

The effects of curcumin as dietary supplement for patients with COVID-19: A systematic review of randomized clinical trials

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SUMMARY Accumulating evidence has been reported regarding the effect of curcumin as a dietary antiviral on patients with COVID-19; however, findings are controversial. Our systematic review aimed to evaluate the effects of curcumin in patients with COVID-19. Electronic databases (PubMed, EMBASE, Scopus, Web of Science, Cochrane Central, and Google Scholar) were systematically searched to identify only randomized clinical trials (RCTs) that assessed curcumin in patients with COVID-19 from inception to September 23, 2021 relevant keywords. The Cochrane risk-of-bias tool for randomized trials was used to evaluate the risk of bias. After a critical review of 1,098 search hits, only six RCTs were selected for discussion. A total of 480 patients were included, with 240 amongst the curcumin groups and 240 in the control group. The lymphocyte count was significantly higher in the curcumin group compared to the placebo group. Curcumin was found to decrease the number of T-helper 17 cells, downregulate T-helper-17 cell-related factors, reduce levels of T-helper-17 cell-related cytokines, yet increase the gene expression of Treg transcription factor forkhead box P3 (FOXP3), and decrease T-Box transcription factor 21 (TBX21). Our review revealed that curcumin might have a positive effect on relieving COVID-19 related inflammatory response due to its powerful immune-modulatory effects on cytokines production, T-cell responses, and gene expression. These findings suggest that curcumin confers clinical benefits in patients with COVID-19. However, due to the limited number of the included studies, further high-quality studies are needed to establish the clinical efficacy of the curcumin.

Keywords curcumin, COVID-19, SARS -CoV-2, cytokines, gene expression, systematic review

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first reported in December 2019 in China, then the virus spread expeditiously worldwide, causing a pandemic that led to health, economic and social disruption. The clinical presentation is variable, ranging from mild symptoms such as cough, myalgias, and headache to serious illnesses like acute respiratory distress syndrome (ARDS), multiorgan failure, and death (1). As of October 17, 2021, 232 million infections,

including 4.87 million deaths, have been recorded globally (2).

SARS-CoV-2 causes overactivation of the immune system, which leads to excessive cytokine production, including interleukin (IL) -6, IL-7, IL-8, IL-18, interferon (IFN)- γ , tumor necrosis factor (TNF)- α , and granulocyte-macrophage colony-stimulating factor (GM-CSF) (1). Excessive cytokine production may cause peripheral lymphopenia, neutrophilia, and cytokine storm (3). Subsequently, ARDS, multisystem organ failure, and death may develop consequently. Medications targeting the suppression of cytokine storms are vital to prevent

permanent parenchymal damage and ARDS caused by COVID-19. Among herbal medicines, curcumin has documented anti-inflammatory, antiviral, and antioxidant effects (4), which could have potential application when used against COVID-19. Curcumin, scientifically known as diferuloylmethane, is derived from the *Curcuma longa* plant and has been traditionally used in many countries as a spice and food coloring due to its yellow color. Interestingly, curcumin has been documented to improve glycemic control (5), have anticancer activity (6,7), and multiple antimicrobial effects, including antifungal, antibacterial, and antiviral (8). The prominent anti-inflammatory and immunomodulatory effects of curcumin make it a promising candidate for the treatment and prevention of COVID-19. Few randomized clinical trials (RCTs) have proposed mechanisms explaining the effect of curcumin on patients with COVID-19. However, no review has been conducted to critically and systematically evaluate these mechanisms.

Thus, this systematic review aims to evaluate the effects of curcumin among patients with COVID-19 to deliver reliable information for clinical decision-making in such cases. Furthermore, the pathophysiological mechanism of COVID-19 induced inflammation is discussed with relevance to the mechanism of action of curcumin in reducing that.

2. Methods

2.1. Protocol and registration

Our systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Cochrane Handbook for Systematic Reviews of Interventions (9,10). We registered our review at OSF Registries with DOI: 10.17605/OSF.IO/RKEMY

2.2. Eligibility criteria

Type of study: RCTs. Type of subject: Patients with COVID-19, no age criterion. Type of intervention: Studies that evaluated the effect of curcumin consumption versus placebo in patients with COVID-19. Primary results: change in the lymphocyte level, cytokines level, and gene expression.

