11 Possible Mechanisms and Special Clinical Considerations of Curcumin Supplementation in Patients with COVID-19

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Abstract

The novel coronavirus outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was recognized in late 2019 in Wuhan, China. Subsequently, the World Health Organization declared coronavirus disease 2019 (COVID-19) as a pandemic on 11 March 2020. The proportion of potentially fatal coronavirus infections may vary by location, age, and underlying risk factors. However, acute respiratory distress syndrome (ARDS) is the most frequent complication and leading cause of death in critically ill patients. Immunomodulatory and anti-inflammatory agents have received great attention as therapeutic strategies against COVID-19. Here, we review potential mechanisms and special clinical considerations of supplementation with curcumin as an anti-inflammatory and antioxidant compound in the setting of COVID-19 clinical research.

Keywords

Curcuminoids · Inflammation · COVID-19 · ARDS

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11.1 Introduction

The novel coronavirus outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was recognized in late 2019, following announcement of a cluster of pneumonia cases in Wuhan, China [1]. World Health Organization declare coronavirus disease 2019 (COVID-19) as a pandemic on 11 March 2020 [2]. According to published reports, the proportion of potentially fatal infections may vary by location, age, and underlying risk factors [3]. Acute respiratory distress syndrome (ARDS) is the most frequent complication and leading cause of death in severely ill

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patients. Cytokine release syndrome characterized by elevated serum levels of proinflammatory cytokines including interleukin (IL)-6, IL-1β, IL-2, IL-8, IL-17, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-inducible protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α), and tumor necrosis factor α (TNF-α) was detected in severe cases of COVID-19 [1, 4, 5]. Unrestrained immune activation and subsequent systemic inflammation result in diffuse alveolar damage and pulmonary capillary endothelial injury that recognized as ARDS [6]. As a consequence, immunomodulatory and anti-inflammatory agents have received great attention in therapeutic strategies for COVID-19[5].

Turmeric, as a precious spice obtained from *Curcuma longa* rhizomes, has a remarkable history in traditional herbal medicine. Curcumin (diferuloylmethane) is a bioactive polyphenolic ingredient of turmeric with manifold pharmacological effects including potent anti-inflammatory and antioxidant properties [7–14]. Studies demonstrated that curcumin shows anti-inflammatory, antioxidant and antineoplastic properties through regulation of cytokines, transcription factors, adhesion molecules and enzymes. Due to such properties, some studies are being conducted to evaluate the probable clinical profit of curcumin for the treatment of COVID-19. In the current study, we focused on probable mechanisms of curcumin against ARDS and acute lung inflammation (ALI) and discussed the special clinical considerations of curcumin supplementation in patients with COVID-19.

11.2 COVID-19-Associated ARDS and Related Cytokines

ARDS is a serious lung inflammatory disorder which mortality rate is estimated to be 30–50% [15]. It was described as a syndrome accompanied by inflammation and enhanced permeability of pulmonary capillary endothelial cells followed by fluid leakage into lung parenchyma and activation of inflammatory responses leading to ALI [16]. It was demonstrated that the severity of ARDS directly depends on the magnitude of induced inflammatory responses [17].

Recent studies reported that the cytokine profile of COVID-19 is similar to ARDS and sepsis. Besides, studies confirmed the relevance of elevated levels of inflammatory cytokines with poor prognosis of COVID-19 patients [18]. The inflammatory cytokines that playing key roles in development and progression of ARDS, are introduced here to better understand the relying mechanisms of curcumin in Table 11.1.

Table 11.1 Role of different mediators playing key roles in ARDS

Mediators affecting ARDS	Function	References
TNF-α	Pro-inflammatory cytokine, neutrophil recruitment, activation of ROS generation	[20, 71]
IL-1β	Pro-inflammatory, neutrophil activation on ARDS	[17]
IL-6	Pro-inflammatory cytokine, leukocytes recruitment and activation, early biomarkers of lung injury	[72]
IL-10	Anti-inflammatory cytokine, suppresses the release of proinflammatory cytokines	[31]
ICAM-1	Neutrophil adhesion and trafficking to the lung tissue	[73]
SP-D	Regulates surfactant hemostasis synthesized in alveolar type II cells and Clara cells of lungs	[38]
Reactive oxygen and nitrogen species	Increased endothelial permeability, promoting the migration of PMNs	[17, 26]
Chemokines	Activate leukocyte integrins, causing firm adhesion and extravasation	[74]
IL-8	Potent neutrophil attractant and activator	[75]

