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Review Article

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# Antiviral Potential of Curcumin in Mitigating COVID-19 Effects and Post-COVID-19 Sequelae

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## ABSTRACT

COVID-19 is a respiratory disease resulting from infection with the Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) virus, which may manifest as mild, moderate, or severe symptoms. Even after recovering from the disease, some individuals may experience persistent symptoms, known as "long COVID". Curcumin, a polyphenol extracted from *Curcuma longa* L., exhibits diverse medicinal properties including antiviral, anti-inflammatory, anti-thrombotic, antioxidant, antiproliferative, and immunomodulatory effects. It can potentially be a therapeutic agent for treating COVID-19 due to its ability to modulate the immune response and inhibit cytokine storms. These actions can help prevent severe difficulties like acute respiratory distress syndrome (ARDS) and multiorgan failure. Curcumin specifically targets viral entry, replication, and the molecular signalling cascade responsible for pathophysiological effects, making it a potential option for combating COVID-19 and addressing its long-term post-COVID effects on health. Using nanocarriers can overcome the limitations of curcumin's poor bioavailability and solubility, allowing for more effective delivery to the target cells and tissues.

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## INTRODUCTION

Turmeric (*Curcuma longa* L.) is a rhizomatous perennial plant that belongs to the Zingiberaceae family. It has various health benefits, including anti-inflammatory, antioxidant, antiviral, antitumor, antiseptic, nephroprotective, cardioprotective, radioprotective, hepatoprotective, and digestive properties (Prasad & Aggarwal, 2011). Its well-known therapeutic qualities are attributed to its three curcuminoids: 77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin (Huang *et al.*, 2020a). Curcumin has been approved by the FDA as "GRAS" (Generally Recognized as Safe), with an Allowable Daily Intake (ADI) of 0-3 mg/kg body weight, according to the European Food Safety Authority (EFSA) and the Joint FAO/WHO Expert Committee on Food Additives (Hewlings & Kalman, 2017).

Curcumin is effective against various viruses, including SARS-CoV, which suggests its potential for treating COVID-19 (Wen *et al.*, 2007). It can regulate the activity of cytokines, inflammatory enzymes, cell survival proteins, and adhesion molecules by modulating the activation of various transcription factors, effectively treating a wide range of diseases and providing direct and indirect health benefits to the body (Goel *et al.*, 2008). Turmeric extract serves as a potential COVID-19 vaccine, aids in patient recovery, and effectively boosts resistance against coronavirus with no reported side effects (Datta, 2021). Additionally, numerous advanced curcumin nanoformulations have been created to significantly enhance the delivery of curcumin, effectively addressing the issue of low therapeutic effects (Karthikeyan *et al.*, 2020).

COVID-19 is a highly contagious respiratory illness that has affected over 775 million people worldwide and caused 7 million deaths, leading to severe complications and long-term health problems (WHO, 2020). It can affect individuals of all age groups, with symptoms ranging from mild to severe and displaying various clinical manifestations (Baj *et al.*, 2020). In the early stages of COVID-19, patients may experience symptoms such as cough, fever, headache, fatigue, hemoptysis, and diarrhoea. The illness can lead to serious complications including acute respiratory distress syndrome (ARDS), acute cardiac injury, pneumonia, dyspnea, RNAemia, and secondary infection (Huang *et al.*, 2020b). COVID-19 patients with pre-existing disorders are more likely to experience serious consequences (Sharif *et al.*, 2023). Mutations in SARS-CoV-2 have the potential to significantly alter the virus's virulence (Yao *et al.*, 2020).

Over half of COVID-19 survivors experience post-COVID, also known as post-acute sequelae of COVID-19 (PASC), a short- or long-term multisystem disease, six months after recovery (Groff *et al.*, 2021). The existing approved antiviral drugs have side effects, making it crucial to find substances that can act against the virus (Ghildiyal *et al.*, 2020). Therefore, curcumin can be used in post-COVID treatment to minimize the permanent and long-term health consequences of COVID-19. This review aims to assess the therapeutic efficacy of curcumin in the context of COVID-19 and post-COVID conditions.

