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The effect of antioxidants supplementation on oxidative stress and proinflammatory biomarkers in patients with chronic kidney disease: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: This systematic review and meta-analysis aimed to address the effect of antioxidant supplementation on oxidative stress and proinflammatory biomarkers in patients with Chronic Kidney Disease (CKD).

MATERIALS AND METHODS: Systematic literature searches from the date of inception up to September 16th, 2022, were performed on PubMed, SCOPUS, and the Cochrane Central Register of Controlled Trials using relevant keywords, i.e., "Chronic Kidney Disease" and "antioxidants", and "supplementation".

All studies relevant to the selection criteria were included in the analysis, focusing on any type of oxidative stress and proinflammatory biomarkers. A meta-analysis of included literature was conducted if sufficient data was obtained.

RESULTS: This systematic review involved 32 published studies, with most having a Jadad score of ≥ 3 (65.6%). Only studies on antioxidants, i.e., polyphenols (n=5) and vitamin E (n=6) in curcumin/turmeric, were sufficient to be included in a meta-analysis. Curcumin/turmeric supplementation was found to significantly reduce the serum c-reative protein (CRP) [standardized mean difference (SMD) -0.5238 (95% CI: -1.0495, 0.0019); p = 0.05; I^2 = 78%; p = 0.001]. Similarly, vitamin E supplementation was found to significantly reduce the serum CRP [SMD -0.37 (95% CI: -0.711, -0.029); p = 0.03; I^2= 53%; p = 0.06] , but not serum interleukin-6 (IL-6) [SMD -0.26 (95% CI: -0.68, 0.16); p = 0.22; I^2 = 43%; p = 0.17] and malondialdehyde (MDA) content [SMD -0.94 (95% CI: -1.92, 0.04); p = 0.06; I^2= 87%; p = 0.0005].

CONCLUSIONS: Our review suggests that curcumin/turmeric and vitamin E supplements effectively lower serum CRP levels in CKD patients, particularly those undergoing chronic dialysis (CKD-5D). Higher scales of randomized controlled trials (RCTs) are still needed for other antioxidants due to inconclusive and contradicting results.

Key Words:
Antioxidants, Oxidative stress, Proinflammatory markers, Chronic kidney disease.

Introduction

Chronic kidney disease (CKD) is a crucial global health issue due to its increasing prevalence and increased risk of cardiovascular disease (CVD)[1,2]. The increased risk of CVD among CKD patients is directly proportional to the progression of CKD, with CKD Stage V on chronic dialysis (CKD-5D) exhibiting the highest risk[3,4]. These specific populations exhibit two interrelated conditions, inflammation and oxidative stress, which are directly associated with each other[2,5,6]. Increased serum CRP is associated with an increased risk of cardiovascular mortality in patients undergoing chronic hemodialysis[7]. A positive correlation of proinflammatory markers [c-reative protein (CRP) and interleukin-6 (IL-6)] with malondialdehyde (MDA) in CKD patients was reported, which was negatively associated with endogenous antioxidants enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GPx)[8].

Interventions that aim to alleviate oxidative stress and chronic inflammation in CKD patients are considered potential treatment options to improve treatment outcomes in these populations. Antioxidants have emerged as plausible treatment agents due to their activities that target the highly oxidative milieu in CKD patients. Buyuklu et al[9] showed that curcumin supplementation effectively alleviated oxidative stress, necrosis,

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and inflammation in animal models with contrast-induced nephropathy. A recent double-blind, randomized controlled trial (RCT) published by Rodrigues et al[10] reported that curcumin supplementation might provide some benefits in reducing oxidative stress but was incapable of lowering proinflammatory markers in CKD-5D patients. Conversely, another RCT from Alvarenga et al[11] showed that turmeric/curcumin supplementation could reduce proinflammatory markers in those populations. This systematic review aimed to assess the efficacy of antioxidant supplementation in reducing oxidative stress and proinflammatory biomarkers in patients with CKD.

Materials and Methods

The primary protocol was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This study was registered in PROSPERO (CRD42022357859).

Eligibility Criteria

Five inclusion criteria were applied for this systematic review: (1) Studies that involved a randomized controlled trial; (2) Studies conducted in adults (> 18 years old) with predialysis CKD or CKD patients (either with hemodialysis or peritoneal dialysis); (3) Studies on any antioxidants interventions; and (4) Studies with outcomes of interest, i.e., relevant to this systematic review. Antioxidants reviewed in this study include vitamins (A, C, and E), carotenoids, polyphenols, trace elements (selenium and zinc), and enzymes (superoxide dismutase, catalase, and glutathione peroxidase). The outcomes of interest included oxidative stress and proinflammatory biomarkers. Excluded from this systematic review were observational and non-randomized controlled trial studies, research on pediatric patients (< 18 years old), abstract-only articles, and non-English language articles.

Search Strategy

This study used electronic databases for a systematic search of the literature, including PubMed, SCOPUS, and the Cochrane Central Register of Controlled Trials. The keywords used to perform a literature search from the date of inception up to September 16th, 2022, were "Chronic Kidney Disease" and "antioxidants", and "supplementation". Any duplicate records were removed after obtaining the initial results. Relevant articles were sorted by screening their titles and abstracts. Lastly, the relevance of the remaining records was assessed based on the inclusion and exclusion criteria.

Data Collection Process and Risk of Bias Assessment

The whole data collection process, comprising the systematic searching of studies through electronic databases, inclusion criteria assessment, and data extraction, was conducted independently by three authors.

