Therapeutic Potential of Curcumin in ARDS and COVID-19

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Abstract

Curcumin is a safe, non-toxic, readily available, and naturally occurring compound, an active constituent of Curcuma longa (turmeric). Curcumin could potentially treat diseases but faces poor physicochemical and pharmacological characteristics. To overcome these limitations, we developed a stable, water-soluble formulation of curcumin (CDC). We have previously shown that direct delivery of CDC to the lung following lipopolysaccharides (LPS) exposure reduces acute lung injury (ALI) and effectively reduces lung injury, inflammation, and mortality in mice following *Klebsiella pneumoniae (KP)*. Recently, we found that administration of CDC led to a significant reduction in angiotensin-converting enzyme 2 (ACE2) and signal transducer and activator of transcription 3 (STAT-3) expression in gene and protein levels following pneumonia, indicating its potential in treating coronavirus disease 2019 (COVID-19). In this review, we consider the clinical features of ALI and acute respiratory distress syndrome (ARDS) and the role of curcumin in modulating the pathogenesis of bacterial/viral-induced ARDS and COVID-19.

1. Introduction

Curcumin is a yellow compound produced by plants of the Curcuma longa (turmeric) species[1]. It is the principal curcuminoid of Curcuma longa, a member of the ginger family, Zingiberaceae [2,3]. It is sold as an herbal supplement, cosmetic ingredient, food flavoring, and coloring. It has various medicinal preparations common in Ayurveda and Chinese medicine. The medicinal properties of curcumin have been known for thousands of years; however, the exact mechanism(s) of action and bioactive components, many of which have yet to be determined, have only recently been investigated [2-4]. Curcuminoids have been approved by the US Food and Drug Administration (FDA)[2], and good tolerability and safety profiles have been shown by clinical trials [3,5]. According to the National Center for Complementary and Integrative Health (NCCIH), turmeric is generally safe, but consuming it in high doses or for extended periods may upset your stomach. Gupta et al. reported the safety of curcumin at doses as high as 12 g/day over 3 months in humans [2].

Curcumin, a polyphenol, has been shown to target multiple signaling molecules while also demonstrating activity at the cellular level, which is most likely implicated in its numerous health benefits [2,3,6]. It has been shown to aid in metabolic syndromes[7], pain [8], and inflammatory conditions [9,10]. The diverse effects of curcumin result from its action on a wide range of cellular targets, including transcription factors, inflammatory cytokines, growth factors, apoptotic proteins, and more[11,12]. With so many varied biological targets, curcumin elicits numerous pleiotropic effects. This renders it therapeutically advantageous because many pathological disease states involve more than one signaling pathway, receptor protein/enzyme, or gene[13].

Curcumin has received worldwide attention for its multiple health benefits, which appear to act primarily through its antioxidant and anti-inflammatory mechanisms[10]. These benefits are best achieved when curcumin is combined with agents such as piperine, which increases its bioavailability significantly[3]. It may also help manage exercise-induced inflammation and muscle soreness and, as a result, enhance recovery and subsequent performance in inactive people. Due to its unique molecular chemical structure and functional groups, curcumin may bind with and either inhibit or activate a variety of endogenous biomolecules, including enzymes, receptors, signaling molecules, metals, transcription factors, and even specific proteins located in cell membranes[13,14].

Curcumin represents one of the most diverse therapeutic agents yet isolated from natural sources[2,10,11]. For example, curcumin can act as a potent immunomodulatory agent that can modulate the activation of T cells, B cells, macrophages, neutrophils, natural killer cells, and

dendritic cells[8,15]. Curcumin can also down-regulate the expression of various proinflammatory cytokines, including tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-2, IL-6, IL-8, IL-12[15,16], and chemokines most likely through inactivation of the transcription factor nuclear factor-κB (NF-κB) [17]. Curcumin has also been shown to activate host macrophages and natural killer (NK) cells and modulate lymphocyte-mediated functions[18].

Notably, most curcumin studies in humans have been in populations with existing health problems. Studies on healthy people can be challenging due to less immediate and measurable benefits if biomarkers are standard at baseline. Therefore, following subjects over time may provide the best insight into any potential health benefits for healthy people. However, the therapeutic application of curcumin is limited by its extremely low solubility in aqueous buffer, instability in body fluids, and rapid metabolism. Nano-delivery systems have shown excellent potential to improve the solubility, biocompatibility, and therapeutic effect of curcumin [19]. Specifically, nanoparticles, including but not limited to liposomes, micelles, nanogels, and niosomes, improve the bioavailability and therapeutic effects of curcumin such as in treating pulmonary tuberculosis using Nanomicelles containing curcumin[20,21]. Moreover, nano-curcumin, a powerful immunomodulatory agent, may help downregulate Th17 cell responses, lessen inflammation, and accelerate patients' rehabilitation with COVID-19[22].