## CURCUMIN AS A POTENTIAL THERAPEUTIC AGENT FOR COVID-19

Curcumin has exhibited significant antimicrobial properties by hindering the proliferation of various fungi, bacteria, and viruses (Jennings & Park, 2020). Curcumin's adaptable chemical structure allows it to interact with a broad range of molecular targets and produce various biological effects, including modifying the cell cycle, promoting differentiation, suppressing growth, raising proapoptotic factors, and preventing the production of reactive oxygen species (Shishodia *et al.*, 2007). Recent studies indicate that curcumin possesses antiviral properties that may effectively combat SARS-CoV-2. Its antiviral properties are characterized by its ability to inhibit cellular entry, prevent viral replication, modulate cellular signalling pathways, and control and repair COVID-19-related damage (Soni *et al.*, 2020). Curcumin demonstrates various clinically relevant benefits such as antioxidant, antiapoptotic, antifibrotic, antiviral, antinociceptive, anti-inflammatory, antipyretic, and antifatigue properties, which may effectively manage COVID-19 symptoms (Babaei *et al.*, 2020). Figure 1 illustrates the effects of curcumin on COVID-19 disease.

Applying curcumin at low, subtoxic concentrations has shown the potential to neutralize SARS-CoV-2 in human cells, reduce virus RNA in cell cultures, and alleviate COVID-19 symptoms (Bormann *et al.*, 2021). Curcumin treatment at a dosage of 100 mg/kg has demonstrated an antipyretic effect (Haider *et al.*, 2013), and is effective in treating chronic fatigue (Gupta *et al.*, 2009). Anosmia and ageusia are the olfactory and gustatory dysfunctions that are common in COVID-19-infected individuals. A single dosage of 1000 mg of a turmeric supplement aids in the full recovery of taste and smell (Chabot & Huntwork, 2021). Curcumin capsules have been shown to improve airway obstruction and may benefit asthma treatment (Abidi *et al.*, 2014). Curcumin can potentially treat pulmonary inflammation, oedema, fibrosis, and cardiovascular damage (Zahedipour *et al.*, 2020). It has been found that curcumin formulations can help reduce COVID-19 symptoms and pro-inflammatory effects while stimulating anti-inflammatory pathways, thereby reducing mortality rates and promoting patient recovery (Vahedian-Azimi *et al.*, 2022).

## TARGETS VIRAL ENTRY AND REPLICATION

Curcumin exhibits properties that may impede the entry and replication of SARS-CoV-2 within cells. The fusion and

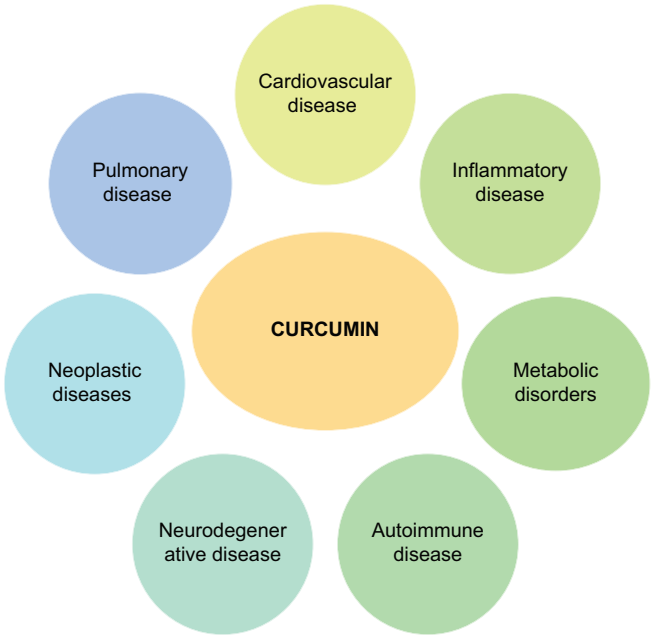


**Figure 1:** Effect of curcumin on COVID-19 disease

internalization of the virus occur through the binding of the viral spike glycoprotein (S) to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells (Hoffmann *et al.*, 2020). Curcumin can modify the host's lipid membranes, which are crucial for viral entry and receptor function (Mounce *et al.*, 2017). It inhibits ACE2 activity, the spike (S) glycoprotein, the interaction between the S protein and ACE2, as well as the endosomal cysteine proteases cathepsin B and L (Cat B/L) and the transmembrane protein serine protease 2 (TMPRSS2). These components are essential for viral entry and S protein priming (Hoffmann *et al.*, 2020; Soni *et al.*, 2020).

