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Mini-Review

Curcumin as a Promising Therapy for COVID-19: A Review

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ABSTRACT

The ongoing COVID-19 pandemic has spurred intense research efforts to identify effective therapeutic options. Among the potential candidates, curcumin, a naturally occurring polyphenol obtained from turmeric, has gained considerable attention due to its diverse pharmacological properties. This review examines the existing literature on curcumin's potential as a new promising treatment for COVID-19. Curcumin demonstrates antiviral effects by modulating key signaling pathways for entry and multiplication of SARS-CoV-2 in host cells. It limits viral entry in host cells as it binds and inhibits S-protein, TMPRSS2, and ADAM17 enzymes required for cytoadherence and membrane fusion. It also downregulates SARS-CoV-2 replication by preventing the release of the viral genomic RNA into the cytoplasm from virus-containing vacuoles and subsequently inhibits enzymes required for viral replication. Rennin–angiotensin–aldosterone system (RAS) dysfunction, especially increased angiotensin-converting enzyme (ACE)-Angiotensin II-AT1R axis activity, is associated with prothrombotic state, acute respiratory distress syndrome, and lung injury in COVID-19 patients. Curcumin increases soluble ACE2 cellular ACE2 activity, restores RAS normal function, and mitigates these complications. Curcumin also exerts anti-inflammatory and immunomodulatory actions. It reduces the secretion of pro-inflammatory cytokines through inhibition of toll-like receptors (TLRs), namely, TLR2, TLR4, and TLR9, and enhances the production of anti-inflammatory cytokines like interleukin-10. In addition, it prevents the progression of tissue damage and inflammation by reactive oxygen species (ROS) through ROS scavenging enzymes. Due to its antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties, curcumin has emerged as an attractive candidate for combating various aspects of COVID-19 pathogenesis, such as excessive inflammation, oxidative stress, viral multiplication, and immune dysregulation. However, limited clinical evidence is currently available to support its efficacy, specifically against COVID-19. Thus, further research, including clinical trials, is warranted to evaluate curcumin's therapeutic potential and determine its optimal dosage, formulation, and safety for COVID-19 patients. Overall, based on its favorable pharmacological properties and promising preclinical data, curcumin holds promise as a treatment for COVID-19, but its clinical utility requires further exploration.

Keywords: Curcumin, *Curcuma longa*, COVID-19, SARS-CoV-2, Phytochemicals

INTRODUCTION

COVID-19 is a serious respiratory illness with potential for multisystem involvement caused by SARS-CoV-2. It emerged as a pandemic in December 2019 and still continues to pose a significant challenge to healthcare systems globally.[1] COVID-19 has been a substantial burden on the healthcare infrastructure, leading to overwhelmed hospitals, increased mortality rates, and economic disruptions.[1] SARS-CoV-2 infects the respiratory system, and various approaches, such as vaccination, development of new therapies, and repurposing of existing therapeutics, have been employed. However, effective medications to diminish and control the disease without significant adverse effects are not yet available.

Curcumin, a polyphenolic compound obtained from turmeric, has been extensively explored for its anti-inflammatory, antimicrobial, antioxidant, and immunomodulatory activities.[2,3] Since alteration of cytokine response, immune dysfunction, and excessive inflammation play a key role in SARS-CoV-2 pathogenesis, curcumin could be beneficial in combating COVID-19.[2] In addition, curcumin exhibits antiviral activity and inhibits the replication of certain viruses.[4] The rationale for the exploration of curcumin as a promising therapy for COVID-19 has been discussed here in light of the currently available research evidence.

MOLECULAR MECHANISMS OF COVID-19 PATHOGENESIS

SARS-CoV-2 primarily infects pneumocytes through the interaction of viral S-protein with the angiotensin-converting enzyme2 (ACE2) on host cells.[5] A cell surface transmembrane protease (TMPRSS2) and a metalloprotease (ADAM17) facilitate the fusion of the SARS-CoV-2 envelope with the host cell membrane. TMPRSS2 cleaves S-protein, leading to its change in conformation.[6] After clathrin-mediated endocytosis, the virus-containing vacuoles undergo acidification and subsequent fusion with endosomes/lysosomes. The viral genome escapes from the vacuole into the cytoplasm through protein pores formed by viral proteins that have undergone conformational changes in an acidic milieu. The replication transcription complex is made by viral nonstructural proteins, and SARS-CoV-2 genome replication starts. The viral enzymes, namely, 3C-like protease (3CLpro) and papain-like protease (PLpro), are important for replication by facilitating proteolytic cleavage. After assembly, new virions are released through exocytosis.