Cyclodextrins (CDs) are cyclic oligosaccharides with a structure of a hollow truncated cone. Due to their hydrophilic outer surface and lipophilic cavity, CDs can solubilize hydrophobic drugs. To address the solubility concern, a novel curcumin formulation (CDC) was developed by complexing the compound with hydroxypropyl-γ-cyclodextrin (CD) [17,23] Specifically, curcumin was prepared at a concentration of 15 g/l. The solution was agitated, and after the complete dissolution of curcumin, the pH was adjusted to 6.0 with a mixture of hydrochloric acid and citric acid. The solution was sterile filtered, filled aseptically into sterile vials, capped, and sealed. The recovered CDC solution contained 12 g/l curcumin and 93 g/l cyclodextrins in 20 mM sodium citrate and 100 mM NaCl solution[23]. This dramatically enhances water solubility and stability, facilitating direct pulmonary delivery[24]. Fluorescence microscopic examination revealed an association of curcumin with cells throughout the lung[17]. *In vitro* studies demonstrated that CDC increased curcumin's association with and transport across Cultured Human Airway Epithelial Cells (Calu-3) monolayers compared with uncomplexed curcumin solubilized using dimethyl sulfoxide (DMSO) or ethanol[17]. The pharmacokinetics of both curcumin and its principal

metabolite (tetrahydrocurcumin) were assessed, leading to the discovery that tetrahydrocurcumin disappeared rapidly (undetectable after 30 minutes)[17,24]. Saber Abdelkader Saidi et al. reported that with improved bioavailability and stability, CDC has homogenous distribution in the hepatic tissue and was rapidly used by liver cells during preservation, indicating efficient uptake[23].

2. Effects of curcumin on NF-κB

Nuclear factor-κB (NF-κB) represents a family of transcription factors that regulate an extensive array of genes involved in different immune and inflammatory responses[25]. Accumulating evidence associates the transcription factor NF-κB as a positive mediator of cell growth, but the molecular mechanism(s) involved in this process remains largely unknown. In addition, NF-κB is critical in regulating the survival, activation, and differentiation of innate immune cells and inflammatory T cells[26]. The activation of NF-κB involves two major signaling pathways, the canonical and the noncanonical. Both are important for regulating immune and inflammatory responses despite their differences in the signaling mechanism[5]. Canonical NF-κB regulates CD4+ T-cell differentiation by regulating cytokine production in innate immune cells and through T-cell intrinsic mechanisms. The noncanonical NF-κB pathway is dispensable for naive T-cell activation[26].

The activation of specific transcription factors, notably NF-κB, and the consequent production of proinflammatory cytokines and other molecules comprise prominent features of inflammation. We have reported that reduced inflammation is reflected in the downregulation of NF-κB activity[17]. In our experiments, the nuclear protein was isolated from the lungs of mice treated with lipopolysaccharide (LPS), and NF-κB activity was determined in the presence and absence of CDC. The increased activity after LPS treatment was significantly reduced by CDC administration directly to the lungs as measured through protein and transcript levels[17]. We reported that the administration of CDC following LPS attenuated inflammation and injury and reduced activation of NF-κBp65[17]. We also recently found that CDC administration significantly reduced the expression of NF-κBp65 at both the transcript and protein levels following *Klebsiella pneumoniae* [24]. Beyond our results regarding mice treated with LPS, CDC has been found to have numerous additional effects. The downstream impacts of NF-κB are pleiotropic, regulating more than 200 genes involved in various cellular processes, including inflammation[27]. Previous studies show that curcumin reduces lung inflammation induced by influenza infection by inhibiting the NF-κB signaling pathway[28]. Crucially, curcumin's downregulation of the NF-κB pathway and

anti-inflammatory effect is dependent on the presence of peroxisome proliferator-activated receptor γ (PPARγ)[26,29]. Finally, further discussed below, NF-κB and curcumin have important implications in the inflammasome activation cascade.

3. Effect of curcumin on Inflammasomes

Inflammasomes are cytosolic multiprotein complexes responsible for innate immunity, eventually resulting in cell death called pyroptosis[26]. Among the various inflammasomes, NOD-like receptor pyrin domain-containing 3 (NLRP3) is the most well-characterized, activated in conditions of tissue damage, metabolic stress, reactive oxygen species (ROS) overload, inflammation, and infection[26,30,31]. Gayatri Puri et al. reported that NLRP3 inflammasome activation by mitochondrial ROS (mtROS) plays a critical role in the pathogenesis of exaggerated inflammation[32].

The NLRP3 complex consists of a sensor protein, an apoptosis-associated speck-like protein, a caspase recruitment domain (ASC), and a protease caspase-1[33,34]. Two different mechanisms can trigger NLRP3 activation. The first mechanism involves inflammatory bacterial products like LPS, which activate the NF-κB pathway to induce NLRP3 and, consequently, pro–IL-1β synthesis [32]. Secondly, some stimuli, such as nigericin, aluminum crystal, and monosodium urate crystal (MSU), can activate the NLRP3 inflammasome and caspase-1 processing[35]. Curcumin can effectively suppress NLRP3 inflammasome activation and IL-1β secretion by regulating NF-κB signaling. In particular, the remarkable ability of curcumin to suppress inflammation is specific to the NLRP3 inflammasome[35,36].

The NLRP3 inflammasome has been shown to play a critical role in the pathogenesis of viral diseases. NF-κB mediates NLRP3 activation in sterile and microbially induced inflammation[37]. Specifically, NF-κB primes the NLRP3-inflammasome for activation by inducing pro-IL-1β and NLRP3 expression[26,31]. Curcumin inhibits the NLRP3 inflammasome and reduces phosphorylation of NF-κB subunits (p65 and p50), inhibiting the degradation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (IκBα) and ultimately inhibiting inflammation[37]. In our previous finding, *Klebsiella Pneumoniae (KP)* led to up-regulation of NLRP-3 inflammasome activity, likely through NF-κB.

