24 24	2.9% 2.9%	-0.70 [-4.35, 2.95] -0.70 [-4.35, 2.95]	•	•••••
2.14 Pomegranate ext Ghavipour et al. 2016 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect:	ract 3.7 oplicabl	3.21 e	30 30	7.9	6.01	25 25	5.5% 5.5%	-4.20 [-6.82, -1.58] -4.20 [-6.82, -1.58]	*	€€€€?€€
2.1.6 Resveratrol Khojah et al. 2018 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect:			50 50 < 0.0000	5.7 01)	2.1	50 50	67.7% 67.7%	-2.60 [-3.35, -1.85] -2.60 [-3.35, -1.85]	,	??
2.1.7 Garlic tablets Moosavian et al. 2020 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect:	plicabl	e	31 31 = 0.07)	5.55	4.5	31 31	8.4% 8.4%	-1.94 [-4.07, 0.19] -1.94 [-4.07, 0.19]		⊕ ⊕ ⊕ ⊕ ⊕ ⊕ ⊕
2.1.8 Conjugated lino Aryaein et al. 2009a Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect:	leic acio –5.13 oplicabl	ds 6.34 e	22 22	-0.68	2.34	7 7	3.8% 3.8%	-4.45 [-7.62, -1.28] -4.45 [-7.62, -1.28]	•	⊕ € ? ? ⊕ ⊕ ⊕
2.1.9 Conjugated lino Aryaein et al. 2009b Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect:	-2.46 pplicabl	4.83 e	22 22	-0.68	2.34	8 8	5.7% 5.7%	-1.78 [-4.37, 0.81] -1.78 [-4.37, 0.81]	•	••••
2.1.10 Vitamin E Aryaein et al. 2009c Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect:		e	21 21 = 0.69)	-0.68	2.34	7 7	4.1% 4.1%	-0.61 [-3.65, 2.43] -0.61 [-3.65, 2.43]	•	••••
2.1.11 Selenium Heinle et al. 1997 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect:			35 35 = 0.62)	20	10.3	35 35	1.7% 1.7%	-1.20 [-5.89, 3.49] -1.20 [-5.89, 3.49]	•	€€\$\$\$
2.1.12 Spa therapy Karagulle et al. 2017 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect:	plicabl		15	36.14	23.09	22 22	0.2% 0.2%	-6.54 [-20.17, 7.09] -6.54 [-20.17, 7.09]	•	€€??₽€€
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diff Risk of bias legend (A) Random sequence (B) Allocation concea (C) Blinding of partici (D) Blinding of outco (E) Incomplete outcon (F) Selective reporting (G) Other biases	Z = 7.9 erences e gener llment (pants a me asso me data	96 (P < s: Chi ² ation ((selection and per assmer a (attri	< 0.0000 = 6.76, (selection ion bias rsonnel nt (dete tion bias	01) df = 8 (on bias) s) (perfor ction bi	p = 0.5 mance	6); I ² =		-2.50 [-3.12, -1.89] Favours	-20-10 0 10 20 (experimental) Favours (control)	

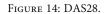
FIGURE 13: Number of tender joints.

results showed that the MDA, NO, DAS28, HAQ, and ESR in the experiment group were lower (SOD (SMD -2.47, 95% CI -4.71 to -2.62, P < 0.00001), NO (SMD -5.03, 95% CI -6.09 to -3.97, P < 0.00001), DAS28 (WMD -2.00, 95% CI -2.83 to -1.17, P < 0.00001), HAQ (SMD -1.01, 95% CI -1.55 to -0.47, P = 0.0002), and ESR (WMD -20.00, 95% CI -34.13 to -5.87, P = 0.006)) (Figures 4, 7, 14, 16, and 17), while the GSH and CAT in the experiment group were higher (GSH (SMD 4.44, 95% CI 3.48 to 5.41, P < 0.00001); CAT (SMD

5.81, 95% CI 4.62 to 7.00, P < 0.00001)) (Figures 9 and 10). The difference of SOD and CRP was of no statistical significance (SOD (SMD 0.44, 95% CI -0.08 to 0.95, P = 0.10); CRP (WMD -8.00, 95% CI -16.08 to 0.08, P = 0.05)) (Figures 6 and 18).

4.5.13. H_2 -Saline. Only one RCT utilized H_2 -saline to treat RA. Ishibashi et al. 2014 reported DAS28, CRP, TNF- α , and IL6. Their study found that H_2 -saline may improve

Study or subgroup	Experi	mental D Total		Contro		Weight	Mean Difference IV, Random, 95% CI	Mean Difference	Risk of Bias
2.3.1 N-acetylcysteine Batooei et al. 2018 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z	4.35 1. licable	2 27 27	4.7	1.5	24 24	7.4% 7.4%	-0.35 [-1.10, 0.40] -0.35 [-1.10, 0.40]	IV, Random, 95% CI	
2.3.2 CoQ10 Abdollahzad et al. 2015 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z	licable	22		1.36	22 22	8.2% 8.2%	-1.70 [-2.34, -1.06] -1.70 [-2.34, -1.06]	•	***
P 2.3.3 Probiotic Zamani et al. 2017 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z		27	3.2	1.1	27 27	9.2% 9.2%	-0.60 [-1.09, -0.11] -0.60 [-1.09, -0.11]	•	*****
2.3.4 Pomegranate extra Ghavipour et al. 2016 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z	4 0. licable	30	4.8	1.36	25 25	8.4% 8.4%	-0.80 [-1.41, -0.19] -0.80 [-1.41, -0.19]	•	*** ***
2.3.5 Quercetin Javadi et al. 2017 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z		20	3.11	1.29	20 20	7.7% 7.7%	-0.46 [-1.17, -0.25] -0.46 [-1.17, -0.25]	•	€€€€€€
2.3.6 Resveratrol Khojah et al. 2018 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z		50	4.78	0.87	50 50	10.3% 10.3%	-1.66 [-1.99, -1.33] -1.66 [-1.99, -1.33]	∓ ♦	••••••
2.3.7 Garlic tablets Moosavian et al. 2020 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z	licable	31 31 31 0.002)	4.45	0.86	31 31	9.8% 9.8%	-0.65 [-1.07, -0.23] -0.65 [-1.07, -0.23]	•	******
2.3.8 Conjugated linole: Aryaein et al. 2009a Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z	–1.93 1.1 licable	22	-0.31	0.98	7 7	6.4% 6.4%	-1.62 [-2.52, -0.72] -1.62 [-2.52, -0.72]	*	***
2.3.9 Conjugated linole: Aryaein et al. 2009a Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z	-1.8 1.0 licable	02 22 22	-0.31	0.98	8 8	7.0% 7.0%	-1.49 [-2.29, -0.69] -1.49 [-2.29, -0.69]	*	***
2.3.10 Vitamin E Aryaein et al. 2009a Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z		21	-0.31	0.98	7 7	6.9% 6.9%	-0.46 [-1.28, -0.36] -0.46 [-1.28, -0.36]	•	***
2.3.12 Spa therapy Karagulle et al. 2017 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z		15	5.34	1.75	22 22	5.8% 5.8%	-0.10 [-1.09, -0.89] -0.10 [-1.09, -0.89]	•	⊕⊕??⊕⊕⊕
2.3.14 Ozone Leon fernandez et al. 20 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z	licable	30	5.2	1.64	30 30	6.8% 6.8%	-2.00 [-2.83, -1.17] -2.00 [-2.83, -1.17]	→	⊕?⊕⊕⊕⊕⊕
2.3.15 H2-saline Ishibashi et al. 2014 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: Z	licable	22 10 10 0.005)	5.1	0.9	10 10	6.1% 6.1%	-1.36 [-2.30, -0.42] -1.36 [-2.30, -0.42]	•	<mark>€€⊕⊕⊕⊕</mark>
Total (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup differ Risk of bias legend (A) Random sequence [(B) Allocation conceali (c) Blinding of particip; (D) Blinding of outcom (E) Incomplete outcom (F) Selective reporting	C = 5.86 (P < ences: Chi2 = generation (snent (selection)ants and persue assessmente data (attritic)	0.00001) 44.22, d election on bias) onnel (p (detecti on bias)	lf = 12 (bias) erforma on bias)	p < 0.	01); I ² 0001); ias)		-1.02 [-1.37, -0 <u>.68]</u> % Favours (-4 -2 0 2 4 (experimental) Favours (co	ntrol)