On infection, the immune system mounts a multifaceted response involving innate and adaptive immune cells. The innate immune response includes activation of macrophages, natural killer (NK), and dendritic cells, which recognize the products of virus and damaged host cells, namely, microbe-associated molecular patterns (MAMPs) and damage-associated molecular patterns (DAMPs) through their pattern recognition receptors (PRR). Pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α), are secreted from these immune cells.[7] Cytokines have a pivotal function in orchestrating the immune response. Nevertheless, in certain instances, an excessive immune response can emerge, resulting in a cytokine storm marked by the excessive production of pro-inflammatory cytokines causing systemic inflammation, tissue damage, endothelial damage, activation of coagulation cascade, hypercoagulability, and multiorgan failure.[8,9] Comprehending the intricate relationship of SARS-CoV-2, inflammation, and cytokine storm is vital for crafting specific therapeutic approaches for COVID-19.

CURCUMIN: SOURCE, PROPERTIES, AND MECHANISMS OF ACTION

Curcumin, is a biological compound of polyphenolic class obtained from *Curcuma longa* rhizome, commonly known as turmeric. Turmeric has been utilized in Ayurveda for centuries in the Indian subcontinent.[10] It possesses various bioactive properties, including anti-inflammatory, antioxidant, antimicrobial, and antineoplastic effects.[10,11] It has been the focus of research to a great extent for its pharmacological properties and its applications in diseases, including cancer, cardiovascular diseases, neurodegenerative disorders, and viral infections.[10,11]

Curcumin applies anti-inflammatory effects through multiple mechanisms. It inhibits the activity of nuclear factor-kappa B, a key transcription factor involved in the liberation of pro-inflammatory cytokines.[12] In addition, curcumin modulates various signaling pathways of inflammation, including MAP kinases and JAK/STAT pathways.[10] Moreover, curcumin possesses immunomodulatory properties by controlling the equilibrium between pro and anti-inflammatory cytokines. It can suppress pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, while enhancing the production of anti-inflammatory cytokines, including IL-10.[13,14]

Curcumin has demonstrated promising antiviral effects against various viral pathogens by targeting stages of viral replication. These antiviral properties are attributed to its ability to target multiple molecular pathways in virus replication and host immune responses. It can directly interfere with viral attachment and cell entry, disrupt viral replication, inhibit viral proteases, and modulate host immune responses against viral infections.[4,15] Moreover, curcumin has demonstrated antiviral action against enveloped viruses such as herpes simplex virus, dengue virus, influenza, and respiratory syncytial virus, and non-enveloped viruses such as norovirus and enterovirus.[15,16]

MECHANISMS OF ANTIVIRAL ACTION OF CURCUMIN AGAINST SARS-COV-2

Curcumin displays unique mechanisms of antiviral action against SARS-CoV-2, affecting each phase in the replicative cycle of the virus in the host cell [Figure 1]. Pertaining to its superior binding capability to cell surface ACE2 and viral S-protein, curcumin interferes with SARS-CoV-2 adherence and entry into host cells. TMPRSS2 and ADAM17 are the essential enzymes mediating the fusion of viral envelopes with cell membranes during viral entry. Curcumin also shows a great propensity to bind with these two enzymes, thereby inhibiting them. Furthermore, pulmonary fibrosis, acute respiratory distress syndrome (ARDS), and lung injury of COVID-19 are related to dysregulation of the renin–angiotensin–aldosterone system.[17] SARS-CoV-2

