REVIEW

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Impact of Curcumin Supplementation on Radiation Dermatitis Severity: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Radiation dermatitis (RD) is a common side effect of radiotherapy in most breast cancer patients. Curcumin has recently attracted more attention for managing the side effects of breast cancer treatments. This review study aimed to investigate the effect of curcumin on the severity of radiation dermatitis in patients with breast cancer. **Methods:** All eligible randomized controlled trials (RCTs) were collected by searching PubMed, Scopus, Cochrane, and Web of Science. The effect size was expressed as weighted mean difference (WMD) and 95% confidence interval (CI). Study heterogeneity was assessed through Q statistics and I-squared. **Results:** Four RCTs with 882 patients were included in the final analysis. The results of the meta-analysis indicated that curcumin supplementation significantly reduced radiation dermatitis severity (RDS) score in the intervention group compared to the control group (WMD=-0.50; 95% CI -0.72 to -0.27, P <0.001). A significant heterogeneity was observed between the studies ($I^2 = 95.7\%$, $P < 0.001$). **Conclusion:** Based on the results of the present study, curcumin has significant effects in reducing the severity of radiation dermatitis in breast cancer patients receiving radiotherapy. Further well-designed longitudinal studies are recommended to confirm these results and to discover the underlying mechanisms of the effects of curcumin on the severity of radiation dermatitis in patients with cancer.

Keywords: Curcumin- breast cancer- radiation- dermatitis

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Introduction

Breast cancer (BC) is the most common cancer in women and a major public health concern around the world. In 2020, there was approximately 2.26 million newly diagnosed female BC worldwide (Chen et al., 2020; Ferlay et al., 2021; Hatami et al., 2022), and the cases are expected to reach 4.4 million in 2070 (Soerjomataram et al., 2021). Additionally, BC accounted for nearly 15.5% of cancer deaths, and is the leading cause of incidence and mortality in over 100 countries in 2020 (Chen et al., 2020). Currently, many types of therapies are available to treat breast cancer, such as hormone therapy, immunotherapy, chemotherapy, and radiotherapy (RT). However, the adverse reactions to therapeutic options for BC have limited their efficacy and new strategies are sought to limit the side effects of the therapies (Akbari et al., 2020; Maughan et al., 2010).

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Approximately 75% of breast cancer patients worldwide are treated with RT as adjuvant therapy after surgery. Despite the reduction in local BC recurrence and related mortality reductions due to RT (Haque et al., 2011), skin damage frequently occurs in patients with BC (Ryan Wolf et al., 2020). Because the skin is a proliferative and self-renewing organ, it is susceptible to damage by ionizing radiation (Hymes et al., 2006). Radiation dermatitis (RD) is one of the most common adverse reaction experienced by 90% of the patients with BC receiving radiotherapy (Ryan et al., 2013). RD is associated with tissue destruction, generation of reactive oxygen species, a decrease in functional stem cells, initiation of epidermal and dermal inflammatory responses, and skin cell necrosis. The severity of RD depends on various factors such as genetics (Bray et al., 2016), total radiation dose, dose fractionation schedule, and amount of organ or tissue is affected (Rosenthal et al., 2019). The severity range of RD is from faint or definite erythema to dry or moist desquamation and ulceration. RD can impair the quality of life and interrupt RT in patients with BC (McQuestion, 2011; Salvo et al., 2010).

Despite the importance of RD, effective treatment for the prevention or control of RD does not exist (Bray et al., 2016; Rosenthal et al., 2019; Ryan Wolf et al., 2018). To manage the adverse effects of RT, the use of herbal medicines and phytochemicals has recently received much attention (Akbari et al., 2020; Mansouri et al., 2020). Amongst the wide range of medical herbs, curcumin is a component of the turmeric plant and a potent antioxidant and anti-inflammatory agent used to treat skin ailments, such as scabies, acne, eczema, wrinkled skin, and wound healing. Some clinical trial studies have shown that the effect of curcumin on breast cancer dermatitis is beneficial(Khameneh et al., 2018; Sarkhosh et al., 2019). For example, Okunieff et al. reported curcumin might reduce cutaneous radiation toxicity in mice (Okunieff et al., 2006). Hemati et al. demonstrated that oral curcumin is effective in the prophylaxis of radiation-induced dermatitis in BC (Hemati et al., 2011). However, some papers found contradictory results. For example, Wolf et al. found no significant effect of curcumin on the treatment group of BC dermatitis during RT (Ryan Wolf et al., 2020). No comprehensive review has been performed on the effect of curcumin on RD in patients with breast cancer. So, this meta-analysis aimed to assess the effect of curcumin on RD severity in patients with BC.

