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REVIEW

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Curcumin (a constituent of turmeric): New treatment option against COVID-19

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Abstract

In late December 2019, the outbreak of respiratory illness emerged in Wuhan, China, and spreads worldwide. World Health Organization (WHO) named this disease severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused by a new member of beta coronaviruses. Several medications are prescribed to patients, and some clinical trials are underway. Scientists are trying to find a specific drug against this virus. In this review, we summarize the pathogenesis, clinical features, and current treatments of coronavirus disease 2019 (COVID-19). Then, we describe the possible therapeutic effects of curcumin and its molecular mechanism against coronavirus-19. Curcumin, as an active constituent of *Curcuma longa* (turmeric), has been studied in several experimental and clinical trial studies. Curcumin has some useful clinical effects such as antiviral, antinociceptive, anti-inflammatory, antipyretic, and antifatigue effects that could be effective to manage the symptoms of the infected patient with COVID-19. It has several molecular mechanisms including antioxidant, antiapoptotic, and antifibrotic properties with inhibitory effects on Toll-like receptors, NF-κB, inflammatory cytokines and chemokines, and bradykinin. Scientific evidence suggests that curcumin could have a potential role to treat COVID-19. Thus, the use of curcumin in the clinical trial, as a new treatment option, should be considered.

KEYWORDS

antiapoptotic, antifatigue, antifibrotic, anti-inflammatory, antiviral, Coronavirus-19, curcumin

1 | INTRODUCTION

In late December 2019, the outbreak of respiratory illness was reported in Wuhan, China. After a while, the cause of this unknown pneumonia was recognized as a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by World Health Organization (WHO) (Zhu et al., 2020; He, Deng, & Li, 2020; Huang et al., 2020).

Coronaviruses (CoVs) are enveloped positive-stranded RNA viruses that cause respiratory, enteric, hepatic, and neurological diseases in humans and animals (Zumla, Chan, Azhar, Hui, & Yuen, 2016). Some human CoVs, such as HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63, create mild respiratory illness, but some others including severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) cause severe diseases (Li, Bai, & Hashikawa, 2020). It is identified that COVID-19

transmitted among humans by respiratory droplets and close contact (Chan et al., 2020). A recent research project revealed that sequence homology between SARS-CoV-2 and SARS-CoV was 79.5% (Wu et al., 2020) and SARS-CoV-2 belongs to the same beta coronavirus (β CoV) clade as MERS-CoV and SARS-CoV (Yu, Du, Ojcius, Pan, & Jiang, 2020). Moreover, it has been identified that SARS-CoV-2 had high homology with bat coronaviruses and likely derived from bats (Zhou et al., 2020), but the intermediate hosts of SARS-CoV-2 have not been determined yet. The recent finding reveals that COVID-19 has similar pathogenesis with SARS-CoV or MERS-CoV (Song et al., 2019) and uses the same receptor as SARS-CoV for entrance to human host cells (Lu et al., 2020; Wan, Shang, Graham, Baric, & Li, 2020).

2 | METHODS

The most important articles about COVID-19 (from starting disease up to now) and curcumin were selected. We considered all articles of curcumin—human and animal studies—that could be effective to treat or rescue COVID-19-infected patients. PubMed and Web of Science were used as databases. As the importance of the subject, some selected papers were in the press. The keywords used for the search were as follows: coronavirus-19, COVID-19, SARS-CoV-2, curcumin, *Curcuma longa*, turmeric, curcumin and antiviral, curcumin and anti-inflammatory, curcumin and antipyretic, curcumin and lung, curcumin and acute lung injury, curcumin and fatigue, curcumin and antioxidant, curcumin and ARDS, curcumin and bradykinin, curcumin and fibrosis, curcumin and Interleukin-6 (IL-6), curcumin and tumor necrosis factor-alpha (TNF-α), curcumin and NF-κB, curcumin and Toll-like receptors (TLRs), curcumin and antiapoptotic.

3 | PATHOGENESIS

The SARS-CoV-2 is an enveloped nonsegmented positive-sense RNA virus. Two-thirds of viral RNA is located in the first open reading frames that encode 16 nonstructural proteins, whereas the remaining part of the genome encodes four essential structural proteins including spike (S) glycoprotein, envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein (Cui, Li, & Shi, 2019).

S protein contributes to virus pathogenesis through binding to cell surface receptor, angiotensin-converting enzyme 2 (ACE2), and the entrance of the virus into the host cell (Zhou et al., 2020). The possible mechanism and molecules involved in membrane invagination during virus endocytosis are still unknown. S protein is divided into the S1 domain that is responsible for receptor binding, and S2 domain that mediates cell membrane fusion (He et al., 2004).

Recent data showed that the 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 (Wrapp et al., 2020). The ACE2 expressed on the surface of cells in the lung, arteries, heart, kidney, and intestine (Hamming et al., 2004). Its concentration in the alveolar cells of men was higher than women, which may correlate with a high incidence rate of COVID-19 among men. Moreover, the expression level of ACE2 in the alveolar cells of Asians was higher than other races, which may lead to high susceptibility to disease and severe outcomes (Sun, Lu, Xu, Sun, & Pan, 2020). The ACE2 is an enzyme that catalyzes vasoactive angiotensin II to vasodilator angiotensin[1–7] (Richards & Raizada, 2018).

On the other hand, the binding of the SARS-CoV spike protein to ACE2 leads to ACE2 downregulation (Kuba et al., 2005). It is not clear that SARS-CoV-2 could downregulate the expression of ACE2 or not as the homology of SARS-CoV-2 with SARS-CoV. ACE2 downregulation resulted in excessive production of angiotensin by the ACE, suggesting lead to pulmonary hypertension, acute lung injury (ALI), and lung fibrosis (Tan, Liao, Zhou, Mei, & Wong, 2018).