TNF-α tumor necrosis factor α, *IL-1β* interleukin 1β, *IL-6* interleukin 6, *IL-10* interleukin 10, *ICAM-1* intercellular adhesion molecule 1, *SP-D* surfactant protein D, *IL-8* interleukin 8

TNF-α and IL-1β are among the first proinflammatory cytokines released into the systemic circulation in response to an infectious stimulus. It was demonstrated that TNF-α and IL-1β both activate neutrophils and in sepsis, they are released within 30–90 min from exposure to lipopolysaccharides (LPS) which stimulate the release of the second inflammatory cascade including cytokines, reactive oxygen species (ROS), and upregulation of cell adhesion molecules. Thereupon, inflammatory cells adhere to vascular endothelial cells and migrate into tissues [19]. Moreover, it was shown that TNF-α caused multi-organ damage through the recruitment of neutrophils [20].

The nuclear factor kappa B (NF-**κ**ß) plays a critical modulatory role in the transcription of adhesion molecules, cytokines and other mediators involved in the function of immune system, inflammatory and acute responses, recruitment of leucocytes to extravascular tissues [21]. The NF-**κ**ß is mainly composed of two subunits which are sequestered in the cytoplasm through integration with I-**κ**ß [22]. When activation mediators such as TNF-α or IL-1β are bound to their receptors, I-**κ**ß becomes phosphorylated resulting in activation of NF-**κ**ß. Afterwards, the complex translocate to the nucleus where enhancing the transcription of its target genes. Rather than TNF-α and IL1 β, viral and bacterial products such as double stranded RNA, LPS, and free radicals are potent inducers of NF-**κ**ß [23]. Studies demonstrated that enhanced activation of NF-**κ**ß pathway results in increased cell viability and decreased apoptosis. In fact, enhanced viability of activated neutrophils in the lung tissue of patients with ARDS, leads to more production of ROS and proinflammatory cytokines which might preserve and prolong pulmonary inflammatory process [24]. Actually, neutrophils play a fundamental role in the development and progression of ARDS. Previous studies confirmed that accumulation of alveolar neutrophils correlated with enhanced lung permeability, hypoxemia, and low survival rates. Increased amount of neutrophils in airspaces led to microvascular and lung tissue damage. IL-8 is also a potent neutrophil attractant which plays a significant role in ALI/ARDS [25]. Reactive oxygen and nitrogen species (ROS and RNS, respectively) are produced by lung endothelial cells, alveolar cells and airway epithelial cells, neutrophils, and macrophages which lead to increased endothelial permeability promoting the migration of polymorphonuclear leukocytes (PMNs) and fluid into the alveolar lumen. This process finally stimulates the release of proinflammatory agents, expression of adhesion molecules needed for leukocyte recruitment and neutrophil migration promoting the lung injury [17, 26].

IL-6 is secreted by almost all stromal cells and immune cells such as macrophages, monocytes and T/B lymphocytes [27]. The presence of IL-6 and other inflammatory agents is essential for host defense against infections. However, elevated levels of IL-6 can lead to severe acute systemic inflammatory responses named cytokine release syndrome (CRS) [28]. Studies indicated that sustained release of IL-6 is correlated with serum viral RNA load in COVID-19 patients which is correlated to disease severity [29]. Additionally, high serum levels of IL-6 in acute phase of disease were associated with lung lesions in coronavirus infected patients [30]. As a result, ongoing clinical trials of tocilizumab (a humanized monoclonal antibody against IL-6 receptor) in severe COVID-19 cases are being conducted worldwide. In contrast, IL-10 is an anti-inflammatory cytokine which suppresses the release of proinflammatory cytokines such as TNF-α, IL-1β and IL-6, thereby limiting the damage to the host tissues [31].

Macrophages play a dual role in ALI and ARDS. In the acute phase, resident alveolar macrophages' main phenotype is M2 which shift into M1 phenotype and release potent proinflammatory cytokines such as interferon gamma (IFN-γ), TNF-α, and IL-1β that demonstrate inflammatory effects in the early stage of disease. Besides, blood monocytes are also recruited which finally differentiate to M1 macrophages. In the later stage of ALI/ARDS, macrophages differentiate into M2 phenotype which is regulated through the release of IL-4, IL-10, IL-13, signal transducer and activator of transcription 6 (STAT6), and interferon regulatory factor 4 (IRF4). This

process finally leads to elimination of debris, pathogens and apoptotic cells exhibiting an anti-inflammatory effect [32].