Additionally, recent studies emphasize the critical role of the NLRP3 inflammasome in the immunopathogenesis of severe COVID-19, especially in patients with increased risk (ex., diabetes, and obesity). Activation of the inflammasome is likely to form a severe "cytokine storm," which

causes ARDS and, ultimately, death. This result positions curcumin to potentially have a role in treating COVID-19. Curcumin's effects on the inflammasome have also been characterized in various other conditions. Li X et al. reported that curcumin could effectively ameliorate MSU crystal-induced gouty arthritis through NLRP3 inflammasome mediation via inhibiting NF-κB signaling *in vitro* and *in vivo*[35].

4. Effect of curcumin on other critical pathways

Curcumin's effects on molecular pathways extend beyond just NF-κB and the NLRP3 inflammasome, including its impact on signal transducer and activator of transcription 3 (STAT-3), hypoxia-inducible factor 1-alpha (HIF-1α), and nuclear factor erythroid 2 related factor 2 (Nrf2) pathways. Briefly, signal transducers and activators of transcription (STAT) are molecular pathways involved in various biological processes such as cell proliferation and apoptosis[38]. Curcumin can affect the STAT signaling pathway in the induction of its therapeutic impacts. Curcumin can enhance anti-inflammatory cytokines and improve inflammatory disorders such as colitis by targeting STAT signaling pathways[2,11]. A recent study shows that STAT-3 can induce inflammatory responses during coronavirus infections[39].

Hypoxia-inducible factor-1 (HIF-1) is a transcription factor that consists of two subunits, HIF-1α and HIF-1β[40,41]. Under hypoxic conditions, HIF-1α is an adaptive system that regulates the transcription of multiple genes associated with growth, angiogenesis, proliferation, glucose transport, metabolism, pH regulation, and cell death[42,43]. However, aberrant HIF-1α activation contributes to the pathophysiology of several human diseases, such as cancer, ischemic cardiovascular disorders, and pulmonary and kidney diseases[44]. A study showed that curcumin significantly decreases hypoxia-induced HIF-1α protein levels in hepatocellular carcinoma cells (HepG2). Moreover, curcumin suppressed the transcriptional activity of HIF-1 under hypoxia, leading to a decrease in the expression of vascular endothelial growth factor (VEGF), a major HIF-1 target angiogenic factor. Curcumin also blocked hypoxia-stimulated angiogenesis *in vitro* and down-regulated HIF-1α and VEGF expression in vascular endothelial cells[45].

Nrf2 is an essential transcription factor that maintains the cell's redox balance state and reduces inflammation in varying adverse stresses[46]. Curcumin can target the Nrf2 signaling pathway to protect the cells against oxidative damage[33]. Accumulating data demonstrates that curcumin applies four distinct methods to stimulate the Nrf2 signaling pathway, including inhibition of kelch-like ECH-associated protein 1 (Keap1), affecting the upstream mediators of

Nrf2, influencing the expression of Nrf2 and target genes, and improving the nuclear translocation of Nrf2[47].

5. Effect of curcumin on treating COVID-19

COVID-19 is a rapidly spread disease, leading to high mortality rates. COVID-19, which created a public health emergency of global concern, is caused by a coronavirus belonging to the Coronaviridae family[48,49] and has been identified in several mammalian hosts, especially in humans and bats. The clinical manifestation of COVID-19 ranges from asymptomatic upper respiratory tract infection to critical illness and pneumonia associated with acute respiratory distress syndrome (ARDS)[50]. COVID–19 causes severe complications, including pneumonia, ARDS, and multiorgan failure. The main risk factors associated with greater severity and mortality caused by COVID-19 include hypertension, diabetes mellitus, cardiovascular disease (CVD), advanced age, and obesity [51-53]. Procoagulant and pro-thrombotic events are recurrent in patients with COVID-19 and can cause significant damage. The virus attaches to the human host target cell receptor, the angiotensin-converting enzyme 2 (ACE2), to cause infection.

The pandemic years have witnessed a boom in the production and export of the humble underground stem called turmeric, along with a renewal of interest among the scientific community in the spice's therapeutic qualities, especially against COVID-19. This coincides with the findings of existing studies[39-41]. We recently found that the CDC administration after *KP* significantly attenuated ACE2 and STAT3 expression protein and gene levels (unpublished data). Ultimately, due to CDC's promising effects on relevant markers, curcumin could be used as supportive therapy to treat ARDS and COVID-19 disease to save lives.

Beyond our lab's findings, several other studies have evaluated curcumin's potential to treat COVID through varying mechanisms. Modeling studies have shown that curcumin inhibits the virus-receptor interaction in two ways, through the spike protein and the ACE2 receptor[22,54,55]. ACE2 is an enzyme located in various body parts, including alveolar epithelial cells of the lung, intestinal absorptive cells or enterocytes of the small intestine, venous endothelial cells of the kidney, endothelial cells of the heart, and renal tubular epithelial cells[56,57]. ACE2 is also present in humans' lower respiratory tract[55,57]. Therefore, potential drug therapies could target and block the cell surface receptors from binding coronavirus and activating specific cell signaling pathways, which help in viral replication. Hamed_et al. reported that nano-curcumin might be an innovative therapeutic agent for COVID-19 patients by regulating the inflammatory response[22].