All authors performed data inquiries using a designated form with information including authors' names, location, study design, subjects (predialysis CKD or CKD-5D), total samples, intervention, and outcome (oxidative stress and proinflammatory markers). All included studies were assessed using the Jadad scale, a risk-of-bias tool that assesses bias based on randomization, blinding, withdrawals, and dropouts. The total score ranged from 0 to 5 points. A Jadad scale of ≤ 2 denotes low quality, while a scale of ≥ 3 denotes high quality. Any disagreement between authors was resolved through a discussion.

Statistical Analysis

A meta-analysis of included studies was conducted if three or more eligible studies were obtained. Statistical analysis was performed using RevMan Software version 5.4 (Review Manager Web, The Cochrane collaboration, Copenhagen, Denmark). Continuous variables of outcomes of interest were analyzed using the inverse variance method to obtain standardized mean difference (SMD) and 95% confidence intervals (CIs). Random-effect models were used for pooled analysis regardless of heterogeneity. *p*-values were two-tailed, and statistical significance was set at ≤ 0.05. Heterogeneity between studies was analyzed using I^2 (I^2) statistics, with a value > 50% or *p*-values < 0.10 suggesting significant heterogeneity. Leave-one-out sensitivity analysis was performed if a significant heterogeneity was present.

Results

Study Selection and Characteristics

Searches on relevant search engines yielded 2,072 records (Figure 1). After duplicate removal, 1,785 records remained. We excluded 1,726 records after the title and abstract screening. Eligibility screening of the remaining 59 full-text articles resulted in the exclusion of 27 articles

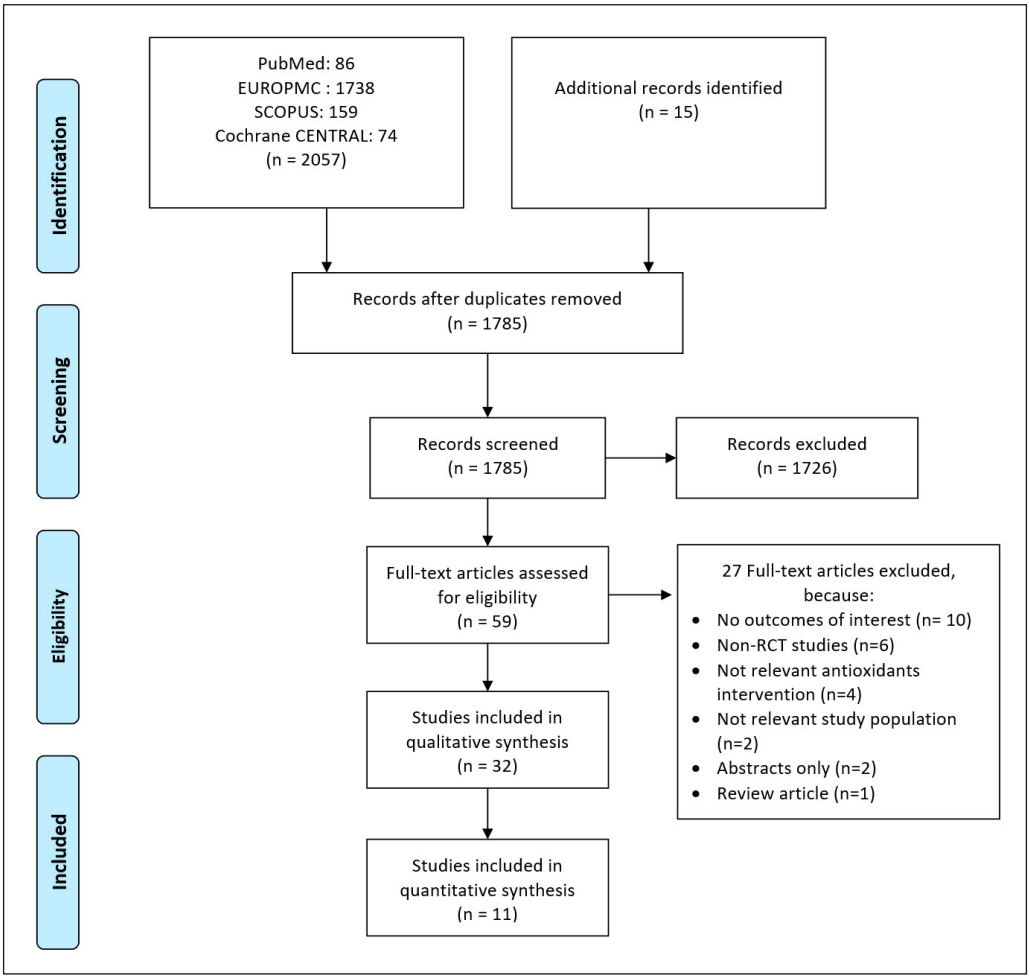

Figure 1. PRISMA Flowchart.

from the final analysis. Reasons for exclusion included no outcomes of interest (n=10), non-RCT studies (n=6), no relevant antioxidants intervention (n=4), irrelevant study population (n=2), abstracts-only articles (n=2), review article (n=1), and study conducted on animals (n=1). Thus, 32 studies were included in this systematic review (Figure 1). Most studies had a Jadad score of ≥ 3 (65.6%). C-reactive Protein (CRP), IL-6, TGF-β, and TNF-α were the most common proinflammatory markers in the included studies. Biomarkers for oxidative stress were measured differently in the included studies: total antioxidant capacity (TAC); serum malondialdehyde (MDA) content; thiobarbituric acid reactive substances (TBARS); carbonyl values; oxygen radical absorbance capacity (ORAC); advanced oxidation products of protein (AOPP); 8-hydroxy-2'-deoxyguanosine (8-OHdG); Lucigenin-enhanced chemiluminescence (LucCL); formamidopyrimidine glycosylase (FPG); catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and superoxide dismutase (SOD) activities. Seven studies[12-18] were conducted in predialysis CKD patients. However, we further excluded one study because it used vitamin D as its primary intervention[17]. The characteristics of the included studies are shown in Table I.