Materials and Methods

Search Strategy

The meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). A systematic search on publications from 2000 to 2021 of the PubMed, Scopus, Cochrane, and Web of Science (WOS), databases was performed using the following Medical Subject Heading (MeSH) search terms: "Curcumin" OR "Curcuma longa" OR "Curcuminoid of turmeric" OR "diarylheptanoid" AND "Chemotherapy" OR "Chemotherapies" OR "Pharmacotherapy" OR "Drug therapy" OR "anti-cancer drugs" AND "Breast cancer" OR "lump in the breast" OR "breast metastasis" OR "breast neoplasms".

Inclusion and Exclusion Criteria

All studies evaluating the effect of curcumin on RD of patients with BC meeting all of the following criteria were considered: i) studies with a randomized controlled trial (RCT) design. ii) studies on the effect of curcumin. iii) studies with sufficient data regarding the mean changes of the RDS score along with standard deviation (SD) for both intervention and placebo groups. Duplicate papers, non-RCTs studies, studies without a placebo group, letters to the editor, animal studies, case reports, narrative reviews, studies that investigated the effect of other interventions along with curcumin in cases but not in the placebo group, and studies with insufficient data were excluded.

Data Extraction

Two authors independently screened the literature and extracted the data according to a predesigned extraction form, and an agreement was reached after consultation with the third author. The following data were extracted: the first author's name, year of publication, country of origin, study design, mean or range of age, the dosage of curcumin supplements (g/day), duration of intervention, sample size, the mean and SD of the RD score.

Data Synthesis and Statistical Analysis

Data were analyzed using STATA version 12.0 software. Standard formulas were applied to convert different data formats to the mean and standard deviations (SDs) (Higgins, 2011; Hozo et al., 2005). For instance, in the absence of SDs of the change, the following formula was uused: SD changes= square root [(SD baseline 2+SD final 2) - (2×R× SD baseline× SD final)]. Also, the standard error of the mean (SEM) to the SD was converted using the following formula: SD = SEM × √n, where "n" is the number of subjects in each group. The random-effects model was used for the meta-analysis of study outcomes. The weighting of studies was done using the generic inverse variance method. In the case of multiple evaluations in a single study group, the values belonging to the longest time point were used for the analyses. The effect size was expressed as weighted mean difference (WMD) and 95% confidence interval (CI). Q Statistics and I-squared (I^2) were used to evaluate the heterogeneity between studies. Insignificant, low, moderate, and high heterogeneity were identified with an I^2 values of 0% to 25, 26% to 50%, 5% to 75%, and 76% to 100%, respectively (Higgins et al., 2003). A sensitivity analysis was applied to assess the contribution of each study to the overall mean diference. The publication bias was assessed using the formal Egger's test (Egger et al., 1997).

Results

The process of extraction and exclusions is shown in Figure 1. After searching the systematic databases, 780 articles were selected, with 756 remaining after

