Review

Efficacy and Safety of Turmeric Dietary Supplementation on Proteinuria in CKD: A Systematic Review and Meta-analysis of RCT

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The beneficial effects of oral turmeric extract on proteinuria levels have been investigated in several human and animal studies. We conducted a systematic review and meta-analysis to evaluate the significance of this new treatment in CKD patients for the first time. We searched ISI Web of Science, PubMed/Medline, Google Scholar, Scopus, SID, and Magiran until March 2021 to identify human-controlled trials that evaluated the effect of turmeric on proteinuria in chronic kidney disease patients. A total of six trials met the selection criteria and were reviewed in our study and four of them were included in the meta-analysis. In these studies, the results showed not only a significant decrease in the level of proteinuria of the trial groups, who had received curcumin but also a significant change in the level of proteinuria between the trial and control groups (SMD = -0.72, 95% CI: -1.10 to 0.35). The results of this meta-analysis demonstrates that turmeric/curcumin oral supplementation significantly improves urinary protein excretion in patients who suffer from chronic kidney diseases with proteinuria; thus, it can be considered as a potential treatment modality in this population.

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INTRODUCTION

The global rise in the prevalence of chronic kidney disease (CKD) in the last decade has made it more reputed as a public health problem.[1] The mortality rate of CKD has been constantly increasing, as its rank has risen from the 17th cause of death in 1990 to the 12th most common cause of death in 2017.[2-3]

According to Kidney Disease Improving Global Outcomes (KDIGO) guidelines, CKD is defined as "persistently elevated urine albumin excretion (≥ 30 mg/g), reduced estimated glomerular filtration rate (eGFR < 60 mL/min/ 1.73 m^2), or both, for > 3 months".[4] While quantitative measurement of urine protein is considered as a marker of kidney damage, which facilitates the diagnosis of CKD, it can also be used as a strong predictor of CKD progression even independent of the GFR level.[5] Albuminuria is categorized in CKD patients based on 24 hours urine albumin excretion rate as normal or mildly increased (< 30 mg/24h), moderately (30 to 300 mg/24h), and severely increased (> 300 mg/24h).[4]

Current treatment options for CKD patients are renin-angiotensin system blockers including angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). Although ACEIs and ARBs are effective in reducing proteinuria, they are associated with potential side effects such as cough, angioedema, and

hyperkalemia.[3,6-8] In recent years, the beneficial effects of herbal drugs on proteinuria levels in CKD patients have been more investigated.[9,10] Curcumin is an active component of turmeric that is extracted from the root of *Curcuma longa*, a medicinal plant of the ginger family. Turmeric has long been used as a spice in Asian countries, especially in India and China. It has antioxidant and anti-inflammatory properties and its effect on the treatment of several chronic diseases has been studied during the past decades.[11,12,13] Its beneficial impact on reducing proteinuria has been reported in both animal and human studies.[14-19] In this systematic review and meta-analysis, we assessed all human randomized clinical trial studies which had been conducted regarding the effect of curcumin on proteinuria in CKD patients for the first time, in order to evaluate the significance of this new treatment.

MATERIALS AND METHODS

This systematic review and meta-analysis were performed under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2015 statement (Figure 1).[20] This study was approved by the local Ethics Committee by the research project number 23037.

Search Strategy

This study aimed to include human randomized controlled trials that examined the effects of curcumin supplementation on reducing proteinuria. The primary outcome of this systematic review and meta-analysis was to evaluate the effect of