2.3. Data sources and search strategy

We identified the studies by searching the electronic databases PubMed, EMBASE, Scopus, Web of Science, Cochrane Central, and Google Scholar. We used the following search terms ((COVID-19 OR covid-19 OR COVID OR coronavirus OR SARS-CoV-2 OR SARS virus) AND (Curcumin OR Turmeric Yellow OR yellow turmeric OR Curcuma OR Turmeric)), and the search terms were modified according to each database (Table

S1, Supplementary Material, <http://www.ddtjournal.com/action/getSupplementalData.php?ID=91>). No language restrictions were carried out. The literature search was conducted on September 23, 2021, and included all studies from inception to that data. We also evaluated the studies mentioned in the bibliographies or suggested by co-authors for eligibility.

2.4. Study selection and data extraction

Two authors independently evaluated the eligibility of studies (AKA and MAE). Any conflict was resolved by a third author (BA). All search results were transferred to Covidence Software (11). In the first phase of the selection, the title and the summary of the search results were evaluated based on the inclusion and exclusion criteria. Then, the pre-selected studies were reviewed in full to determine eligibility. From the studies that met our inclusion criteria, two authors (AKA and MAE) extracted the following information: authors, publication year, study design, study duration, subject baseline characteristics (sample size, mean age, gender, lymphocyte count, platelet counts, C-reactive protein), intervention design (type of curcumin, dose, and control group), and outcome measures of interest (interleukins, genes). Tahmasebi *et al.* conducted two RCTs on the same patient sample, but they published two articles discussing different outcomes measured, and they divided the patient into mild and severe COVID-19 (12,13). We reported each patient group separately (mild vs. severe) in our tables as each had unique baseline characteristics.

2.5. Risk of bias assessment

We used the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials for risk of bias assessment (14). Two authors (AKA and MAE) separately classified the included RCTs as having a low, high, or unclear risk of bias. Each RCT was evaluated for the following biases: selection, performance, detection, attrition, and reporting bias. BA resolved discrepancies between the reviewers. We used Review Manager V. 5.3 to create the graphs for the risk of bias assessment (15).

2.6. Outcomes of interest

Our outcome of interest was the effect of curcumin on lymphocyte count, change in cytokine levels, and gene expression of transcription factors and cytokines in patients with COVID-19.

3. Results

3.1. Study identification and selection

We identified a total of 1,098 studies from our literature

search. We removed 584 studies as duplicate and 499 studies based on the title and abstract screening. The remaining fifteen studies were read in full for eligibility. Nine studies were excluded; five had wrong study designs (16-20), one had a wrong population (21), and three were protocols. As a result, six RCTs met our inclusion criteria for the systematic review (12,13,22-25) (Figure 1).

3.2. Characteristics of included studies

RCTs evaluating the effect of curcumin on patients with COVID-19 were included in this systematic review. Two RCTs were triple blinded (22,23), and four were double-blinded (12,13,24,25). One RCT was done in India (24), and the rest in Iran (12,13,22,23,25). The RCTs included in our systematic review differ in the type and dose of Curcumin dosage, which ranged from 80 mg to 160 mg for 2-3 weeks in five RCTs (12,13,22,23,25), and 950 mg for two weeks in the last RCT (24). The total number of patients included was 480 patients

(240 patients in each group), with a mean age of 51 years. All RCTs involved both genders with a male predominance (58% total patients). Table 1 and Table 2 show the characteristics of the included studies, patient demographics, and baseline characteristics as reported by the authors.

3.3. Risk of bias of the included studies

Figure 2 shows the risk of bias summary and graph. All RCTs were classified as having a low risk of bias for random sequence generation except Valizadeh *et al.*, who used the intervention method to divide the patients (25). Five RCTs had an unclear risk of bias for allocation concealment. One RCT was at low risk of bias, as they used a randomization application to create the allocation sequence (24). Performance bias was deemed low risk in all included RCTs as they were double or triple blinded. Detection bias was low risk in Hassaniyazad *et al.* since they used coded capsule containers to achieve the triple blindness of the participants, physicians, nurses, and