Thennakoon et al. recently reported that Nanocellulose/polyvinyl alcohol/curcumin (CNC/PVA/curcumin) nanoparticles with enhanced drug loading properties were developed by the dispersion of nanocellulose in curcumin/polyvinyl alcohol aqueous medium. The enhancement of curcumin's solubility will significantly improve drug loading in nanocellulose, and this curcumin presents a promising nano-based approach for treating COVID-19[58]. Silymarin, extracted from milk thistle, has a protective effect during lung injury because of its ability to decrease the production of nitric oxide and the infiltration of inflammatory cells[59]. Additionally, silymarin has recently been considered a potent inhibitor for angiotensin converting enzyme-2, preventing its host-cell entry[60]. Nemany et al. recently found Silymarin/curcumin-loaded albumin nanoparticles coated with chitosan and used in a muco inhalable delivery system had anti-inflammatory and anti-COVID-19 effects [61].

Studies on viral infections have shown overactive inflammasome and thus destructive and systemic inflammation in patients[62]. The NLRP3 inflammasome has been shown to play a critical role in the pathogenesis of viral diseases[34,55,62]. The proliferation of SARS-CoV-2 in a wide range of cells can be combined with numerous observations of direct and indirect inflammasome activation by other coronaviruses.

6. Effect of curcumin in long Covid-19

Despite ongoing vaccination efforts, there is an urgent demand for safe and effective treatments to help reduce the debilitating effects of SARS-CoV-2 disease. The pathophysiology of COVID-19 is highly heterogeneous, and the way COVID-19 modulates the different systems in the host remains unknown. This complex and multifactorial response requires a comprehensive therapeutic approach. Curcumin has beneficial effects on the progression of inflammatory diseases due to its numerous action mechanisms: antiviral, anti-inflammatory, anticoagulant, antiplatelet, and cytoprotective. These features make it a promising therapeutic in the long adjuvant treatment of COVID-19[34,63,64].

Kirti et al. reported that the administration of oral curcumin with piperine as symptomatic adjuvant therapy in COVID-19 treatment could substantially reduce morbidity and mortality and ease the logistical and supply-related burdens on the healthcare system. Curcumin could be a safe and natural therapeutic option to prevent post-Covid thromboembolic events.[54] Amir Vahedian-Azimi et al. conducted a meta-analysis in June 2021 to find studies assessing the effects of curcumin-related compounds in mild to severe COVID-19 patients. Six studies showed that

curcumin supplementation led to a significant decrease in typical symptoms, duration of hospitalization, and deaths. Curcumin administration leads to a substantial reduction in proinflammatory cytokines, such as IL-1β and IL6, with a significant increase in anti-inflammatory cytokines, including IL-10, IL-35, and Transforming growth factor alpha **(**TGF-α**)**. These findings suggested that curcumin exerts beneficial effects by partially restoring the proinflammatory/anti-inflammatory balance during COVID-19 infection[65].

Gholamreza et al. reported that forty-six outpatients with COVID-19 disease were randomly allocated to receive two capsules of curcumin-piperine for 14 days. There was a significant improvement in dry cough, sputum cough, ague, sore throat, weakness, muscular pain, headache, and dyspnea in curcumin-piperine groups[66]. Gajendra Kumar et al. reported that using curcumin, Piper Nigrum Piperin, and catechin could cure and prevent COVID-19 outbreaks and infection. Curcumin and piperine interact and form a π—π intermolecular complex, which enhances curcumin's bioavailability. Additionally, the molecules curcumin and catechin bind directly to the receptor binding domain of spike protein and ACE-2 receptors of the host cell, inhibiting the virus entry in the host cell[67].

Anish et al. recently reported curcumin as a potential therapeutic candidate against the SARS-CoV-2 Omicron variant among seven phytochemicals studied[68]. It is reported to cause impaired heart function, lung injuries, and increased C-reactive protein levels in severely ill patients[68]. Asha et al. reported that a nano curcumin-based formulation (NCF) with improved bioavailability showed several holistic therapeutic effects, including myocardial protection, edema prevention, anti-inflammatory and antioxidant properties, and metabolic and mitochondrial homeostasis maintenance under hypoxic conditions[69].

Saber-Moghaddam et al. reported that an open-label, nonrandomized clinical trial evaluated the efficacy of nano curcumin oral formulation in 41 hospitalized patients with mild-moderate COVID-19. Most symptoms, including fever and chills, tachypnea, myalgia, and cough, resolved significantly faster in the curcumin group[70]. Thimmulappa et al. evaluated phytochemical curcumin for the treatment of COVID-19 in a randomized clinical trial. They found that curcumin showed broad-spectrum antiviral activity against enveloped viruses, and curcumin may suppress SARS-CoV-2 infection by directly modifying the spike protein and ACE2. Additionally, curcumin exerts immunomodulatory activity by blocking NF-κB, inflammasome, High mobility group box 1 (HMGB1), and IL-6-driven inflammatory responses[63].

Nrf2 is a central transcription factor that regulates the antioxidant defense system and is considered a modifier for several inflammatory diseases. It has previously been reported that curcumin is a promising Nrf2 agonist, and the administration of curcumin activates the Nrf2 pathway in the lungs of mice[63,71]. Saber-Moghaddam et al. suggest that curcumin's anti-inflammatory properties and inhibition of p21-activated kinases (PAK1), Activator protein 1 (AP1), and NF-κB could be a potentially beneficial treatment for COVID-19-related ARDS. So, curcumin may also exert antiviral activity against SARS-COV-2 by activating the Nrf2 pathway[70].