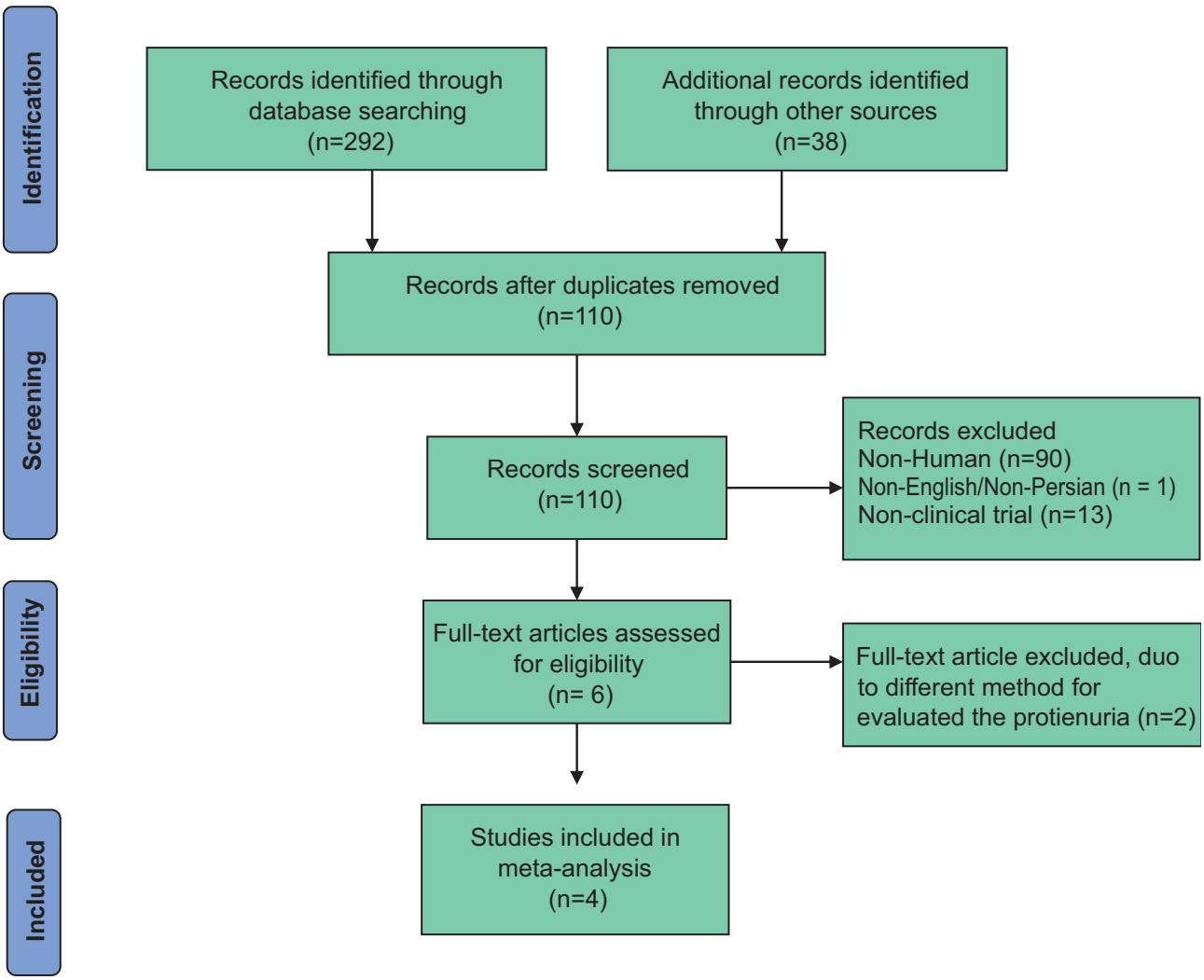

Figure 1. PRISMA Flow Chart

turmeric on proteinuria. The secondary outcome was to determine the optimal dosage and duration of treatment and its associated side effects. Two independent investigators (LM and AH) conducted a systematic search in online international databases (ISI Web of Science, PubMed/Medline, Google Scholar, and Scopus) and national ones (SID, Magiran) to identify relevant studies published in English and Persian up to March 2021 (no restrictions by publication date). The keywords searched were "Turmeric" or "Curcumin" or "curcuma" combined with the general term "chronic kidney disease", "diabetic nephropathy", "diabetic kidney disease", "lupus nephritis", "end-stage kidney disease", and specific term "proteinuria", "albuminuria", "microalbuminuria" and "urinary albumin excretion".

The studies were meticulously checked for the following criteria. Inclusion criteria were: 1) Human randomized controlled trial studies, 2) Studies that examined the effects of Turmeric/Curcumin supplementation on reducing proteinuria, and 3) Studies in the English or Persian language. Exclusion criteria were: 1) Observational studies, 2) Case reports or animal studies, and 3) Non-English or studies in Persian language.

Literature Selection and Data Extraction

Data were collected based on the paper titles by two reviewers (LM and AH), separately. First, the titles and abstracts were screened. Afterwards each paper was briefly read by two authors to exclude the unrelated and duplicate studies. Finally, the relevant studies were reviewed and the references were explored to find related studies. The information that was extracted from the studies included title, author's name, year of the study, country, population, sample size, and results of the study.

Quality Assessment and Risk of Bias

The authors independently performed the quality assessment and risk of bias using the Cochrane Risk of Bias Tool,[21] and disagreements were resolved through the consensus method.

Patient and Public Involvement

Patients and the general population were not involved in the design and conduct of this review.