The results of a clinical trial in critically ill patients with ALI/ARDS demonstrated that the levels of inflammatory biomarkers including inflammatory cytokines (IL-6 and IL-8), protein C, surfactant protein D (SP-D), intercellular adhesion molecule 1 (ICAM-1), plasminogen activator inhibitor (PAI), tumor necrosis factor receptor (TNFR), and von Willebrand factor (VWF) were significantly lower in surviving patients when compared to non-survivors. However, among all these, the best prognostic biomarkers were IL-8 which is a potent neutrophil attractant and SP-D [33].

Immune system possesses a complex structure and describing all the details of known mechanisms involved in ARDS pathophysiology is so intricate. The main purpose of this part was to classify inflammatory and anti-inflammatory biomarkers and to briefly describe the role of each cytokine in the process to better understanding the potential pathways that curcumin involves and modulates the immune system responses.

11.3 Potential Anti-Inflammatory Mechanisms of curcumin Against ARDS

Studies have indicated that curcumin shows anti-inflammatory, antioxidant and anti-neoplastic activities [34, 35] which are regulated through several molecular targets such as cytokines (e.g. TNF-α, IL-10, IL-6), transcription factors (e.g. NF-κß), enzymes (e.g. matrix metalloproteinases [MMPs]) and adhesion molecules (e.g. ICAM-1) playing key roles in inflammation and carcinogenesis [36]. In this part we are going to study the effects and anti-inflammatory mechanisms of curcumin in the setting of ALI/ARDS resulted by different underlying causes.

Sepsis, severe pneumonia, aspiration, toxic inhalation and trauma are the major underlying conditions leading to ARDS [17]. Xiao et al. prepared rat models of sepsis-induced ALI using cecal ligation puncture (CLP) model. Then, they studied the effect of different doses of curcumin on various cytokines' concentrations and the final survival rate. The results revealed that the use of curcumin downregulated the pro-inflammatory cytokines such as TNF-α and IL-8. Besides, the results showed that the treatment with curcumin led to improvement of the survival rate by 40–50% in CLP induced ALI model [37]. Additionally, it reduced the oxidative stress in the lung tissue through reduction of myeloperoxidase (MPO), malondialdehyde (MDA) and enhancement of superoxide dismutase (SOD) activity. As demonstrated above, ROS react with macromolecules, produce lipid peroxidases and mutate DNA leading to host tissues toxicity. SOD is an anti-oxidant enzyme which scavenges superoxide substrate and studies demonstrated that its concentration is decreased in sepsis induced ARDS.

In a rat model of intestinal ischemia and reperfusion induced ALI, oral treatment with curcumin further confirmed the antioxidant activity of curcumin. The results indicated the reduction of elevated tissue MDA levels, enhancement of SOD and glutathione peroxidase. Also there was a significant reduction in inducible nitric oxide synthase activity and enhanced the expression of SP-D in lung tissue [38]. SP-D plays vital roles in innate host defense of the lung tissue and regulates surfactant homeostasis [39].

Another interesting mechanism was highlighted in a study by chai et al. They showed that curcumin promoted T regulatory (Treg) cells differentiation and enhanced Treg-derived IL-10 in serum and broncho-alveolar lavage fluid (BALF). Enhancement of Treg-derived IL-10 is the main factor affecting macrophage polarization and conversion of M1 macrophages to M2 [40].

Madathilparambil et al. demonstrated that the administration of cyclodextrin-curcumin complex in LPS induced ALI in mice led to reduced pulmonary edema and neutrophil accumulation in BALF and lung tissue. Besides, the proinflammatory transcription factor, NF-κß was decreased causing the reduction of severe inflammation and lung injury [41]. Qingquan et al. showed that the levels of cytokine-induced neutrophil chemoattractant-1 (CINC-1) in rat model of LPS induced

ALI was remarkably increased. They demonstrated that curcumin pretreatment resulted in inhibition of lung CINC-1 expression leading to suppression of neutrophil recruitment and activity in the lung tissue [42].