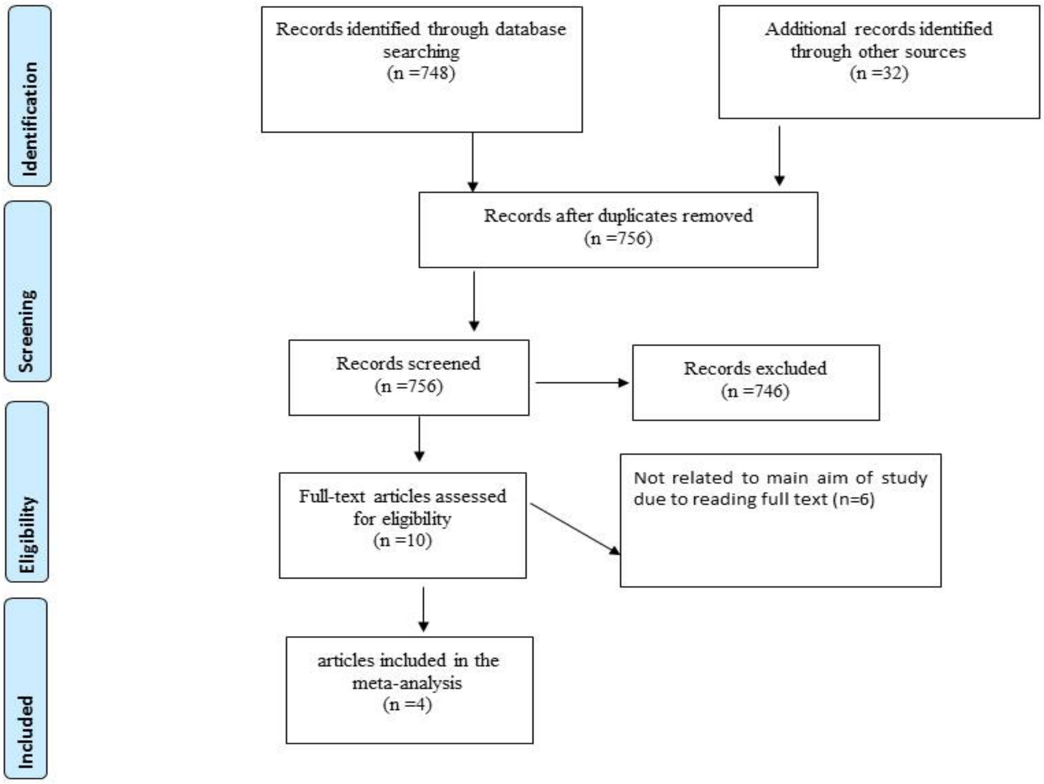

Figure 1. Flow Chart of the Included Studies, Including Identification, Screening, Eligibility and the Final Sample Included.

eliminating duplicate studies. Then, 746 articles were excluded after reviewing the abstract or title according to the inclusion criteria, and 6 articles were excluded after retrieving the full text of the remaining 10 articles. Finally, four studies met the eligibility criteria and were included in the statistical analysis (Table 1).

Effect of Curcumin Supplementation on RDS Score

A meta-analysis of a random effect model on 4 clinical trials showed that curcumin supplementation significantly reduced RDS score compared to the control group (WMD − 0.50; 95% CI − 0.72 to -0.27, P <0.001). However, between-studies heterogeneity was high (I^2 = 95.7%, P < 0.001) (Figure 2).

Sensitivity Analysis

To discover the effect of each study on the pooled effect size for RDS score, the trials were discarded step-by-step

