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Effects of Curcumin Supplementation on Inflammation and Metabolic Profiles in Hemodialysis Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

To the Editor:

Curcumin (diferuloylmethane) is the active component in turmeric (*Curcuma longa*) and the one responsible for its yellow color and its anti-inflammatory/antioxidant activity.[1] Curcumin is believed to have anti-inflammatory effects by downregulating the expression of the Nuclear factor κB (NF-κB) which results in significant reduction of major inflammatory cytokines and adhesion molecules, for example, proinflammatory interleukins.[2,3] Hemodialysis (HD) patients are at high risk of malnutrition and cardiovascular complications due to oxidative stress and inflammation. It is estimated that 40%–60% of HD patients have inflammation.[4]

Anti-inflammatory benefits of curcumin supplementation in HD patients have been examined in several studies. In 2014, Pakfetrat et al[5] published the first randomized controlled trial (RCT) comparing curcumin supplementation versus placebo (PBO) in patients with chronic kidney disease (CKD) on HD, which showed significant reduction in inflammation represented by reduction in the high-sensitivity C-reactive protein (hs-CRP) level among the curcumin group. Since then, many RCTs have compared curcumin supplementation versus PBO with conflicting findings.[6–9] Therefore, we conducted this systematic review and meta-analysis to evaluate the impact of curcumin supplementation on inflammation and metabolic profiles among HD patients.

All RCTs that compared curcumin supplementation with PBO in patients with CKD on HD and reported the difference in inflammation represented by hs-CRP were eligible for inclusion. We excluded observational studies or studies that included patients with CKD who are not on HD. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines to select the final studies.[10] Two investigators (A.B. and O.S.) independently performed the search and shortlisted the studies for final review. Discrepancies were resolved by a third reviewer (K.S.).

The primary outcome of our study was the anti-inflammatory effect of curcumin represented by the change in the hs-CRP level. The secondary outcomes were the lipid profile including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) in addition to fasting blood sugar (FBS).

We performed a meta-analysis of the included studies using comprehensive meta-analysis (Biostat, Englewood, CO). The median and interquartile ranges were converted to mean and SD where applicable.[11] The random-effects model was used to calculate the standardized mean difference (SMD) with 95% confidence intervals (CIs). A P value <0.05 was considered statistically significant. Where the mean and SD of the change from baseline to end point were not reported in the original studies, an imputed value for the correlation coefficient (r) was used to calculate them.[12] We performed a sensitivity analysis using r of 0.4, 0.5, and 0.6 for our meta-analyses, and the results did not significantly change, indicating that our analyses were robust to this assumption.[12] We used r of 0.5 in our meta-analysis.[13] The heterogeneity was evaluated using the I^2 statistic as defined by the Cochrane handbook for systematic reviews. The I^2 value of $\geq$50% was considered significant heterogeneity for all outcomes.[14]

To confirm the robustness of our results, sensitivity analysis for hs-CRP using leave-one-out meta-analysis was performed to see whether it had a significant influence on the meta-analysis result (ie, jack-knife sensitivity analysis). The Jadad composite scale was used to assess the methodological quality of the clinical trials based on randomization, blinding, and withdrawals.[15] The scale ranged from 0 to 5 points.[15] Studies with a total score of $\geq$3 were considered to have a low risk of bias. Two authors (O.S. and A.B.) independently assessed each study for bias. Discrepancies were resolved by a third reviewer (K.S.).

A total of 7 RCTs[5–9,16,17] with 413 patients with CKD on HD (204 received curcumin supplementation and 209 received PBO) were included. All the included RCTs were published between January 2014 and June 2021 and included hemodialysis patients. Based on country of origin, 5 studies originated from Iran and 2 studies from Brazil. Regarding the design of studies, all of them were RCTs. The follow-up duration ranged

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from 8 to 12 weeks. Although 6 studies[5,8,9,16,17] provided curcumin supplementation in capsule forms, one study 6 provided the curcumin supplementation in a form of juice. All the included RCTs scored ≥3 according to the Jadad composite scale.