the clinical symptoms of RA patients (decreased DAS28) (P < 0.05) (Figure 14), while it has no obvious improvement effect on CRP (P > 0.05) (Figure 18). The indicators of TNF- α and IL6 could not be extracted, but the author reported that there was no significant change between the two compared with the placebo group (P > 0.05).

4.5.14. Alpha-Lipoic Acid. Two RCTs utilized alpha-lipoic acid to treat RA. Mirtaheri et al. 2015 reported SOD, TAC, GPx, TNF- α , IL6, and CRP; Bae et al. 2009 reported CRP, TNF- α , and IL6. The summary results showed that the difference of TNF- α between two groups was of no statistical significance (SMD 0.09, 95% CI -0.36 to 0.55, P = 0.69).

Study or subgroup	Ez	kperimei	ntal		Control		Weight	Std. Mean Difference	Std. Mean Difference	Risk of Bias
study of subgroup	Mean	SD	Total	Mean	SD	Total	weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
2.5.1 N-acetylcysteine Batooei et al. 2018 Subtotal (95% CI)	50	7.8	27 27	66.9	19.4	24 24	9.6% 9.6%	-1.15 [-1.75, -0.55] -1.15 [-1.75, -0.55]		••••
Heterogeneity: Not applie Test for overall effect: Z =	cable = 3.78 (P =	= 0.0002)							
2.5.2 CoQ10 Abdollahzad et al. 2015 Subtotal (95% CI)	7.05	10.54	22 22	48.86	23.09	22 22	8.1% 8.1%	-2.29 [-3.06, -1.51] -2.29 [-3.06, -1.51]	•	
Heterogeneity: Not applie Test for overall effect: Z =		= 0.0000	1)							
2.5.3 Probiotic										
Zamani et al. 2017	27	15.6	27	35.9	26.8	27	10.1%	-0.40 [-0.94, 0.14]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Subtotal (95% CI) Heterogeneity: Not applie Test for overall effect: Z =		= 0.15)	27			27	10.1%	-0.40 [-0.94, 0.14]		
2.5.5 Quercetin										
Javadi et al. 2017 Subtotal (95% CI)	21.45	15.88	20 20	40.25	27	20 20	9.2% 9.2%	-0.83 [-1.48, -0.18] -0.83 [-1.48, -0.18]	•	$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Heterogeneity: Not applie			20			20	51270	0.05 [1110, 0.10]	-	
Test for overall effect: Z =	= 2.51(<i>P</i> =	= 0.01)								
2.5.7 Garlic tablets Moosavian et al. 2020	59.35	13.3	31	69.19	18.4	31	10.4%	-0.61 [-1.12, -0.10]		
Subtotal (95% CI)		15.5	31	09.19	10.4	31	10.4%	-0.61 [-1.12, -0.10]	•	
Heterogeneity: Not applie Test for overall effect: Z =		= 0.02)								
2.5.8 Conjugated linoleic		,								
Aryaein et al. 2009a		20.21	22	-7.73	33.08	7	7.4%	-0.64 [-1.51, 0.23]		⊕ ⊕ € ? ? ⊕ ⊕
Subtotal (95% CI) Heterogeneity: Not applie	cable		22			7	7.4%	-0.64 [-1.51, 0.23]		
Test for overall effect: $Z =$		= 0.15)								
2.5.9 Conjugated linoleic	acids +Vi	it E								
Aryaein et al. 2009b Subtotal (95% CI)	-40.23	34.14	22 22	-7.73	33.08	8 8	7.5% 7.5%	-0.93 [-1.78, 0.09] -0.93 [-1.78, 0.09]	•	⊕ ? ? ? ⊕ ⊕ ⊕
Heterogeneity: Not applie										
Test for overall effect: Z =	= 2.16 (P =	= 0.03)								
2.5.10 Vitamin E Wittenborg et al. 1998	4.9	3	42	5	2.6	43	11.1%	-0.04 [-0.46, 0.39]	<u> </u>	•••••
Aryaein et al. 2009c	-6.43		21	-7.73	33.08	7	7.5%	-0.06 [-0.80, 0.91]	<u> </u>	••••
Subtotal (95% CI) Heterogeneity: Tau ² = 0.0	00; Chi ² =	0.04, df	63 = 1 (p =	= 0.85); 1	$I^2 = 0\%$	50	18.6%	-0.02 [-0.40, -0.36]		
Test for overall effect: Z =	= 0.09 (P =	= 0.93)								
2.5.11 Selenium										
Peretz et al. 2001 Subtotal (95% CI)	35	23	28 28	38	22	27 27	10.2% 10.2%	-0.13 [-0.66, -0.40] -0.13 [-0.66, -0.40]	•	3 3 3 4 4 4
Heterogeneity: Not applie Test for overall effect: Z =		= 0.63)								
2.5.12 Spa therapy Karagulle et al. 2017	34	19.77	15	50.27	29.94	22	9.0%	-0.60 [-1.28, -0.07]	-	
Subtotal (95% CI) Heterogeneity: Not applie	cable		15			22	9.0%	-0.60 [-1.28, -0.07]	•	
Test for overall effect: $Z =$		= 0.08)								
Total (95% CI)			277			238	100.0%	-0.66 [-1.02, -0.31]	◆	
Heterogeneity: $Tau^2 = 0.2$ Test for overall effect: Z =				<i>p</i> = 0.00	01); $I^2 =$	71%			-4 -2 0 2 4	-
Test for subgroup differen				(<i>p</i> < 0.0	0001); I ²	= 74.3%			Favours (experimental) Favours (control)	
Risk of bias legend (A) Random sequence ge	neration	(selection	n bias)							
(B) Allocation concealme	ent (select	ion bias))	man 1	iac)					
(c) Blinding of participan(D) Blinding of outcome	assessmen	nt (detec	tion bia	mance b as)	ias)					
(E) Incomplete outcome (F) Selective reporting (re			5)							
(G) Other biases	-roning t									

FIGURE 15: VAS.