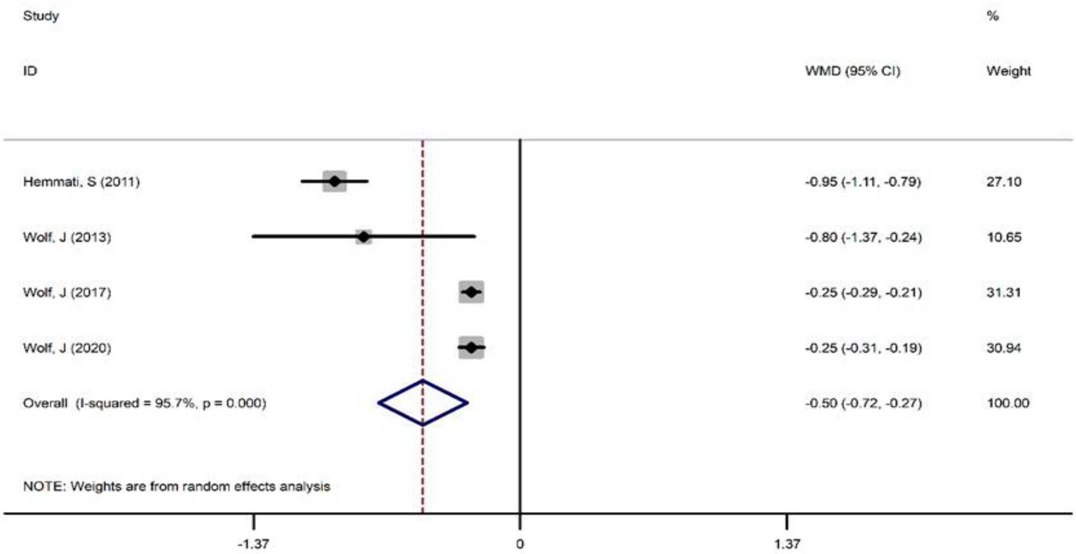

Figure 2. Forest Plot of Randomized Controlled Trials Investigating the Effects of Curcumin Supplementation on Radiation Dermatitis Severity (RDS)

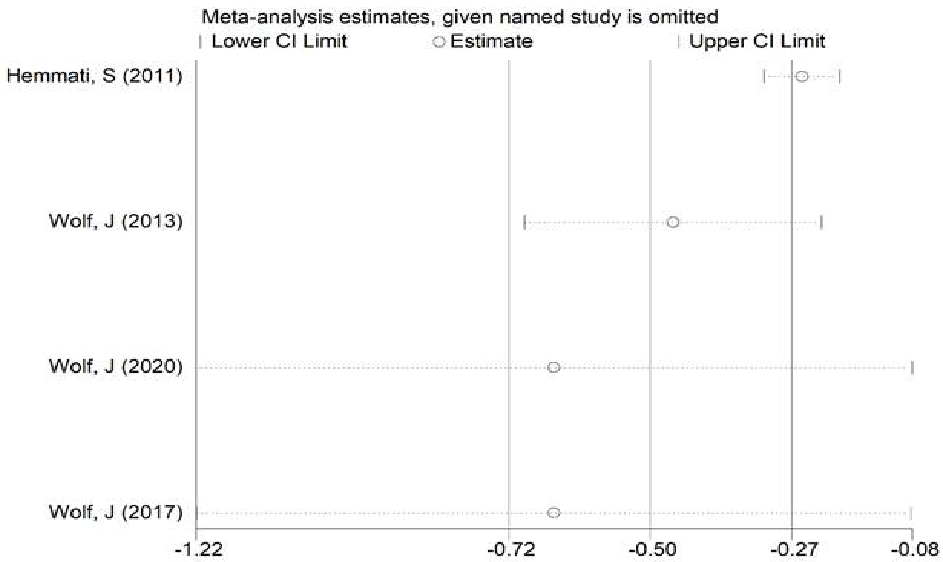

Figure 3. Sensitivity Analysis of the Weighted Mean Difference (WMD) Radiation Dermatitis Severity (RDS) Score Changes

from the analysis. The leave-one-out sensitivity analysis indicated the robustness of the results (Figure 3).

Publication bias

The results of the publication bias analysis based on the Egger's linear regression test and the visual inspection of the funnel plot. No evidence for publication bias based on the Egger's tests were detected (P = 0.308) (Figure 4).

Discussion

To the best of our knowledge, this is the first meta-analysis of RCTs evaluating the effect of curcumin on radiation dermatitis in BC patients. The present study identified that curcumin supplementation may be associated with reduced severity of RD induced by RT in patients with BC. Curcumin was reported to reduce chemotherapy-induced side-effects such as gastrointestinal toxicity, cardiotoxicity, hepatotoxicity, nephrotoxicity, neurotoxicity, ototoxicity (Liu et al., 2018). Several RCTs have been conducted to assess the effect of curcumin on the severity of RD in patients with BC. Hemati et al., (2011) in 2011 included 40 radiotherapy candidates BC patients randomly assigned to two groups: the intervention group received four 500 mg curcumin capsules, 3 times a day for 2 days, and the control group received a placebo for 2 days. The severity of RD was evaluated in weekly visits. The results indicated a faster increase in the mean score of RD in the placebo group, and curcumin supplementation was suggested to be used as prophylaxis in RD. Ryan et al., (2013) performed a RCT that assessed the curcumin effect to reduce RD severity in 30 breast cancer patients.