Polyphenols Antioxidants

Fourteen studies[10-15,19-26] have reported antioxidative interventions of polyphenols. Curcumin/turmeric were the most common antioxidants in this group, with turmeric doses ranging from 1.5 g to 2.5 g/day[10-13,19-21]. Other reported[14,15,23-26] antioxidants include resveratrol, pomegranate, and antioxidant-containing grapes (grape juice, seed extract, or powder).

Table I. The characteristics of the included studies.

No.	Author, Country	Blinding, Placebo Controlled	Subjects (Predialysis or CKD-5D)	Total Samples (Intervention *vs.* Control)	Age (mean/ median)	Intervention	Route (IV/SC/PO)	Control	Duration (Week)	Outcome		Jadad Score
										Oxidative Stress biomarkers	Pro-inflammatory biomarkers	
Polyphenols (n = 14)												
1	Jimenez-osorio et al[12], Mexico	Double-Blind, Placebo-controlled	Predialysis	101 (DM: 28 *vs.* 23) and (Non-DM: 24 *vs.* 26)	48.2 ± 7.6	Turmeric (Curcumin 320 mg/day)	PO	Placebo	8	**+ TAC - MDA** ~GPx, GR, SOD, CAT	NA	2
2	Alvarenga et al[11], Brazil	Double-Blind, Placebo-Controlled	CKD-5D	28 (14 vs. 14)	53.5 ± 13.3	2.5 gr Turmeric (Curcumin 95%) three times a week	PO	Placebo	12	NA	**- hs-CRP, NF-kB mRNA expression** ~Nrf2, NLRP3, IL-lb	5
3	Rodrigues et al[10], Brazil	Double-Blind, Placebo-Controlled	CKD-5D	43 (20 *vs.* 23)	55 (42-64)	Curcumin 1 g/day	PO	Placebo	12	**+CAT** ~MDA, GPx, GR	~hs-CRP	5
4	Pakfetrat et al[19], Iran	Double-Blind, Placebo-Controlled	CKD-5D	100 (50 *vs.* 50)	53.3 ± 15.8	Turmeric 1.5 gr/day (66.3 mg Curcumin)	PO	Placebo	8	NA	**-hs-crp:**	5
5	Pakfetrat et al[20], Iran	Double-Blind, Placebo-Controlled	CKD-5D	48	49.4 ± 14.7	Turmeric 1.5 gr/day (66.3 mg Curcumin)	PO	Placebo	8	**+CAT -MDA** ~GR, GPx	NA	4
6	Afshar et al[21], Iran	Double-Blind, Placebo-Controlled	CKD-5D	54 (27 *vs.* 27)	57.2 ± 10.7	Nano-curcumin 120 mg/day	PO	Placebo	12	NA	**-Hs-crp, ICAM-1, VCAM-1**	4
7	Khajehdehi et al[13], Iran	Double-Blind, Placebo-Controlled	Predialysis	40 (20 *vs.* 20)	52.8 ± 9.3	Turmeric 1.5 gr/day (66.3 mg Curcumin)	PO	Placebo	8	NA	**-TGF** ~IL-8, TNF	3
8	Samadian et al[22], Iran	Double-Blind, Placebo-Controlled	CKD-5D	71 (35 *vs.* 36)	49.6 ± 16.8	Turmeric 1.5 gr/day (66.3 mg Curcumin)	PO	Placebo	12	NA	~Hscrp, IL-6, TNF-α Kj	5
9	Corredor et al[23], Spain	Open Label	CKD-5D	39 (25 *vs.* 14)	66.16 ± 2.55 *vs.* 59.71 ± 4.61	100 ml unfermented grape juice (poly-phenol 588±262 mg/L; anthocyanin 1,515± 98 mg/L) thrice a week	PO	Placebo	24	**-DNA oxidative damage**	~CRP	1
10	Turki et al[14], Tunisia	Double-Blind, Placebo-Controlled	Predialysis	33 (23 *vs.* 10)	62.7 ± 2.4 *vs.* 62.3 ± 1.9	Six capsule of Grape Seed Extract (total 2 gr/day)	PO	placebo	24	**-MDA, protein carbonylation, + CAT, SOD**	~CRP*	2
11	Janiques et al[24], Brazil	Double-Blind, Placebo-Controlled	CKD-5D	32 (16 *vs.* 16)	53.0 ± 9.8 *vs.* 52.7 ± 13.7	Grape powder supplementation (500 mg of polyphenols/day)	PO	Placebo	5	+GPx	~CRP*	3

Continued

Table I (continued). The characteristics of the included studies.