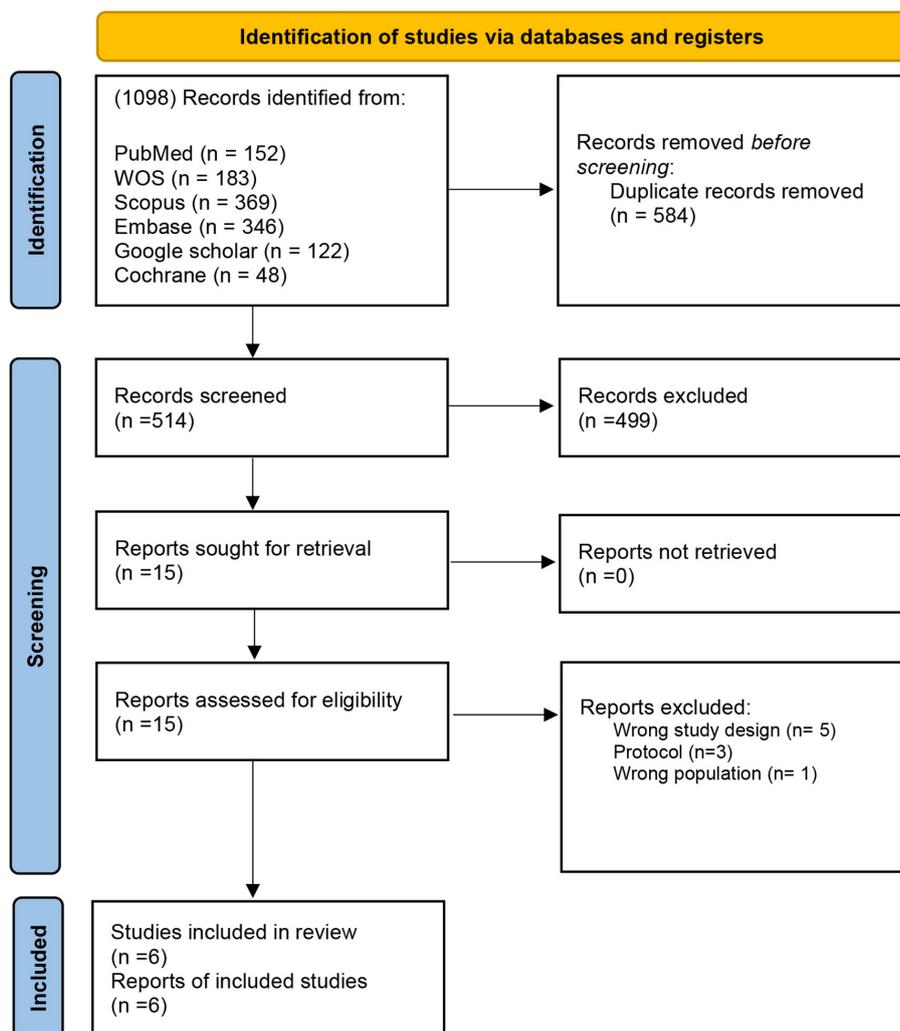


Figure 1. PRISMA 2020 flow diagram for updated systematic reviews, which included searches of databases, registers, and other sources.

Table 1. Summary of included studies

Author, Year	Study design	Year of Research	Hospital, Country	Duration (weeks)	Sample size (n)	Treatment group (n)	Control (n)	Curcumin Dose and form	Outcomes measured
Ahmadi <i>et al.</i> , 2021 (22)	Triple-blinded RCT	2020	Imam Reza Hospital, Iran.	16	60	30	30	Two soft gels (40 mg of nano-curcumin capsule) twice a day for 14 days.	CRP, lymphocyte count.
Hassaniyazad <i>et al.</i> , 2021 (23)	Triple-blinded RCT	2020	Shahid Mohammadi hospital, Iran	2	40	20	20	40 mg of the nano-curcumin capsule, four times per day for 14 days.	INF γ , IL-4, IL-17, TGF- β , CRP, lymphocyte count, lactate dehydrogenase, gene expression of TBX21, GATA3, RORC, and FOXP3 genes.
Valizadeh <i>et al.</i> , 2020 (25)	Double-blinded RCT	2020	Imam Reza hospital, Iran	2	80	40	40	160 mg of nano-curcumin (four 40 mg capsules) daily for 14 days	Lymphocyte count, platelet count, creatinine, lactate dehydrogenase, gene expression of IL-1 β and IL-6.
Tahmasebi, Saeed, <i>et al.</i> , 2021 (12)	Double-blinded RCT	2020	Imam Reza hospital, Iran	3	80	40	40	Two doses of nano-curcumin (Sina Curcumin) in an 80 mg capsule, two times for 21 days.	TGF- β , CRP, lymphocyte count, platelet count, creatinine, lactate dehydrogenase, gene expression of Treg transcription factor forkhead box P3 (FoxP3), and cytokines (IL-10, IL-35, and TGF- β).
Tahmasebi, El-Esawi, <i>et al.</i> , 2021 (13)	Double-blinded RCT	2020	Imam Reza hospital, Iran	3	80	40	40	Two doses of nano-curcumin (Sina Curcumin) in 80 mg capsule, two times for 21 days.	In mild and severe COVID: Th-17 frequency, serum level of Th17, mRNA expression levels of Th-17, cytokines secretion levels of Th-17, gene expression levels of Th17 cells, serum levels of IL-23, 21, GM-CSF.
Pawar <i>et al.</i> , 2021 (24)	Double-blinded RCT	2021	India	2	140	70	70	Curcumin (diferuloylmethane; 5 25 mg) with 2.5 mg Bioperine twice a day for 14 days	Absolute neutrophil to absolute lymphocyte ratio > 3.5; PaO ₂ /FIO ₂ ratio < 300; rising CRP, ferritin, D-dimer, LDH, and triglycerides; troponin I positive and positive CK-MB.