Across all the 7 studies, our meta-analysis showed a significant reduction in hs-CRP levels among HD patients compared with placebo (SMD −0.41; 95% CI −0.61 to −0.21; P <0.001; I^2 = 0%; Figure 1A). The results remained consistent on leave-one-out sensitivity analysis. Three studies7, 9, 17 reported the effect of curcumin supplementation on glycemic profile. There was no significant effect of curcumin on FBG (SMD −0.30; 95% CI −0.60 to 0.007; P = 0.056; I^2 = 0%; Figure 1B).

Three studies[6,9,17] reported the effect of curcumin supplementation on lipid profile, which included total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels. There was no significant effect of curcumin intake on TG (SMD −0.17; 95% CI −0.51 to 0.16; P = 0.31; I^2 = 0%; Figure 2A), TC (SMD −0.25; 95% CI −0.62 to 0.11; P = 0.17; I^2 = 12.7%; Figure 1A), LDL (SMD −0.28; 95% CI −0.69 to 0.13; P = 0.175; I^2 = 27.6%; Figure 2C), or HDL (SMD 0.21; 95% CI −0.13 to 0.55; P = 0.23; I^2 = 0%; Figure 2D).

We thoroughly investigated the impact of curcumin supplementation on inflammation and metabolic profile among patients with CKD on HD in this meta-analysis of RCTs. We observed a significant improvement in the inflammation (ie, hs-CRP levels) with curcumin supplementation in HD patients. However, there was no significant change in the metabolic profile (lipid profile and glycemic profile).

Our results regarding the effects of curcumin on the inflammation and metabolic profiles were in line with the trial by Vafadar-Afshar et al,[9] which showed significant reduction in the proinflammatory markers such as increased levels of hs-CRP and adhesion molecules such as: intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) among the HD patients who received curcumin supplementation compared with the placebo group (P <0.05). However, curcumin supplementation did not significantly improve the