No.	Author, Country	Blinding, Placebo Controlled	Subjects (Predialysis or CKD-5D)	Total Samples (Intervention *vs.* Control)	Age (mean/ median)	Intervention	Route (IV/SC/PO)	Control	Duration (Week) Stress	Outcome		Jadad Score
										Oxidative inflammatory biomarkers	Pro-biomarkers	
12	Wu et al[25], USA	Double-Blind, Placebo-Controlled	CKD-5D	27 (13 *vs.* 14)	52.6 ± 3.3 *vs.* 55.9 ± 2.6	1,000 mg purified pomegranate polyphenol extract once a day.	PO	Placebo	24	~ORAC (oxygen radical absorbance capacity), AOPP (advanced oxidation products of protein), 8-OhdG	~CRP, IL-6	3
13	Saldanha et al[15], Brazil	Double-Blind, Placebo-Controlled	Predialysis	20 (9 placebo first, 11 resveratrol first *vs.* 0)	62 ± 8	The "placebo first" group: wheat flour 500 mg, 1 capsule a day for 4 weeks, continued with 8 weeks washout, and lastly gave resveratrol 500 mg, 1 capsule a day for 4 week The "Resveratrol first": was given an opposite sequence from the previous group.	PO	Placebo	16 (4 weeks intervention, 8 weeks washout, 4 weeks intervention)	~SOD, GPx, CAT	~CRP, TNF-alpha	5
14	Ortiz et al[26],	Mexico	CKD-5D	40 (20 *vs.* 20)	37.0 ± 11.5	Resveratrol + curcumin (oral dose of 500 mg of resveratrol and 500 mg of curcumin/day)	PO	Placebo	12	~TBARS, carbonyl values	**-Ferritin**	2
Vitamin Antioxidants (n=11)												
Vitamin E (n=7)												
1	Hodkova et al[27], Czech Republic	Open Label	CKD-5D	29 (15 *vs.* 14)	63 ± 6 *vs.* 60 ± 8	α-TP alpha tocopherol 888 IU	PO	No Supplementation	5	NA	~CRP	2
2	Coloma and Jocson[28], Phillipine	Double-Blind, Placebo-Controlled	CKD-5D	50 (25 *vs.* 25)	60.04 ± 12.45 *vs.* 59.32 ± 14.17	α-TP 400 IU	PO	Placebo	2 months	NA	~CRP	4
3	Ahmadi et al[29], Iran	Open Label	CKD-5D	41 (17 *vs.* 24)	44.8 ± 12.7 *vs.* 48.9 ± 12.5	α-TP 400 IU	PO	Placebo	2 months	~MDA	-Il-6	2
4	Daud et al[30], USA	Double-Blind, Placebo-Controlled	CKD-5D	81 (41 *vs.* 40)	59 ± 12 *vs.* 58 ± 13	Tocotrienols 180 mg	PO	Placebo	4 months	NA	~CRP, IL-6 IL-6:	5

Continued

Table I (continued). The characteristics of the included studies.

No.	Author, Country	Blinding, Placebo Controlled	Subjects (Predialysis or CKD-5D)	Total Samples (Intervention *vs.* Control)	Age (mean/ median)	Intervention	Route (IV/SC/PO)	Control	Duration (Week)	Outcome		Jadad Score
										Oxidative Stress biomarkers	Pro-inflammatory biomarkers	
5	Sohrabi et al[31], Iran	Open Label	CKD-5D	46 (23 *vs.* 23)	58 ± 8.7 *vs.* 55 ± 6.5	α-TP 600 IU	PO	No Supplementation	2 months	**-MDA**	**- IL-6** ~hs-CRP	3
6	Asemi et al[32], Iran	Double-Blind, Placebo-Controlled	CKD-5D ~MDA, TAC,	60 (30 *vs.* 30)	61.2 ± 16.6 *vs.* 59.9 ± 15.7	α-TP 400 IU	PO	Placebo	3 months	**+TAC**	~CRP:	5
7	Koay et al[16], Malaysia	Double-Blind, Placebo-Controlled	Predialysis	59 (31 *vs.* 28)	66 ± 13 *vs* 70 ± 13	200 mg tocotrienol-rich vitamin E twice daily (400 mg/day)	PO	Placebo	12 months	NA	~TGF-β1, VEGF-A	5
Vitamin C (n= 4)												
1	Martins et al[34], Brazil	Double-Blind	CKD-5D	18 (6 *vs.* 6 *vs.* 6)	54.0 (53.0-55.0) *vs* 61.0 (27.0-66.0)	20 gr Whey Protein *vs.* 250 mg vitamin C *vs.* combination (20 g whey protein + 250 mg Vitamin C)	PO	Whey protein	8 week	~GSH, GSSG, GSH:GSSG ratio, GPx-1, MDA	NA	3
2	Fumeron et al[35], France	Open Label	CKD-5D	40 (20 *vs.* 20)	52.3 ± 14.8 *vs.* 51.8 ± 13.6	Vitamin C 250 mg three times per week	PO	No Supplementation	8	~GSSG/GSH	~CRP ratio	1
3	Zhang et al[36], China	Open Label	CKD-5D	100 (48 *vs.* 52)	64.1 ± 12.1	Vitamin C 200 mg/day in the first 3 months, withdrawn in the next 3 months.	PO	Vitamin C 200 mg/day not given in the first 3 months, administered in the next 3 month.	24	NA	-Hs-CRP	2
4	Chen et al[37], Taiwan	Open label, Placebo-controlled	CKD-5D	29 (18 *vs.* 11)	64	Vitamin C 300 mg after HD session	IV	Placebo	One dose only	+LucCl	NA	2
Trace Elements antioxidants (n= 4)												
1	Zachara et al[38], Poland	Double-Blind, Placebo-Controlled	CKD-5D	42 (22 *vs.* 20)	59.6 ± 10.4 *vs.* 55.8 ± 12.5	Supplemented with 200 µg Se (as Se-rich yeast) per day	PO	Placebo	12	-FPG	NA	2
2	Zachara et al[39], Poland	Double-Blind, Placebo-Controlled	CKD-5D	58 (30 *vs.* 28)	61.0 ± 11.6 *vs.* 56.0 ± 12.0	Supplemented with 200 µg Se/day (as Se-rich Yeast)	PO	Placebo	12	~GSH-Px.	NA	2
3	Omrani et al[40], Iran	Double-Blind, Placebo-Controlled	CKD-5D	64 (32 *vs.* 32)	57.34 (± 13.23) *vs.* 59.53 (± 14.68)	Selenium Capsule 200 µg/day	PO	Placebo	12	NA	~CRP, ESR	3

Continued

Table I (continued). The characteristics of the included studies.