The data representation of the CRP in Mirtaheri et al. 2015 and Bae et al. 2009 is median (interquartile range), and both two RCTs showed that the results showed that the difference of CRP between the experimental group and the control group was of no statistical significance (P > 0.05). The data representation of the IL6 in Mirtaheri et al. 2015 is also median (interquartile range), but both two RCTs reported that the difference of IL6 between the experimental group and the control group was of no statistical significance (P > 0.05) (Figure 20). Mirtaheri et al. 2015 also showed that the difference of SOD, TAC, and GPx between two groups was of no statistical significance (TAC (SMD 0.44, 95% CI

Ci. 1 1	Ex	perime	ental	Control			X47. 1. 1. 4	Std. mean difference	Std. mean difference	Risk of bias
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
2.4.1 N-acetylcysteine										
Batooei et al. 2018 Subtotal (95% CI)	13.9	9.6	27	24.1	14	24 24	16.5% 16.5%	-0.85 [-1.42, -0.27] -0.85 [-1.42, -0.27]	→	++++++++++++++++++++++++++++++++++++
Heterogeneity: Not applicab Test for overall effect: $Z = 2$.		.004)								
2.4.4 Pomegranate extract Ghavipour et al. 2016 Subtotal (95% CI)	0.8	0.63	30 30	1.2	0.88	25 25	18.7% 18.7%	-0.52 [-1.06, -0.02] -0.52 [-1.06, -0.02]	-	€€€€?€€
Heterogeneity: Not applicab Test for overall effect: $Z = 1$.		06)								
2.4.5 Quercetin										
Javadi et al. 2017 Subtotal (95% CI)	0.35	0.28	20 20	0.68	0.41	20 20	12.7% 12.7%	-0.92 [-1.58, -0.27] -0.92 [-1.58, -0.27]		+++++ +++++++++++++++++++++++++++++++
Heterogeneity: Not applicab Test for overall effect: $Z = 2$.		.006)	20				120,70			
2.4.7 Garlic tablets										
Moosavian et al. 2020 Subtotal (95% CI)	0.5	0.3	31 31	0.7	0.4	31 31	21.2 21.2	-0.56 [-1.07, -0.05] -0.56 [-1.07, -0.05]	- ♦	+++++ ++
Heterogeneity: Not applicab Test for overall effect: $Z = 2$.		.03)								
2.4.12 Spa therapy										
Karagulle et al. 2017 Subtotal (95% CI)	0.79	0.64	15 15	1.23	0.75	22 22	12.1% 12.1%	-0.61 [-1.28, -0.06] -0.61 [-1.28, -0.06]	− ♦	
Heterogeneity: Not applicab Test for overall effect: $Z = 1$.		.08)								
2.4.14 Ozone										
Leon fernandez et al. 2016 Subtotal (95% CI)	0.7	0.06	30 30	1.1	0.55	30 30	18.8% 18.8%	-1.01 [-1.55, -0.47] -1.01 [-1.55, -0.47]	- ◆	⊕?⊕⊕⊕⊕⊕
Heterogeneity: Not applicab Test for overall effect: $Z = 3$.		.0002)				50		-1.01 [-1.55, -0.47]		
Total (95% CI)			153			152	100.0%	-0.74 [-0.97, -0.50]	•	
Heterogeneity: $Tau^2 = 0.00$; Test for overall effect: $Z = 6$				0.76); I ²	= 0%			-	-10 -5 0 5 10	_
Test for subgroup difference				= 0.76),	$I^{2} = 09$	6		Fav	vours (experimental) Favours (control)	
Risk of bias legend (A) Random sequence gene	ration (sel	ection	bias)							
(B) Allocation concealment	(selection	bias)								
(C) Blinding of participants					ıs)					
 (D) Blinding of outcome ass (E) Incomplete outcome dat 			on dias)							
(F) Selective reporting (repo										
(G) Other biases										

FIGURE 16: HAQ.

-0.06 to 0.93, P = 0.08), SOD (SMD -0.11, 95% CI -0.59 to 0.38, P = 0.66), and GPx (SMD 0.16, 95% CI -0.33 to 0.65, P = 0.52)) (Figures 5, 6, and 8).

4.6. Publication Bias of Outcomes. Finally, there are 10 outcomes with more than 5 RCTs: MDA, TAC, number of tender joints, number of swollen joints, DAS28, VAS, HAQ, ESR, CRP, and TNF- α . (1) For the oxidative stress index, the publication bias detection showed that the RCTs included in MDA may have publication bias (P = 0.094)(Figure 21(a)), while the that in TAC may not have publication bias (P = 0.329) (Figure 21(b)). (2) For clinical efficacy indexes, the publication bias detection showed that the RCTs may have publication bias (number of tender joints: P =0.793, number of swollen joints: P = 0.791, DAS28: P =0.476, HAQ: P = 0.66, and VAS: P = 0.126) (Figure 22). (3) For inflammation indexes, the publication bias detection showed that the RCTs included in ESR and CRP may have publication bias (ESR: P = 0.064; CRP: P = 0.014) (Figures 23(a) and 23(b)), while that in TNF- α may not have publication bias (P = 0.351) (Figure 23(b)).

5. Discussion

5.1. Summary of Main Outcomes. A total of 24 RCTs (28 records) and 1277 participants were included. The time span of RCTs is from 1986 to 2020. These RCTs involve 16 types of antioxidants or antioxidant therapies, and these therapies have varying degrees of improvement on oxidative stress in RA patients. (1) N-acetylcysteine: it may reduce the MDA and NO levels in RA patients, and the addition of Nacetylcysteine to conventional therapy will not increase the occurrence of adverse events. Meanwhile, it may relieve pain and improve the quality of life of patients (reduce VAS and HAQ). (2) Coenzyme Q10: it may reduce the MDA, ESR, and TNF- α in RA patients, and the addition of coenzyme Q10 to conventional therapy will not increase the occurrence of adverse events. Meanwhile, it may relieve pain and improve the patient's condition (reduce VAS and DAS28). Whether it can reduce IL6 is still inconclusive. (3) Probiotics: it may reduce the MDA and CRP levels and improve the patient's condition (reduce DAS28). It has not been observed to improve TAC, SOD, GPx, and CAT. (4) Pomegranate extract: interestingly, the MDA in