Curcumin serves as both an S-protein and an ACE-2 inhibitor. Both the keto and enol forms of curcumin can interact with the spike glycoprotein, anchoring the ACE2 residues. This blocks their interaction with the human ACE2 receptor, potentially controlling viral infection (Shanmugarajan *et al.*, 2020). Curcumin exhibits a strong binding affinity to the spike glycoprotein, creating six hydrogen bonds that inhibit the virus from binding to the host cells (Maurya *et al.*, 2020). Additionally, curcumin firmly binds to the "RBD/ACE2-complex" interface, thereby preventing the development of the S protein-ACE2-complex (Jena *et al.*, 2021). Curcumin can also inhibit the TMPRSS2 protein, thereby preventing SARS-CoV-2 from entering host cells (Motohashi *et al.*, 2020; Prasansuklab *et al.*, 2021).

Curcumin can inhibit the replication of SARS-CoV-2 by targeting the 3-chymotrypsin-like main protease ($3CL^{pro}$), papain-like protease ($PL^{pro}$ or nsp3), and RNA-binding domain of the SARS-CoV-2 nucleocapsid protein. These viral replication proteins can be potential targets for treating COVID-19 (Sheam *et al.*, 2020; Singla *et al.*, 2020). Two types of proteinases, $3CL^{pro}$ and $PL^{pro}$, are responsible for viral proteolysis (Sheam *et al.*, 2020). Curcumin inhibited SARS-CoV replication and

suppressed 3CL$^{pro}$ in Vero E6 cells (Wen *et al.*, 2007). They fit perfectly into the 3CL$^{pro}$ pocket (Huynh *et al.*, 2020), form hydrogen bonds with the 3CL$^{pro}$ residues Gln192 and Arg188 (Bahun *et al.*, 2022), and neutralize it which contributes to a quicker reduction of viral loads (Rajagopal *et al.*, 2020). Curcumin has shown significant effectiveness as a 3CLpro inhibitor (Das *et al.*, 2021).

Curcumin inhibits PL$^{pro}$ more effectively than quercetin and other natural products. The Pro248 residue of PL$^{pro}$ forms C-H bonds with curcumin derivatives (Alici *et al.*, 2022). It also has strong affinities to nucleocapsid and nsp10, which are important for viral RNA detection and processing (Suravajhala *et al.*, 2021). Curcumin affects the intercellular signaling pathways crucial for efficient virus replication by reducing NF-κB and PI3K/Akt signaling. Additionally, it influences post-transcriptional and post-translational modifications in cells, limiting viral multiplication by disrupting crucial phases of the replication cycle, like viral attachment and genome replication (Zahedipour *et al.*, 2020).

## INHIBITS THE MOLECULAR SIGNALLING CASCADE THAT CAUSES PATHOPHYSIOLOGICAL EFFECTS

Curcumin can control several cell-signaling pathways that are crucial for many chronic diseases. Since most chronic diseases are caused by uncontrolled inflammation, the anti-inflammatory properties of curcumin make it a promising treatment option. Curcumin is a highly pleiotropic compound that can help prevent various diseases by targeting different molecular factors such as cytokines (TNF-α, IL-6, IL-1β, IL-8, IL-2, IL-12, MIP, IFN-γ, and MCP-1), transcription factors (Nrf2, NF-κB, PPAR-γ, AP-1, STAT-3, and HIF-1), protein kinases (mTOR, ERK, JAK, and p38MAPK), enzymes (5-LOX, COX-2, GST, MMP, iNOS, HO-1, and ATPase), receptors (HER-2, EGFR, and CXCR-4), and growth factors (VEGF, EGF, FGF, NGF, HGF, and PDGF) (Zhou *et al.*, 2011; Prasad *et al.*, 2014).

