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Curcumin therapy: Immune booster in present and post-pandemic (COVID-19) Era

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Abstract

COVID-19 pandemic, which has traumatized the world population, in principle, is an inflammatory lung disease secondary to SARS-COV2 virus infection. Inflammatory lung injury progressing to Acute Respiratory Distress Syndrome (ARDS) is a recognized clinical feature of the disease. Inflammatory cytokines released in response to COVID-19 activate the transcription factor - the nuclear factor-κB (NF-κB) and series of pro-inflammatory cytokines, which are responsible for lung injury. Accurate yet precise treatment of coronavirus disease still remains inconclusive, and intervention is mainly symptomatic treatment, respiratory support, antiviral therapies and vaccination. Currently, the major focus of therapy is on reducing lung inflammation by elevating the host immunity. In this scenario, NF-κB inhibition can be conceptualized as a promising approach to down-regulate the overproduction of cytokines, such that inflammatory lung tissue injury could be prevented in COVID-19 infected patients. Towards this, curcumin from *Curcuma longa* (Turmeric) would play a vital role in the intervention and suppress NF-κB activation via translocation of p65 into the nucleus. Moreover, Curcumin is a proven therapeutic agent against various inflammatory pathologies as it also has the potential to inhibit the expression of certain genes that are critical for the regulation of inflammation. Keeping this phenomenon and the current medical significance in view, we have explored and computed the anti-inflammatory properties of curcumin to develop it as a potent therapeutic agent to prevent NF-κB induced lung tissue injury in COVID-19 with the main goal of elevating immunity in the post-covid-19 situations as well as in healthy human beings.

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INTRODUCTION

The inflammatory disease of the upper and lower respiratory system caused by SARS-COV2 virus, termed coronavirus disease-19 (COVID-19) by WHO, was reported first in Wuhan, China in December 2019. The hypoxia that develops in COVID-19 patients is predominantly due to the amalgamation of local subpleural interstitial edema and vasoplegia. Autopsy studies of patients who attained mortality due to severe SARS- COV2 infection revealed the presence of diffuse alveolar damage, which is

consistent with ARDS and associated thrombus formation in pulmonary capillaries (Attaway *et al.*, 2021). During the course of the pandemic, the explicit virus mutations in the SARS - COV2 genome were isolated from patients, which includes B.1.1.7, P.1 and B.1.351, while B.1.1.7 has shown a high rate of infectivity and spread (Vranken *et al.*, 2021). As per WHO, there is a global decline in the number of COVID-19 cases as well as death by September 2021, which accounts to 10%. But, more number of COVID-19 cases present in the Geographic areas includes Mediterranean region (17%), Western Pacific Region (15%), USA (14%), African region (12%) and South-east Asian region (10%) (www.who.int/covid19).

During the pandemic, the virus mutated several times, but the line of treatment still remains symptomatic. As SARS-COV2 genome variation does not linked with the pathogenicity, precise treatment for SARS-COV2 positive patients is still enigmatic. Thus, emphasis has been given to boost the host immunity through vaccination or other allied medicinal preparations. In the past, various vaccines have been developed and approved as emergency drugs against SARS- COV2 and are being administered in several countries across the world. However, it is still unclear which vaccine strategy is the most effective and successful (Jeyanathan *et al.*, 2020). Accordingly, WHO states that ~13 different types of vaccines developed against COVID-19 that are available in the market are approved as emergency drugs (vaccines). The vaccines help the host immune system to recognize viral antigens and block or curtail their action. One group of vaccines administers inactivated or weakened viruses, which are avirulant but trigger the host immunity to generate antibodies. There are protein-based vaccines available which use benign fragments of protein or protein shell that mimic the COVID-19 virus to generate an immune response. There are viral vector vaccines, which are based on COVID-19 spike proteins, which trigger the immune system to produce antibodies and other immune cells. The mRNA based vaccines introduce mRNA into muscle cells. The muscle cells copy the spike protein of COVID-19, and then mRNA degrades quickly. The spike protein elicits a series of immune responses and the production of antibodies. Recently, the first DNA based vaccine has been approved by DCGI, India, which uses circular strands of DNA to trigger the immune system against the SARS-COV2 virus. Eventually, as most of the vaccines are approved on an emergency basis and still many vaccines are under different phases of human trials, concerted efforts are still underway across the world for the development of highly efficacious and safe vaccines. Despite the complete vaccination regime, breakthrough infections occur, the vaccines offer a better threshold against severe forms of COVID-19 related illnesses and morbidity as compared to non-vaccinated cases. However, the long-term efficacy and side effects of the vaccines still needs to be assessed. Moreover, the CDC and US-FDA have now recommended booster shots of the COVID-19 vaccine to people who are moderately and severely immunocompromised.