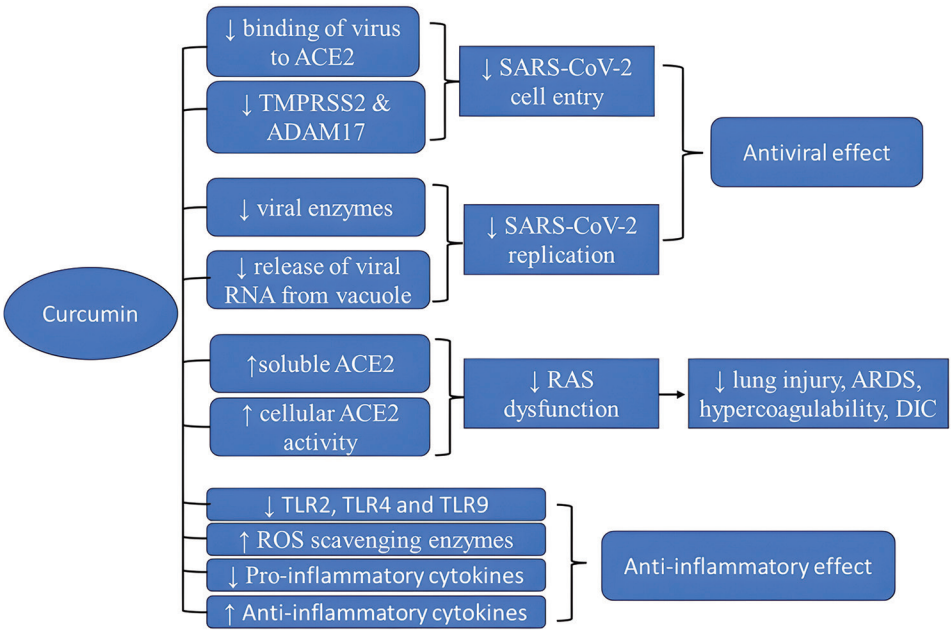

Figure 1: Mechanisms of biological actions of curcumin in COVID-19. ACE2: Angiotensin-converting enzyme 2, TMPRSS2: Transmembrane serine protease 2, ADAM17: A desintegrin and metalloproteinase domain 17, TLR: Toll-like receptor, ROS: Reactive oxygen species, ARDS: Adult respiratory distress syndrome, DIC: Disseminated intravascular coagulation, RAS: Renin-angiotensin system.

downregulates ACE2 in pulmonary tissue and, thereby, shifts the balance toward the ACE-angiotensin II-AT1R axis over the ACE2-Ang1-7-MasR axis. This leads to endothelial injury, prothrombotic state, pulmonary fibrosis, and ARDS. Curcumin increases soluble ACE2, which binds with SARS-CoV-2 competitively, minimizing its access to cell surface ACE2. This not only leads to reduced host cell infection but also restores cellular ACE2 activity, which is essential for maintaining a balance of the renin-angiotensin system.[18] Apoptosis and release of lysosomal enzymes give rise to greater inflammatory damage in COVID-19. Unlike cancer cells, curcumin prevents apoptosis and autophagy in SARS-CoV-2-infected pneumocytes by inhibiting caspase-3 activation. Curcumin stabilizes the virus-containing vacuole membrane, impedes the fusion with lysosomes, and minimizes the extent of viral replication. SARS-CoV-2 protein translation is also impeded by curcumin as it binds and inhibits viral enzymes, such as 3CLpro and PLpro.

Curcumin's immunomodulatory properties are implicated in its potential role in defending against SARS-CoV-2. Innate immune cells such as macrophages, NK cells, and dendritic cells recognize the molecular patterns (MAMPs and DAMPs) associated with virus and virus-infected cells through their PRR such as Toll-like receptors (TLR) and contribute to inflammation by producing pro-inflammatory cytokines. Curcumin inhibits TLR2, TLR4, and TLR9, reducing the secretion of inflammatory cytokines such as INF-α and TNF-α. Furthermore, curcumin blocks CD2/CD3/CD28-initiated helper CD4+ T-cell activation and NFAT-regulated expression of cytokines. Reactive oxygen species (ROSs) are generated by neutrophils through oxidative metabolism. These molecules damage cellular structures and DNA as a part of inflammation. Curcumin upregulates the generation of catalase, superoxide dismutase, glutathione-S-transferase, etc. ROS scavenging enzymes and prevents the progression of inflammatory damage to host cells and macromolecules. This multipronged inhibition reducing cytokine production from T lymphocytes, macrophages, NK cells, dendritic cells, and reducing macromolecule damage by ROS opens the prospect for curcumin to be used in COVID-19 treatment to mitigate cytokine storm and inflammation.