The death of severely ill COVID-19 patients is associated with respiratory failure or multiorgan failure caused by ARDS and septic shock[63]. ARDS and sepsis pathogenesis involves an early hyperactivated inflammatory response characterized by a cytokine storm[19]. Due to anti-inflammatory and anti-inflammasome properties, without any side effects, curcumin can potentially play a role in treating pneumonia and COVID-19 infection along with other drug regimens. The present data reveal that oral curcumin therapy in COVID-19 treatment could dramatically reduce morbidity and mortality (Figure 1).

7. Curcumin and the ACE 2 receptor

Angiotensin-converting enzyme 2 (ACE2), a carboxypeptidase that degrades angiotensin II into angiotensin, has been identified as a potent receptor for SARS-CoV-2. ACE inhibition has assumed a central role in reducing cardiovascular and renal events. However, with the advent of COVID-19, attention has been turned to ACE2 as a possible target to reduce virus binding to different human cells[72]. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) for host cellular entry. This is mediated via spike proteins on SARS-CoV-2, especially the spike glycoprotein receptor binding domain. ACE2 is present in the lung, heart, kidney, venous endothelial cells, and arterial smooth muscle cells. Furthermore, ACE2 is abundantly present in humans in the epithelia of the lung alveolar epithelial cells and small intestine, which might provide possible routes of entry for SARS-CoV[73].

Atish et al. found negligible expression of ACE2 in non-COVID-19 lungs irrespective of gender and a uniform increase in ACE2 expression in all severe COVID-19 lungs in their study. It seems unlikely that baseline pulmonary ACE2 expression levels contribute to the risk of developing COVID-19[74]. Dhivya et al. reported that ACE2 is mediated via proteins of SARS-CoV-2, especially the spike glycoprotein receptor binding domain. Accordingly, their study of virus replication and binding to the host system led to probing curcuminoids' efficiency towards

essential surface drug target proteins using the computational biology paradigm approach. Fourteen natural curcuminoids were studied for their possibility of inhibiting SARS-CoV-2[75].

Mahendra Pal et al. reported that SARS-CoV-2 are enveloped viruses containing non-segmented positive-sense, single-stranded ribonucleic acid (RNA)[76]. Recent data showed that the spike protein (S protein) of SARS-CoV-2 binds to ACE2 with a higher affinity than SARS-CoV. For this reason, it spreads rapidly in human populations[77]. Recent studies show curcumin maintains binding efficiency to the receptor-binding domain (RBD) of the viral spike COVID-19 protein and human ACE2, triggering the blockage of the ACE2 receptor and resulting in inhibition of the viral attachment with the host cell[75,78]. In addition, Zhang et al., 2020 reported that curcumin could potentially increase soluble ACE2 protein, which may competitively attach with COVID-19 to neutralize the virus and rescue cellular ACE2 activity, which negatively controls the renin-angiotensin system (RAS) to protect the lung from injury[77,79].

Atish et al. reported that a relatively large cohort of patients with fatal COVID-19 demonstrated high pulmonary expression of ACE2 protein in their post-mortem lung tissues compared to negligible expression in control lung tissues, highlighting the critical role of ACE2 protein in the pathogenesis of SARS-CoV-2 infection[74]. The level of ACE2 expression in the lung correlates with an increased risk of severe infection and complications in COVID-19. Ultimately, the broad, multifaceted, and beneficial effect that curcumin has on the progression and severity of COVID-19 makes it a promising therapeutic.

8. Effect of curcumin in treating ALI/ARDS

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are characterized by rapid-onset respiratory failure following various direct and indirect insults to the parenchyma or vasculature of the lungs[80]. ALI remains a significant cause of morbidity and mortality in critically ill patients[81]. ALI is characteristic of the wholesale destruction of the lung endothelial barrier, which results in protein-rich lung edema, the influx of proinflammatory leukocytes, and intractable hypoxemia, contributing to high mortality[82]. Despite an improved understanding of the pathogenesis of ALI, supportive care with a lung-protective strategy of mechanical ventilation remains the only treatment with a proven survival advantage[83,84]. Most ALI patients die or are weaned from supportive therapy within 1–2 weeks, although up to 10% of patients require prolonged treatment (30 days or more). Ultimately, there is an urgent need to develop therapies to halt the progression of this devastating syndrome. Most people who get ARDS are already at the

hospital for trauma or illness. Pathologically, ARDS is characterized by diffuse alveolar damage, alveolar-capillary leakage, and protein-rich pulmonary edema leading to the clinical manifestation of poor lung compliance, severe hypoxemia, and bilateral infiltrates. Most clinical trials in ALI have targeted mechanically ventilated patients. Past pharmacological agents may have failed to demonstrate efficacy due partly to the resultant delay in initiation of therapy until several days after the onset of lung injury[85].

Acute lung injury and its excessive inflammatory responses in the lung, known as "cytokine storms," result in pulmonary edema, atelectasis, and fatal acute respiratory distress syndrome (ARDS)[28]. ARDS, the most severe form of acute lung injury, is a clinical manifestation of the response of the lung to pulmonary insults brought on by infectious, non-infectious, and other damaging events. It affects up to 200,000 patients annually in the US, with a mortality rate approaching 50%, with inflammation and tissue fibrosis being the leading cause of morbidity and mortality[86]. Factors predisposing patients to ARDS include sepsis, aspiration, and pneumonia[28,87,88].