Previous studies have shown the protective role of ACE2 against various types of pulmonary illnesses such as acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), pulmonary hypertension, ALI, and asthma (Jia, 2016). It has been suggested that increasing ACE2 levels such as using angiotensin II receptor blocker medications could be effective to treat COVID-19 (Gurwitz, 2020). However, another study showed that decreasing ACE2 activity might be protective (Zhang, Penninger, Li, Zhong, & Slutsky, 2020). Thus, these hypotheses might be the basis for more research to clarify new therapeutic options.

3.1 | Clinical signs and symptoms in patients

The patients mainly were 30–79 years old (Wu & McGoogan, 2020). A few cases were children below 15 years old such as 15 days old in Iran (Kamali Aghdam, Jafari, & Eftekhari, 2020). There were one or more coexisting medical conditions, including hypertension, diabetes, and cardiovascular disease in about half the patients (Chen et al., 2020). These coexisting medical conditions lead to a high mortality rate in COVID-19 patients (Wu & McGoogan, 2020). There was a spectrum of clinical features ranging from asymptomatic infection to severe respiratory failure. The most prevalent manifestations include fever, fatigue, dry cough, myalgia, dyspnea, and anorexia (Qin et al., 2020; Rodriguez-Morales et al., 2020). The uncommon symptoms were sputum production, headache, hemoptysis, diarrhea, nausea, and vomiting (Huang et al., 2020; Qian et al., 2020; Rodriguez-Morales et al., 2020).

3.2 | Laboratory findings

According to laboratory examination, lymphopenia, hypoalbuminemia, and high levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and lactate dehydrogenase (LDH) were the most prevalent results in the patients (Mo et al., 2020; Qin et al., 2020; Rodriguez-Morales et al., 2020; Talebpour, Hadadi, Oraii, & Ashraf, 2020; Wang, Yang, Li, Wen, & Zhang, 2020).

TABLE 1 Some protocols used for the treatment of COVID-19

Study details	Treatment protocol	Reference
41 patients, Wuhan, China	Oxygen support, antibiotics (*N*), antiviral (oseltamivir), corticosteroid (methylprednisolone), renal replacement therapy	Huang et al. (2020)
69 patients, Wuhan, China	Oxygen support, antibiotics (*N*), antiviral (*N*), corticosteroid (*N*), antifungal (*N*), arbidol, moxifloxacin, interferon therapy (*N*)	Wang, Yang, et al. (2020)
135 patients, Northeast Chongqing, China	Oxygen support, antibiotics (*N*), antiviral (Kaletra), corticosteroid (*N*), traditional Chinese medicine therapy, renal replacement therapy	Wan, Xiang, et al. (2020)
155 patients, Wuhan, China	Oxygen support, corticosteroid (*N*), expectorant, antiviral: arbidol, lopinavir, ritonavir, interferon inhalation, immune enhancer (thymalfasin, immunoglobulin)	Mo et al. (2020)
One patient Case report, United States	Antipyretic therapy: acetaminophen (650 mg, every 4 hr), and ibuprofen (600 mg, every 6 hr), expectorant: guaifenesin (600 mg), oxygen support, antibiotics (vancomycin and cefepime), antiviral (remdesivir)	Holshue et al. (2020)
99 patients, Wuhan, China	Oxygen support, antibiotics: cephalosporins, quinolones, carbapenems, tigecycline against methicillin-resistant Staphylococcus aureus, linezolid, Antiviral: oseltamivir (75 mg, every 12 hr), ganciclovir (0.25 g, every 12 hr), and lopinavir and ritonavir (500 mg, twice daily), corticosteroid: methylprednisolone sodium succinate, methylprednisolone, and dexamethasone, antifungal (*N*), renal replacement therapy, immunoglobulin therapy (IV)	Chen et al. (2020)
More than 100 patients Wuhan, Jingzhou, China	Chloroquine phosphate	Gao, Tian, and Yang (2020)
20 patients, Marseille, France	Hydroxychloroquine (600mg, daily)	Gautret et al., (2020)

Note: N: not mentioned.

Patients with severe symptoms had raised levels of coagulation indexes (prothrombin time, activated partial thromboplastin time, and D-dimer), procalcitonin, IL-6, and serum ferritin, and multiple organ involvement, such as liver (increased lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase levels), kidney (increased blood urea nitrogen and creatinine levels), and heart and muscle (increased creatinine kinase levels) compared with patients with mild symptoms. Also, there was higher neutrophil-to-lymphocyte ratio (NLR) and lower percentages of monocytes, eosinophils, and basophils in complete blood count (Qian et al., 2020; Qin et al., 2020; Talebpour et al., 2020; Wan, Xiang, et al., 2020).

The elevated levels of IL-1B, interleukin-1 receptor antagonist (IL1RA), IL-7, IL-8, IL-9, IL-10, basic fibroblast growth factors (FGF), granulocyte colony-stimulating factor (GCSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-gamma (IFNγ), interferon γ-induced protein 10 kDa (IP-10), monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein-1 alpha (MIP1-α), macrophage inflammatory protein-1β (MIP-1β), platelet-derived growth factor (PDGF), tumor necrosis factor-alpha (TNF-α), and vascular endothelial growth factor (VEGF) were observed in serum sample of patients. Plasma levels of IL-5, IL-12p70, IL-15, eotaxin, and RANTES (chemokine (C-C motif) ligand 5, CCL5) were similar between healthy adults and patients infected with SARS-COV-19. Moreover, plasma concentrations of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNF-α were higher in the intensive care unit (ICU) patients compared with non-ICU patients. These data suggest that the initial response of the immune system may lead to the production of cytokines and chemokines, which damage normal host organs such as lung and heart. Also, hypersensitive troponin I (hs-cTnI) was increased in patients with virus-related cardiac injury (Huang et al., 2020).