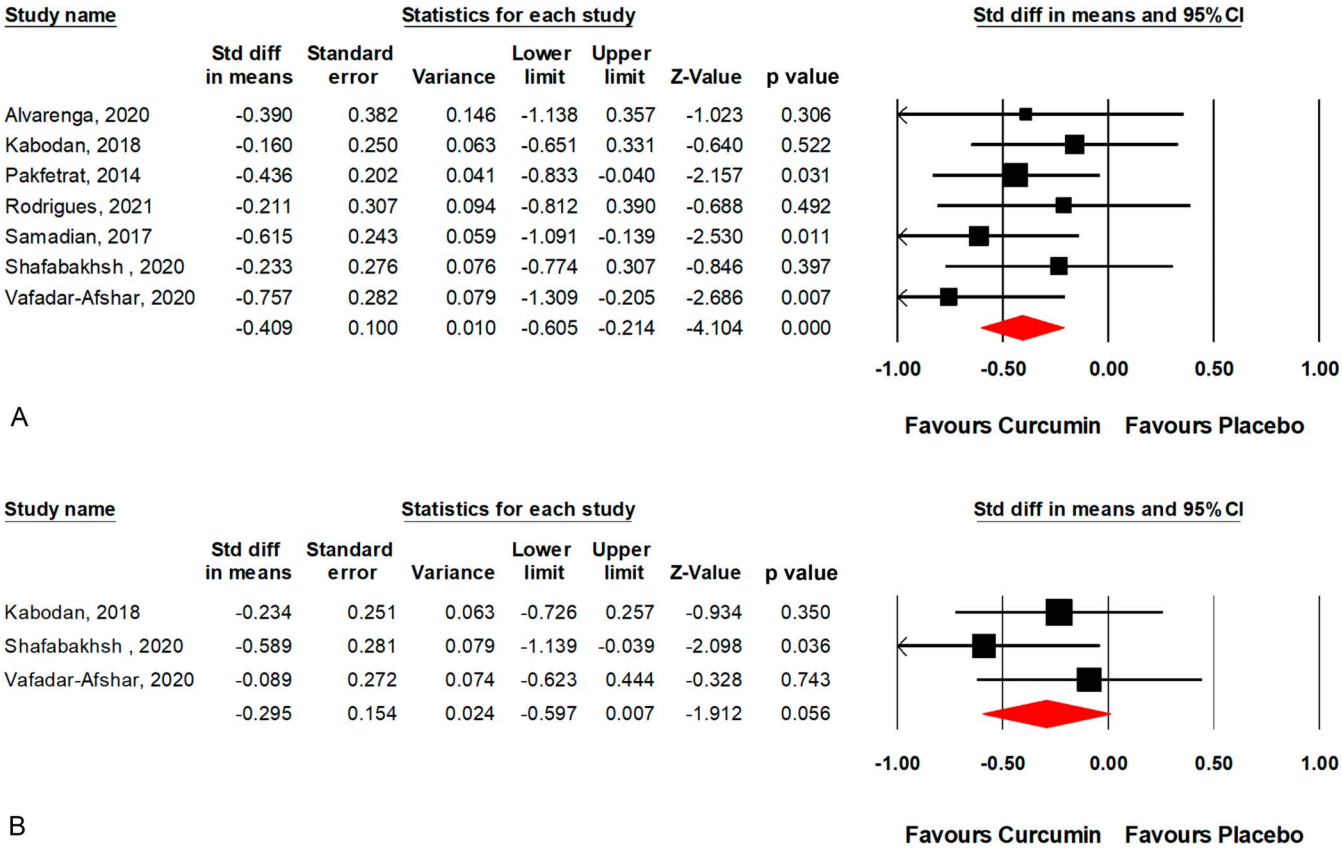

FIGURE 1. Forest plots comparing between curcumin and placebo regarding (A) hs-CRP and (B) fasting blood sugar.

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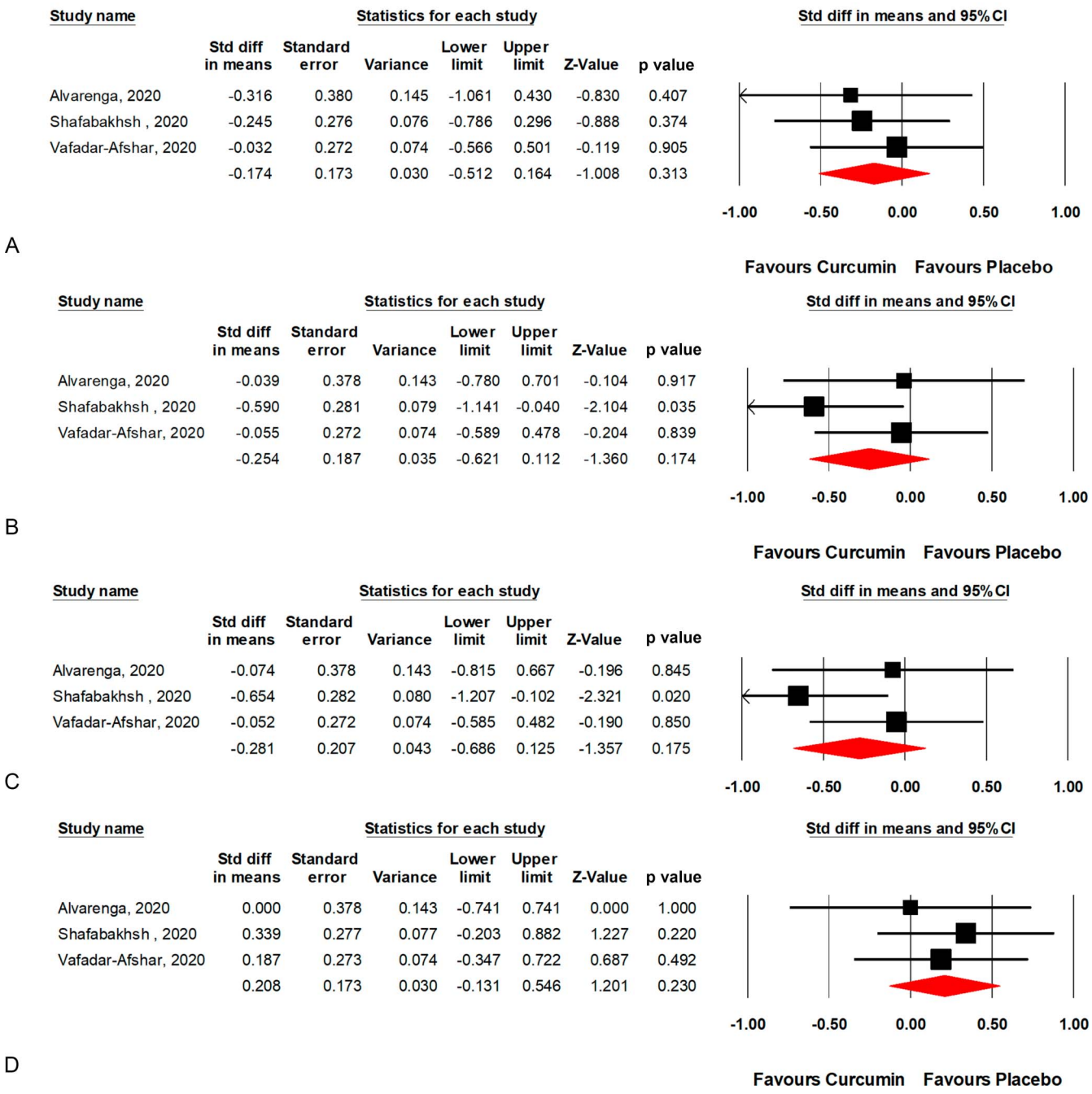