No.	Author, Country	Blinding, Placebo Controlled	Subjects (Predialysis or CKD-5D)	Total Samples (Intervention *vs.* Control)	Age (mean/ median)	Intervention	Route (IV/SC/PO)	Control	Duration (Week)	Outcome		Jadad Score
										Oxidative Stress biomarkers	Pro-inflammatory biomarkers	
4	Salehi et al[41], Iran	Double-Blind, Placebo-Controlled	CKD-5D	80 (40 *vs.* 40)	50 ± 15.4 *vs.* 55 ± 13	Capsule of Selenium in the form of Selenium Yeast 200 µg daily.	PO	Placebo	12	**-MDA**	**+IL-6** ~hs-CRP	4
Combinations and other antioxidants (n=3)												
1	Moreillon et al[18], USA	Double-Blind, Placebo-Controlled	Predialysis	16 (9 *vs.* 7)	56 ± 16	Curcumin and Boswellia serrata (1648 mg of purified turmeric extract with 95% curcuminoids, and 1032 mg of Boswellia serrata extract, 10% 3-acetyl-11-keto-β-boswellic acid / day)	PO	Placebo	8	NA	~IL-6, CRP, TNFα	4
2	Xie et al[42], China	Double-Blind, Placebo-Controlled	CKD-5D	124 (41 *vs.* 39 *vs.* 44)	52.8 ± 13.6	10g fiber (Group A), 20g fiber (Group B), or placebo) once a day	PO	Placebo	6	**+TAC** **-MDA** ~SOD, GPx	**-IL-6, IL-8 and Hs-CRP** ~TNFα	4
3	Gokbel et al[43], Turkey	Double-Blind, Placebo-Controlled	CKD-5D	23 (12 *vs.* 11)	46.6 ± 11.9	200mg CoQ10 once daily	PO	Placebo	12	~GPx, MDA, SOD	NA	4

ORAC: oxygen radical absorbance capacity; AOPP (advanced oxidation products of protein), 8-OhdG: 8-hydroxy-2'-deoxyguanosine (8-OHdG); fpg: formamidopyrimidine glycosylase; MDA: Malondialdehyde; CRP: C-Reactive Protein; TNF-alpha: tumor necrosis factor-alpha; TGF-beta: Transforming growth factor beta; ESR: Erythrocyte Sedimentation Rate; SOD: Superoxide Dismutase; TAC: Total Antioxidant Capacity; 25-hydroxyvitamin D3 (25OHD3); LucCL:, Lucigenin-enhanced chemiluminescence; NA: Not Available. **Bolded fonts means significant effect. + increased significantly; - decreased significantly; ~no significant effect.**

Among the 12 studies[10,11,13-15,21,22-26] reporting the antioxidant activity of polyphenols on proinflammatory markers, four[15,22,23,25] reported insignificant changes in the level of proinflammatory markers, including CRP, IL-6, and/or TNF-alpha. Similarly, Samadian et al[22] reported an insignificant reduction in CRP levels after 12 weeks of turmeric supplementation (1.5 g/day). In addition, pomegranate polyphenol extract, unfermented grape juice, and resveratrol were reportedly[15,23,25] unsuccessful in reducing CRP and TNF, while other grape-containing interventions were able to prevent significant increments of CRP[14,24].

Turmeric supplementation significantly reduced serum CRP in four studies[10,11,19,21] (Table I). A pooled meta-analysis[10,11,19,21] showed that turmeric supplementation significantly reduced CRP [SMD -0.5238 (95% CI: -1.0495, 0.0019); p = 0.05; I^2 = 78%; p = 0.001] (Figure 2). Leave-one-out sensitivity analysis by Afshar et al[21] demonstrated the antioxidant activity of nano-curcumin contributing to this heterogeneity (I^2 = 0%).

Changes in the content of biomarkers for oxidative stress were reported in eight studies[10,12,14,15,20,23,24,26], with three[15,25,26] of them reporting changes in their levels. Saldanha et al[15] reported no differences in serum SOD, GPx, and catalase activity in CKD patients after receiving 500 mg of resveratrol/day for four weeks. Combinatory supplementation with resveratrol and curcumin did not significantly reduce TBARS and carbonyl values[26]. Similarly, Wu et al[25] reported that polyphenols extract of pomegranate did not reduce ORAC, AOPP, and 8-OhdG compared with placebo. Meanwhile, a significant reduction in serum MDA content with turmeric/curcumin (n=2) and GSE (n=1) supplementation has been reported[12,14,20]. Additionally, Jimenez-Osorio et al[12] reported a significant increase in TAC after turmeric supplementation for eight weeks.