Study or subgroup	Exp Mean	erimen SD		Mean	Control SD	Total	Weight	Mean Differen IV, Random, 959		Mean Differer IV, Random, 95	Risk of Bias A BC D E F C
3.1.1 N-acetylcysteine Hashemi et al. 2019 Batooei et al. 2018 Subtotal (95% CI)	21.39 25.2	3.9 19.8	23 27 50	22.21 27.8	2.73 23.7	19 24 43	11.0% 6.0% 17.0%	-0.82 [-2.83, 1.0 -2.60 [-14.67, 9 -0.87 [-2.87, 1.1	.47]		++++++++++++++++++++++++++++++++++++++
Heterogeneity: $Tau^2 = 0.00$; Test for overall effect: $Z = 0$			= 1 (p	= 0.78)	$I^2 = 0\%$						
3.1.2 CoQ10 Abdollahzad et al. 2015 Zhu et al. 2020 Subtotal (95% CI) Heterogeneity: Tau ² = 0.00;	Chi ² = 0.	10.92 .06, df =		33.16		22 45 67	9.5%	-12.72 [-26.10, 0 -14.54 [-20.11, - -14.27 [-19.41, -	8.97]	•	₽???®®€ ₽₽₽₽₽€
Test for overall effect: $Z = 5$	5.44 (P <	0.00001	.)								
3.1.4 Pomegranate extract Ghavipour et al. 2016 Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: $Z = 2$	ble	15.64 0.03)	30 30	34.1	15.74	25 25	7.9% 7.9%	-9.40 [-17.73, -1 -9.40 [-17.73, -1		•	€€€€€€
3.1.5 Quercetin Javadi et al. 2017 Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: Z = 1		9.61 .25)	20 20	21.95	17.52	20 20	7.7% 7.7%	-5.10 [-13.86, 3 -5.10 [-13.86, 3		•	******
3.1.6 Resveratrol Khojah et al. 2018 Subtotal (95% CI) Heterogeneity: Not applica		9.7	50 50	41.7	20.4	50 50		-18.20 [-24.46, -1 -18.20 [-24.46, -1			<u>??●●⊕</u> ⊕€
Test for overall effect: $Z = 5$ 3.5.7 Garlic tablets	5.70 (P <	0.00001	.)								
Moosavian et al. 2020 Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: $Z = 0$			31 31	20.74	13.26	31 31	9.0% 9.0%	-1.71 [-8.23, 4.4 -1.71 [-8.23, 4.4		•	••••
3.1.8 Conjugated linoleic ad Aryaein et al. 2009a Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: Z = 1	cids 19.14 ble	10.94	22 22	27.04	18.95	7 7	4.9% 4.9%	-7.90 [-22.66, 6. -7.90 [-22.66, 6.		•	
3.1.9 Conjugated linoleic at Aryaein et al. 2009b Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: $Z = 1$	17.77 ble	12.2	22 22	27.04	18.95	8 8	5.1% 5.1%	-9.27 [-23.36, 4 -9.27 [-23.36, 4		•	•••••
3.1.10 Vitamin E Aryaein et al. 2009c Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: Z = 0			21 21	27.04	18.95	7 7	4.1% 4.1%	5.24 [-11.89, 22. 5.24 [-11.89, 22.		•	•••••
3.1.11 Selenium Tarp et al. 1986 Peretz et al. 1992 Peretz et al. 2001 Subtotal (95% CI)	44 28 30	33 12 20	20 8 28 56	46 35 38	31 13 23	20 7 27 54	3.3% 5.7% 6.3% 15.3%	-2.00 [-21.84, 17 -7.00 [-19.72, 5 -8.00 [-19.41, 3 -6.69 [-14.50, 1	.72] .41]	•	
Heterogeneity: $Tau^2 = 0.00$; Test for overall effect: $Z = 1$			= 2 (p	= 0.87)	; 1- = 0%						
3.1.14 Ozone Leon fernandez et al. 2016 Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: $Z = 2$	ble	21.91 0.006)	30 30	40	32.86	30 30		-20.00 [-34.13, - -20.00 [-34.13, -		•	€?₽₽₽₽€
Total (95% CI) Heterogeneity: Tau ² = 43.01 Test for overall effect. Z = 3 Test for subgroup differenc Risk of bias legend (A) Random sequence genn (B) Allocation concealmen (c) Blinding of participants (D) Blinding of outcome as (E) Incomplete outcome da (F) Selective reporting (rep	3.58 (P = es: Chi ² = eration (s t (selection seessment tata (attriti	0.0003) 53.96, election on bias) onnel (c (detection on bias)	df = 1 n bias) perfor tion bi	0 (<i>p</i> < 0	0.0001);		1%	-7.89 [-12.21, -3	-100	-50 0 experimental) Favo	п 00

FIGURE 17: ESR.

pomegranate extract was higher, which is different from the results of other supplements. It has not been observed to improve GPx. Meanwhile, it may also reduce inflammation and relieve the condition (reduce number of swollen joints, number of tender joints, DAS28, and ESR). (5) Quercetin: it may reduce the MDA level in RA patients. Meanwhile, it may relieve pain and improve the quality of life of patients (reduce VAS and HAQ). (6) Resveratrol: the results showed that it may alleviate the patient's condition (reduce number of swollen and tender joints and the DAS28) and improve