Lipopolysaccharide (LPS) is a bacterial bio-active component found in gram-negative bacteria and involved in many pathological conditions due to its role in activating the inflammatory cascade[17]. The mechanism of LPS causing ALI depends on its proinflammatory activities[17]. LPS is proposed to recruit and promote monocyte infiltration and aggregation, promote provocative cytokine synthesis and secretion and induce apoptosis in alveolar epithelial cells[48]. Previous studies from our lab demonstrated that targeted delivery of CDC to lung cells following exposure to LPS reduces the severity of ALI in mice[17]. In another study, the novel curcumin analog c26 was found to have remarkable protective effects on rats' LPS-induced ALI. These effects may be related to its ability to suppress the production of inflammatory cytokines through the extracellular signal-regulated kinases (ERK) pathway. Compound c26, with improved chemical stability and bioactivity, may have the potential to be further developed into an anti-inflammatory candidate for the prevention and treatment of ALI[89].

Importantly, curcumin has been found to have broad anti-inflammatory activities both *in vitro* and *in vivo*. Additionally, other studies indicate that pretreatment with curcumin showed beneficial effects on ALI induced by oleic acid[90], sepsis[91,92], and aspiration[93]. Finally, curcumin is an effective inhibitor of bleomycin (BLM)-induced inflammation, apoptosis, and migration of basal alveolar epithelial cells[94]. Ultimately, the full potential benefits of curcumin and its

mechanisms of action have just begun to be elucidated to treat pulmonary diseases, including fibrosis and ALI/ARDS[24,28] (**Figure 2).**

9. Effect of curcumin on treating bacterial pneumonia

Pneumonia is a significant cause of morbidity and mortality worldwide and causes a substantial burden on healthcare systems[95]. The main types of pneumonia are bacterial, viral, and mycoplasma pneumonia. The bacteria and viruses that most commonly cause pneumonia in the community differ from those in healthcare settings, some of which are discussed here[92,93]. A common cause of bacterial pneumonia is *Streptococcus pneumoniae* (SP)[96]. Ventilator-associated pneumonia (VAP) is when someone gets pneumonia after being on a ventilator, a machine that supports breathing[97,98]. *Klebsiella pneumoniae* (*KP*) is a gram-negative pathogen with a large accessory genome of plasmids and chromosomal loci[99,100]. The gram-positive bacterium, methicillin-resistant *Staphylococcus aureus* (MRSA), is resistant to β-lactam antibiotics because of the lowered β-lactam affinity to penicillin-binding proteins (PBP) and PBP2a[101,102]. *Pseudomonas aeruginosa* is an important pathogen frequently associated with healthcare-associated infections, particularly in critically ill or immunocompromised patients[96].

Plant compounds such as curcumin may serve as a source of novel antibiotics[103]. One study found synergistic effects of curcumin and common antibiotics against 60 strains of gram-positive and gram-negative biofilm-producing bacteria, including common pneumonia-causing pathogens introduced earlier[104]. *In vitro* disc diffusion assays have demonstrated that extracts from plants in the Curcuma genus can inhibit the growth of several pneumonia-causing bacteria, such as *K. pneumoniae*[2,89]. Promisingly, curcumin has effectively inhibited the development of several species of multidrug-resistant bacteria[3,100.101]. Additionally, Hayati et al. found *in vitro* antibacterial activity of curcumin against methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus faecalis*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli (E.coli),* and *Klebsiella pneumoniae* using the microdilution broth susceptibility test method [105]. One study found that MRSA and MSSA have demonstrated *in vitro* sensitivities to curcumin[105]. This finding could suggest that curcumin acts on cellular targets that bypass the resistance mechanisms of MRSA[96]. On another note, Alikiaii reported that curcumin lessens pneumonia severity by reducing neutrophil infiltration and ameliorating the exaggerated immune response in preclinical pneumonia models[106].

Our studies demonstrate that CDC administration improves cell survival and reduces injury, inflammation, and mortality in a murine model of lethal gram-negative (*KP)* pneumonia. CDC, therefore, has promising anti-inflammatory potential in pneumonia and likely other inflammatory lung diseases, demonstrating the importance of optimizing the physicochemical properties of active natural products to optimize their clinical application.[24]

10. Other therapeutic effects of curcumin

It has been found that cyclodextrin-encapsulated curcumin (CDC) has a greater cellular uptake and a longer half-life in cells than free curcumin, indicating that CDC has superior attributes to free curcumin for cellular uptake. In addition, the improvement of curcumin permeability across mammalian cells and animal tissue was observed in CD-encapsulated curcumin and was about 1.8-fold compared with the free curcumin. Thus, these studies suggest that CDC has improved *in vitro,* and *in vivo* bioavailability and chemotherapeutic efficacy compared to curcumin alone.

Multiple studies have demonstrated the safety and efficacy of curcumin in numerous animals, including rodents, monkeys, horses, rabbits, and cats. They have provided a solid basis for evaluating its safety and effectiveness in humans. More than 65 human clinical trials of curcumin, which included more than 1000 patients, have been completed, and as many as 35 clinical trials are underway. Curcumin is a free radical scavenger and hydrogen donor and exhibits pro-oxidant and antioxidant activity. It binds metals, particularly iron and copper, and can function as an iron chelator. Curcumin is remarkably non-toxic and exhibits limited bioavailability. Curcumin shows excellent promise as a therapeutic agent. It is currently in human clinical trials for various conditions, including multiple myeloma, pancreatic cancer, myelodysplastic syndromes, colon cancer, psoriasis, and Alzheimer's disease. Curcumin protects against hepatic disorders, chronic arsenic exposure, and alcohol intoxication. Dose-escalating studies have indicated the safety of curcumin at doses as high as 12 g/day over 3 months. Various formulations of curcumin, including nanoparticles, liposomal encapsulation, emulsions, capsules, tablets, and powder, have been examined. Additionally, curcumin treatment is suitable for mental health conditions and reduces antidepressant and anxiolytic effects.