RCT: randomized control trial; n: Number; y: year; SD: standard deviation; CRP: C-reactive protein; IL: interleukin; INF: Interferon; TGF: tumor growth factor; CK-MB: Creatine kinase-MB.

Table 2. Baseline characteristics of the included patients

Author, Year	Population number		Age (mean \pm SD)		Sex (M: F)		Lymphocyte count (number/ μ L)		creatinine (μ mol/L)		lactate dehydrogenase (U/L)		C-reactive protein (mg/L)	
	CUR	CO	CUR	CO	CUR	CO	CUR	CO	CUR	CO	CUR	CO	CUR	CO
Ahmadi <i>et al.</i> , 2021 (22)	30	30	41.33 \pm 12.04	44.97 \pm 11	20:10	15:15	2,016 \pm 1,294	1,557 \pm 1648	NA	NA	NA	NA	3 (0-3)**	3 (1-3)**
Hassaniyazad <i>et al.</i> , 2021 (23)	20	20	48.7 \pm 10.8	48.3 \pm 11	10:10	12:8	* > 0.99 20.6%	* > 0.99 21.2%	NA	NA	606	602	* Zero 2, (10%) * +1 3, (15%) * +2 6, (30%) * +3 9, (45%)	* Zero 2, (10%) * +1 3, (15%) * +2 5, (25%) * +3 10, (50%)
Valizadeh <i>et al.</i> , 2020 (25)	20	20	53.3 \pm 8.4	51.4 \pm 7.9	15:5	16:4	< 1.0 $\times 10^9$ /L, 13 ≥ 1.0 , 7	< 1.0 $\times 10^9$ /L, 11 ≥ 1.0 , 9	* ≤ 133 , 18, (90%) * > 133, 2, (10%)	* ≤ 133 , 17, (85%) * > 133, 3, (15%)	* ≤ 245 , 13, (65%) * > 245, 7, (35%)	* ≤ 245 , 13, (65%) * > 245, 7, (35%)	NA	NA
Tahmasebi <i>et al.</i> , 2021 (12,13) (for mild COVID-19 patients)	20	20	54.2 \pm 9.1	52.4 \pm 8.5	24:16	24:16	* < 1.0 $\times 10^9$ /L, 14, (70%) * ≥ 1.0 , 6 (30%)	* < 1.0 $\times 10^9$ /L, 15, (75%) * ≥ 1.0 , 5 (25%)	* ≤ 133 , 15, (75%) * > 133, 4, (20%)	* ≤ 133 , 16, (80%) * > 133, 4, (20%)	≤ 245 , 14, (70%) > 245, 6, (30%)	* ≤ 245 , 11, (55%) * > 245, 9, (45%)	* ≥ 10 13, (65%)	* ≥ 10 9, (45%)
Tahmasebi <i>et al.</i> , 2021 (12,13) (for severe COVID-19 patients)	20	20	54.2 \pm 9.1	52.4 \pm 8.5	24:16	24:16	* < 1.0 $\times 10^9$ /L, 15, (75%) * ≥ 1.0 , 5, (25%)	* < 1.0 $\times 10^9$ /L, 14, (70%) * ≥ 1.0 , 6, (30%)	* ≤ 133 , 16, (80%) * > 133, 4, (20%)	* ≤ 133 , 17, (85%) * > 133, 3, (20%)	* ≤ 245 , 11, (55%) * > 245, 8, (40%)	* ≤ 245 , 9, (45%) * > 245, 11, (55%)	* ≥ 10 17, (85%)	* ≥ 10 14, (70%)
Pawar <i>et al.</i> , 2021 (24)	70	70	51.5 \pm 14.13	54.25 \pm 12.44	45:25	54:16	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