FIGURE 2. Forest plots comparing between curcumin and placebo regarding (A) triglycerides, (B) total cholesterol, (C) LDL, and (D) HDL.

metabolic profiles (FBS and lipid profile) ($P > 0.05$).[9] The anti-inflammatory effect of curcumin in HD patients may be explained by its ability to inhibit oxidative stress and reactive oxygen species generation in addition to what mentioned above.[18]

There are certain limitations to our study that should be acknowledged. First, despite pooling 7 RCTs, the number of patients included in this meta-analysis was relatively small (413 patients). Therefore, further large-scale RCTs are necessary to confirm our findings. Second, the included RCTs in our analysis were conducted in 2 countries (Brazil and Iran), which may affect generalizability to other populations. Third, although the random-effects

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model was used in our analysis, there was mild to moderate heterogeneity noted in the measurement of TC and LDL. This might be driven by differences in patient characteristics, inconsistent follow-up duration, the variations in the curcumin dosage, and formulas used in the included studies. Fourth, the lack of patient-level data did not allow to control for the presence of other confounding factors. Finally, we could not assess publication bias because of the limited number of included studies. Despite the limitations, to the best of our knowledge, this is the first meta-analysis of RCTs to compare the effect of curcumin versus placebo on inflammation and metabolic profiles in HD patients.

In conclusion, our meta-analysis demonstrated a significant improvement in inflammatory biomarkers among HD patients without substantial effects on lipid and glycemic profiles. Curcumin supplementation may have an anti-inflammatory effect in this selected patient population. However, further trials with larger sample size and longer duration of follow-up are needed to validate our findings.

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The authors have no conflicts of interest to declare.

O. Srour and A. Beran: study design; data acquisition and interpretation, statistical analysis; manuscript drafting. M. Mhanna, S.-E. Mahas, W. Khokher, and O. Alhasanat: data acquisition and interpretation; manuscript drafting. K. Srour: study supervision; critical revision for intellectual content.

Data availability statement: The authors declare that all the data supporting the findings of this study are available within the manuscript.

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