Multiple scientific studies have evidenced the efficacy of curcumin in mitigating the inflammatory response induced by COVID-19 (Babaei *et al.*, 2020; Liu & Ying, 2020; Soni *et al.*, 2020; Zahedipour *et al.*, 2020; Que *et al.*, 2022; Vahedian-Azimi *et al.*, 2022). Curcumin regulates the inflammatory processes triggered by COVID-19 through various mechanisms, such as reducing the proinflammatory effects of the Angiotensin II-AT1 receptor, suppressing cytokine storms, modulating host factors NF-κB, NRF2, NLRP3, and HMGB1 pathways, inhibiting mTOR and STAT3 activity, and suppressing the activation of inflammasomes. This can delay the progression of the disease and prevent cell damage. The SARS-CoV-2 virus induces oxidative stress, fibrosis, and inflammation in the body, by activating the Angiotensin II/AT1 receptor axis, which can lead to respiratory failure (Pagliaro & Penna, 2020). However, curcumin can reduce respiratory failure in COVID-19 patients by inhibiting the inflammatory effects of AngII-AT1R (Manoharan *et al.*, 2020; Soni *et al.*, 2020; Yao *et al.*, 2020).

SARS-CoV-2 activates NF-κB excessively, leading to overproduction of pro-inflammatory cytokines and chemokines in lung epithelial cells, causing inflammatory dysfunction. This can further amplify NF-κB activation through self-activation or other pathways, resulting in an inflammatory cytokine storm (Zhou *et al.*, 2024). In COVID-19 patients, cytokine storms can lead to serious complications such as coagulopathy, ARDS, thromboembolic diseases and multi-organ failure (Bhaskar *et al.*, 2020). Curcumin has shown effectiveness in reducing viral load, regulating the cytokine-mediated inflammatory pathway, and mitigating the "cytokine storm." It has also demonstrated a significant decrease in morbidity and mortality associated with COVID-19 (Liu & Ying, 2020).

Curcumin works by inhibiting the signalling of various cytokines such as TNF-α, NF-κB, IL-1β, IL-6, MCP-1, and MAPK, which are involved in cytokine production (Singh, 2020; Yao *et al.*, 2020). Additionally, curcumin inhibits the expression of NLRP3 (NOD-like receptor pyrin domain-containing inflammasome 3) and subsequent production of IL-1β, thus controlling NF-κB signalling and suppressing inflammation (Yin *et al.*, 2018; Hasanzadeh *et al.*, 2020; Rattis *et al.*, 2021). It can also block the signalling of Toll-like receptors (TLRs) and the subsequent activation of NF-κB, STAT3, the NLRP3 inflammasome, and other signalling pathways makes it an effective treatment for inflammatory diseases (Jagetia & Aggarwal, 2007; Shuto *et al.*, 2010; Peng *et al.*, 2021). By inhibiting NF-κB activation mediated by STAT3 and IκB, curcumin reduces the levels of pro-inflammatory cytokines such as IL1α, IL-6, and TNF-α (Rattis *et al.*, 2021).

Curcumin is a powerful drug that controls several important signalling pathways regulating antioxidative factors, such as Nrf2, and anti-inflammatory effects by inhibiting the activity of significant target proteins, such as iNOS and COX-2, by maintaining NF-κB transcription (Hassan *et al.*, 2019). Curcumin has been shown to increase Nrf2 transcription, which in turn protects alveolar stem cells, as well as increasing HO-1 (heme oxygenase 1) expression, which has been related to COVID-19 severity and susceptibility (Dai *et al.*, 2018; Hooper, 2020). It reduces oxidative stress by strengthening antioxidant defences, inhibiting the production of reactive oxygen species (ROS) by inhibiting NADPH oxidase, improving the Nrf2 signalling pathway, and exerting antiviral effects against SARS-CoV-2. Additionally, curcumin reduces the proviral host factor HMGB1 expression, attenuates HMGB1-mediated proinflammatory responses, and protects against SARS-CoV-2 susceptibility (Thimmulappa *et al.*, 2021).