Recent progress has revealed the great need for self immunity-boosting agents with proven scientific evidence against viral respiratory infections, which can specifically act against COVID-19 infection and are used by every individual on a routine basis to strengthen their immune system. In this regard, immune-boosting antioxidant and anti-inflammatory food and supplements are in great demand now. Towards this, parallel research is being carried out in repurposing several natural compounds for alternative therapeutics of COVID-19. These natural compounds have been known to mankind for years and are known to boost immunity even when consumed in the form of food and nutraceuticals. Therefore, these compounds could offer long term benefits even in the post-COVID-19 era too. (Sarada *et al.*, 2015)

Historically, the Indian system of medicine - the Ayurveda, which is a plant science-based medicine system, is well known for treating respiratory diseases. Turmeric or Haldi has been in use as a potent therapeutic agent for more than a thousand years, as documented in the ayurvedic system of medicine. The rhizome, botanically known as *Curcuma longa*, belongs to the family *Zingiberaceae*. Major health benefits like potent antioxidant and anti-inflammatory and anti-thrombolytic activity shown by turmeric is due to its active principle molecule, the curcumin (Sirsidthi *et al.*, 2016). Here, we intend to unravel a promising field of research to envisage the possible use of curcumin as a potential therapeutic agent against SARS-COV2 induced inflammatory lung injury leading to COVID-19 disease, as the use of curcumin might decelerate the thrombus formation in pulmonary capillaries, which is a consistent autopsy finding in COVID-19 patients with proven ARDS. Interestingly, the inflammatory lung injury in COVID-19, similar to SARS-COV1, could be linked to the nuclear factor kappa B (NF-κB) signaling pathway. The curcumin is known to possess transcription regulatory effects on the NF-κB pathway via a down-regulation mechanism, which in turn decelerates the pro-inflammatory pathways. These transcription regulatory effects of curcumin could be of great value

in attenuating the pulmonary tissue inflammation and as a potential immunomodulatory treatment in alleviating the severe form of COVID-19 (Hariharan *et al.*, 2021). As stated above, presently, no definitive therapy for COVID-19 disease exists and the assessment of the long term efficacy of vaccines is still underway. Hence, the curcumin based immune-boosting therapy could serve as a valuable tool in adjuvant therapeutics of COVID-19.

Pathogenesis and clinical manifestations

The clinical symptoms produced by SARS-COV1, MERS and SARS-COV2, are comparatively similar to its initial symptoms, which includes - initial fever progressing to cough, sore throat and dyspnea. The development of ARDS was observed after 8 days which further required ventilator support and extra-corporeal membrane oxygenation (ECMO). When the atypical nature of SARS-COV2 infection is considered, it was observed that patients with COVID-19 Pneumonia fulfilling the Berlin Criteria of ARDS presented with an atypical form of the syndrome. As observed by the respiratory physicians, there was dissociation between their lung mechanics and the severity of hypoxemia (Gattinoni *et al.*, 2020).

