

REVIEW ARTICLE

Curcumin: From Ancient Spice to Modern Anti-Viral Drug in COVID-19 Pandemic

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ABSTRACT

A viral disease such as COVID-19 (Corona Virus Disease-2019) is a major health problem and worsens the complications of various diseases including cardiovascular diseases, hypertension, diabetes, and cancers. The current study summarises the therapeutic progress and efficacy of curcumin for the cure and prevention of severe acute respiratory syndrome (SARS) and SARS-related COVID-19. Curcumin is extracted from the herb *Curcuma longa* L., known for its various therapeutic functions such as anti-inflammatory, anti-obesity and anti-cancer activities. Very little is known about its therapeutic importance for the prevention and treatment of COVID-19 infections and complications. Curcumin has the ability to interact with spike protein or ACE2 protein in COVID-19-induced signal transduction pathway. Curcumin also suppresses several important signaling pathways in viral infection such as the well-known transcription factors including NF- κ B, STAT-3, Wnt/ β -catenin, Nrf2, p38/MAPK. Curcumin inhibit virus-induced inflammation by modulating the manifestation of various factors such as IL-10, IL-8, IL-6, TNF- α/β , and COX-2 in COVID-19 diseases. The modulation of multiple molecular targets by treatment with curcumin and anti-inflammatory effects of curcumin make it an ideal candidate phytochemical for the treatment of SARS and SARS-related COVID-19.

Key Words: Curcumin, COVID-19, Cell Signaling, Inflammation, SARS.

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Introduction

Curcumin is the major chemical constituent of *Curcuma longa* L. (turmeric), which belongs to the family of Zingiberaceae. Curcumin is mostly used as a food coloring, spice and food-flavoring ingredient as well as herbal supplement, cosmetic and therapeutic agent. The medicinal properties of turmeric have been reported in different pathological conditions by regulating multiple signaling pathways at transcription and translational level.^{1,2} *Curcuma longa* L. traditionally has been utilized as a preventive remedy for various diseases due to its

antioxidant, anti-inflammatory, antimicrobial, and anticancer properties.^{1,3-5} Curcuminoids are phenolic compounds of turmeric with several beneficial effects such as an antioxidant, anti-inflammatory, neuroprotective and antitumor.² Curcuminoids such as curcumin, demethoxycurcumin, bisdemethoxycurcumin, are "Generally Recognized as Safe" (GRAS) by the US Food and Drug Administration (FDA) (GRAS Notice (GRN) No. 822).⁶ The underlying mechanism of action and pharmacological effects such as anti-inflammatory, antioxidant, anti-hypertensive, anti-cancer, antiviral, anti-infective and wound-healing properties have been studied extensively. The most attractive action of curcumins are the anti-inflammatory effects mediated by reducing the expression level of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and down regulation of P-selectin, nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B), JNK, p38 and STAT-3 in endothelial cells.⁷ The potent anti-inflammatory effect of curcumin also greatly attributes to the treatment of osteoarthritis

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diseases. Curcumin inhibits the progression of osteoarthritis by blocking translocation of the p65 subunit of NF-κB complexes into the nucleus and reduces the inflammatory responses in the chondrocytes.⁸ Curcumin also targets various inflammatory mediators such as cyclooxygenase-2, inducible nitric oxide synthase, and NF-κB in angiogenesis, tumor growth, and metastasis.⁹ In one study, curcumin efficiently inhibited LPS-induced TNF-α, IL-6 and microRNA-155 (miR-155) in Raw264.7 and THP-1 cells.¹⁰ Similarly, the anti-inflammatory and anti-oxidant effects of curcumin were tested in Astrocytes and SH-SY5Y neuronal cells. Curcumin treatment suppressed the mitogen-activated protein kinase (MAPK) pathway, reduced the levels of inflammatory markers such as IL-6, Nox-2, COX-2 and reduced reactive oxygen species (ROS) levels.^{7,11,12}

Recently, it has been shown that curcumin effectively inhibited the expression of insulin and IGF-1 receptors as well as a MYC oncogene in SW480 and 5FU-SW480 cancer cells.¹³ Curcumin anti-cancer activities are mediated by modulation of different signaling such as NF-κB, STAT3, AP-1, NRF-2, PPARγ, HIF-1α, VEGFR, EGFR, HER2 IGF-1R, PI3K, AMPK, BCR-ABL, and Raf/Ras etc.^{14,15} Curcumin has the ability to block the progression of the cell cycle at G1/S and G2/M phase of the selected cancer cell lines.¹⁶ The multi-factorial function of curcumin as having an anti-inflammatory effect in obesity and obesity-related metabolic diseases was also explored.^{17,18}

There is compelling evidence that curcumin has been effective against various viruses such as vesicular stomatitis virus, parainfluenza virus, flock house virus, herpes simplex virus, and respiratory syncytial virus by inhibiting viral encapsulation and proteases, followed by modulation of inflammatory cellular signaling pathways.¹⁹

In this review antiviral effects of curcumin are discussed as a base for clinical applications of curcumin for the treatment and prevention of newly emerged COVID-19 infection and COVID-19 related pneumonia.