	Evi	arima	intal	(Contr	al		Mean difference	Mean difference	Risk of bias
Study or subgroup	-	perime SD		Mean			Weight	IV, Random, 95% CI	IV, Random, 95% CI	A B C D E F G
3.2.1 N-acetylcysteine Hashemi et al. 2019 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z		0.5 P = 0.5	23 23 58)	6.31	1.51	19 19	24.3% 24.3%	-0.20 [-0.91, 0.51] -0.20 [-0.91, 0.51]	•	*** **
3.2.2 CoQ10 Zhu et al. 2020 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z		5.92 P = 0.0	45 45 003)	13.08	6.61	45 45	6.8% 6.8%	-3.92 [-6.51, -1.33] -3.92 [-6.51, -1.33]		*****
3.2.3 Probiotic Zamani et al. 2017 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z	4.61 cable = 2.73 (2.71 P = 0.0	27 27 006)	8.47	6.82	27 27	6.2% 6.2%	-3.86 [-6.63, -1.09] -3.86 [-6.63, -1.09]	*	••••
3.2.4 Pomegranate extrac Ghavipour et al. 2016 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z	7.2 cable	4 P = 0.8	30 30 37)	7	4.88	25 25	7.7% 7.7%	0.20 [-2.19, 2.59] 0.20 [-2.19, 2.59]	+	**** ? * *
3.2.5 Quercetin Javadi et al. 2017 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z		2.34 P = 0.5	20 20 50)	2.69	2.41	20 20	14.4% 14.4%	-0.51 [-1.98, 0.96] -0.51 [-1.98, 0.96]	•	******
3.2.6 Resveratrol Khojah et al. 2018 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z		0.4 P < 0.0	50 50 0001)	2.6	0.7	50 50	29.8% 29.8%	-0.50 [-0.72, -0.28] -0.50 [-0.72, -0.28]	7	****
3.2.7 Garlic tablets Moosavian et al. 2020 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z	cable	10.58 P = 0.1	31	14.23	16.22	31 31	1.2% 1.2%	-5.61 [-12.43, 1.21] -5.61 [-12.43, 1.21]	•	******
3.2.8 Conjugated linoleic Aryaein et al. 2009a Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z	5.48 cable	5.6 P = 1.0	22 22 00)	5.48	5.6	7 7	2.4% 2.4%	0.00 [-4.76, 4.76] 0.00 [-4.76, 4.76]	•	••••
3.2.9 Conjugated linoleic Aryaein et al. 2009b Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z	3.17 cable	3.9	22 22 28)	5.48	5.6	8 8	3.0% 3.0%	-2.31 [-6.52, 1.90] -2.31 [-6.52, 1.90]	•	
3.2.10 Vitamin E Aryaein et al. 2009c Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z	4.76 cable	5.21	21 21	5.48	5.6	7 7	2.5% 2.5%	-0.72 [-5.43, 3.99] -0.72 [-5.43, 3.99]	•	
3.2.11 Selenium Peretz et al. 2001 Heinle et al. 1997 Subtotal (95% CI) Heterogeneity: Tau ² = 0.0 Test for overall effect: Z				29 26 1 (<i>p</i> = 0	24 37).48);	27 35 62 $I^2 = 0\%$	0.2% 0.7%	-11.00 [-21.82, -0.18] -4.00 [-20.21, 12.21] -8.84 [-17.84, 0.16]		*** *\$\$\$\$\$
3.2.14 Ozone Leon fernandez et al. 201 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z	cable		30 30 30)5)	13 2	1.91	30 30	0.9% 0.9%	-8.00 [-16.08, 0.08] -8.00 [-16.08, 0.08]	*	**** ***
3.2.15 H2-saline Ishibashi et al. 2014 Subtotal (95% CI) Heterogeneity: Not appli Test for overall effect: Z			10 10 14)	16 2	8.7%	10 10		-7.70 [-27.20, 11.80] -7.70 [-27.20, 11.80]		•••••
Total (95% CI) Test for subgroup differe Test for overall effect: Z Test for subgroup differe Risk of bias legend (A) Random sequence go (B) Allocation concealm (c) Blinding of participa (D) Blinding of participa (F) Selective reporting (r (G) Other biases	= 2.71 (nces: Cl eneratio ent (selents and assessin data (at	P = 0.0 $hi^2 = 2.0$ on (selection person nent (contraction)	007) 3.34, d ection bias) inel (p letection bias)	f = 12 (bias) erforma	p < 0	.03); I ² .02); I ²	= 45%	-1.06 [-1.83, -0.29] -	 ↓ −20 −10 0 10 20 vours (experimental) Favours (contr 	- ol)

FIGURE 18: CRP.

inflammation (reduce CRP, ESR, TNF- α , and IL6). (7) Garlic tablets: it may reduce the MDA level in RA patients and increase the TAC of RA patients. It may also relieve pain and improve the quality of life of patients (reduce VAS and HAQ) and reduce inflammation (reduce TNF- α). (8) Vitamin E and conjugated linoleic acids: whether conjugated linoleic acids were used alone (reduce the number of tender joints, number of swollen joints, and DAS28) or in combination with vitamin E (reduce number of swollen joints, VAS, and DAS28), it may improve the patient's condition.

Study or subgroup		operime			Contro		Weight	Std. Mean Difference		Risk of bias
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
3.3.1 N-aceticysteine										
Hashemi et al. 2019 Subtotal (95% CI)	2.57	0.53	23 23	2.77	0.88	19 19	15.0% 15.0%	-0.28 [-1.89, -1.33] -0.28 [-1.89, -1.33]	•	
Hetrogenity: Not applic Test for overall effect: Z		9 = 0.37)								
3.3.2 CoQ10										
Zhu et al. 2020	2.72	0.78	45	3.29	0.87	45	18.4%	-0.68 [-1.11, -1.26]	-	
Subtotal (95% CI)			45			45	18.4%	-0.68 [-1.11, -1.26]	•	
Hetrogenity: Not applic										
Test for overall effect: Z	= 3.15 (P	' = 0.002	.)							
3.3.5 Quercetin										
Bae et al. 2009a	3.32	1.32	6	3.44	1.75	5	7.5%	-0.07 [-1.26, -1.12]	—	• • • • • • •
Subtotal (95% CI) Hetrogenity: Not applic	abla		6			5	7.5%	-0.07 [-1.26, -1.12]		
Test for overall effect: Z		e = 0.91)								
3.3.6 Resveratrol										
Khojah et al. 2018	18.3	6.2	50	29.7	11.8	50	18.4%	-0.20 [-1.63, -0.77]	-	
Subtotal (95% CI)	10.5	0.2	50	29.7	11.0	50	18.4%	-0.20 [-1.63, -0.77]	•	
Hetrogenity: Not applic	able									
Test for overall effect: Z	= 5.51 (P	< 0.000	01)							
3.3.7 Garlic tablets										
Moosavian et al. 2020	19.04	13.67	31	32.1	23.8	31	16.8%	-0.66 [-1.18, -0.15]	-	
Subtotal (95% CI)			31			31	16.8%	-0.66 [-1.18, -0.15]	•	
Hetrogenity: Not applic Test for overall effect: Z		0.01)								
Test for overall effect: Z	= 2.54 (P	= 0.01)								
3.3.16 Alpha- lipic acid									\perp	
Mirtaheri et al. 2015 Bae et al. 2009b	4.67	2.42	33 5	4.4	2.3	32 4	17.3%	0.11 [-0.37, -0.60]		
Subtotal (95% CI)	3.33	1.41	5 38	3.44	1.75	36	6.5% 23.8%	-0.06 [-1.38, -0.25] 0.09 [-0.36, -0.55]		
Hetrogenity: Tau ² = 0.00	0; $Chi^2 = 0$	0.06, df	= 1 (P	= 0.81);	$I^{2} = 0$ %					
Test for overall effect: Z	=0.39 (P	= 0.69)								
Total (95% CI)			193			186	100.%	-0.49 [-0.89, -0.09]	•	
Hetrogenity: Tau ² =0.17	; Chi ² =18	8.46, df =	= 6 (P =	0.005);	$I^{2} = 68$	%				-
Test for overall effect: Z									-4 -2 0 2 4	
Test for subgroup differ Risk of bias legend	ences: Chi	$i^2 = 18.4$	0, $df = 5$	5(P = 0)	.002), I	2 = 72.89	%		Favors (experimental) Favors (control)	
(A) Random sequence s	generation	ı (selecti	on bias)						
(B) Random sequence g										
(C) Blinding of particip					e bias)					
(D) Blinding of outcom (E) Incomplete outcom				bias)						
 (E) Incomplete outcome (F) Selective reporting(1) 			as)							
(G) Others biases										

FIGURE 19: TNF-α.