The pathogenicity of the virus (SARS- COV1) increases with its affinity to the Receptor Binding Domain (RBD) of the S- protein. SARS- COV2 also behaves the same way, but it shows more affinity than the SARS-COV 1 and single nucleotide mutation on RBD, which increases the pathogenicity of the COVID-19 (Wan *et al.*, 2020). To understand it better, the virus genome sequence is warranted. However, as the respiratory tract gets inoculated with the viral loads of COVID-19, the disease manifests as upper respiratory syndrome due to the release of interleukins IL1b and IL. Toll-like receptors (TLR) trans-membrane signaling receptors in the innate immune system are usually expressed on macrophages and dendritic cells, which identify structural molecules from viruses that link the immune system and inflammation. This process of ligation by exogenous and endogenous ligands triggers a pro-inflammatory reaction by signaling cascade (Conti *et al.*, 2020). Among excessive cytokines produced by activated macrophages, IL-6 is one of the key cytokines. The elevated cytokine levels may also be responsible for the lethal complications of COVID-19. Patients with COVID-19 presented with elevated T-helper-2 cytokines in addition to T helper- 1 cytokines compared to those in patients with SARS- COV1 or MERS. Therefore possible blockade of pro-inflammatory cytokines (IL-6, IL-1, IL-b and IFN) could be a possible therapy for COVID- 19. Consistently elevated IL-6 levels reported in several studies of COVID-19 shall be one of the biomarkers of the disease (Cruz *et al.*, 2021). The clinical data and animal studies have proved that inhibition of NF-κB and reduced levels of IL-6 increased animal survival. To this, the modern therapeutics of inflammatory diseases mainly relies on steroids, which inhibit NF-κB activity. Unlike steroids, curcumin in neutrophil driven diseases is highly appreciated since neutrophils are one of the key components of ARDS like syndromes and immunomodulation therapy, and hence pre-treatment with curcumin might be useful to curtail ALI/ARDS/COVID-19 (Langeresis *et al.*, 2014; De Girolamo *et al.*, 2020). But a systematic study for their long term usage is warranted.

Clinical relevance of SARS-COV2 genome in COVID-19

The genomic sequence of SARS-COV2 has a great role not only in drug development and mitigation of several serious clinical symptoms but also facilitates the detection of the mutated virus since its occurrence in Wuhan. With the emergence of new variants, the genome sequence of the COVID-19 virus is being viewed as a crucial device in fighting the pandemic, monitoring the progress of the disease and response to drugs and vaccines, which majorly depends on the molecular basis of evidence. DNA and RNA based vaccines are being highly considered as promising candidates to conventional COVID-19 vaccines as these vaccines are being predicted to be brought into clinical trials in less than 16 weeks when the precise sequence of the virus genome is known. Interestingly, the genomic sequence of SARS-COV2 has 86% similarity to SARS-COV1 and 50% similarity to MERS-COV (Lu *et al.*, 2020). The SARS-COV2, using angiotensin-converting enzyme 2 (ACE2) as its main receptor, inoculates on the surface layer of human airway epithelial cells similar to SARS-COV1 and affects the cell activity and stops the ciliary movements, thus aggravating the inflammatory response in airway epithelial cells. Further, the SARS-COV2 shows more affinity than the SARS-COV1 to Receptor Binding Domain (RBD) of the S-protein due to a single nucleotide mutation on RBD, implying enhanced pathogenicity (Wan *et al.*, 2020). Toll-like receptors (TLR), which are trans-membrane signaling receptors in the innate immune system, identify structural molecules from viruses that link the immune system and inflammation. This process of linkage (ligation) by exogenous and endogenous ligands triggers a pro-inflammatory reaction via signaling cascade. Ligation of SARS-COV2 to the TLR releases the pro-IL-1b, which is the main cause of clinical manifestations like pulmonary destruction, fever, and

fibrosis (Conti *et al.*, 2020). The exceptional affinity of SARS-COV2 to ACE2 receptors is well established. Similar to SARS- COV1, the SARS-COV2 virus preferably infects the ciliary epithelium of the respiratory system. Therefore, there exists a close similarity between clinical features of SARS-COV1 and 2, as both the viruses target the same respiratory epithelial lining tissue. (Aggarwal *et al.*, 2006)