Complications of COVID-19 and the Cytokine Storm

The Corona virus uses its spike protein for attachment to target cells. Spike proteins interact with the ACE2 (angiotensin-converting enzyme 2)

located on the surface of the cell, which reduces the inhibitory effect of the ACE2 receptor on *angiotensin II* (AngII).^{20,21} The spike protein binding to ACE2 receptor in the lung cells induces a series of signaling that causes the activation of NF-κB, AngII, TNF-α and the soluble form of IL-6Ra (sIL-6Ra) via disintegrin and metalloprotease 17 (ADAM17) leading to a cytokine storm.²² The activation of inflammatory signaling causes the binding of IL-6 to sIL-6R through gp130, forming a complex of IL-6-sIL-6R. This complex further activates STAT3 in non-immune cells. STAT3 together with NF-κB induces amplification of IL-6 amplifier (IL-6 Amp) consequently activates several known pro-inflammatory cytokines and chemokines, including VEGF, MCP-1, IL-8, and IL-639. IL-6.^{23,24} This impaired signaling of the infected cells results in the secretion of several antiviral factors interferons (IFNs) and pro-inflammatory cytokines, chemokine and other immune modulating factors. Several pro-inflammatory cytokines or chemokines have been detected in COVID-19 patient blood samples such as IL-1β, IL-6, TNF-α, CCL-2, CCL-3, CCL-5, IFN-I or IFN-α/β, IFN-γ, IP-10, MCP-1, IL-4, IL-10, MCP-1, and NF-κB.²⁵ Thus, the activation of several important inflammatory molecules in SARS-CoV-2 may cause cytokine storms (Figure 1).

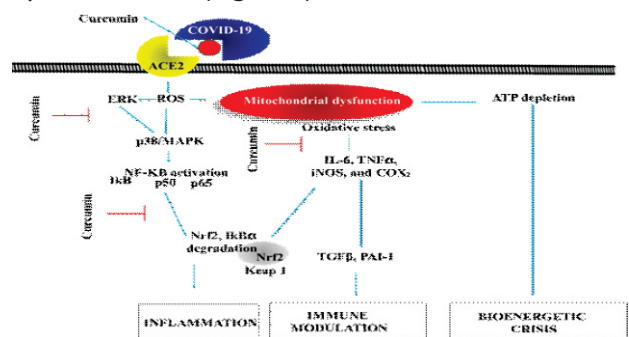


Fig 1: The figure represent the binding of the COVID-19 spike protein with the ACE2 activate the cytokine storm and how the curcumin inhibit these signaling pathways at various targeted points. Activation: Inhibition: ⊥

Recently, Renmin Hospital of Wuhan University (Wuhan, China) analyzed the sera of 102 COVID-19 patients for major molecules involved in cytokine storm. The serum samples analysis shows that IL-10 and IL-6 molecules could be utilized as a diagnostic marker for speedy diagnosis of patients infected with COVID-19 and who are at high risk of disease deterioration.²⁶

Anti-viral activity of Curcumin

Among natural compounds, curcumin has displayed effective antiviral activity against various type of viruses and viral infections. Curcumin inhibits viruses by suppressing the expression of capsid protein. It also reduces viral RNA expression, protein synthesis and virus titer. Furthermore curcumin can protect the host cells against virus-induced apoptosis and cytopathic activity. Previously, it was reported that curcumin inhibited enveloped virus infectivity and modified virus lipid bilayer, consequently influencing their membrane protein function.²⁷ In another study, antiviral effect of curcumin has been reported in two flaviviruses, JEV (Japanese encephalitis virus (JEV) and Dengue virus type II (DENV). This study concluded that curcumin completely degraded the envelopes of these viruses, abrogated the infectivity and inhibited the viral attachment in a co-treatment experiment (curcumin was treated throughout the time of infection and addition of curcumin upon the viral attachment (i.e. co-treatment) strongly inhibited its attachment and severity).²⁸ This shows that curcumin antiviral effect is multipronged and involves inhibition of envelopes and attachment of viruses besides the many other mechanisms.