Statistical Analysis (Meta-analysis)

Meta-analysis was performed using STATA 13 (College Station, TX, USA) statistical software. At first, we calculated the before and after changes in the level of proteinuria for the two groups (trial and control); then, the effect size of the difference of the two groups was calculated and combined in metan package. The amount of the heterogeneity of the studies was indicated by I-squared. The fixed-effect model was used because heterogeneity was not significant. Also, the forest plot was provided for each study and pooled data. Publication bias was assessed by Egger's method. Because we included fewer than 10 trials, we did not create a funnel plot. We did not do subgroup or sensitivity analyses. And the significance level and its confidence interval (CI) was considered 95% in all tests.

RESULTS

Literature Search

A total of 292 abstracts were identified in databases. Additional records identified through other resources were 38. Two hundred and twenty duplicate records were removed. Among the total of 110 records screened, 104 were excluded. A total of 6 full-text RCTs were assessed for eligibility and reviewed (Figure 2).[22-27]

Meta-analysis

Among 6 studies that were reviewed, 2 were excluded for meta-analysis due to lack of sufficient similarity to other studies and considering different study methods in the measurement of proteinuria or drug dosage, that could not be converted to the same values in other included studies.

Summary of the Studies Included

Characteristics of the included studies are reported in Table 1. Of the total of 6 reviewed studies,[10,22-24,26,27] four studies were done on diabetic kidney disease (DKD) patients[22,24-26] and two on lupus nephritis patients.[23,27] Three studies measured 24-hour urine protein.[22,23,26] Three others measured 24-hour urine protein,[24] overnight proteinuria[25] and protein to creatinine ratio,[27] respectively. The curcumin dosage varied between 60 to 1500 mg/d and the duration of treatment varied between 15 days to 4 months.[24,25,27]