Curcumin, in inflamed organs, reduces the expression levels of NLRP3, IL-1β, IL-18, and caspase-1, inhibiting the inflammasome. In LPS-stimulated mouse macrophages, curcumin inhibits the activity of the NLRP3 inflammasome. Curcumin activated Nrf2 and inhibited NF-κB. In the lungs, curcumin effectively prevented the increase of Neurogenic locus notch homolog

protein 1 (Notch1). Curcumin has a regulatory effect on several molecules in the intracellular signal transduction pathways involved in inflammation, including extracellular signal-regulated kinase 1 (ERK1), STAT3, and AMP-activated protein kinase (AMPK). Curcumin down-regulates the expression of inflammatory enzymes, such as cyclooxygenase-2 (COX2) and inducible nitric oxide synthase (iNOS) and inhibits proinflammatory enzymes and chemokines. Studies have shown that curcumin inhibits severe inflammation and cytokine storm in COVID-19 infection, which may help prevent ARDS, ALI, and multiple organ dysfunction syndromes (MODS) such as in the lungs, liver, kidneys, brain, and eventually death. Oral curcumin supplementation may inhibit COVID-19-caused inflammation alongside other drug regimens by affecting these pathways and molecules and applying anti-inflammatory, antioxidant, and anti-apoptotic properties without specific side effects. Ultimately, curcumin shows massive potential as a therapeutic agent in different contexts.

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AUTHOR DISCLOSURE

None of the authors has a financial relationship with a commercial company.

DATA AVAILABILITY STATEMENT

All data collected and analyzed within this study are available from the corresponding author upon request.

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FIGURE LEGENDS

Figure 1. The schematics represent the potential mechanisms by which CDC (curcumin) effectively protects against ARDS/COVID-19. Antiviral curcumin against SARS-CoV-2 mediated by distracting the ACE2, which prevents the entry of the virus into the cells. CDC induces antiviral responses by positively repressing the expression of ACE2, NRF2, STAT3, and C–X–C motif chemokine 10 (CXCL10). CDC mediates immunomodulatory responses by inhibiting inflammation, cytokines, apoptosis, and oxidative stress, thus mitigating the progression to KP/ARDS following SARS-CoV-2 infection.

Figure 2: The proposed mechanism model responsible for curcumin's protective effects in mice following LPS/KP. CDC inhibits the production of proinflammatory cytokines by targeting the

NF-κB pathway. CDC targets NF-κB signaling by inhibiting the activation of IL-1β, IL-6, and Monocyte chemoattractant protein-1(MCP1).