M: male; F: female; SD: standard deviation; CUR: curcumin; CO: control; L: liter. *Data are presented as the variable's value, patient number, (patient percentage compared to total patients included). **Data of C-reactive protein is reported using the qualitative method rather than the quantitative method used in the rest of the studies.

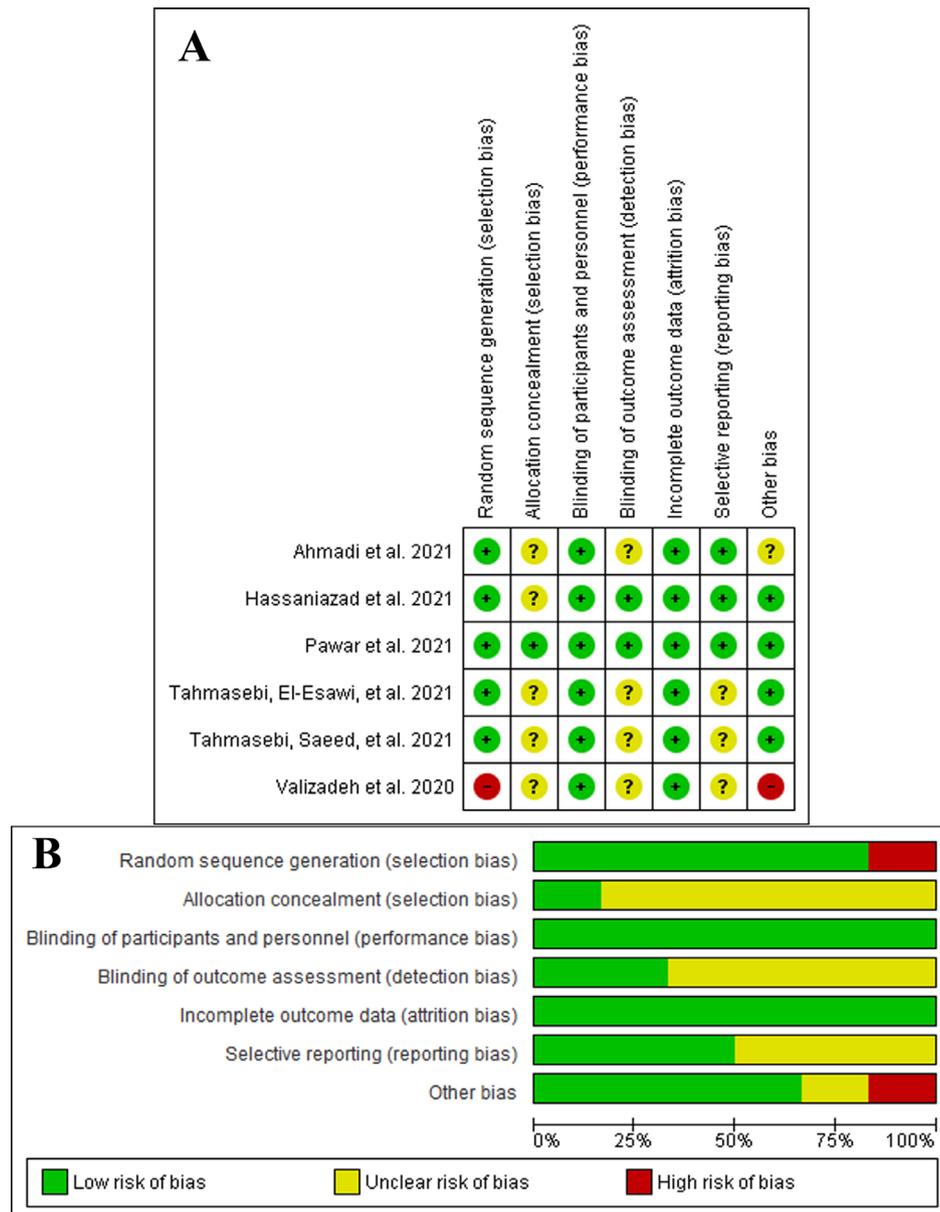


Figure 2. Risk of bias assessment. A: Risk of bias summary: review authors' judgments about each risk of bias item for each included study. The items are scored (+) low risk; (-) high risk; (?) unclear risk of bias. B: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