In a double-blind RCT conducted by

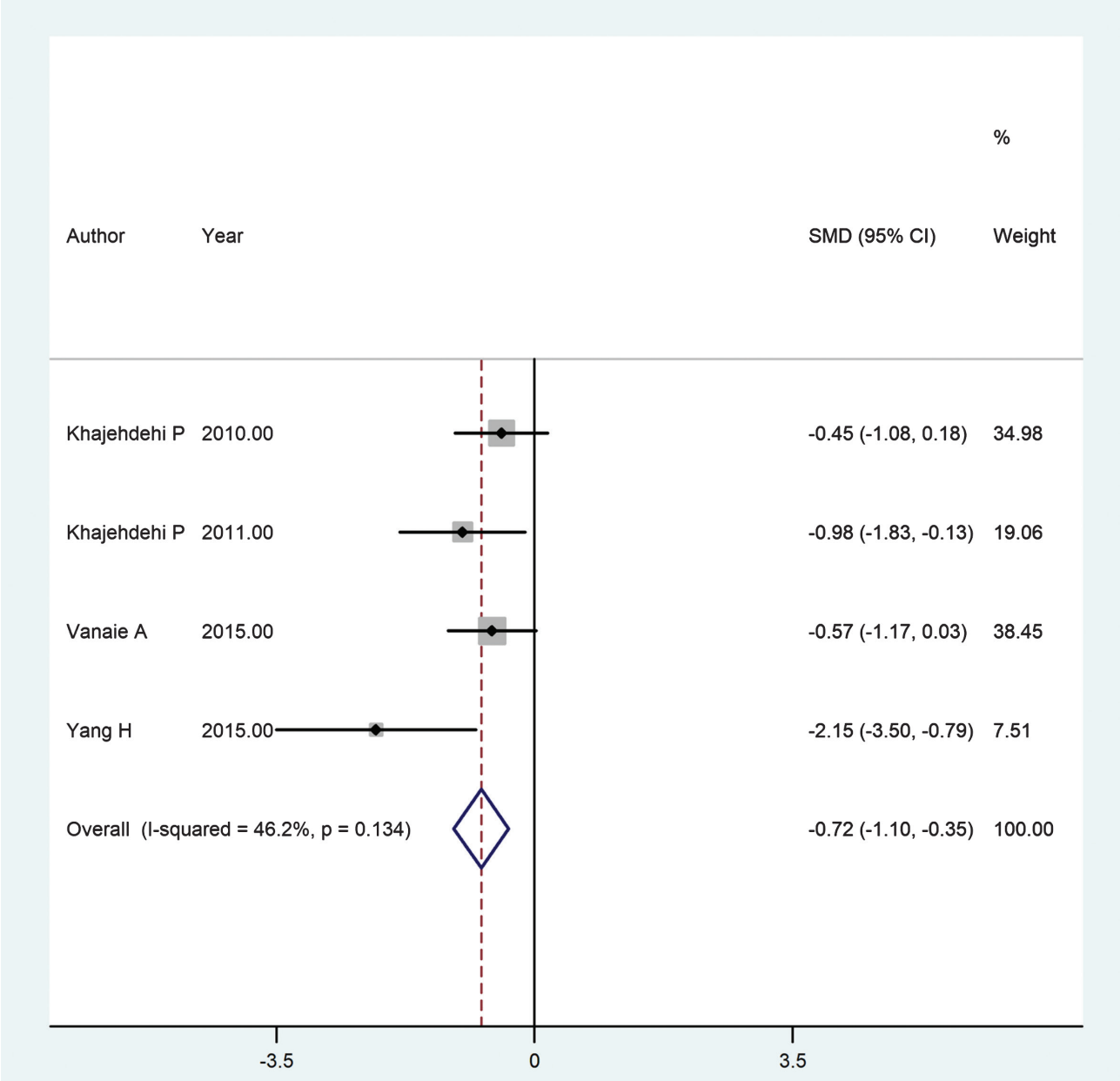

Figure 2. Forest Plot for Individual and Combined Effect Size of Difference in the Proteinuria Level Between the Study and Control Group

Khajehdehi *et al.* patients who were diagnosed with type II diabetes mellitus (T2DM) for more than 7 years and DKD with overt proteinuria (≥ 500 mg/d) were enrolled.[22] The 24-hour urine protein measurement before and after the study period showed a significant decrease in the trial group (4328.7 ± 338.2 to 2354.7 ± 800.1 mg/24h (P = .001)) and a non-significant decrease in the control group (4695.4 ± 3413.2 to 4169.6 ± 2981.4 mg/24 h, (P > .05)). Another study carried out by Khajehdehi *et al.* was a randomized placebo-controlled study in which the efficacy of curcumin in refractory biopsy-proven lupus nephritis patients was evaluated.[23] Measurement of the level of 24-hour urine protein in the trial group showed a significant decrease after 1, 2, and 3 months of curcumin therapy (954.2 ± 836.6 to 448.8 ± 633.5, 235.9 ± 290.1, and 260.9 ± 106.2 mg/24h; respectively (P < .01)). In the control group, there was no significant decrease in the proteinuria level.[23] In a double-blind RCT conducted by Vanaie *et al.*, the effect of curcumin on patients with T2DM

Table 1. Characteristics of the Randomized Controlled Trials Included

Study	Patient	Turmeric Dosage (Curcumin Dose of each Capsule)	Study Group		Turmeric/Curcumin Side Effects
			Trial	Control	
Khajehdehi et al. 2010, Iran (22)	40, overt type 2 diabetic nephropathy	Turmeric capsule 500 mg (22.1 mg), TID, 2 months	20, Turmeric capsule	20, capsule containing starch	No side effect
Khajehdehi et al. 2011, Iran (23)	24, relapsing or refractory Lupus nephritis	Turmeric capsule 500 mg (22.1 mg), TID, 3 months	12, Turmeric capsule	12, capsule containing starch	No side effect
Vanaie et al. 2019, Iran (24)	46, overt type 2 diabetic nephropathy	Capsule 500 mg (10-40 mg) TID, 4 months	27, Curcumin capsule	19, Placebo capsule	One case of epigastric pain
Yang et al. 2015, China (25)	14, type 2 diabetic nephropathy or preclinical stage or normal renal function	Capsule 500 mg, (10-40 mg), QD, 15 days	7 patients with diabetic nephropathy, Curcumin	7 patients with normal renal function, Curcumin	Not reported
Jimenez- Osorio et al.* 2016, Mexico (26)	50, Non-diabetic proteinuric CKD	Turmeric capsule 500 mg (107 mg) TID, 2 months	24,Turmeric capsule	26,starch capsule	Not reported
	51, diabetic proteinuric CKD		28,Turmeric capsule	23,starch capsule	
Wahono et al.* 2016, Indonesia (27)	40, Lupus nephritis patients with low vit D3	Extract of Curcuma Xanthorrhiza (20 mg) TID, 3 months	20, Curcumin plus vit D3	20, Placebo plus vit D3	Not reported