Vitamin Antioxidants

Antioxidative interventions with vitamins, i.e., E (n=7) and C (n=4), have been reported in 12 studies[10,16,27-36] included in this systematic review. Only the studies[16,27-32] on the antioxidant activity of vitamin E were sufficient for further meta-analysis related to proinflammatory (CRP and IL-6) and oxidative stress biomarkers (Figure 3). Vitamin E supplementation significantly reduced serum CRP [SMD -0.37 (95% CI: -0.711, -0.029); p = 0.03; I^2 = 53%; p = 0.06] (Figure 3A), but not serum IL-6 [SMD -0.26 (95% CI: -0.68, 0.16); p = 0.22; I^2 = 43%; p = 0.17] (Figure 3B) and MDA content [SMD -0.94 (95% CI: -1.92, 0.04); p = 0.06; I^2 = 87%; p = 0.0005] (Figure 3C). Removal of Coloma and Jocson[28] and Sohrabi et al[31] studies in leave-one-out sensitivity analysis reduced outcome heterogeneity involving serum CRP and MDA, respectively. Similarly, Vitamin C supplementation successfully reduced serum CRP in one study[36], while Chen et al[37] reported a significant increment of oxidative stress biomarkers after ascorbic acid supplementation. Additionally, Martins et al[34] and Fumeron et al[35] showed no significant differences in oxidative stress biomarkers after vitamin C supplementation.

Trace Elements Antioxidants

Antioxidant activity of trace elements has been demonstrated in four studies[38-41] included in this review. These studies involved the administration of selenium at 200 mcg/day for 12 weeks to CKD-5D patients. FPG and MDA were reportedly reduced by selenium supplementation in two of the studies[38,41], while insignificant changes in serum CRP and erythrocyte sedimentation rate (ESR) were reported in the remaining studies[40,41]. Moreover, Salehi et al[41] recorded a significant increase in serum IL-6 among patients supplemented with selenium compared with a placebo.

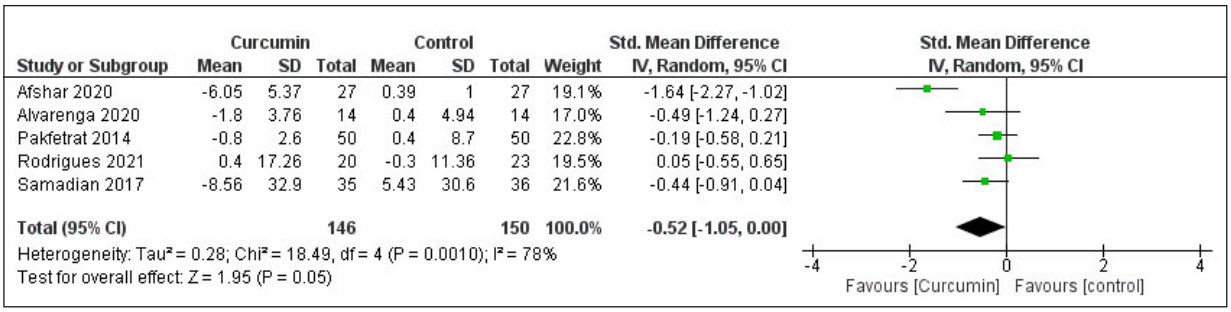

Figure 2. Forest plot of Curcumin/Turmeric supplementation and serum CRP.