Immune regulation in COVID-19 therapeutics

Pathogen derived molecules, cytokines and lipopolysaccharides are known to activate multiple inflammatory pathways that play a major role in inflammatory pathosis of several diseases, including COVID-19. The transcription factor NF-κB, which is one of the key regulators of inflammatory pathways, cause various human diseases. The NF-κB is a family of rapid-acting primary transcription factors that remains inactive within the cytoplasm in association with IκB proteins. Activation of IκB kinases (IκKα, IκKβ, and NF-κB essential modulator [NEMO/IκKγ) result in the phosphorylation of the inhibitory IκB (IκBα, IκBβ, and IκBε) proteins bound to NF-κB. NF-κB is consequently released and translocates to the nucleus, wherein it interacts with other transcription factors and co-factors to regulate the expression of an array of genes, many of which are involved in inflammatory signaling as well as proliferation and apoptosis. NF-κB is activated within minutes by a variety of stimuli, including inflammatory cytokines such as TNF-α and IL-1, T-cell activation signals, etc. NF-κB as a transcription factor regulates the expression of many genes that are involved in innate and adaptive immunity and inflammation (Albert and Baldwin, 2001).

Since, patients with COVID-19 exhibit elevated levels of T-helper-2 cytokines in addition to T- helper-1 cytokines, blockade of pro-inflammatory cytokines (IL-6, IL-1, IL-b and IFN) could be a possible immunotherapeutic action against COVID-19 (Wang *et al.*, 2020). Thus, inhibition of NF-κB results in decreased IL-6 levels, and as IL-1 and IL-6 are suppressed, a significant decrease in interleukin production is obvious, which in turn reduces the pulmonary inflammation (Langeresis *et al.*, 2010). Thus, an appropriate drug candidate inhibiting NF-κB is warranted.

Curcumin in immunotherapeutics of COVID-19

Curcumin is largely known for its inhibitory effect over NF-κB as well as its pleiotropic effects because it has the ability to prevent pulmonary dysfunction and attenuate organ damage due to lung injury caused by inflammation, oxidative stress and tissue remodeling (Huscher *et al.*, 2009). Such that Curcumin extracted from *C. longa* attenuates pulmonary inflammation secondary to inhibition of COX-2, 5-LOX pathway, NF-κB signaling and AP-1pathway. Experimentally, the effect of curcumin on the downregulation of pro-inflammatory cytokines IL-1 (IL-1α and IL-1β) via modulation of AP-1 and NF-IL6 has been well demonstrated using the mice model (Jeon *et al.*, 2000). Here, Curcumin treatment has shown significant down-regulation of both m-RNA expression and 17 kDa protein level, IL-1α in the liver of mice. This data suggest the positive role of curcumin in an inflammatory response. In addition, the importance of curcumin therapeutics in inflammatory lung diseases like asthma, COPD, ARDS, ALI and pulmonary fibrosis (Lelli *et al.*, 2017) is also well explored. Further, rats pre-treated with curcumin and then treated with oleic acid to induce ALI effectively mitigated both pro-inflammatory as well as anti-inflammatory factors. It curtailed undesired effects of oleic acid on pulmonary compliance, as well as improved pulmonary function (Zhu *et al.*, 2008).

So, Curcumin exerts its therapeutic effects by inhibiting the degradation of IκB-α and subsequent inactivation of NF-κB and initiating a cascade of downstream inflammatory and immunogenic events as a key immunomodulator. Curcumin mediated inactivation of NF-κB inhibits expression of a number of pro-inflammatory cytokines and down-regulation of the mRNA expression of several pro-inflammatory enzymes, which could be a major advantage of using curcumin in immune modulation in COVID-19 therapeutics. It is observed that drugs that inhibit NF-κB activation leads to both reduction in inflammation and lung pathology in infected culture cells of SARS-COV1 (Avasarala *et al.*, 2013), the congener of SARS-COV2. Hence, curcumin may act as a major NF-kB inhibitor to curtail lung inflammation.