Table 1. Continued

Other Drugs Used in Each groups			Outcome Measure	Result in		
Drugs and dosage	Trial Group n (%)	Control Group n (%)		Trial group	Control group	Comparing groups
ACE-I or ARB drugs (dosage not reported)	Not reported	Not reported	24-hour Proteinuria	Significant decrease ($P = 0.001$)	Non-significant decrease ($P = 0.43$)	Significant change ($P = 0.03$)
Cyclophosphamide Intravenous 1 g Mycophenolate mofetil Oral 2 g/day Prednisone 1 mg/kg/day Captopril 50-100 mg/day Losartan 50 mg/day Diltiazem HCL 120 mg/day Furosemide 40 mg/day Hydrochlorothiazide 50 mg/day	11 (91.6) 1 (8.3) 12 (100) 10 (83.3) 2 (16.7) 4 (33.3) 12 (100) 2 (16.7)	11 (91.6) 1 (8.3) 12 (100) 11 (91.6) 3 (25) 6 (50) 11 (91.6) 1 (8.3)	24-hour Proteinuria	Significant decrease After1,2 and 3 months ($P < 0.01$)	Non-significant decrease	Significant change after 2 months ($P < 0.04$)
ACE-I or ARB drugs (dosage not reported	20 (75)	12 (65)	24-hour Albuminuria	Significant decrease ($P = 0.002$)	Non-significant decrease ($P = 0.43$)	Significant change ($P = 0.01$)
Insulin Metformin Roziglitazone Glibenclamide Gliclazide Acarbose Aspirin	2 (28.5) 3 (42.8) 0 (0) 0 (0) 3 (42.8) 3 (42.8) 1 (14.2)	3 (42.8) 2 (28.5) 2 (28.5) 1 (14.2) 1 (14.2) 1 (14.2) 0 (0)	12-hour Overnight urine microalbumin	Significant decrease after 15 days ($P < 0.05$)	Not reported	Significant Change ($P < 0.05$)
Not reported	Not reported	Not reported	24-hour Proteinuria	Non-significant	Non-significant	Not reported
				Non-significant	Significant decrease, ($P < 0.05$)	Not reported
Chlorquine Cyclosporine Cyclophosphamide Azathioprine	7 (17.9) 0 (0) 5 (12.8) 14 (35.9)	10 (25.6) 2 (5.1) 1 (2.6) 10 (25.6)	Protein-Creatinine Ratio	Significant decrease ($P = 0.000$)	Significant decrease ($P = 0.000$)	Non-significant change ($P = 0.482$)

*Excluded studies in the meta-analysis

Abbreviations: CKD, chronic kidney disease; TID, three times a day; QD, ones a day; ACE-I, angiotensin converting enzyme inhibitor; ARD, angiotensin receptor blocker.

and DKD with overt proteinuria was evaluated. The results showed that albuminuria diminished significantly from 900.4 ± 621.9 at the baseline to 539.68 ± 375.16 mg/24h at the end of the study (P = .002). In the placebo group, no statistically significant change was observed (519.94 ± 214.33 to 444.00 ± 219.10 mg/24h; P > .05). In the study by Yang *et al.* the effect of curcumin on urinary micro-albumin (U-mAlb) in T2DM and DKD patients was evaluated. Half of the patients were diagnosed as overt DKD or preclinical stage of DKD and the other half were diabetics with normal renal function.[25] The average content of U-mAlb before curcumin treatment in all patients was 214.9 ± 104.5 mg/L, which was dramatically reduced after 15 days of curcumin therapy to 69.7 ± 41.9 mg/L (P < .05).[25] The reduction in U-mAlb was significantly more in DKD patients than those with normal renal function (69.8% ± 8.0 reduction vs. 15.2% ± 1.7, P < .05). The patients with overt DKD also got extra 15 days of curcumin therapy and the effect of curcumin in reducing U-mAlb continued in all of them (670.0 ± 260.2 mg/L at day 0 vs. 211.0 ± 131.1 mg/L at day 15, P < .05 and 163.5 ± 96.4 mg/L at day 30, P < .05).[25]

In a double-blind placebo-controlled RCT study by Jimenez-Osorio *et al.*, the curcumin effect was evaluated in 2 groups of CKD patients with persistent proteinuria, ≥ 1000 mg/d, with or without diabetes mellitus.[26] In each group, almost half of the patients received turmeric capsule. While the results did not show any significant decrease in the level of proteinuria, in either diabetic or non-diabetic CKD patients who were treated with curcumin, proteinuria in the control group of diabetic CKD patients showed a significant decrease (5.1 ± 0.9 to 4.1 ± 0.7 g protein /24h.; P < .05).

Wahono *et al.* performed a double-blind RCT to evaluate the effect of adding curcumin to vitamin D3 supplementation in systemic lupus erythematosus patients who had low vitamin D3 level. At the end of the study, they showed a significant decrease in protein/creatinine ratio both in the trial group who received vitamin D plus curcumin (P < .000) and the control group who received vitamin D alone as placebo (P < .000). Although there was a significant decrease in protein/creatinine ratios before and after treatment in both groups, the comparison of delta levels was not significant (P > .05).[27]

Pooled estimation of changes in proteinuria before and after the intervention for the trial and control groups are displayed in Figure 2 as forest plots and summarized in Table 2. Combined (overall) effect size extracted from meta-analysis showed that turmeric in comparison to placebo led to reduction of the proteinuria level (SMD = -0.72, 95% CI: -1.10 to 0.35). Based on Cochrane's Q test, significant heterogeneity was not observed among the studies (I^2 = 46.2, P > .05). Egger's test also indicated that the publication bias was not significant (P > .05).