3.3 | Pathology

The pathological features of COVID-19 were similar to SARS-CoV and MERS-CoV infection (van den Brand, Smits, & Haagmans, 2015; Hui & Zumla, 2019; Nassar, Bakhrebah, Meo, Alsuabeyl, & Zaher, 2018). Moreover, moderate microvascular steatosis, mild lobular, and portal activity were observed in the liver biopsy samples. The heart tissue also showed interstitial mononuclear inflammatory infiltrates. The CD4 and CD8 T cells were decreased in flow cytometric analysis of peripheral blood. Also, X-ray images showed a rapid progression of pneumonia in lung tissues (Xu et al., 2020).

4 | COVID-19 AND CURRENT DRUG DEVELOPMENT RESEARCH PROJECTS

Countries use various strategies to treat COVID-19 patients. Some protocols for the treatment are summarized in Table 1. Some clinical trials try to find an effective drug (Li & De Clercq, 2020). Organ dysfunction, including shock, ARDS, acute cardiac injury, acute kidney injury, liver dysfunction, and secondary inflammation are causes of death among COVID-19 patients (Chen et al., 2020; Huang et al., 2020; Wan, Xiang, et al., 2020; Wang, Hu, et al., 2020). Current medical therapies are symptomatic treatment or supportive care. There is no definitive treatment yet for this

disease. Therefore, finding effective strategies to treat infected patients and protect organs is necessary to decrease the mortality rate.

4.1 | Curcumin as a new option

Curcumin, as a potential agent, could be considered to treat COVID-19. Curcumin, as an active constituent of rhizomes of *C. longa* (turmeric), is a hydrophobic polyphenol (Figure 1) (Akbar et al., 2018; Soleimani, Sahebkar, & Hosseinzadeh, 2018). Curcumin is used as a spice in foods and for different purposes such as cosmetic and pharmaceutical industries in world (Hosseini & Hosseinzadeh, 2018). Curcumin has several pharmacological effects such as antioxidant, anticancer, antibacterial, antiviral, and antidiabetic effects (Fan et al., 2015; Moghadamtousi et al., 2014; Zhu et al., 2017), as well as anti-inflammatory activity (Cheng, Yang, Hu, Zhu, & Liu, 2018). As the potential role of curcumin to treat many inflammatory disorders, at the first step we will describe all effects of curcumin that may be useful to treat COVID-19, and then, we explain the possible molecular mechanisms of it.

5 | THERAPEUTIC EFFECTS OF CURCUMIN AGAINST COVID-19

5.1 | Antiviral effects

Curcumin prevented the replication of SARS-CoV and inhibited 3Cl protease in Vero E6 cells. Also, it significantly has an inhibitory activity against the cytopathogenic effect of SARS-CoV in Vero E6 cells (Wen et al., 2007). Curcumin was effective against other viruses such as influenza A virus, HIV, enterovirus 71 (EV71), herpes simplex virus (HSV), hepatitis C virus (HCV), and human papillomavirus (HPV) with several mechanisms that made it valuable for antiviral therapies (Moghadamtousi et al., 2014; Praditya et al., 2019; Qin et al., 2014).

Recently, it has shown that the transformation of curcumin into carbon quantum dots could boost antiviral effects of curcumin with different mechanisms against EV71 in vitro and in vivo (Lin et al., 2019). The interesting issue about carbon quantum dots is that it alone was effective against human coronavirus (HCoV) by inhibiting the entry receptor of HCoV-229E (Łoczechin et al., 2019).

5.2 | Antiemetic effect

C. longa L, as herbal medicine, is used to treat vomiting from ancient times in Asian countries (Liu et al., 2018). Curcumin (20 mg/kg, intragastric, 3 days) improved appetite of rats in chemotherapy induced by fluorouracil (5-FU) (Yao et al., 2013). It may be effective against vomiting due to COVID-19.

5.3 | Reduces myalgia and fatigue

In an animal study, oral administration of curcumin has an antifatigue function and improved physical function in mice (Huang et al., 2015). Administration of curcumin (1,000 mg/d, 30 days) reduced stress and fatigue in the subjects that experiencing occupational stress-related anxiety and fatigue in a randomized double-blinded placebo-controlled study (Pandaran Sudheeran et al., 2016). Curcumin (2.5 g, two times a day) reduced delayed-onset muscle soreness of healthy men who have a heavy eccentric exercise (Nicol, Rowlands, Fazakerly, & Kellett, 2015). The use of curcumin in myalgic encephalomyelitis/chronic fatigue syndrome as a novel therapeutic option was mentioned (Morris et al., 2019). Curcumin inhibited sepsis-induced muscle wasting by inhibiting catabolic response in skeletal muscle via blocking NF-κB (Alamdari, O'Neal, & Hasselgren, 2009). Curcumin (Meriva®, 1 g, 3 months) prevented muscle loss and improved physical performance in healthy elder subjects and delayed the onset of sarcopenia in them (Franceschi et al., 2016). These results suggest that curcumin may be effective to manage myalgia and fatigue symptoms induced by COVID-19.