Meanwhile, the addition of vitamin E to conventional therapy will not increase the occurrence of adverse events. (9) Selenium: current research has not shown that selenium has a therapeutic effect on RA. What is interesting is that for VAS, RCT showed different results. Because the data is expressed in different ways, it cannot be combined, so it is impossible to draw a certain conclusion. (10) Spa therapy: it has no significant improvement on MDA and SOD, and it may reduce number of swollen joints. Meanwhile, spa therapy may not increase adverse events. (11) Vitamins A, E, and C combination: this combination may decrease MDA and increase GSH. (12) Ozone: it may reduce MDA and NO levels and increase CAT and GSH levels in RA patients. Meanwhile, it may also reduce inflammation and relieve the condition (reduce DAS28, HAQ, and ESR). (13) H₂-saline: The H₂-saline may improve the clinical symptoms of RA patients (decreased DAS28). (14) Alpha-lipoic acid: current research has not shown that alpha-lipoic acid has a therapeutic effect on RA.

In short, most antioxidants or antioxidant therapies can reduce MDA levels in RA patients, and a small number of therapies can increase GSH or TAC levels. And several antioxidants or antioxidant therapies may relieve pain and improve the quality of life of patients and the patient's condition. However, pomegranate extract may cause an increase in MDA. However, since there is only one RCT in most subgroups, the interpretation of the results still requires caution.

5.2. Possible Mechanism of Antioxidant Treatment of RA. In 1986, Koster et al. found that compared with healthy controls, the serum sulfhydryl concentration of RA patients was lower [47]. Considering that the sulfhydryl group may act as a scavenger of peroxides, this discovery had already indicated that the oxidative stress in RA patients was excessive. Subsequently, the characteristics of oxidative stress in the pathogenesis of RA have been reported successively [14, 48–51]. Oxidative stress is a state where the body's oxidation and antioxidant effects are out of balance and tend to be oxidized. Oxidative stress can cause inflammatory infiltration of neutrophils and promote the massive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) free radicals [13, 52]. ROS mainly includes superoxide anion (O_2 -) [53], hydrogen peroxide (H_2O_2)

Study or subgroup	Ex	perime	ntal		Contro		Weight	Std. Mean difference	Std. Mean difference	Risk of bias	
study of subgroup	Mean	SD	Total	Mean	SD	Total	weight	IV. Random, 95% CI	IV. Random, 95% CI	ABCDEF	
3.4.1 N-acetylcysteine											
Hashemi et al. 2019 Subtotal (95% CI)	4.22	0.5	23 23	3.86	0.36	19 19	21.4% 21.4%	0.80 [-0.16, 1.43] 0.80 [-0.16, 1.43]	•	•••••••••••••••••••••••••••••••••••••••	
Heterogenity: Not appli Test for overall effect: Z		P = 0.00)1)								
3.4.2 CoQ10											
Zhu et al. 2020 Subtotal (95% CI)	0.1	0.03	45 45	0.12	0.04	45 45	22.6% 22.6%	-0.56 [-1. 98, -1.14] -0.56 [-1. 98, -1.14]	•		
Heterogenity: Not appli Test for overall effect: Z		P = 0.00	19)								
3.4.5 Quercetin											
Bae et al. 2009a Subtotal (95% CI)	3.79	1.44	6 6	3.94	1.73	5 5	17.3% 17.3%	-0.09 [-1. 27, -1.10] -0.09 [-1. 27, -1.10]	•		
Heterogenity: Not appli Test for overall effect: Z		P = 0.89))								
3.4.6 Resveratrol											
Khojah et al. 2018 Subtotal (95% CI)	23.5	7.1	50 50	51.2	22.1	50 50	22.4% 22.4%	-1.67 [-2. 13, -1.22] -1.67 [-2. 13, -1.22]	↓		
Heterogenity: Not appli Test for overall effect: Z		P < 0.00	001)								
3.4.16 Alpha-lipoic acid	1										
Bae et al. 2009b Subtotal (95% CI)	4.22	1.82	5 5	3.94	1.73	$\frac{4}{4}$	16.3% 16.3%	0.14 [-1.18, 1.46] 0.14 [-1.18, 1.46]	—		
Heterogenity: Not appli Test for overall effect: Z		P = 0.84)								
Total (95% CI)			129			123	100.0%	-0.32 [-1.28, 0.63]	•		
Heterogenity: Tau ² = 1. Test for overall effect: Z				<i>P</i> < 0.00	001), I	² = 90%				_	
Test for subgroup differ	ences: Cl	$ni^2 = 41.$	72, df =	4 (P < 0)	0.00001), $I^2 = 90$	0.4%		Favours (experimental) Favours (control)		
Risk of bias legend											
(A) Random sequence				as)							
(B) Allocation concealr (C) Blinding of particip				rforman	ce bias)						
(D) Blinding of outcom					cc 0148)						
(E) Incompelete outcon				,							
(F) Selective reporting											
(G) Other biases											

FIGURE 20: IL6.

[54, 55], hypochlorous acid (HClO) [56], and hydroxyl radical (OH) [57]. RNS mainly includes nitrogen monoxide (NO) [58-61] and peroxynitroso (ONOO-) [62, 63]. In addition, a variety of highly active molecules including oxidative stress will be produced under pathological conditions [56, 63, 64]. In addition to increasing the number of ROS/RNS under oxidative stress, antioxidants will also remove ROS/RNS substances or compounds, thereby inhibiting the oxidative stress process in cells [65]. Current research shows that there are mainly two different types of antioxidants, namely, enzymatic system and nonenzymatic system. The first type is mainly composed of SOD [65-67], CAT [68], GPx [69], glutathione reductase (GR) [70], and thioredoxin reductase [71]. O2- and H2O2 are the most ROS produced during oxidative stress [52, 69]. The former is cleared by SOD [65], and the latter is cleared by CAT [68], GPx [69], and perredoxin (PRX) [72]. The nonenzymatic antioxidant system is mainly composed of vitamins (A, C, and E), beta carotene, antioxidants, and minerals such as copper, ferritin, zinc, manganese, and selenium [52, 73].