IN VITRO STUDIES ON ACTIONS OF CURCUMIN ON SARS-COV-2

Various *in vitro* studies have investigated curcumin's biological effects on SARS-CoV-2.[19-22] These studies have explored curcumin's actions on SARS-CoV-2 entry, replication, viral load, cytokine profile, immune cells, and inflammation [Table 1]. In one study, curcumin suppressed entry of Omicron variant SARS-CoV-2 through disrupting the Omicron S-protein - hACE2 complex.[19] The authors studied seven phytochemicals and found that curcumin had the greatest capacity to counter Omicron S-protein due to

Table 1: Studies on effects of curcumin in COVID-19.

Author, year	Type of study	Formulation used	Research outcome
Nag *et al*., 2022[19]	*In vitro* study	Curcumin	Curcumin showed most effective binding and inhibition of Omicron S-protein.
Allam *et al*., 2020[20]	*In vitro* study	Curcumin	Apart from S-protein, curcumin also interacted with Adenosine triphosphatase (ATPase) domain of GRP78 on molecular docking analysis.
Guijarro-Real *et al*., 2021[21]	*In vitro* study	Methanolic extract of turmeric rhizomes and commercial curcumin	Turmeric extract had substantial inhibition of the 3CLPro enzyme of SARS-CoV-2, while commercial curcumin was less effective
Bormann *et al*., 2021[22]	*In vitro* study	Turmeric root extract, curcumin capsule, and pure curcumin	All three curcumin formulations neutralized and rendered SARS-CoV-2 to subtoxic level at in Vero E6 and human Calu-3 cells and also reduced SARS-CoV-2 RNA concentration in the supernatants significantly
Cho *et al*., 2007[14]	*In vitro* study	Curcumin	Curcumin showed inhibitory action on production of IL-1ß, IL-6, IL-8 and TNF-α, etc., pro-inflammatory cytokines and cyclin E in HaCaT cells
Abo-Zaid *et al*., 2020[23]	Animal experiment	Curcumin administered by intraperitoneal injection	Curcumin prevented carbon tetrachloride induced hepatic cirrhosis in rats and had substantially increased IL-10 and decreased TNF-α and TGF-1β levels
Bereswill *et al*., 2010[24]	Animal experiment	Curcumin dissolved in 2% Carboxy-Methyl-Cellulose administered per orally	Curcumin protected mice from acute ileal inflammation and associated with improved gut barrier function, increased regulatory T cells, epithelial cell regeneration, higher anti-inflammatory cytokines and lower pro-inflammatory cytokines
Chai *et al*., 2020[25]	Animal experiment	Curcumin administered by intraperitoneal injection	Curcumin suppressed inflammation and ameliorated lung injury in mice. Curcumin facilitated Treg differentiation, increased IL-10 production, while reducing IL-17A levels, MPO-producing neutrophils, and NF-κB p65 expression
Pawar *et al*., 2021[26]	Clinical trials	Curcumin with Piperine (525 mg+2.5 mg) twice a day for 14 days	Curcumin treatment group showed early recovery, less deterioration, fewer red flag signs, better oxygen saturation, reduced duration of hospital stay, less mortality in COVID-19 infection
Askari *et al*., 2022[27]	Clinical trials	Curcumin with Piperine (500 mg+5 mg) twice a day for 14 days	Curcumin treatment group showed significant reduction in weakness associated with COVID-19 infection. Cough, sore throat, muscular pain, headache and dyspnea improved in both treatment group and placebo group
Valizadeh *et al*., 2020[2]	Clinical trials	Nano-curcumin (40 mg) four capsules daily for 14 days	Nano-curcumin treatment group showed a substantial decrease in mRNA expression and secretion of IL-6 and IL-1β in COVID-19 patients.
Asadirad *et al*., 2022[28]	Clinical trials	Nano-curcumin 240 mg/day for 7 days	Nanocurcumin group showed improvement in clinical and laboratory parameters, mortality rate in COVID-19 patients with significant decrease in IFN-γ, IL-1β, IL-6 gene expression and IL-1β serum levels
Hassaniazad *et al*., 2021[29]	Clinical trials	Nano-micelles containing curcumin (40 mg) 4 times daily for 14 days	Curcumin nano-micelles group showed decline in TBX21 gene expression and serum levels of IFN-γ and IL-17 with increase in FOXP3 gene expressions and serum levels of IL-4 and TGF-β in COVID-19 patients