5.4 | Antinociceptive, anti-inflammatory, and antipyretic effects

The antinociceptive and anti-inflammatory effects of curcumin in animal and human studies were reviewed by Eke-Okoro, Raffa, Pergolizzi, Breve, & Taylor, 2018 (Eke-Okoro et al., 2018). About the important molecular mechanism of these effects, it will discuss later that curcumin could be effective as a novel treatment against COVID-19. Also, in an animal study, curcumin (100 mg/kg, i.p.) has an antipyretic effect in rats (Haider et al., 2013). It seems that curcumin overcomes the fever of COVID-19-infected patients.

5.5 | Inhibitory effects on cytokines and chemokines

Two meta-analyses of randomized controlled trials have shown that curcumin reduced circulating IL-6 and TNF-α levels that both are the key inflammatory mediators and increase in inflammatory diseases (Derosa, Maffioli, Simental-Mendía, Bo, & Sahebkar, 2016; Sahebkar,

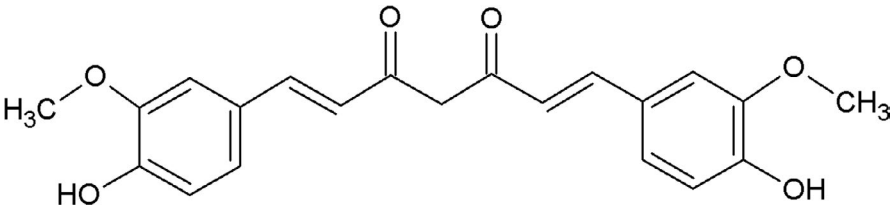

FIGURE 1 Chemical structure of curcumin

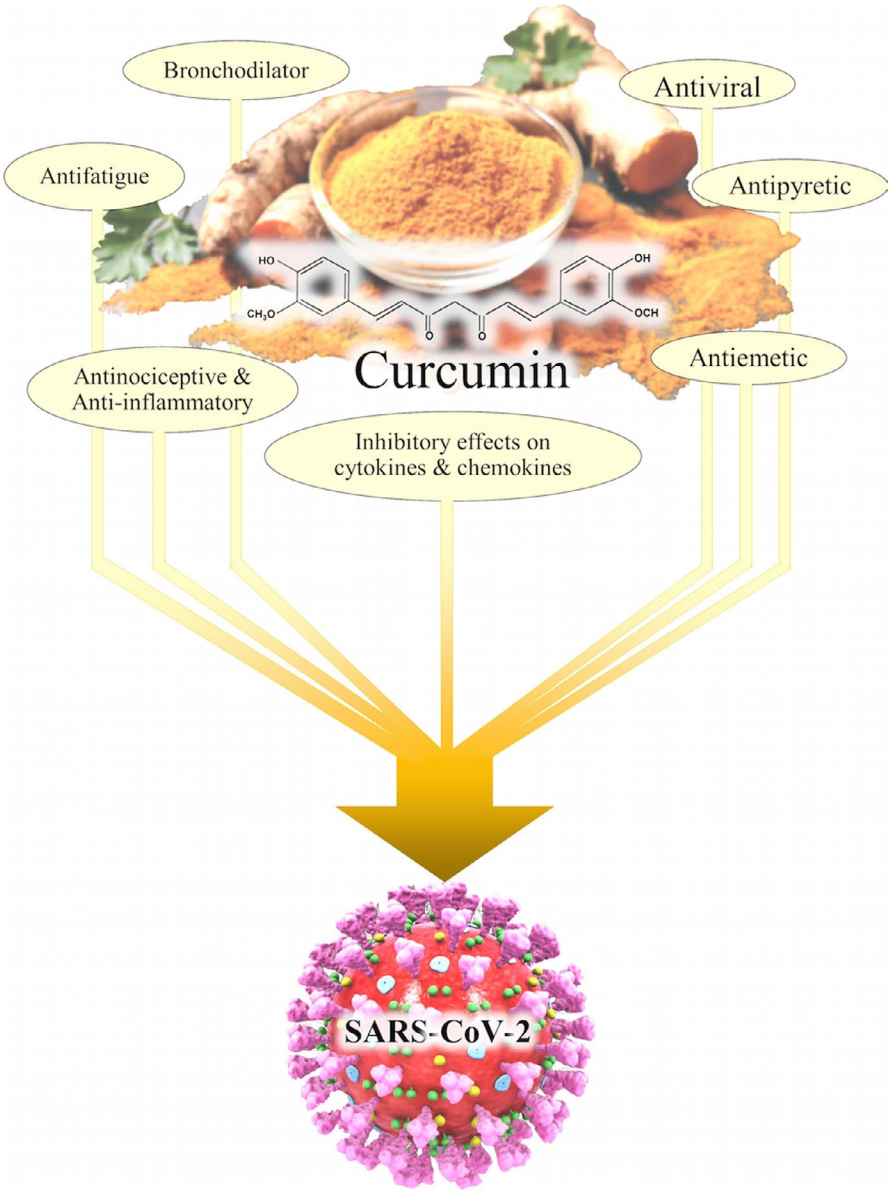

FIGURE 2 Possible clinical effects of curcumin in the treatment of COVID-19. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Cicero, Simental-Mendía, Aggarwal, & Gupta, 2016). Curcumin also reduced the expression of IL-1β in M1 macrophages from Behcet's disease patients (Palizgir et al., 2018). Also, curcumin protected human genital mucosal epithelial cells against HIV-1 replication by inhibiting activation of proinflammatory chemokines such as IL-8 and RANTES (Ferreira, Nazli, Dizzell, Mueller, & Kaushic, 2015). The summary of the clinical effects of curcumin that may be useful to treat COVID-19 is illustrated in Figure 2.