Current basic research shows that oxidative stress plays a key role in the initiation and maintenance of systemic inflammation in RA [32, 45, 74, 75]. Under the pathological conditions of RA, ROS and RNS are produced by neutrophils, monocytes, and macrophages in joint tissues [76]. They can damage different types of cell structures in joints, including DNA, carbohydrates, proteins, and lipids [14, 17, 43, 74], leading to an imbalance of oxidative stress in joint tissues. Among them, the most common oxidation promoting factor (ROS/RNS) in RA joints is composed of O2-, H₂O₂, OH, NO, ONOO-, HOCl, and LOO [32, 45, 74, 75]. In addition, in the occurrence and progression of RA joint damage, the oxidative stress imbalance and the inflammatory biological network are interconnected in multiple directions, which eventually leads to RA (synovitis) and forms a vicious circle. For example, ROS increases in RA patients [10] (mainly H₂O₂), which in turn activates the NF- κ B pathway [77]. NF- κ B signal transduction immunity promotes more IL-1 and TNF- α . Activated macrophages and T cells in the synovium may induce the production of ROS through the release of TNF and IL-1. This way further amplifies the inflammation of synovitis, forming a positive feedback, and worsening the process of RA synovitis [78, 79]. It is specifically manifested in the disease progression of RA patients. Compared with inactive RA patients, RA patients with active disease show higher ROS levels, more severe inflammatory factor levels, and lower antioxidant potential. Moreover, compared with healthy controls, these active RA patients have worse antioxidant capacity [74]. It is manifested by a higher degree of lipid peroxidation found in the synovial fluid and blood samples of these patients with possible RA [80, 81].

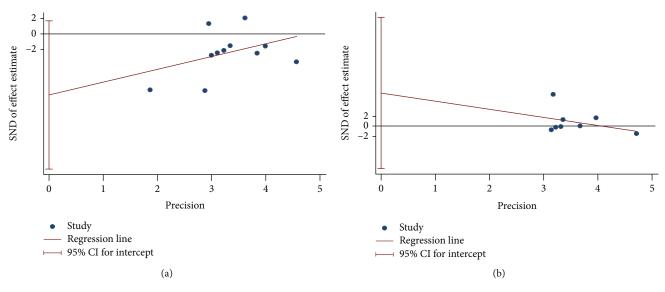


FIGURE 21: Publication bias of oxidative stress index: (a) MDA; (b) TAC.

In addition, the increase in intra-articular pressure caused by chronic long-term inflammation in the joints of RA patients may lead to chronic hypoxia, which in turn increases the production of ROS in the joints of RA individuals [82]. The oxidation of type II collagen in the joints of patients with RA [10] and the increased production of matrix metalloproteinases [33] will cause oxidative damage to the matrix (extracellular environment) of the joints [10]. These oxidative stress factors can also induce stromal cells and joint cells (chondrocytes) to undergo programmed cell death caused by endoplasmic reticulum oxidative stress, which in turn leads to early joint damage in RA [10]. Further studies have also shown that oxidative stress can also cause other complications in RA patients. For example, high levels of inflammation and oxidative stress in RA patients can cause endothelial dysfunction and cause vascular damage to the circulatory system [83, 84]. Controlling the oxidative stress imbalance and inflammation in the preclinical and chronic stages of RA can avoid complications in the circulatory system of RA patients [84]. Aiming at the mechanism of oxidative stress in the clinical diagnosis and treatment of RA patients, oxidative stress biomarkers have been used as relevant markers and protocols to assess the disease activity and prognosis of RA patients [50, 82]. For example, Quiñonez-Flores et al. [50] found that lipid peroxidation (through MDA level) can be used to detect disease activity in RA patients (disease activity score DAS28), which expands the potential applicability of oxidative biomarkers in the diagnosis and prognosis of RA patients.

5.3. Characteristic Analysis of Included Studies. A total of 24 RCTs were included in this study, with a time span from 1986 to 2020. These 24 RCTs used a total of 14 different therapies; they were N-acetylcysteine, CoQ10, probiotic, pomegranate extract, quercetin, resveratrol, garlic tablets, vitamin E and conjugated linoleic acids, selenium, spa therapy, vitamins A, E, and C, ozone, H_2 -saline, and alpha-lipoic acid. Hashemi et al. 2019 [16], Batooei et al. 2018 [17],

Abdollahzad et al. 2015 [19, 20], Zhu et al. 2020 [30], Vaghef-Mehrabany et al. 2016 [31], Zamani et al. 2017 [32], Ghavipour et al. 2016 [33], Javadi et al. 2017 [24, 25], Moosavian et al. 2020 [26, 27], Aryaeian et al. 2009 [36], Karagülle et al. 2017 [43], and León Fernández et al. 2016 [45] described the random sequence generation methods. Hashemi et al. 2019 [16], Batooei et al. 2018 [17], Zhu et al. 2020 [30], Vaghef-Mehrabany et al. 2016 [31], Zamani et al. 2017 [32], Ghavipour et al. 2016 [33], Javadi et al. 2017 [24, 25], Moosavian et al. 2020 [26, 27], and Karagülle et al. 2017 [43] described allocation concealment methods. The other RCTs failed to described the random sequence generation methods and/or allocation concealment methods. Since the main outcome of this meta-analysis is an objective indicator, it is less affected by whether or not blinding is used. Hence, although only Hashemi et al. 2019 [16], Batooei et al. 2018 [17], Zamani et al. 2017 [32], and Moosavian et al. 2020 [26, 27] uses blinding, all RCTs are assessed as low risk of bias regarding blinding. However, the implementation of blinding methods is still very important. Hashemi et al. 2019 [16], Batooei et al. 2018 [17], Vaghef-Mehrabany et al. 2016 [31], Ghavipour et al. 2016 [33], and Bae et al. 2009 [34] have incomplete outcome data. In addition, 2 RCTs were from Belgium; 2 RCTs were from China; 2 RCTs were from Germany; 8 RCTs were from Iran; Bae et al. 2009 was from Korea; Khojah et al. 2018 was from Egypt; Edmonds et al. 1997 was from the UK; Tarp et al. 1986 was from Denmark; Karagülle et al. 2017 was from Turkey; Jaswal et al. 2003 was from India; León Fernández et al. 2016 was from Cuba; and Ishibashi et al. 2014 was from Japan. The included RCTs in this study showed that the included patients were mainly women. This is consistent with the facts: the incidence of RA is higher in women than in men, and women are 2 to 3 times that of men, and it occurs more frequently in 30-50 years of age [85-87]. Therefore, the results of this study mainly show the effect of antioxidant therapy in women with RA. Although it also shows potential effects for men, more samples are needed to further

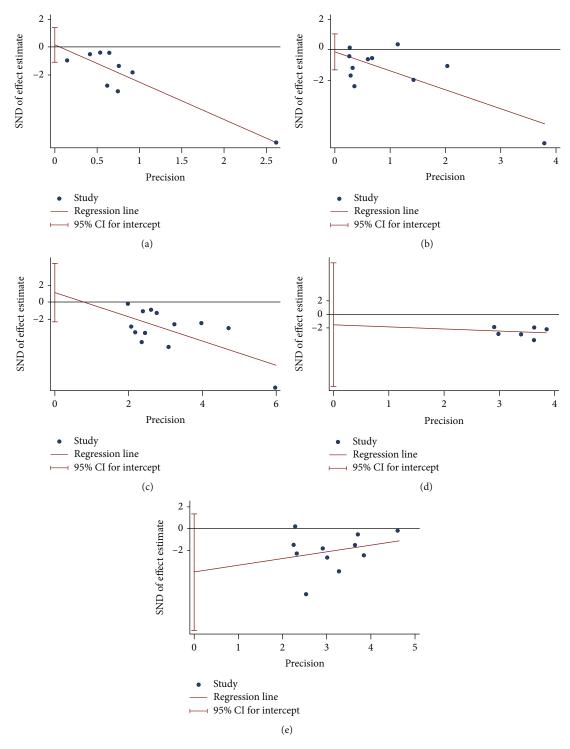


FIGURE 22: Publication bias of clinical efficacy indexes: (a) number of tender joints; (b) number of swollen joints; (c) DAS28; (d) HAQ; (e) VAS.