It also acts as an mTOR inhibitor (Kotha & Luthria, 2019) and activates PPARγ to inhibit the NF-κB pathway (Zhu *et al.*, 2019). Curcumin-mediated mTOR inhibition may improve recovery speed in elderly SARS-CoV-2-infected patients (Kotha & Luthria, 2019). It also activates the inflammatory signalling pathway (JAK/STAT) transcription and regulates signal transducer/Janus kinase (Ashrafizadeh *et al.*, 2020). SARS-CoV-2 primarily targets lymphocytes, particularly T lymphocytes, triggering a cytokine storm and a cascade of immune responses that cause organ damage (Qin *et al.*, 2020).

The cytokine response in diseases like SARS-CoV, MERS-CoV, and SARS-CoV-2 has been associated with the activation of T-helper 17 (Th17) cells, which differentiate from CD4+ lymphocytes, and can cause high levels of immune cell activation (Mahmudpour *et al.*, 2020; Tahmasebi *et al.*, 2021). COVID-19 patients produce inflammatory cytokines like IFN-γ, IL-1β, IP10, and MCP1, which trigger Th17 cell responses and cause lung damage (Huang *et al.*, 2020b). Curcumin inhibits the activation of Th17 cells, and related cytokines, and reduces the inflammatory response associated with COVID-19 (Abdelazeem *et al.*, 2022). This is achieved by preventing the differentiation of Th17 cells by suppressing STAT3 phosphorylation (Chang *et al.*, 2021).

## NANOCURCUMIN IMPROVES CURCUMIN PROPERTIES AGAINST SARS-COV-2

Due to curcumin's poor pharmacokinetic properties, low water solubility, and low bioavailability, its therapeutic use is severely limited (Hay *et al.*, 2019). However, nano curcumin, a nanoparticle-based delivery system, is at least nine times more effective than curcumin with piperine in treating SARS-CoV-2 (Shaikh *et al.*, 2009). To enhance the bioavailability of oral curcumin, nanotechnological carriers such as liposomes, micelles, nanoemulsions, exosomes, nanostructured lipid carriers, biopolymer nanoparticles, and phospholipid complexes have been utilized (Bertoncini-Silva *et al.*, 2024). Functionalized curcumin nanoparticles have been shown to prevent viral entry into cells and reduce pro-inflammatory cytokines (Bisht *et al.*, 2007; Tiyaboonchai *et al.*, 2007).

Patients with COVID-19 could benefit from a 14-day daily administration of 160 mg of nano-curcumin. This treatment may modulate the elevated levels of inflammatory cytokines, leading to improved clinical outcomes, enhanced recovery, and reduced mortality rates (Valizadeh *et al.*, 2020). A clinical trial suggests that an oral curcumin nano-formulation (Sinacurcumin soft gel, containing 40 mg of curcuminoids) taken twice daily at a dosage of 80 mg can significantly improve recovery time and COVID-19 symptoms in hospitalized patients (Saber-Moghaddam *et al.*, 2021). Sinacurcumin® (80 mg capsule) taken twice daily for 21 days may reduce Th17 cells and decrease Th17 cell-related cytokine levels in COVID-19 patients (Tahmasebi *et al.*, 2021). Sinacurcumin has been found to reduce recovery time in patients (Ahmadi *et al.*, 2021). Consuming 150 mg of highly bioavailable curcumin, Theracurmin Super, or Theracurmin per day for 12 weeks has been shown to reduce common cold symptoms (Kuwabara *et al.*, 2024). The curcumin-loaded thermosensitive hydrogel can increase neurotransmitter concentration in the brain and has potential for treating depression (Qi *et al.*, 2020). Therefore, nano-curcumin could be used to treat COVID-19 patients by modulating their inflammatory response.