DISCUSSION

The results of this meta-analysis on the efficacy and safety of turmeric/curcumin on proteinuria in CKD disease confirmed the effect of curcumin on decreasing proteinuria in patients with kidney disease. A total of six RCTs[22-27] were reviewed in this study out of which, four were done on CKD patients with diabetic nephropathy[22,24-26] and two on patients with lupus nephritis. The results of four

Table 2. Combined Effect Size of the Difference (After-Before) in the Proteinuria Level Between the Study and Control Groups

Author		Year	SMD	95% CI		Weight
Khajehdehi P		2010	-0.45	-1.08	0.180	31.63
Khajehdehi P		2011	-0.98	-1.83	-0.13	23.23
Vanaie A		2015	-0.57	-1.17	0.03	32.91
Yang H		2015	-2.15	-3.50	-0.79	12.24
Overall	Index		-0.72	-1.10	-0.35	100
	z			3		
	P			.003		
I^2(%) [a]	Value			46.2		
	P			> .05		
Egger's test [b]	Bias			6.54		
	95% CI for Bias			(-19.44 -32.53)		
	P			> .05		

[a]proportion of total variation in effect estimate due to between-study heterogeneity, [b]Egger's test for small-study effects.

studies showed not only a significant decrease in the amount of proteinuria in the trial groups who received curcumin, but also a significant change in the proteinuria between the trial and control groups was detected.[22-25] The other two studies reported no significant effect of curcumin in reducing proteinuria.[26-27] One of them was performed on lupus nephritis patients who had low serum vitamin D3 levels and did not show any significant effect by adding curcumin and vitamin D3 supplements in decreasing proteinuria;[27] the other was done in two groups of diabetic and non-diabetic CKD patients and the results showed a significant decrease in proteinuria in the diabetic control group.[26] In five studies CKD patients were randomly categorized into the trial group (curcumin) and control (placebo) groups.[22-24,26,27] In one study, the trial and control groups were chosen from diabetic nephropathy patients with normal kidney function who were all treated with curcumin.[25] The duration of curcumin treatment was different in each study (15 days to 4 months), and it was prescribed at a wide range of doses (60 to 1500 mg/d).[22-27] Considering the limited number of studies performed in humans, determining a distinct dosage and duration of therapy was not possible.

Turmeric has been recognized as a potential treatment option for different aspects of CKD.[28-30] Its effect in reducing proteinuria is one of the main topics, investigated in various animal studies. In a study conducted by Kim *et al.*, the effect of curcumin on proteinuria has been evaluated in T2DM rats, and the results showed a significant decrease in 24-hour urinary albumin-creatinine ratio levels in the T2DM group treated with curcumin (100 mg/kg/d) compared to those that received oral saline ($P < .05$). The results of another study conducted by Sharma *et al.*[15] in which the effect of 15 and 30 mg/kg oral curcumin for 2 weeks on proteinuria in streptozotocin-induced diabetic rats was evaluated, showed a significant decrease in urine albumin excretion in the curcumin groups) compared with the controls ($P < .05$). Lee *et al.* investigated the effect of curcumin on proteinuria in lupus nephritis, New Zealand black/white mice, and showed a significant decrease in urine protein in curcumin-treated mice compared with the control group ($P < .01$).

The mechanism by which curcumin attenuates proteinuria can be explained by referring to recent investigations regarding its anti-inflammatory effects. Tumor necrosis factor-α (TNF-α) is an inflammatory mediator, secreted by native kidney cells or macrophages, and is responsible for the release of other cytokines, acute phase proteins, and consequent glomerular cell apoptosis. It has a potential effect on the progression of diabetic nephropathy by several mechanisms including breakdown of glomerular filtration barrier, which subsequently leads to proteinuria.[31] Proteinuria, which is a known marker of kidney disease, has a potential role in the activation of nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) system, which in turn results in glomerular and/or tubulointerstitial fibrosis, and consequent loss of kidney function.[32,33] Angiotensin converting enzyme inhibitor (ACE-I) drugs can effectively reduce proteinuria by inhibiting the formation of Angiotensin II, which is an inflammatory molecule that stimulates tumor necrosis factor α (TNF-α) production in the kidney.[34] Another effect of ACE-I drugs is reversal of macrophage infiltration in kidney tissue, as reported by Mizobuchi *et al.*[35] A study conducted by Ghoss *et al.*[36] which compared the beneficial role of curcumin with enalapril, in amelioration of renal injuries, showed equal effectiveness of both compounds in reducing the amount of proteinuria. The study also showed a significant reduction of macrophage infiltration in the glomerulointerstitium of animals treated by either curcumin or enalapril as well as a significant effect of curcumin in reducing TNF-α in the serum and kidney.