give better evidence. Most RCTs reported disease duration, baseline CRP, baseline ESR, and baseline DAS28, while a small number of RCTs did not report these baseline data. Baseline data suggest that the disease duration of most patients is more than 5 years, and most RCTs select moderate to severe patients in the active phase for the study.

In general, the quality of RCTs is medium to high. However, since most RCTs are not blinded, and a small number of studies have not conducted allocation concealment and description of random sequence generation methods, the interpretation of the results still needs to be cautious.

5.4. Strengths and Limitations of This Research and Inspiration for Future Research. The strengths of this research is that it is the first meta-analysis involving the improvement of oxidative stress in RA patients with

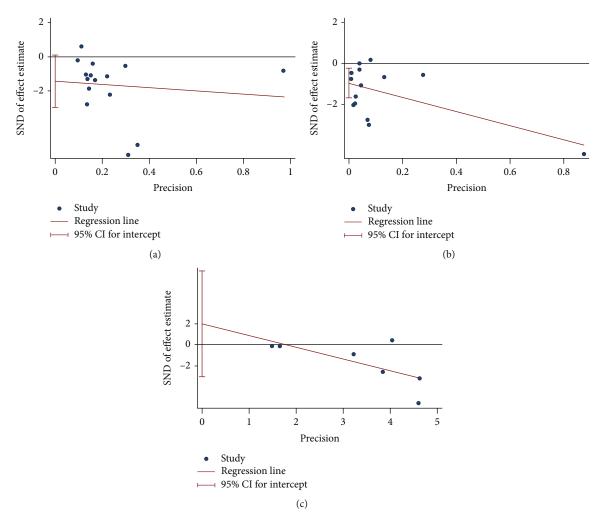


FIGURE 23: Publication bias of inflammation indexes: (a) ESR; (b) CRP; (c) TNF- α .

antioxidants and antioxidant therapies. The RCTs collected in this study span 34 years (1986-2020) involving 1277 participants, and a comprehensive systematic review and metaanalysis of previous related studies have been extensively conducted. The quality of RCT is generally high. In addition, the RCTs included this time involve multiple countries and ethnic groups, including Belgium, China, Cuba, Denmark, Egypt, the UK, Germany, India, Iran, Japan, Korea, and Turkey, which makes the results more applicable.

The limitations of this research is that most subgroups have only one RCT (such as the N-acetylcysteine, pomegranate extract, quercetin, garlic tablets, spa therapy, vitamins A, E, and C combination, and ozone subgroup in MDA; all subgroups of SOD, NO, GPx, CAT, and GSH). This affects the credibility of the results, because only one RCT cannot represent all the population. Meanwhile, there are many RCTs that do not involve indicators of oxidative stress, such as Yin et al. 2017 [18], Bae et al. 2009 [34], Khojah et al. 2018 [35], Aryaeian et al. 2009 [36], Tarp et al. 1986 [39], Peretz et al. 1992 [40], Peretz et al. 2001 [41], Heinle et al. 1997 [42], and Ishibashi et al. 2014 [46]. Therefore, more research on the effects of these therapies on oxidative stress indicators in RA patients is needed. Meanwhile, the intervention duration of these RCTs is different, which

may affect the effect of drug intervention in RA. In addition, although most RCTs are considered to be of high quality, blinding methods (such as Yin et al. 2017 [18], Abdollahzad et al. 2015 [19, 20], Zhu et al. 2020 [30], Vaghef-Mehrabany et al. 2016 [31], Ghavipour et al. 2016 [33], Javadi et al. 2017 [24, 25], Bae et al. 2009 [34], Khojah et al. 2018 [35], Aryaeian et al. 2009 [36], Edmonds et al. 1997 [37], Wittenborg et al. 1998 [38], Tarp et al. 1986 [39], Peretz et al. 1992 [40], Peretz et al. 2001 [41], Heinle et al. 1997 [42], Karagülle et al. 2017 [43], Jaswal et al. 2003 [44], León Fernández et al. 2016 [45], and Ishibashi et al. 2014 [46]) are not used. The main reason they were rated as low risk of bias was that the main outcome indicators were objective indicators (serum MDA, etc.). However, we still need to be vigilant, because the failure to implement blinding may affect other outcome indicators that are not focused on in this study. Therefore, in the future, more well-designed, randomized controlled double-blind clinical trials are needed to verify or modify the outcome indicators.

In MDA outcomes, there was a result contrary to most results: the MDA in the pomegranate extract group was higher than that of the control group. This is a very interesting result, because it suggests that pomegranate extract may have a reverse effect. However, since there is only one RCT, the result is unstable. Therefore, we look forward to more pomegranate extract-related RCTs in the future. In addition, although current RCTs show that antioxidants or antioxidant therapies do not increase the incidence of adverse events, most RCTs do not report safety outcomes. Therefore, it is expected that future RCTs will report more on the incidence of corresponding adverse events to determine the safety of those therapy.

6. Conclusion

Oxidative stress plays an important role in the pathophysiology of RA. This study showed through systematic reviews and meta-analysis that although there are currently fewer RCTs for antioxidant therapy, the existing evidence shows potential benefits, mainly in reducing MDA and increasing TAC and GSH. Meanwhile, it was also found that the combination of antioxidant therapy and conventional therapy is the main choice for reducing RA disease and preventing cardiovascular complications in the future. However, considering the small number of patients recruited, the study design varies greatly between different RCT studies, and the characteristics of RA participants included in different RCT studies are not the same; it is difficult to immediately extrapolate these results to general RA patients. In the future, more large samples and higher quality RCTs are needed to provide high-quality evidence, so as to provide more clinical reference information for the antioxidant treatment of RA.

Data Availability

All data generated or analyzed during this study are included in this published article.

Conflicts of Interest

We declare no competing interests.

Authors' Contributions

Liuting Zeng and Ganpeng Yu contributed equally to this work. Liuting Zeng and Ganpeng Yu should be considered joint first authors. Hua Chen is the first corresponding author because he supervised the study.

Supplementary Materials

Supplementary 1. Table S1: search strategies for PubMed and Embase.

Supplementary 2. PRISMA 2020 checklist: checklist.

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