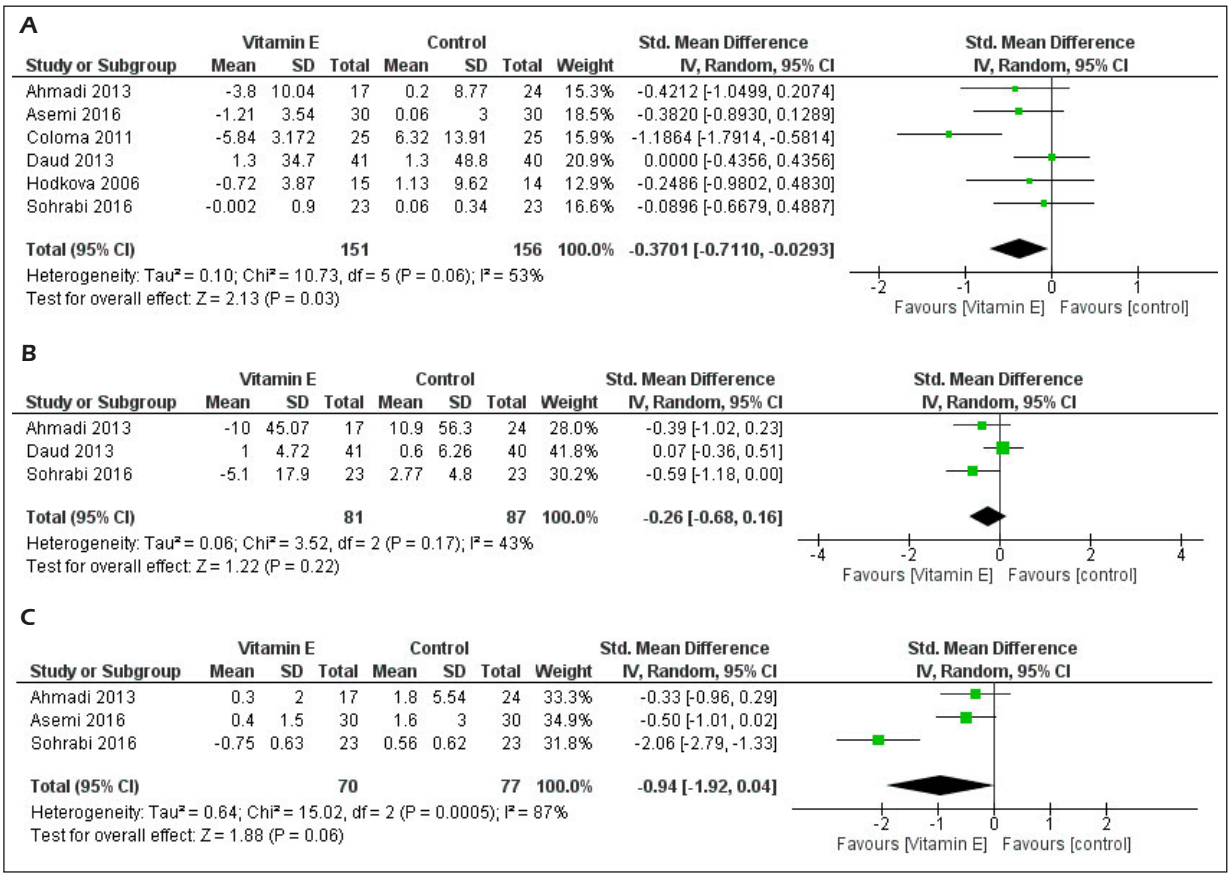

Figure 3. Forest plot of Vitamin E supplementation and serum CRP (**A**), serum IL-6 (**B**), and MDA (**C**).

Combinations and Other Antioxidants

Three studies[18,42,43] included in this review discussed other antioxidant interventions, including the combination of curcumin and *Boswellia serrata*, fermentable fiber, and coenzyme Q10 (CoQ10). Moreillon et al[18] reported insignificant changes in serum IL-6, CRP, and TNF-α among patients receiving the combination of curcumin and B. serrata for eight weeks. Additionally, supplementing patients with dietary water-soluble fiber at a minimum of 10 g/day significantly reduced proinflammatory markers (IL-6, IL-8, and CRP) and MDA content while increasing serum TAC significantly[42]. Gokbel et al[43] reported no changes in serum MDA level, GPx, and SOD activity of CKD-5D patients receiving 200 mg of CoQ10 for 12 weeks compared with placebo in a double-blind, randomized crossover trial.

Discussion

This systematic review highlighted numerous RCTs conducted to attest to the efficacy of antioxidant supplementation in reducing oxidative stress and proinflammatory biomarkers in CKD patients. This review found that only the studies[10,11,16,19,21,27-32] on the antioxidant activities of curcumin/turmeric polyphenol extract and vitamin E were sufficient for further meta-analysis. Also provided in this review is the clinical evidence[10,11,19,21,27-32] related to the reduction of serum CRP with curcumin/turmeric and vitamin E supplementation in patients with CKD. However, a pooled analysis of vitamin E supplementation could not demonstrate a significant reduction in serum IL-6 and MDA content compared with a placebo. The effects of other antioxidants reviewed in this study, such as other vitamins, trace elements (selenium), and combined antioxidant

agents, on oxidative stress and proinflammatory biomarkers are still contradictory.

Polyphenols are a group of natural antioxidants classified into flavonoids, phenolic acids, lignans, stilbenes, and other polyphenols[44]. These antioxidants can improve oxidative stress through several mechanisms, including the augmentation of ROS-scavenging activity, endogenous antioxidant production, activity enhancement *via* activation of Nrf2-mediated pathway, and counteracting ROS production *via* the regulation of microRNAs[45]. Curcumin ($C_{21}HOO_6$) is a bioactive polyphenol with a lipophilic substance obtained from turmeric rhizomes (*Curcuma longa L*)[46]. Its hydroxyl and methoxy functional groups contribute to several functions, including antioxidant, antimicrobial, anti-inflammatory, anti-angiogenic, and antimutagenic properties[46,47]. These properties are also associated with the regulation of proinflammatory cytokines, nitric oxide synthase (iNOS) enzymes, cyclooxygenase-2 (COX-2), lipoxygenase, xanthine oxidase, and reduction of malondialdehyde (MDA)[48]. Furthermore, a previous study[49] showed that curcumin inhibited the hypoxia-inducible factor 1α (HIF-1α)-induced apoptosis and inflammation *via* extracellular signal-regulated kinase (ERK) signaling pathways.

Two previous meta-analyses[47,50] conducted in non-specific adult populations proved that curcumin supplementation could reduce oxidative stress and proinflammatory biomarkers. Our meta-analysis further supported the evidence concerning the effectiveness of curcumin/turmeric supplementation in reducing proinflammatory biomarkers in patients with CKD, particularly the patients undergoing chronic dialysis (CKD-5D). A significant increment in oxidative stress biomarkers, including TAC and catalase activity, and reduction of MDA after curcumin/turmeric supplementation have been reported[10,12,20]. However, further quantitative analysis of the median difference was not conducted due to insufficient studies. Additionally, the high heterogeneity in the curcumin studies could be due to the variation in curcumin/turmeric doses (66.3-2,375 mg/day) and their formulations. The use of nano-formulation for curcumin (nanocurcumin) was reported in Afshar et al[21]. Curcumin prepared with a nano-encapsulation technology exhibited a higher efficacy, i.e., enhanced oral bioavailability, than that of native curcumin. The technology overcomes the downsides of naturally-occurring curcumin, including its poor absorption, low bioavailability, high metabolic rates, and rapid excretion from the body[51].

Malnutrition, insufficient vitamin intake, and loss of vitamins and trace elements in the dialysis process jeopardize antioxidant defense mechanisms in CKD patients[52,53]. Thus, vitamin and trace elements supplementation is believed to reverse oxidative stress and improve the proinflammatory biomarkers in CKD patients. Vitamin E, in the form of α-Tocopherol (α-TP) or tocotrienols (TT), is the most common vitamin E supplementation given to CKD patients[52,54]. Tocopherol (TP) and TT inhibit the activity of cyclooxygenase-2 (COX-2), with TP further inhibiting the activation of NF-κB by scavenging the ROS and upregulating peroxisome proliferator active receptors (PPAR)[55,56].