High-mobility group box 1 (HMGB1) is one of the important inflammatory inducers which is produced by activated monocytes and macrophages. Binding of HMGB1 to receptor for advanced glycation end products (RAGE) stimulates NF-κß signaling pathway, promoting the expression of pro-inflammatory cytokines. Studies indicated that the administration of curcumin to the rat model of LPS-induced ALI led to upregulation of peroxisome proliferator-activated receptor γ (PPAR γ) pathway, further inhibiting the HMGB/RAGE pro-inflammatory pathway [43].

Avasarala and collogues also demonstrated that the use of curcumin affects both pro-inflammatory and anti-inflammatory biomarkers causing a remarkable decrease in development of ARDS and lung injury [44]. They showed that the mechanism was regulated through downregulation of NF-κß and reduction of transforming growth factor beta (TGF-ß) receptor II in virus-induced ARDS resulting in inhibition of inflammatory responses and further lung fibrosis.

Taken together, the precise modulatory mechanisms of curcumin in ARDS has not been defined yet. However, in the current section, we pointed out some of the prominent pathways by which curcumin affects the inflammatory cascade in ARDS.

11.4 Curcumin Formulations

Multiple drug delivery systems such as micelles, liposomes, phospholipid complexes, emulsions, micro-emulsions, nano-emulsions, solid lipid nanoparticles, nanostructured lipid carriers, biopolymer nanoparticles, and micro-gels have been formulated to enhance oral absorption, bioavailability, and therapeutic outcomes of curcumin. Compared with unformulated curcumin, significant enhancement of absorption and bioavailability have been obtained with the micellar and micronized formulations (>100-fold) [45–47].

11.5 Curcumin Dosage

Although the results from both in-vivo and in-vitro studies on curcumin have been promising, clinical trials in patients with viral pneumonia and/or ARDS have not yet been reported. Therefore, in case of curcumin supplementation in COVID-19 patients with or without ARDS, it should be used in typical doses for other medical conditions ranging from 500–4000 mg per day [7, 48]. However, dose adjustment should be made with respect to bioavailability-enhanced preparations as these formulae may cause systemic concentrations in the order of hundreds to thousands of times higher those obtained with unformulated curcumin.

11.6 Common Adverse Effects Between COVID-19 and Curcumin

Previous studies have been investigated the safety and clinical benefits of curcumin in a broad range of diseases including gastrointestinal diseases, rheumatic diseases, pulmonary diseases, diabetes, cardiovascular diseases, liver diseases, pancreatic diseases, neurologic and neurodegenerative diseases, infectious disease and malignancies [7, 8, 49–52]. In accordance with the results of clinical trials, curcumin has a long-established record of tolerability and safety in human studies. An acceptable daily intake (ADI) of 0–3 mg/kg of body weight per day for curcumin was established by JECFA (The Joint United Nations and World Health Organization Expert Committee on Food Additives) and EFSA (European Food Safety Authority) [7, 53]. Although generally well tolerated, curcumin may cause mild nausea, dyspepsia, diarrhea, yellow stool, headache, and rash in some patients [54–56]. Nausea, diarrhea, rash, and headache occur in patients with COVID-19 as well. Therefore, initiation of curcumin supplementa-

tion in patients with COVID-19 may increase the risk or intensity of mentioned side effects. Furthermore, curcumin supplementation causes increased bile formation and demonstrates cholekinetic effects [57, 58]. Moreover, curcumin presents antiplatelet, anticoagulation, and fibrinolysis activities [59, 60]. In addition, curcumin supplementation increases insulin sensitivity and subsequently leads to lower blood glucose levels among diabetic patients who were taking diabetes medications [61, 62]. As a result, curcumin supplementation should be avoided in COVID-19 patients with gallbladder diseases, bleeding disorders, and diabetes.