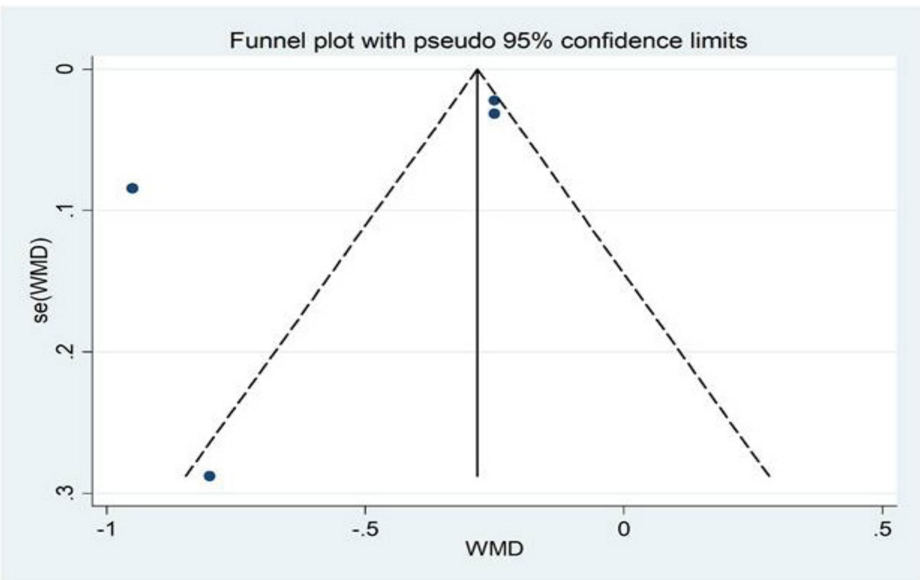

Figure 4. Funnel Plots for Evaluation of Publication Bias of Radiation Dermatitis Severity (RDS).

The patients received 2 grams of curcumin or placebo orally three times per day (i.e., 6.0 grams daily) throughout their course of RT. This study reported that oral curcumin supplementation could reduce RD severity in BC patients and significantly decrease moist desquamation, but not erythema (Ryan et al., 2013). Ryan et al., (2020) conducted a RCT to assess the effect of topical curcumin on the severity of RD in BC patients. This study did not find any significant difference in radiation dermatitis severity at the end of RT between the groups. In another study, 686 BC patients received four 500-mg capsules of placebo or curcumin three times daily throughout their prescribed course of RT until 1-week post-RT. This RCT indicated that oral curcumin did not reduce the severity of the RDS score. In another study, administration of two capsules containing curcumin 150 mg twice daily to patients with T2DM for 8 weeks significantly decreased CRP, IL-6 and TNF-α levels (Usharani et al., 2008). Afshar et al., (2020) suggested that 120 mg nanocurcumin supplementation for 12 weeks reduced inflammation markers such as hs-CRP, ICAM, VCAM. Delavarian et al., (2019) assessed the effect of curcumin to prevent RD severity in head and neck cancers. This study reported that nanomicelle curcumin is an effective agent in the prevention of OM or reducing its severity.

Saadipoor et al., (2019) included 64 eligible patients with prostate cancer. The intervention group received 120mg/day capsules, 3 times a day filled with curcumin, there was no significant difference between two groups in radiation-induced cystitis.

The exact mechanisms of the effect of curcumin on RD are not yet clear. One of the radioprotective mechanisms of curcumin can be the downregulation of the expression of fibrogenic cytokines, transforming growth factor (TGF)-β, IL-1, IL-6, IL-18, tumor necrosis factor (TNF)-α, lymph toxin-beta, cyclooxygenase 2 (COX2), and nuclear factor-kappa B (NFkB) in cutaneous tissues (Akbari et al., 2020; Kim et al., 2016). The oxidative stress causes skin reactions and inflammatory factors (Akbari et al., 2020), and curcumin may reduce levels of proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-8 (Gorabi et al., 2021). Sahebkar et al., (2014) demonstrated that curcuminoids were significantly associated with lower serum levels of the C-reactive protein (CRP). This meta-analysis reported that curcuminoid effects may be dependednton the bioavailability of curcuminoid compounds, and curcumin can be associated with a significant reduction in serum CRP levels (Panahi et al., 2015). Derosa et al., (2016) found a significant reduction of IL-6 serum levels after the use of curcuminoids supplementation. Tabrizi et al., (2018) indicated that curcumin may decrease inflammatory factors and oxidative stress. Also, consuming curcumin significantly reduced MDA levels in patients with MetS. The anti-inflammatory effects of curcumin might be related to its phytochemical compounds. IL-6 can activate the expression of CRP and inhibit the NF-κB signaling pathway, which has a key role in producing pro-inflammatory markers.