In this section, we summarize the important molecular mechanisms of curcumin that show potential ability against COVID-19. Figure 3 presents a summary of the possible molecular mechanisms of curcumin against COVID-19 via different signaling pathways in the pulmonary system. This figure shows the inhibitory effects of curcumin on TLRs, NF-κB, cytokines, chemokines, bradykinin, oxy-radicals, transforming growth factor-beta1 (TGF-β1), cyclooxygenase (COX), plasminogen activator inhibitor-1 (PAI-1), IL-17A, and caspase-3 (Cas-3).

5.6 | Antioxidant effects

In severe COVID-19 infection, pneumonia may cause hypoxemia, which, in turn, disturbs cell metabolism and reduces the energy supply, and increases anaerobic fermentation. Then, acidosis happens and causes oxygen free radicals to destroy the phospholipid layer of the cell membrane (Li, Yang, et al., 2020). Therefore, treatment with a drug that has antioxidant properties will be good for these patients and curcumin has this effect. Several studies have shown that curcumin is a strong antioxidant (Abrahams, Haylett, Johnson, Carr, & Bardien, 2019; Farzaei et al., 2018; Mary, Vijayakumar, & Shankar, 2018; Trujillo et al., 2013). Curcumin (1 mg/kg, 5 mg/kg) increased the superoxide dismutase (SOD) level in acute lung injury induced by intestinal ischemia–reperfusion in mice (Fan et al., 2015). Furthermore, curcumin (200 mg/kg) reduced malondialdehyde (MDA) level and recovered the levels of xanthine oxidase (XO) and total antioxidative capacity (TAOC) in ventilator-induced

lung injury in rats (Wang, An, et al., 2018). Similarly, curcumin (200 mg/kg) increased SOD activity and decreased MDA content in the lung in acute injury induced by sepsis (Xiao, Yang, Sun, & Sun, 2012).

5.7 | The anti-inflammatory effects in acute lung injury/acute respiratory distress syndrome (ALI/ARDS) models

ARDS is a clinical syndrome and is associated with increased permeability pulmonary edema, severe arterial hypoxemia, and impaired carbon dioxide excretion, eventually resulting in respiratory failure. It may occur due to a pulmonary or extrapulmonary infectious or noninfectious insult (Matthay, Ware, & Zimmerman, 2012).

Major inflammatory mediators in ADRS include cytokines (TNF-α, IL-1β, IL-6, IL-8, IL-10), chemokines such as macrophage inhibitory factor (MIF), and macrophage chemoattractant protein, metabolites of arachidonic acid (prostanoids and leukotrienes), and oxyradicals. Until yet, mechanical ventilation is only a proven strategy for treatment to improve the survival of patients (Matuschak & Lechner, 2010). Recently, rescue therapy with high-dose vitamin C has been suggested to use for these patients (Fowler et al., 2019). Therefore, finding new treatments to overcome these mediators and preventing respiratory failure are necessary. On the other hand, the protective effects of curcumin were studied in several pulmonary diseases such as COPD, ARDS, pulmonary fibrosis, and asthma in animal studies (Lelli, Sahebkar, Johnston, & Pedone, 2017; Venkatesan, Punithavathi, & Babu, 2007). In this part of the review, we explain molecular