Our findings support the results from the previous meta-analysis by Khor et al[57], which demonstrated that vitamin E supplementation significantly reduced serum CRP in CKD-5D patients. Further analysis[29-32] revealed that Vitamin E supplementation could not reduce serum IL-6 and MDA content in CKD patients. The findings also demonstrated a high heterogeneity in the included studies[16,27-32] regarding forms, dose, and duration of vitamin E supplementation. Additionally, two trials[16,30] using the TT form of vitamin E reported an insignificant reduction of serum CRP, IL-6, TGF-β, and vascular endothelial growth factor A (VEGF-A). The dose of vitamin E in the included trials[16,27-32] varied from 400 IU to 888 IU/day for α-TP and 180 mg to 400 mg for TT, while the duration ranged from 5 to 48 weeks. It is deduced that the dose and duration of vitamin E supplementation might affect the efficacy of antioxidative interventions. An RCT for vitamin E supplementation for CKD patients and the secondary prevention with antioxidants of cardiovascular disease in end stage renal disease (SPACE) trial[58] used 800 IU of α-TP with a median intervention duration of 519 days (74 weeks). Only one trial[27] was included in this meta-analysis using more than 800 IU of α-TP per day. However, the trial was open-labeled and non-placebo controlled with a small sample size. Therefore, well-designed, larger-scale trials are needed to support these findings.

Vitamin C or ascorbic acid is a water-soluble compound that can rapidly be oxidized, thereby reducing ROS, particularly superoxide anion radicals[59,60]. This ROS-scavenging reaction is the primary mechanism of action of vitamin C in reducing oxidative stress. Additionally, vitamin C inhibits ROS formation by mediating the Jak2/Stat1/IRF1 signaling pathway and inducible nitric oxide synthase[61]. Pro-oxidative properties of vi-

tamin C due to its reactions with metal ions are well-known[37] and have brought wariness among clinicians. Chen et al[37] reported that ROS generation was 16 times higher than the placebo group in CKD-5D patients receiving vitamin C supplementation. The evidence[34-37] of vitamin C supplementation as an intervention to reduce oxidative stress and proinflammatory biomarkers is still conflicting. More trials are still needed to further clarify its efficacy in CKD patients.

Selenium (Se) is an essential trace element and micronutrient. It acts as an integral structural component or a cofactor of glutathione peroxidase (GSH-Px), one of the key enzymes that play a vital role in ROS metabolism and decrease oxidative stress by reducing ROS[62,63]. Patients undergoing hemodialysis generally have lower blood Se concentration than the general population due to decreased intestinal absorption or loss during dialysis[5,53]. Moreover, Se promotes the conversion of arachidonic acid into prostaglandin J2, an anti-inflammatory prostaglandin that inhibits NF-κB, which helps to decrease the inflammatory reaction[64]. Several studies[38,41] have shown that Se supplementation could reduce oxidative stress and inflammation. Salehi et al[41] reported that Se yeast supplementation at 200 μg/day for 12 weeks significantly decreased MDA content and serum IL-6 compared with the placebo group. At a similar dose, Se supplementation could also reduce formamidopyrimidine glycosylase (FPG), a marker for DNA oxidative damage[38].

However, two other RCTs[39,40] did not report significant changes in GPx, serum CRP, and ESR. Previously, several systematic reviews on RCT[57,65-67] have been published due to the abundant literature available. The previous two systematic reviews[66,67] focused on the role of omega-3 fatty acids, which are considered nutritional supplementation with antioxidative properties. Both studies[66,67] showed that fish oil and omega-3 fatty acids supplementation could reduce serum CRP levels in patients with CKD. Khor et al[57] included 46 RCTs involving different nutritional interventions (including antioxidants) and provided evidence that omega-3 fatty acids and vitamin E supplementation could improve inflammation in patients with CKD-5D. Another meta-analysis by Marx et al[65] using various polyphenols in antioxidative interventions reported no significant reduction in serum CRP and IL-6 levels in patients with CKD-5D. Our systematic review focused on the efficacy of all common antioxidant supplementation, including vitamins, polyphenols, trace elements, and a combination of antioxidants, in reducing oxidative stress and proinflammatory biomarkers in patients with CKD.

Limitations

There were several limitations in this systematic review. This review did not include nutritional interventions other than common antioxidants found from the searches using the keyword "antioxidants". Thus, this review did not include some dietary supplements not categorized as conventional antioxidants, such as omega-3 fatty acids and vitamin D. Moreover, this review only included papers written in English. Additionally, due to the highly varied proinflammatory and oxidative stress biomarkers measured in the included studies, only curcumin/turmeric and vitamin E supplementation were found sufficient for meta-analysis. Most of the included studies were conducted on a small scale, while some were open-label trials. The included studies mostly involved patients with CKD-5D. Thus, the results obtained from this meta-analysis should not be extrapolated to patients with predialysis CKD. Consideration should also be given to the varied dose and duration of antioxidant supplementations reported in the included studies.

Conclusions

The evidence suggests that curcumin/turmeric and vitamin E effectively lowered the level of serum CRP in CKD patients, particularly those undergoing chronic dialysis (CKD-5D). Future clinical trials utilizing these antioxidants to reduce mortality and improve cardiovascular outcomes are also necessary for CKD patients to achieve clinically significant results. Other antioxidants likewise require larger-scale RCTs due to conflicting and ambiguous effects.

Availability of Data and Materials

The data used to support the findings of this study are included in the article.

Conflict of Interests

The authors declare no conflict of interests.

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