However, this study had some limitations. The trials were designed in different ways regarding intake of curcumin. Due to the lack of sufficient studies information

Table 1.The Characteristics of the Studies on the Effect of Curcumin Supplementation on Radiation Dermatitis Severity

Author's name, year	Country	Mean Age	Type of treatment	Type of cancer	Study design	Duration of intervention	Radiation dose	Dose	Intervention and Placebo	Curcumin administration	Outcome
Julie L Ryan et al. 2013	USA	58.1	Radiation therapy	Breast cancer	Randomized double-blind trial	7 weeks	All patients received standard fractionated RT (~1.8–2.4 Gy per session) for four to seven weeks with or without boost for a total radiation dose of ≥42 Gy.	2 g orally 3 times a day	Curcumin=18 Placebo=17	Oral	Oral curcumin supplementation could reduce RD severity in BC patients and significantly decrease moist desquamation, though not erythema
Wolf et al. 2020	USA	59.8	Radiation therapy	Breast cancer	Randomized double-blind trial	7 weeks	Eligible RT regimens included 1.8 to 2.0 Gy fractions for 22 to 36 sessions (total radiation dose of 44 to 66 Gy)	500 mg 3 Curcumin gel 3 times daily	Curcumin=59 HPR PLUS=58 Placebo=52	Oral	This study did not find any significant difference in radiation dermatitis severity at the end of RT between the groups
Wolf et al. 2018	USA	57.6	Radiation therapy	Breast cancer	Randomized double-blind trial	6 weeks	Conventional Fractionation on 611 patients and	500 mg 3 times a day	Curcumin=349	Oral	This RCT indicated that oral curcumin did not reduce the severity of the RDS score
Hemati et al. 2011	Iran	47.1	Radiation therapy	Breast cancer	Randomized double-blind trial	3 weeks	Conventional Fractionation on 40 patients with Fractionation 180 -200 Gy	500 mg, 3 times a day	Curcumin=20 Placebo=20	Oral	The results indicated a faster increase in the mean score of RD in the placebo group, and curcumin supplementation was suggested to be used as prophylaxis in RD

about some variables, it was not possible to perform subgroup analyses. Also, exclusion of non-English-language studies appeared to result in a high risk of bias in some areas of research such as complementary medicine (Song et al., 2010). Radiotherapy and chemotherapy are usually not given at the same time and curcumin supplementation needs to be further investigated in relation to chemotherapy.

In conclusion, the results suggest that curcumin can be considered as an effective factor in inhibiting and controlling RD in patients with BC and improving clinical symptoms. Curcumin might reduce RD severity of RD compared to placebo through various molecular pathways, such as reducing the levels of inflammatory cytokines. However, additional RCTs are still required to empower the findings of the current meta-analysis and reach a conclusion on the effects of curcumin on the severity of RD.

Author Contribution Statement

MGh, SD and MHS designed the study, and were involved in the data collection, analysis, and drafting of the manuscript. SM, SB AA were involved in the design of the study, analysis of the data, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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This study was conducted at the school of Nutrition and Food Sciences and shahid beheshti University of Medical Sciences, Tehran, Iran.

Ethics Approval and Consent to Participate

All patients signed an informed consent form at baseline. This study was approved by the ethical committee of Shahid-Beheshti University of Medical Sciences, Tehran, Iran (code: IR.SBMU.PHNS.REC.1399.038).

Consent for Publication

Institutional consent forms were used in this study.

Availability of Data and Material

Not applicable

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Conflict of Interests

The authors declare that they have no conflict of interests.

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