data collectors (23). Pawar *et al.* was also classified as a low risk of detection bias as the researchers assessing outcomes and analyzing data were masked to group assignment (24); the remaining RCTs were at unclear risk of bias. Attrition bias was low risk in all RCTs. Finally, selective reporting bias was deemed low risk in three RCTs and unclear risk in Valizadeh *et al.* (25) and both RCTs by Tahmasebi *et al.* (12,13).

3.4. Outcomes of interest

All RCTs evaluated the effects of curcumin on the lymphocyte count, reporting that lymphocyte count was significantly higher in the curcumin group than in the placebo group (12,13,22-25).

Four RCTs reported outcomes evaluating the effect of curcumin on gene expression of transcription factors and cytokines (12,13,23,25). Tahmasebi, El-Esawi *et al.* reported a significant decrease in the number of T-helper 17 cells, downregulation of T-helper 17 cell-related factors (RAR-related orphan receptor γ t, IL-17, IL-21, IL-23, and GM-CSF), and decreased levels of T-helper 17 cell-related cytokines were found in both mild and severe COVID-19 patients treated by curcumin compared to the placebo group (13). In addition, Tahmasebi, Saeed *et al.* reported that curcumin upregulates the frequency of T regulatory cells leading to an increase in the gene expression transcription factor forkhead box P3 (FOXP3) and cytokines (IL-10, IL-35, and TGF- β) (12). Those findings were consistent with Hassaniazad *et al.*, who

also reported that curcumin significantly increased gene expressions of *FOXP3* and decreased T-Box transcription factor 21 (*TBX21*) genes (23). Finally, Valizadeh *et al.* assessed the mRNA expression and cytokine secretion levels of IL-1 β , IL-6, TNF- α , and IL-18, and curcumin decreased IL-6 and IL-1 β expression and secretion but did not affect TNF- α and IL-18 (25).

4. Discussion

Due to the lack of strict regulation, the need to demonstrate the efficacy, safety, and quality of a marketed product is less reinforced by manufacturers of dietary supplements than in the pharmaceutical sector. As a result, many of the available products can be ineffective (26,27). However, systematic reviews and meta-analyses are at the top of the clinical evidence hierarchy and can decide whether nutraceutical agents should be used in the clinical setting. Fortunately, there were recent advances in the management of COVID-19, including antiviral agents, monoclonal antibodies along with supportive care measures, oxygen therapy, and usage of corticosteroids (28-30). The purpose of this systematic review is to highlight the multi-therapeutic effects of curcumin as a dietary supplement in reducing inflammation, relieving the symptoms of COVID-19, and accelerating the recovery process. To the best of our knowledge, the present review is the first to gather and present the currently available evidence on the effects of curcumin on COVID-19 patients.

Regulatory T-cells are involved in the downregulation of immune responses by producing inhibitory cytokines like TGF- β , IL-10, and IL-35. On the other hand, T helper 17 cells enhance the inflammatory response by producing IL-17, IL-21, IL-22, and GM-CS. An imbalanced ratio of T regulatory/T helper 17 cells is one of the underlying mechanisms of immune system dysregulation and hyper inflammation in COVID-19 that is associated with high mortality rates (31). According to Valizadeh 2020 *et al.* (25), cytokine storm might be the cause of the higher mortality rates observed in the placebo group 40% (8 out of 20) in comparison to the curcumin group that had a mortality rate of 20% (4 out of 20); moreover, Tahmasebi 2021 *et al.* (12) stated mortality rates in the curcumin group of 0% (0 out of 20) and 5% (1 out of 20), compared to the placebo group with 5% (1 out of 20) and 25% (5 out of 20) in the mild and severe group, respectively. Furthermore, studies (12,23) indicate that curcumin has a significant effect on gene expression, which can subsequently modulate the immune response in COVID-19 patients compared to placebo. Curcumin can attenuate the T helper 1 inflammatory response by downregulating the *TBX21* gene (the transcription factor involved in developing T helper cells to the T helper lineage). Curcumin also downregulates T helper 17 and the expression of the RAR Related Orphan Receptor (ROR) C gene, which is the transcription factor ROR γ t

for T helper 17 cell differentiation (23). Moreover, curcumin acts as a modulator of T regulatory cells by upregulating *FOXP3* and *GATA* binding protein 3 genes. With the effects of curcumin detailed above, it is reasonable to infer that curcumin may restore normal homeostasis in COVID-19 patients by suppressing T helper 1 and T helper 17 cell responses and augmenting the T regulatory cell responses.