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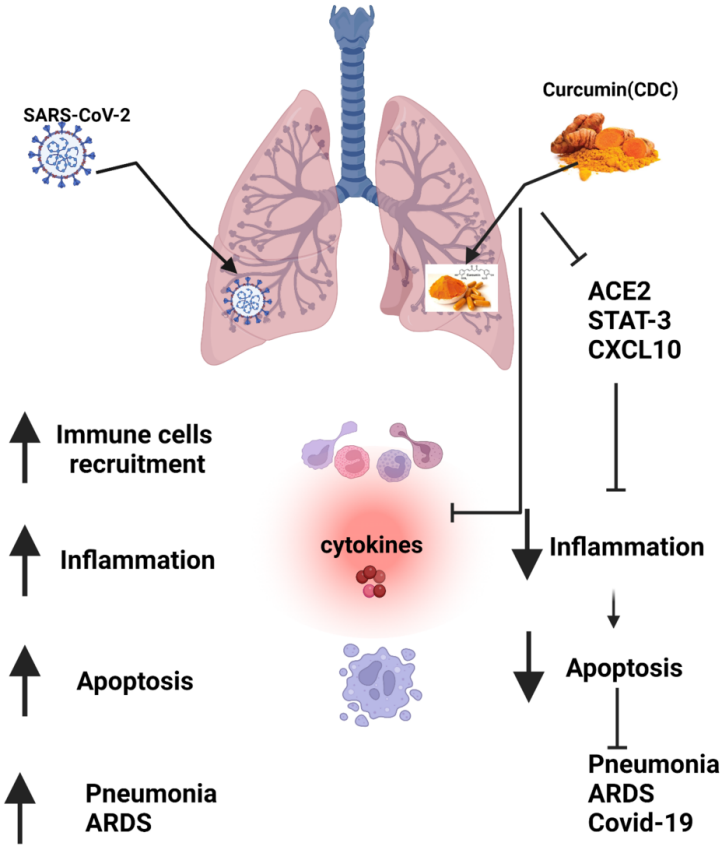
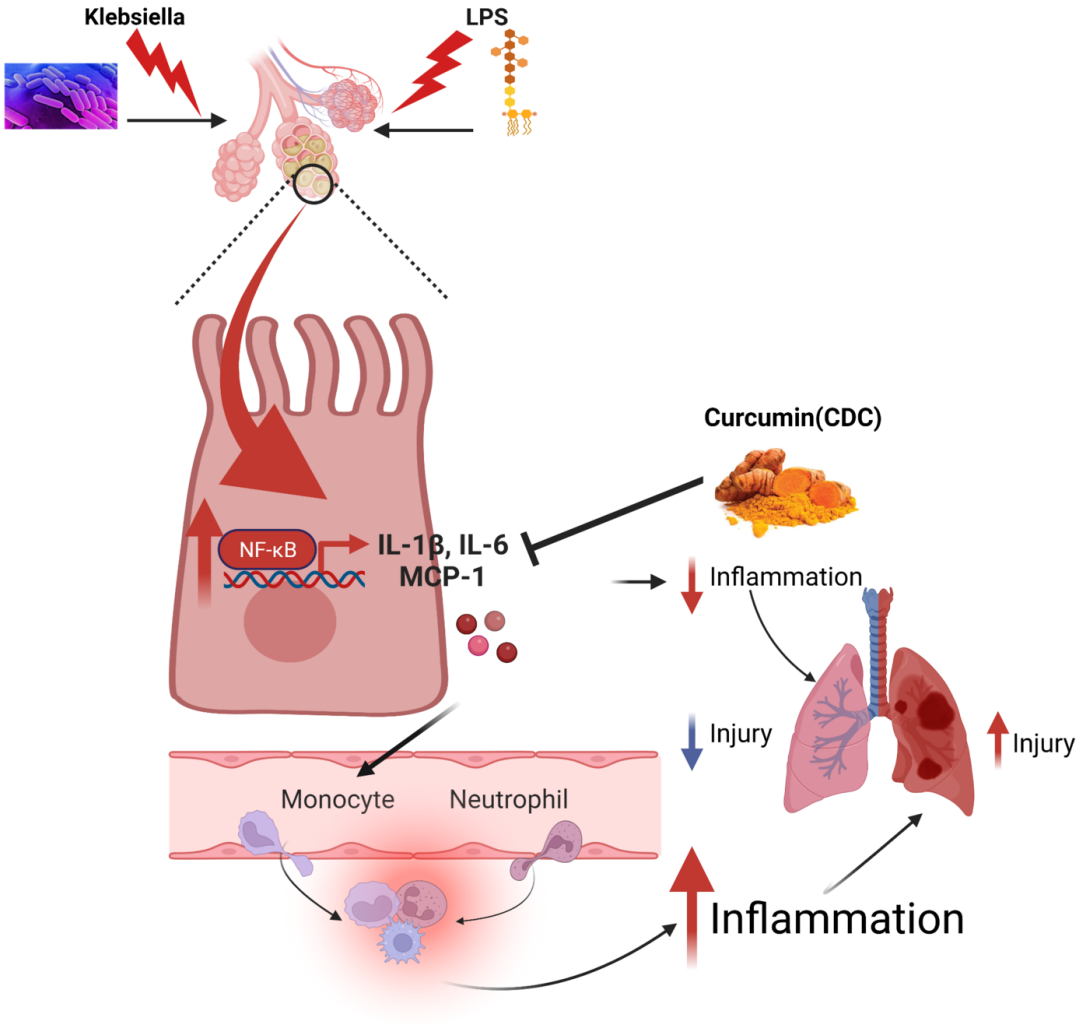


CEP_13744_CDC Figure-1.png



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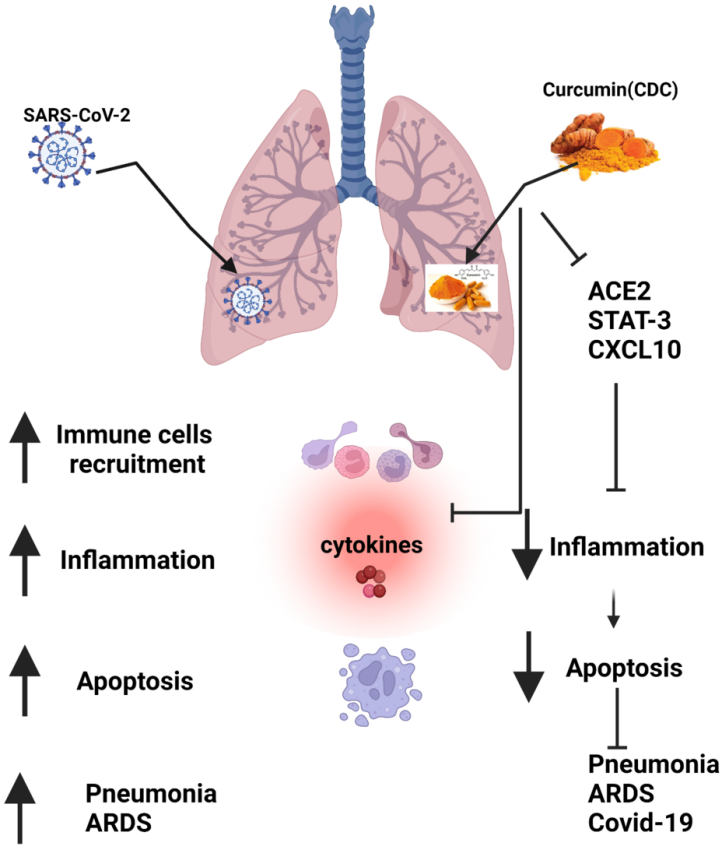

CEP_13744_Graphical abstract image.png

Graphical Abstract Text

Acute respiratory distress syndrome (ARDS) is a deadly lung injury triggered by sepsis, pneumonia, and COVID-19. Curcumin is a safe, non-toxic, readily available, and naturally occurring compound with potent anti-inflammatory properties. We demonstrated oral administration of water-soluble curcumin complex prevents ARDS with potential for COVID-19.