3CLPro: 3C-like protease, IL: Interleukin, TNF-α: Tumor necrosis factor-alpha, NF-κB: Nuclear factor-kappa B, GRP78: Glucose-regulating protein 78, TGF: Transforming growth factor, MPO: Myeloperoxidase, IFN-γ: Interferon gamma, mRNA: Messenger RNA

its stable binding. Besides ACE2, glucose-regulating protein 78 (GRP78) is another cell-surface receptor implicated in SARS-CoV-2 cell entry. Allam *et al*. (2020) observed that curcumin could block GRP78-dependent cell entry as it binds with the S-protein binding site and ATPase site of GRP78.[20] Furthermore, in their study, Guijarro-Real *et al*. (2021) demonstrated that extracts from turmeric rhizomes effectively inhibited 3CLpro, an essential enzyme for SARS-CoV-2 replication in host cells.[21] However, the inhibitory action of commercial curcumin was lower in comparison to the extract, indicating the potential presence of other bioactive components of turmeric rhizomes, which might have suppressed SARS-CoV-2 replication. Yet, another study identified that curcumin remarkably neutralized

SARS-CoV-2 in human Calu-3 and Vero E6 cells.[22] Moreover, curcumin has shown potential in modulating the host immune response during SARS-CoV-2 infection. It repressed inflammatory chemokines, namely, TNF-α, IL-1β, and IL-6, thereby attenuating cytokine storm associated with COVID-19 complications.[14]

EVALUATION OF CURCUMIN'S EFFECTS IN COVID-19 USING ANIMAL MODELS

Curcumin's capacity for immunomodulation is an essential attribute that holds promise for improving treatment outcomes for COVID-19 [Table 1]. The activity of curcumin concerning cytokine profile and hepatic fibrosis has been explored in experimentally induced hepatic cirrhosis models in rats.[23] A substantial increase in IL-10, an anti-inflammatory mediator, along with a marked reduction in hepatic fibrosis and pro-inflammatory TNF-α and transforming growth factor 1 beta (TGF-1β), was observed in curcumin-treated animal groups as compared to the control group. Curcumin's anti-inflammatory and immunomodulatory action was noted in another study utilizing an intestinal inflammation model in mice.[24] Curcumin supplementation was associated with an increase in Treg cells, enhanced ileal epithelial cell regeneration, restoration of the beneficial intestinal microbiome, and repression of TNF-α, interferon-gamma (IFN-γ), IL-6, IL-23p19, and monocyte chemoattractant protein-1.[24] ARDS is a rapidly developing, life-threatening pulmonary disorder characterized by the leakage of fluid into the alveolar space pertaining to direct lung injury, inflammation, or systemic factors. ARDS is a sequelae of severe COVID-19 and a major contributing factor to mortality. Curcumin significantly alleviated lung pathology and diminished the extent of inflammatory chemokines in the murine model of ARDS.[25] The authors also demonstrated that differentiation from naive T-cells to Treg cells, differentiation of M2 macrophages, and IL-10 secretion was stimulated by curcumin.

CLINICAL TRIALS ON CURCUMIN THERAPEUTIC INTERVENTION FOR COVID-19

Although insufficient in number, clinical trials have yielded valuable evidence regarding the potential therapeutic efficacy of curcumin in managing COVID-19 [Table 1]. In a clinical trial, oral curcumin and piperine supplementation was found to significantly decrease the duration and intensity of symptoms among COVID-19 patients in contrast to a placebo group.[26] Curcumin-treated patients had early recovery, shorter hospital stays, and regularly maintained more than 94% oxygen saturation on room air. While the anti-inflammatory properties of curcumin accelerated the recovery from COVID-19, its antimicrobial properties reduced secondary bacterial and fungal infections.[26] In another clinical trial, Askari *et al*. (2022) assessed the effectiveness of 500 mg curcumin with 5 mg piperine in twice daily dosage for two weeks on the duration, severity, symptoms, and inflammatory indices in COVID-19 patients.[27] A significant reduction in weakness among the patients in the treatment group was observed when compared to those in the placebo group. A clinical trial conducted by Valizadeh *et al*. (2020), studied nanocurcumin's immunomodulatory effects in terms of expression of cytokines in COVID patients.[2] Nanocurcumin is a formulation in which curcumin is nano-encapsulated or processed into nanoparticles to enhance solubility, stability, bioavailability, and cellular uptake. A notable reduction in expression and synthesis of IL-6 and IL-1β was documented in the COVID-19 group following therapy with nano curcumin.[2] Similar evidence was obtained with nano curcumin in other clinical trials. Asadirad *et al*. (2022), identified a substantial decrease in the expression as well as blood levels of IFN-γ, IL-1β, and IL-6 in the nanocurcumin-treated group as compared to the control group.[28] Hassaniazad *et al*. (2021), reported a marked decline in TBX21 gene expression as well as serum levels of IFN-γ and IL-17, and an increase in FOXP3 gene expressions and serum levels of IL-4 and TGF-β were noted in the nanocurcumin group after 14 days of therapy.[29] These clinical trials support the potential therapeutic value of curcumin and its formulations in COVID-19 management, emphasizing its ability to improve symptoms, reduce inflammatory markers, and enhance patient outcomes. However, large-scale clinical trials are warranted to validate these findings and establish optimal dosage and treatment protocols for curcumin in COVID-19 patients.