COVID-19 patients had a significantly higher neutrophil-to-lymphocyte ratio compared to their healthy counterparts. Neutrophil to lymphocyte ratio also correlates with disease severity and could potentially be used to predict disease outcomes in COVID-19 (32). Surprisingly, curcumin has been shown to increase lymphocyte percentage, decrease the neutrophil percentage, and decrease neutrophil to lymphocyte ratio in COVID-19 patients (23). This can be explained by curcumin's ability to inhibit the nuclear factor- κ B (NF- κ B) pathway in addition to other proinflammatory pathways (*i.e.*, mitogen-activated protein kinase (MAPK) and the Janus kinase (JAK) (33). These pathways promote neutrophil apoptosis and suppression of sustained inflammatory response.

Additionally, curcumin significantly suppresses mRNA expressions of proinflammatory markers IL-1 β and IL-6 markers in COVID-19 patients, as was experimentally measured by (25). But, it did not decrease the level of IL-18 and TNF- α . Interestingly, IL-6 was significantly elevated in critically ill COVID-19 patients with ARDS than patients without ARDS and was strongly associated with death (34). Thus, curcumin may improve mortality by reducing inflammatory cytokines (mainly IL-6). Curcumin has also demonstrated molecular effects by adjusting several inflammatory molecules like histone acetylase, histone deacetylase, protein kinases, protein reductases, glyoxalase I, proteasome, and carrier proteins (35). The antioxidant effect of curcumin occurs by increasing the activity of superoxide dismutase and enhancing the expression of glutamate-cysteine ligase, both of which control the production of the cellular antioxidant glutathione (36). Glutathione is essential for the regulation of cellular proliferation, apoptosis, and immune response (37).

Curcumin is generally considered safe in its use as a food additive by the Food and Drug Administration. The allowable daily intake of curcumin is 0-3 mg/kg body weight (38). Potential adverse effects have been documented and include diarrhea, headache, rash, and yellow stool (39), but no serious adverse effects have been reported to date. One limitation of using curcumin as a therapeutic agent is its poor bioavailability. It is poorly absorbed, has a rapid metabolism, and is subsequently eliminated rapidly from the body. Several formulations have been prepared to enhance its bioavailability. For example, The combination of curcumin with piperine, the main active ingredient of black pepper, was associated with a 2,000% increase

in curcumin bioavailability (19,40). Nano-formulations of curcumin improve curcumin's solubility in aqueous solutions (41) and have improved concentration in the blood (42).

Curcumin effectively improves myalgia, cough, taste, and olfactory disturbances in COVID-19 patients (22). In addition, another open-label nonrandomized clinical trial has documented that Curcumin alleviated COVID-19 related symptoms like fever, chills, tachypnea, myalgia, and cough (20). These characteristics add to the curcumin activity in reducing inflammation, accelerating the healing process, and decreasing the mortality in COVID-19 patients through the above-noted mechanisms. Therefore, curcumin is considered a potential therapeutic agent for COVID-19. However, further RCTs are required to evaluate the bioavailability, efficacy, and safety of the use of Nanocurcumin in COVID-19 patients.

The main limitation of this systematic review was that we could not perform a meta-analysis. Statistical analysis was not applicable due to the insufficient number of the RCTs in each outcome and lack of homogeneity between the RCTs. Other limitations are related to the included RCTs, such as a short course of follow-up, a small sample size, and different dosages of curcumin used among the trials. This may lead to heterogeneity in clinical effects and further affect the results. Finally, the external validity and applicability of the results to other populations are questionable as most of the RCTs were conducted in Iran. Therefore, more RCTs should be conducted to study curcumin's application as a potential treatment of COVID-19.

5. Conclusion

In conclusion, the results of the present review suggest that curcumin is a promising herbal medicine that may be effective in treating COVID-19 due to its powerful immune-modulatory effects on cytokines production, T-cell responses, and gene expression. However, it is noteworthy that further high-quality studies are required to confirm our results based on the limited available data.

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