Similarly, curcumin has the ability to inhibit Zika, chikungunya and HCV virus infections by preventing their attachment to target cells. Curcumin treatment with a dose range of 1 mM inhibited about 75-99% of their infectivity through lipophilic inhibition and blocked viral cellular attachment and entry into the target cells.²⁹⁻³¹ In another study, EBOV (Ebola Virus) was exposed to various concentrations of curcumin, curcuminoids, and tetrahydrocurcumin. All chemical constituents of turmeric successfully inhibited the VP24 capsid protein of EBOV virus and reduced the viral infection.³² Recently, curcumin activity was assessed in influenza A virus (IAV). Influenza A virus pathogenicity involves oxidative stress, TLR-MAPK/NF- κ B and Nrf2-HO-1 signaling pathways. Curcumin inhibited influenza A virus induced oxidative stress, GSTA3 and IFN- β , increased HO-1, Nrf2, NQO1, production as well as inhibited IAV-induced activation of TLR2/4/7, Akt, p38/JNK MAPK and NF- κ B pathways.³³

Anti-COVID-19 Activity of Curcumin

During random experimentation in 2007, total of 221 phytochemicals including curcumin were checked

against SARS-CoV. Curcumin suppressed SARS-CoV replication by inhibiting SARS-CoV 3CL protease activity as seen with SARS-CoV infected Vero E6 cell-based cytopathogenic effect (CPE) assay.³⁴ This study provides a base for use of curcumin as a potential natural product against SARS-CoV-2 for further study.

The initial encouraging result of curcumin against COVID-19 was reported recently in a study conducted in 2020 in a co-treatment of curcumin (known for the inhibition of envelop viral entry) with Zn (that is known for the *RNA polymerase inhibition*).³⁵ Curcumin can positively boost the immune system and had antiviral action against the COVID-19 pneumonia.³³ The molecular docking studies further explored the real function of unknown molecules as well as underlying interaction mechanism between ligands and receptors. The recent identification of the ligand-receptor interaction of curcumin with Covid-19 protease shows promising results for future investigation in detail.³⁶

In another recent study, using systems biology experimentation concluded that combination of glycyrrhizic acid, vitamin C and curcumin was used as potential therapeutic remedies against CoV infection.³⁷ These studies and analytical approaches warrant further validation in vitro/in vivo experiments.

Cytokine storm in COVID-19 and curcumin

SARS-CoV-2 and beta-coronaviruses follow the same route for entering and affecting the host cell. COVID-19 attaches to the ACE2 receptor located on the lung cells and leads to cytokine storm and pathogenicity.^{38,39} ACE2 receptors can also be found in several other organs including the heart and kidney. The ACE2 expression increases in Covid-19 lungs and influenza patients autopsy samples as compared to control group (healthy group), which advocate that ACE2 expression was increased in Covid-19 infections. It is evident that ACE2 expression is proportional to spike protein expression.⁴⁰

In a docking experiment, the dual binding affinity of curcumin for both the viral S protein and ACE2 has been revealed. There is compelling evidence that curcumin binds to receptor-binding domain (RBD) site of viral S protein and as well as to the ACE2

receptor justifying the potential inhibitory effect of curcumin and its analog against SARS-CoV-2 by inhibiting ACE2 mediated cytokine storm.^{41,42} In a molecular docking experiment, curcumin and its derivatives were found to inhibit the COVID-19 main protease (Mpro), which has a main role in the prevention of disease.^{41,43} In line with this, Nrf2 activators play a very important role in regulation of respiratory viral infection by regulating the level of oxidative stress and numerous studies have shown the improving effect of curcumin redox status by regulating the level of Nrf2.⁴⁴

Clinical trials

Numerous clinical trials have addressed the antiviral effect of curcumin in different SARS-2 related respiratory illnesses and pneumonia. Well planned studies and clinical trials are required for deducing the therapeutic efficacy of curcumin against COVID-19 infections and are in early stages. Curcumin has the ability to bind with a number of SARS-CoV-2 proteins, such as nucleocapsid phosphoprotein (PDB ID: 6VYO), spike glycoproteins (PDB ID: 6VYB), membrane glycoprotein (PDB ID) structures. Thus, the binding affinity of curcumin with SARS-CoV-2 proteins make it a favorable candidate to be screened in clinical trials.⁴⁵

An Israeli Pharmaceuticals has started a Phase II clinical trial of curcumin with artemisinin, a drug derived from the Asian plant *Artemisia annua*, for the cure of patients suffering from SARS-2 infection at the Nazareth Hospital EMMS. It has been known that ArtemiC is an anti-inflammatory drug, which further boosts the efficacy of curcumin in viral infections and other inflammatory complications.⁴⁶ This will be a double-blind, placebo-controlled Phase II trial, which will investigate the safety and efficacy of ArtemiC, a natural formulation intended for immune-modulation. The aim is to treat the pathophysiological complications of Covid-19. MGC Pharmaceuticals will conduct the trial in a total of 50 patients at Israel's Nazareth Hospital EMMS and Hillel Yaffe Hospital, which received human research ethics committee approval last month.⁴⁶

The above findings suggest that curcumin are promising candidates of phytochemical that can be practiced for the treatment and prevention of COVID-19 related complications. Furthermore, the higher safety, low cost and ease of availability of

curcumin make it advisable that curcumin be investigated as a part of the therapeutic regime for COVID-19 infection.

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