## POTENTIAL TO PREVENT LONG-TERM COMPLICATIONS/POST COVID EFFECT

COVID-19 survivors may show long-term sequelae and delayed viral clearance even after vaccine treatment. Even after recovering from COVID-19, immune memory of infection is likely to persist, raising the risk of reinfection (Bhaskar *et al.*, 2020). The chronic post-COVID symptoms can last for weeks or months and may reappear. Symptoms associated with long-COVID-19 include shortness of breath, chronic fatigue, cardiovascular issues, brain fog, autoimmunity, dysautonomia, headaches, mental health disorders and clotting due to inflammation (Makhluf *et al.*, 2024). Figure 2 shows the symptoms of the post-COVID-19 syndrome.

Curcumin has several properties, such as anti-inflammatory, antipyretic, antiviral, anti-fatigue, and anti-infective, which make it effective in managing post-COVID-19 symptoms. The administration of curcumin at a dosage of 1,000 mg daily for 30 days resulted in a reduction in stress and fatigue (Sudheeran *et al.*, 2016). These results imply that curcumin may be useful in treating myalgia and fatigue following COVID-19. Curcumin analogues C2 and C3 can alleviate the damaging effects of reactive oxygen species on the brain by reducing oxidative stress and increasing antioxidant systems, which can help alleviate depression associated with psychological and oxidative stress (Hussain *et al.*, 2022a). Moreover, curcumin has been found to reduce the risk of bleeding and long-term thromboembolic effects in COVID-19 patients (Pawar *et al.*, 2021). The majority of COVID-19 patients exhibit coagulation disorders and thrombosis as significant pathophysiological changes. These are characterized by a low platelet count, prolonged prothrombin time, elevated D-dimer levels, and other abnormalities (Chen *et al.*, 2022). Research has indicated that curcumin can inhibit platelet activation and aggregation and improve platelet count (Hussain *et al.*, 2022b). Therefore, curcumin can be utilized in post-COVID therapy to reduce the prolonged and persistent adverse effects of COVID-19.

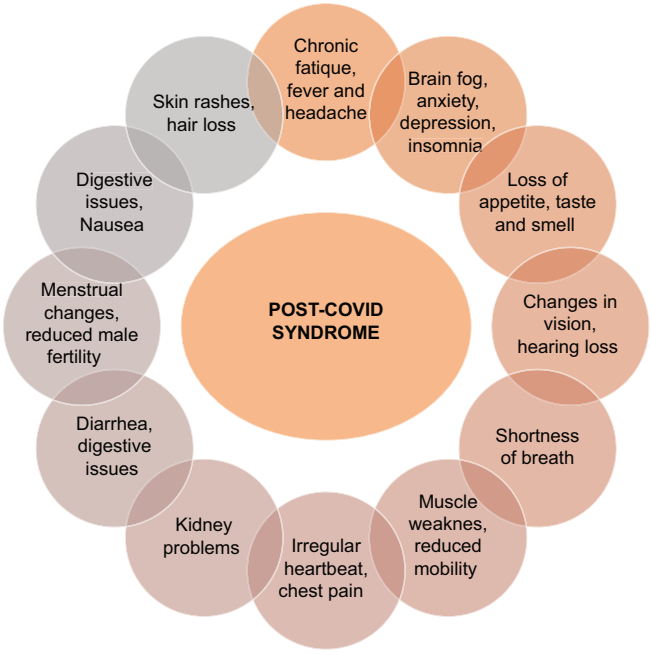


**Figure 2:** Symptoms of post-COVID-19 syndromes

## CONCLUSION

The COVID-19 pandemic constitutes a worldwide public health crisis with anticipated long-term and profound consequences. Studies have raised concerns about vaccine side effects and virus mutations. Curcumin has shown potential in inhibiting several coronaviruses and respiratory viral infections, suggesting that it could be effective against COVID-19. Curcumin targets the pathophysiological effects of COVID-19 via molecular signaling cascade, viral replication, and viral entry into host cells. Its multiple beneficial effects make it a potential candidate for COVID-19 treatment by reducing cellular damage, enhancing immunity, and alleviating post-COVID symptoms. There is strong evidence supporting the effectiveness of curcumin in treating COVID-19 and post-COVID syndromes due to its ability to target viral entry into host cells, viral replication, and the molecular signaling cascade that exhibits the pathophysiological effects of COVID-19.

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