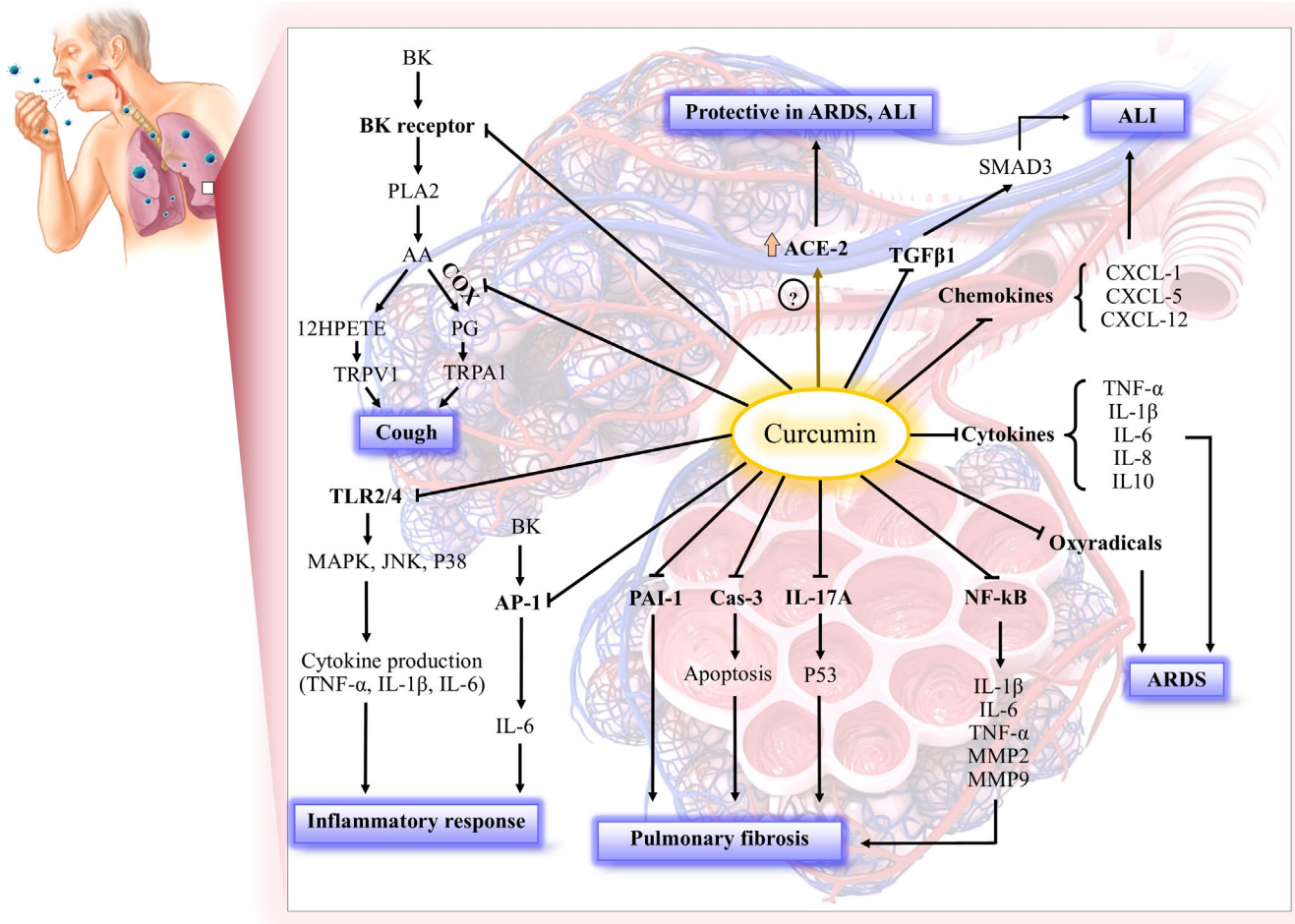

FIGURE 3 Possible molecular mechanisms of curcumin against COVID-19 in the pulmonary system. AA: arachidonic acid, ALI: acute lung injury, AP-1: activator protein 1, BK: bradykinin, ACE2: angiotensin-converting enzyme 2, Ang II: angiotensin II, ARDS: acute respiratory distress syndrome, Cas-3: caspase 3, COX: cyclooxygenase, CXCL: chemokine (C–X–C motif) ligand, 12-HPETE: 12-hydroperoxyeicosatetraenoic acid, JNK: c-Jun N-terminal kinase, 12 LOX: 12-lipoxygenase, MMP: matrix metalloproteinase NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, MAPK: mitogen-activated protein kinase, PAI-1: plasminogen activator inhibitor-1, PLA2: phospholipase A2, PG: prostaglandin, SMAD3: mothers against decapentaplegic homolog 3, TGF-β1: transforming growth factor-beta 1, TNF-α: tumor necrosis factor-α, TLR: Toll-like receptor, TRPA1: transient receptor potential channel subfamily vanilloid member 1, TRPV1: transient receptor potential channel subfamily A member 1

mechanisms that curcumin may be useful to prevent or treat the ARDS.

5.7.1 | NF-κB activity and inflammatory cytokines and chemokines

ALI is a model that is used for the ARDS animal study (Karunaweera, Raju, Gyengesi, & Münch, 2015; Olivera et al., 2012; Tian et al., 2006; Wang, Tang, Duan, & Yang, 2018), and curcumin exhibits its effects by predominantly targeting proinflammatory NF-κB pathway (Ahn, Sethi, Jain, Jaiswal, & Aggarwal, 2006; Karunaweera et al., 2015; Olivera et al., 2012; Puar et al., 2018; Wang, Tang, et al., 2018). Curcumin decreased IL-6 level and myeloperoxidase (MPO) activity, intercellular adhesion molecule-1 (ICAM-1) expression, and bronchoalveolar lavage fluid (BALF) protein in ALI induced by intestinal ischemia–reperfusion in mice that all of them are known as inflammatory indexes. It seems that curcumin by inhibiting NF-κB could have anti-inflammatory effects (Fan et al., 2015). Curcumin not only decreased the level of keratinocyte-derived chemokine (KC), IL-1β, macrophage inflammatory protein (MIP)-2, TNF-α, IL-6, and TGF-β in the BALF but also downregulated the expression of their genes except IL-6 in ALI induced by *Staphylococcus aureus* in mice. Also, curcumin inhibited the activation of NF-κB by downregulating phosphorylation of IκB-α in bone marrow-derived macrophages (BMDM) that were stimulated with *S. aureus*. It has been suggested that some part of the anti-inflammatory effects of curcumin are due to regulating NF-κB activity (Xu et al., 2015).

Curcumin downregulated the production of proinflammatory cytokine (TNF-α, IFN-α, and IL-6) in influenza A virus-infected human macrophages and BAL fluid of infected mice. Similar to other noted studies, curcumin downregulated the expression of NF-κB and increased the cytosolic IκBα and inhibited its phosphorylation in the cytoplasm in human macrophages (Xu & Liu, 2017). In this way, curcumin reduced TNF-α, MIP-2, and IL-6 in lipopolysaccharide (LPS)-induced ALI in mice. It has been suggested that curcumin inhibits the release of cytokines by activation of 5′ adenosine monophosphate (AMP)-activated protein kinase (AMPK) (Kim et al., 2016).

Curcumin reduced the production of TNF-α, IL-1β, IL-6, and IL-8, MMP-2, and MMP-9 both in mice and in A549 cells infected with influenza A virus. These cytokines exacerbate the ALI (Dai et al., 2018). The inhibitory role of curcumin on the expression of proinflammatory cytokines such as TNF-α, IL-1, and IL-6 was reviewed in ALI and fibrosis by Gouda and Bhandary (2019). It seems that the most important molecular mechanism of curcumin on IL-6 activities may be related to the downregulation or inhibition of IL-6 signaling in different inflammatory diseases (Ghandadi & Sahebkar, 2017). Furthermore, curcumin has an inhibitory effect on IL-17 A that plays a pivotal role in the inflammation of the alveolar epithelial cells in ALI studies. In other words, IL-17 by activating P53 causes the stabilization of the PAI-1, which in turn mediates the accumulation of extracellular matrix (ECM) and subsequent development of pulmonary fibrosis in alveolar type II (ATII) cells, and curcumin inhibits IL-17A-mediated changes in the p53-fibrinolytic system (Figure 3) (Gouda & Bhandary, 2018, 2019). Curcumin also reduced the gene expression of chemokines such as chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL5, and CXCL12 that is increased during inflammation in the airway epithelial cells in bleomycin-induced ALI in mice (refer to Figure 3 for more details) (Gouda & Bhandary, 2018).