LIMITATIONS OF CURRENT STUDIES ON CURCUMIN AND COVID-19

Despite the promising findings of the studies I reviewed, there are several limitations. First, the majority of studies available are *in vitro* or animal model studies, which may not fully reflect the complex pathophysiology of human disease.[26] In addition, there is a lack of standardized protocols regarding curcumin dosage, formulation, and treatment duration, making it challenging to compare results across different studies.[27] Furthermore, curcumin's limited bioavailability remains a significant hurdle, as its limited gastrointestinal absorption and rapid metabolism may compromise its therapeutic potential.[30] Finally, most of the studies conducted thus far have focused on curcumin's anti-inflammatory and antiviral effects, whereas its potential interactions with other drugs or therapies commonly used in COVID-19 treatment have not been extensively explored.

CHALLENGES IN CLINICAL APPLICABILITY

Curcumin exhibits poor bioavailability, and this attribute limits its therapeutic efficacy. Its metabolism may vary among individuals. Several approaches have been investigated to augment the bioavailability of curcumin. One approach is the use of adjuvants such as Piperine, a bioenhancer derived from black pepper.[31] Another strategy is using lipid-based systems, such as nanoemulsions or liposomes. These formulations enhance curcumin's solubility and also improve bioavailability and tissue distribution.[32] In addition, the encapsulation of curcumin in nanoparticles, such as polymeric nanoparticles or lipid nanoparticles, can protect it from degradation and facilitate targeted delivery.[30]

Curcumin is generally considered safe with a low toxicity profile. Studies have reported no significant adverse effects associated with curcumin administration, even at high doses.[33] Some studies reported mild and transient nausea, diarrhea, and abdominal discomfort, following curcumin supplementation.[10] In addition, curcumin possesses antiplatelet activity and may interfere with blood clotting mechanisms.[34] Therefore, it should be used with caution in individuals taking anticoagulants or patients with bleeding disorders. When considering curcumin as a therapeutic intervention, it is imperative to be aware of its interactions with other medications. Curcumin modulates various cellular pathways and enzymes involved in drug metabolism, such as cytochrome P450 enzymes, P-glycoprotein, and UDP-glucuronosyltransferases.[35,36]

CONCLUSION

It is evident from the *in vitro* studies, animal models, and human clinical trials that curcumin displays potent antiviral, anti-inflammatory, immunomodulatory, and anti-fibrotic effects and thereby can play a critical role in mitigating SARS-CoV-2 treatment. However, several avenues for future research and investigation remain. First, clinical trials with larger sample sizes and diverse populations are warranted to establish the efficacy, optimal dosage, and treatment duration. Comprehensive studies are needed to explore the interactions of curcumin with other commonly used therapeutic agents in COVID-19 management. Studies on the long-term safety and adverse effects of curcumin in COVID-19 patients are indispensable to ensure its clinical applicability. Investigating the molecular mechanisms of curcumin's antiviral activity can provide insights to develop novel antiviral strategies. The use of curcumin nanosystems holds promise by enhancing its bioavailability and targeted delivery to specific tissues or organs. Finally, investigations into the function of curcumin in post-COVID-19 complications, such as long-term COVID-19 and persistent inflammation, can provide valuable insights into its potential preventive and therapeutic effects. Overall, future research should aim to address these gaps and further explore the therapeutic prospective of curcumin in COVID-19.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that they have not used artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript or image creations.

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