Although the effect of curcumin on decreasing proteinuria has been evaluated in a large number of animal studies and few human research, no meta-analysis has been performed in this regard so far. This is the first systematic review and meta-analysis that provides information on this subject, and the strength of this study is the consideration of extremely strict inclusion criteria, which results in selecting human RCTs and rigorous data analysis. While a number of studies have confirmed the efficacy of this herbal medicine with no serious side effects, authors believe that conducting more human studies with larger sample sizes and longer durations should be considered.

Limitation

Our goal was to study the effect of turmeric

on proteinuria in CKD patients in human RCTs. Unfortunately, as turmeric has not been studied much in controlled trials in human, few studies are included in this meta-analysis One of the major problems for conducting such RCTs might be poor bioavailability and absorption of turmeric.[36] Although there are many animal studies in this field, adding animal studies to this meta-analysis could create high heterogeneity in the results. Obviously, future studies will be helpful.

CONCLUSION

Turmeric/curcumin has been shown to be useful in patients who suffer from proteinuric kidney diseases, and it can be used as an appropriate therapeutic option in these patients. Further evaluation in order to determine the optimal dosage and duration of curcumin/turmeric treatment.

AUTHORS' CONTRIBUTIONS

All authors have contributed to the concept and design of the research and to the writing and/or revision of the manuscript, and have approved the manuscript for submission.

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REFERENCES

1. Levey AS, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: approaches and initiatives-a position statement from Kidney Disease Improving Global Outcomes. Kidney Int. 2007;72(3):247-59.
2. Carney EF. The impact of chronic kidney disease on global health. Nat Rev Nephrol. 2020;16(5):251.
3. Ramos AM, Fernandez-Fernandez B, Perez-Gomez MV, et al. Design and optimization strategies for the development of new drugs that treat chronic kidney disease. Expert Opin Drug. 2020;15(1):101-15.
4. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98(4s):S1-s115.
5. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63(5):713-35.
6. Zhong J, Yang HC, Fogo AB. A perspective on chronic kidney disease progression. Am J Physiol Renal Physiol. 2017;312(3):F375-f84.
7. Montinaro V, Cicardi M. ACE inhibitor-mediated angioedema. Int J Immunopharmacol. 2020;78:106081.
8. Palmer BF. Potassium Binders for Hyperkalemia in Chronic Kidney Disease-Diet, Renin-Angiotensin-Aldosterone System Inhibitor Therapy, and Hemodialysis. Mayo Clin Proc. 2020;95(2):339-54.
9. Silveira MAD, Teles F, Berretta AA, et al. Effects of Brazilian green propolis on proteinuria and renal function in patients with chronic kidney disease: a randomized, double-blind, placebo-controlled trial. BMC Nephrol. 2019;20(1):140.
10. Xiao, Y, Liu Y, Yu K, et al. The Effect of Chinese Herbal Medicine on Albuminuria Levels in Patients with Diabetic Nephropathy: A Systematic Review and Meta-Analysis. Evidence-Based Complementary and Alternative Medicine, 2013. 2013: p. 937549.
11. Esatbeyoglu T, Huebbe P, Ernst IM, Chin D, Wagner AE, Rimbach G. Curcumin--from molecule to biological function. Angewandte Chemie. 2012;51(22):5308-32.
12. Chattopadhyay I, Biswas K, Bandyopadhyay U, Banerjee RK. Turmeric and curcumin: Biological actions and medicinal applications. Current Science. 2004;87(1):44-53.
13. Kim S, Chen J, Cheng T, et al. PubChem in 2021: new data content and improved web interfaces. Nucleic Acids Res. 2021;49(D1):D1388-D95.
14. Kim BH, Lee ES, Choi R, et al. Protective Effects of Curcumin on Renal Oxidative Stress and Lipid Metabolism in a Rat Model of Type 2 Diabetic Nephropathy. Yonsei Med J. 2016;57(3):664-73.
15. Sharma S, Kulkarni SK, Chopra K. Curcumin, the active principle of turmeric (Curcuma longa), ameliorates diabetic nephropathy in rats. Clin Exp Pharmacol Physiol. 2006;33(10):940-5.
16. Suresh Babu P, Srinivasan K. Amelioration of renal lesions associated with diabetes by dietary curcumin in streptozotocin diabetic rats. Mol Cell Biochem. 1998;181:87-96.
17. Soetikno V, Sari FR, Veeraveedu PT, et al. Curcumin ameliorates macrophage infiltration by inhibiting NF-κB activation and proinflammatory cytokines in streptozotocin induced-diabetic nephropathy. Nutr Metab. 2011;8(1):35.
18. Lee, H, Kim H, Lee G, et al. Curcumin attenuates lupus nephritis upon interaction with regulatory T cells in New Zealand Black/White mice. Br J Nutr, 2013.110(1): p. 69-76.
19. Wang Y, Wang Y, Luo M, et al. Novel curcumin analog C66 prevents diabetic nephropathy via JNK pathway with the involvement of p300/CBP-mediated histone acetylation. Biochim Biophys Acta. 2015;1852(1):34-46.
20. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Sys Rev. 2015;4(1):1.