5.7.2 | TLRs in lung injury

The inhibitory effects of curcumin on the different subtypes of TLRs including extracellular TLR2 and TLR4 and TLR8 and intracellular TLR9 have been reported, which result in the therapeutic effects of curcumin in inflammation, infection, autoimmune, and ischemic disease (Boozari, Butler, & Sahebkar, 2019). Curcumin at low concentrations (10, 20 μM) prevented apoptosis and cytokine production (TNF-α, IL-6) induced by 19-kDa *Mycobacterium tuberculosis* protein (P19) in human macrophages. Curcumin also reduced the expression of TLR2/JNK that may be involved in the apoptosis of macrophages (Li et al., 2014). ALI/ARDS could be the consequence of severe influenza A virus infection with substantial morbidity and mortality. On the other hand, curcumin decreased TLR2/4 gene expression and inhibited phosphorylation of p38, JNK, and NF-κB in infected A549 cells with influenza A virus. It seems that curcumin regulates the TLR-MAPK/NF-κB signaling pathways involved in the replication and influenza pneumonia (Figure 3). However, other mechanisms have been suggested for the antiviral effects of curcumin. Furthermore, curcumin increased the survival rate in infected mice with this virus (Dai et al., 2018).

5.7.3 | Antiapoptotic and antifibrotic effect

Pulmonary pathology of COVID-19 pneumonia in two patients with lung cancer showed the edema and prominent proteinaceous exudates, vascular congestion, and inflammatory clusters with fibrinoid material. Also, reactive alveolar epithelial hyperplasia and fibroblastic proliferation were reported in them (Tian et al., 2020). On the other hand, PAI-1 plays a key mediator role in pulmonary fibrosis. Furthermore, PAI-1 and apoptosis have an important role in the progression and pathogenesis of pulmonary fibrosis (Johnson, Shaikh, Muneesa, Rashmi, & Bhandary, 2020). Therefore, this issue led us to point out the antiapoptotic and the antifibrotic effects of curcumin here. The antiapoptotic effects of curcumin were found in different organ injuries including diabetes, nephrotoxicity, intestinal inflammation, neurotoxicity with several mechanisms (Loganes et al., 2017; Qihui, Shuntian, Xin, Xiaoxia, & Zhongpei, 2020; Soetikno et al., 2019; Sun et al., 2014). Both antiapoptotic and antifibrotic effects of curcumin were shown on the ALI model in mice. Curcumin reduced the expression of p53, PAI-1, and chemokines in bleomycin-induced ALI. Also, curcumin inhibited apoptosis mediated by IL-17 and downregulated cleaved caspase-3 in alveolar epithelial cells. The results suggest that the cross talk between the

inflammatory, fibrinolytic, and apoptotic pathways is interrupted by curcumin (Gouda & Bhandary, 2018). Similar results of curcumin were found with the bleomycin model in human alveolar basal epithelial cells (A549) (Gouda, Prabhu, & Bhandary, 2018). Also, curcumin decreased PAI-1 with cytokines and chemokines in ALI induced by staphylococcus aureus (Xu et al., 2015). On the other hand, curcumin inhibited the expression of TGF-β1 and SMAD3 pathway in ALI induced by sepsis in rats that may involve in the pathogenesis of ALI (Xu et al., 2013). Curcumin reduced expression fibrosis markers including smooth muscle actin (α-SMA), and Tenascin-C in reovirus 1/L-induced ALI/ARDS in mice (Avasarala et al., 2013). Intranasal curcumin reduced matrix metalloproteinases-9 (MMP-9)/tissue inhibitors of metalloproteinase (TIMP-1) expression and increased α-SMA, as a myofibroblast marker, which involves in muscle thickening in paraquat lung injury model in mice. It seems that pretreatment of curcumin prevented the early phase of pulmonary fibrosis by inhibiting inflammatory cells and producing fibrotic factors (Tyagi, Dash, & Singh, 2016) (Figure 3).

5.8 | The inhibitory effects of curcumin on bradykinin to suppress cough

Bradykinin has an important role in the inflammatory events during acute and chronic inflammatory diseases such as respiratory tract infection and asthma (Broadley, Blair, Kidd, Bugert, & Ford, 2010; Hewitt et al., 2016). Furthermore, it seems that bradykinin could trigger cough in these inflammatory diseases or other conditions such as in patients with cough associated with captopril and enalapril as ACE inhibitors (Hewitt et al., 2016; Katsumata, Sekizawa, Ujiie, Sasaki, & Takishima, 1991) Curcumin is an inhibitor of activated protein-1 (AP-1) (Singh & Aggarwal, 1995). Curcumin prevented the expression of IL-6 induced by bradykinin in human airway smooth muscle cells via this inhibition (Huang, Tliba, Panettieri, & Amrani, 2003).