11.7 Clinically Significant Drug Interaction Between Curcumin and Conventional Medications

Natural products including herbal medications and dietary supplements can interact with co-administered conventional medications, potentially lead to unexpected side effects, toxicity, and/or suboptimal therapeutic responses [63, 64]. Also curcumin is a safe natural product, clinically significant drug interactions must be avoided in the setting of clinical trials especially in critically ill patients with polypharmacy. Curcumin supplementation can lead to reduced activities of cytochrome p450 monooxygenase (CYP1A1, 2A6, 1B1, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4), P-glycoprotein (P-gp), organic anion-transporting polypeptide (OATP), glutathione-S-transferase (GST), and uridine dinucleotide phosphate glucuronosyltransferases (UDPG) [65–68]. Clinically important drug interactions of curcumin are summarized in Table 11.2. Although, limited trials have investigated the pharmacokinetic and/or pharmacodynamic interactions between curcumin and conventional medications. We recommend to exclude the COVID-19 patients who take listed medications from curcumin supplementation trials. However, included patients must be investigated and monitored closely due to the lack of adequate and well-designed clinical trials that investigate the pharmacokinetic and pharmacodynamic drug interactions between curcumin and other conventional medications. Furthermore, there is possible drug interactions between curcumin and antiviral agents for the treatment of COVID-19. For example, remdesivir is an adenosine nucleotide prodrug that converted to the pharmacologically active nucleoside triphosphate form (GS-443902) into cells and subsequently intervene in the viral RNA-dependent RNA polymerase action. Remdesivir is metabolized by CYP (2C8, 2D6, and 3A4), OATP1B1/1B3, and P-glycoprotein/ABCB1 enzyme systems [69–71]. So, pharmacokinetic drug interactions are possible in patients who administrated curcumin and COVID-19 specific therapies. Although, clinical data are not available in this area.

11.8 Conclusion

Ongoing COVID-19 pandemic is the pressing global health challenge of our time and our information about COVID-19 is being updated almost on a daily basis. Immunomodulatory and anti-inflammatory agents have received great attention during this period of time based on the inflammatory nature of disease. However, one should minimize any unnecessary co-medication in the setting of COVID-19 due to the lack of clinical and/or experimental information and potential risk of toxicity. We suggest not using curcumin supplementation outside of the setting of clinical trials given the lack of clear clinical evidences on the benefit of curcumin in COVID-19 patients. Further clinical investigations should be performed to clarify the role of curcumin supplementation in the setting of COVID-19. It is also unknown if curcumin can help the patients during the initial phase of the disease or might be more effective in later phases to ameliorate complications.

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Table 11.2 Curcumin-conventional drug interactions

Concomitant medication	Outcome	Mechanism	References
Cardiovascular medications			
Losartan	Increased C_{max} and total AUC of losartan	Decreased P-gp activity	[77]
Talinolol	Decreased C_{max} and total AUC, increased total clearance of talinolol	MRP2 upregulation	[78]
Celiprolol	Increased C_{max} and total AUC, decreased clearance of celiprolol	Decreased P-gp level	[79]
Rosuvastatin	Increased C_{max} and total AUC of rosuvastatin	Decreased OATP activity	[80]
Anticoagulants			
Warfarin	Increased C_{max} and total AUC, decreased clearance of warfarin No effect on pharmacodynamic parameters such as anticoagulation rate and INR	Decreased P-gp activity	[81, 82]
Clopidogrel	Increased C_{max} and total AUC, decreased clearance of clopidogrel No effect on pharmacodynamic parameters such as platelet aggregation and in-vivo bleeding time.	Decreased P-gp activity	[81–83]
Antibiotics			
Norfloxacin	Increased total AUC and absorption rate constant, decreased overall elimination rate constant of norfloxacin.	Decreased UDPG levels Decreased CYP3A4 activity Decreased P-gp activity	[84]
Antihistamines			
Loratadine	Increased C_{max} and total AUC of loratadine	Decreased CYP3A4 activity Decreased P-gp activity	[85]
Antineoplastic agents			
Paclitaxel	Increased total AUC and bioavailability of paclitaxel	Decreased P-gp level Decreased CYP3A2 level	[86]
Docetaxel	Increased C_{max}, total AUC, half-life, and bioavailability, decreased clearance of docetaxel	Decreased OATP1B1 and OATP1B3 activity	[87, 88]
Etoposide	Increased C_{max}, total AUC, and bioavailability of etoposide	Decreased CYP3A4 activity Decreased P-gp activity	[89]
Tamoxifen	Increased C_{max} and total AUC of tamoxifen	Decreased CYP3A4 activity Decreased P-gp activity	[90]
Everolimus	Decreased C_{max} and AUC of everolimus	Increased CYP3A4 activity Decreased P-gp activity	[91]
Phospho-sulindac	Increased C_{max} and total AUC of phospho-sulindac	Decreased P-gp activity	[92]

C_{max} maximum serum concentration, *AUC* area under the curve, *P-gp* P-glycoprotein, *MRP2* multi-drug resistance protein 2, *OATP* organic anion-transporting polypeptide, *UDPG* uridine dinucleotide phosphate glucuronosyltransferases, *CYP* cytochrome p450 monooxygenase

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