21. Higgins J, Deeks J, Altman D. Cochrane Handbook for systematic reviews of interventions version 5.1. 0. Higgins J, S G, editors2011.
22. Khajehdehi P, Pakfetrat M, Javidnia K, et al. Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: a randomized, double-blind and placebo-controlled study. Scand J Urol Nephrol. 2011;45(5):365-70.
23. Khajehdehi P, Zanjaninejad B, Aflaki E, et al. Oral supplementation of turmeric decreases proteinuria, hematuria, and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis: a randomized and placebo-controlled study. j ren nutr. 2012;22(1):50-7.
24. Vanaie A, Shahidi S, Iraj B, et al. Curcumin as a major active component of turmeric attenuates proteinuria in patients with overt diabetic nephropathy. J Res Med Sci. 2019;24:77.
25. Yang H, Xu W, Zhou Z, et al. Curcumin attenuates urinary excretion of albumin in type II diabetic patients with enhancing nuclear factor erythroid-derived 2-like 2 (Nrf2) system and repressing inflammatory signaling efficacies. Exp Clin Endocrinol Diabetes. 2015;123(6):360-7.
26. Jimenez-Osorio AS, Garcia-Nino WR, Gonzalez-Reyes S, et al. The Effect of Dietary Supplementation With Curcumin on Redox Status and Nrf2 Activation in Patients With Nondiabetic or Diabetic Proteinuric Chronic Kidney Disease: A Pilot Study. J Ren Nutr. 2016;26(4):237-44.
27. Wahono CS, Wahyuni ZD, Kalim O. Effect of curcuma xanthorrhiza suplementation in vitamin D3 administration towards proteinuria, serum anti-dsDNA and IL-17 levels on systemic lupus erythematosus (sle) patients with hypovitamin D. Int J Clin Rheumtol. 2017;12:121.
28. Hernandez-Resendiz S, Correa F, Garcia-Nino WR, et al. Cardioprotection by curcumin post-treatment in rats with established chronic kidney disease. Cardiovasc Drugs Ther. 2015;29(2):111-20.
29. Wang D, Yang Y, Zou X, Zheng Z, Zhang J. Curcumin ameliorates CKD-induced mitochondrial dysfunction and oxidative stress through inhibiting GSK-3β activity. J Nutr Biochem. 2020;83:108404.
30. Pakfetrat M, Basiri F, Malekmakan L, Roozbeh J. Effects of turmeric on uremic pruritus in end stage renal disease patients: a double-blind randomized clinical trial. J Nephrol. 2014;27(2):203-7.
31. Lampropoulou IT, Stangou M, Papagianni A, Didangelos T, Iliadis F, Efstratiadis G. TNF-α and microalbuminuria in patients with type 2 diabetes mellitus. J Diabetes Res. 2014;2014:394206.
32. Zoja C, Abbate M, Remuzzi G. Progression of renal injury toward interstitial inflammation and glomerular sclerosis is dependent on abnormal protein filtration. Nephrol Dial Transplant. 2015;30(5):706-12.
33. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? J Am Soc Nephrol. 2006;17(11):2974-84.
34. Das UN. Is angiotensin-II an endogenous pro-inflammatory molecule? Med Sci Monit. 2005;11(5):155-62.
35. Mizobuchi M, Morrissey J, Finch JL, et al. Combination therapy with an angiotensin-converting enzyme inhibitor and a vitamin D analog suppresses the progression of renal insufficiency in uremic rats. J Am Soc Nephrol. 2007;18(6):1796-806.
36. Ghosh SS, Massey HD, Krieg R, et al. Curcumin ameliorates renal failure in 5/6 nephrectomized rats: role of inflammation. Am J Physiol Renal Physiol. 2009;296(5):F1146-57.

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