On the other hand, it has shown that curcumin has a greater affinity to bradykinin B_1 receptor (BK1) with strong inhibition activity (Ki value = 2.173 μg/ml) compared with BK2 receptor (Ki value = 58 μg/ml) (Yimam et al., 2016). The possible molecular mechanism of bradykinin for sensitizing cough reflex is through activation B_2 receptors, which in turn stimulate the release of COX and 12-lipoxygenase (12-LOX) metabolites; then, these metabolites activate transient receptor potential (TRP) channel subfamily vanilloid member 1 (TRPV1) and subfamily A member 1 (TRPA1) channels result in an increase in both cough response and airway obstruction (Al-Shamlan & El-Hashim, 2019) (Figure 3). On the other hand, there are many studies due to the inhibitory effects of curcumin on 5-LOX and COX-2 (Rao, 2007). Furthermore, curcumin has shown these inhibitory effects in the airway studies (Kumari, Singh, Dash, & Singh, 2019; Yuan, Liu, Ma, Zhang, & Xie, 2018). Thus, curcumin is likely to inhibit the activity of bradykinin by inhibiting the COX enzyme (Figure 3).

5.9 | Bronchodilator effect of curcumin

Curcumin (20 mg/kg, p.o.) significantly inhibits ovalbumin (OVA)-induced airway constriction and airway hyperreactivity to histamine in sensitized guinea pigs (Ram, Das, & Ghosh, 2003). Also, curcumin (2.5 and 5 mg/kg, intranasal) significantly reduced bronchoconstriction in the mouse model of asthma (Subhashini et al., 2013).

Moreover, *C. longa* extract (1.5, 3 mg/ml) reduced tracheal contractile response to OVA and maximum response to methacholine in rats. It also decreased interstitial fibrosis (Shakeri, Roshan, & Boskabady, 2020). Standard therapy with capsule curcumin 500 mg BD daily for 30 days in patients of bronchial asthma significantly improved forced expiratory volume one second (FEV1) compared with standard therapy. However, the mean scores for cough, dyspnea, wheezing, chest tightness, and nocturnal symptoms were insignificant. Curcumin is recommended to use as an add-on therapy for bronchial asthma (Abidi, Gupta, Agarwal, Bhalla, & Saluja, 2014).

5.10 | Effect of curcumin on ACE2 expression

Dietary administration of curcumin (150 mg kg^{-1} day^{-1}, gavage during Ang II infusion) decreased the protein level of the AT1 receptor and enhanced the expression of the AT2 receptor/ACE2 and results in the attenuation of myocardial fibrosis in a rat model of angiotensin II infusion (Pang et al., 2015). These data suggest that similar events happen in the lung tissues to prevent fibrosis. However, this hypothesis needs further studies (Figure 3). Possibly curcumin will be useful in combination therapy with angiotensin-converting enzyme (ACE) inhibitors and AT1 antagonist (angiotensin II receptor blockers) to overcome fibrosis in COVID-19 patients. On the other hand, recently, Monteil et al. have revealed the human recombinant soluble ACE2 (hrsACE2) could inhibit the growth of SARS-CoV-2 in Vero-E6 cells, human capillary, and kidney organoids through preventing entry into host cells. However, they did not study lung organoids that are the major target organ for COVID-19 (Monteil et al., 2020).

6 | ADVANTAGE OF CURCUMIN OVER THE OTHER NATURAL AGENTS

Advantage of curcumin over other important natural agents with reported anti-inflammatory activities such as zerumbone (Prasannan et al., 2012), thymoquinone (Siveen, Mustafa, et al., 2014), honokiol (Rajendran et al., 2012), escin (Tan et al., 2010), pinitol (Sethi, Ahn, Sung, & Aggarwal, 2008), and tocotrienols (Siveen, Ahn, et al., 2014) is that it has additional antiviral, antiemetic, antinociceptive, antifatigue, and bronchodilator effects that previously has been discussed in this review. Also, it has significant protective effects in the ARDS model in animal studies. These mentioned effects help us to conclude that curcumin has the potential to be effective against COVID-19 infection.

7 | SAFETY AND BIOAVAILABILITY OF CURCUMIN

To date, over 100 clinical trials have been completed with curcumin and safety, tolerability, and outcome have been reported in all of them (Kunnumakkara et al., 2017). An oral dose of 500 mg (two times a day, 30 days) was reported safe for curcumin (Soleimani et al., 2018). Curcumin up to 8,000 mg/day was safe, tolerable, and effective in humans, and higher doses were with toxicity (Kunnumakkara et al., 2019; Shanmugam et al., 2015). Curcumin has low bioavailability, but a lot of data from clinical trials showed the high efficacy of curcumin or turmeric against several diseases (Kunnumakkara et al., 2019). However, various strategies are used including analogs of curcumin and formulations such as adjuvants, nanoparticles, liposomes, micelles, and phospholipid complexes to improve its bioavailability (Kunnumakkara et al., 2017). Recently, it has been shown that the encapsulation of curcumin into specific nanocarrier could enhance its therapeutic efficacy (Moballegh Nasery et al., 2020).

8 | CONCLUSION

COVID-19 is spreading worldwide, leading a pandemic. There is no definitive treatment yet for this disease. In this review, we summarized clinical and molecular mechanisms that curcumin might be effective to treat COVID-19. Research evidence suggests that curcumin will be useful to treat patients especially in ARDS cases with high mortality risk. Curcumin has several therapeutic effects including antiviral, antinociceptive, anti-inflammatory, antipyretic, and antifatigue effects with several molecular mechanisms such as antioxidant, antiapoptotic, antifibrotic effects, and inhibitory effects on NF-κB, inflammatory cytokines and chemokines, Toll-like receptors, and bradykinin. The importance of this review is due to the fact that curcumin is a nutraceutical that could be a new treatment option to combat the COVID-19 pandemic. Designing the best formulation with high efficacy and good bioavailability is necessary. Further clinical studies should focus on curcumin against COVID-19 infection.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICAL APPROVAL

The study did not involve any human or animal testing.

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