The role of curcumin in Covid-19 pathogenesis

The role of curcumin in modulating the pathogenesis of viral-induced ALI/ARDS leading to acute pneumonia and prevention of hypoxia is well studied. Reovirus 1/L-ALI/ARDS induced mice explicit severely damaged lungs due to the infiltration of the interstitium and alveolar spaces by fibroblasts and excessive collagen. The inflammatory and fibrotic changes were significantly reduced when 1/L-ALI/ARDS induced mice were treated with curcumin (Avasarala *et al.*, 2013).

To support this, autopsy studies of patients who died due to severe SARS-COV2 infection have also revealed the presence of diffuse alveolar damage associated with thrombus formation in pulmonary

capillaries (Attaway *et al.*, 2021). Curcumin and its derivatives also have shown thrombin and FXa inhibitory activity. Earlier, curcumin and its derivative (Bisdemethoxycurcumin) showed anticoagulant activity *in vivo* with prolonged PTT and PT as well as cell-based thrombin and FXa activity (Kim *et al.*, 2012). In view of this, we are of the opinion that curcumin is a highly valuable compound in ARDS cases, owing to its anticoagulant property, which may prevent the thrombus formation in pulmonary capillaries and its subsequent embolic effects.

Recently, curcumin, as a potential candidate in the treatment of COVID-19 therapeutics, has aptly demonstrated antiviral properties (Rattis *et al.*, 2021). Despite its high therapeutic value, bioavailability and poor solubility in an aqueous solution act as a major challenge to using it as a potent drug. To exert its full range of anti-inflammatory activity, Curcumin has to undergo oxidative activation into reactive metabolites. Whereas synthetic curcumin analogs that undergo oxidative transformation potently inhibit the pro-inflammatory transcription factor NF-κB, while stable, non-oxidizable analogs are less active. Accordingly, the reactive metabolites covalently adduct the cellular protein, thereby modulating the function (Edward *et al.*, 2017). Therefore, methods that improve the binding of curcumin covalently to cellular protein facilitate to improve the functionality and to exploit the complete benefits of curcumin *in vivo.*

In this direction, several carriers, including hydrophobically modified starch, PVA hydrogel, and polymeric nanoparticles, have been explored to improve the bioavailability of curcumin with different rates of success. The solubility of curcumin is increased by 1670 times due to hydrogen bonds between them, which is established by encapsulating curcumin with hydrophobically modified starch (Yu and Huang, 2010). Bioavailability of curcumin is also increased by synthesis of polymeric nanoparticle encapsulated formulation of curcumin-nano curcumin utilizing the micellar aggregates of cross-linked and random copolymers of Nisopropylacrylamide (NIPAAM) with N-vinyl-2-pyrrolidone (VP) and poly (ethylene glycol) monoacrylate (PEG-A) (Bisht *et al.*, 2007). Pharmaceutical grade cyclodextrins used to load curcumin exhibit great success in attaining delivery of this insoluble natural polyphenol to a therapeutic level.

Traditionally, the general home remedy in the Indian subcontinent is consuming milk boiled with turmeric for respiratory conditions. Keeping this phenomenon in view, one of the authors (Manjunatha) has practiced Curcumin therapy for over a year and believed it to be a great relief during the pandemic time. The scientific rationale behind this is a conjugation of curcumin with the 'milk' protein, the casein - β-casein in particular shows improved and consistent bioavailability. Casein being a rich source of calcium and essential amino acids, has unique properties to fabricate delivery systems for food and pharmaceutical compounds. The β-casein is an amphiphilic self-assembling protein that forms small oblate micelles with a diameter of approximately 13 nm in an aqueous solution (Dauphas, 2005). It makes up 30-35% of the total available protein in the whole milk. β-casein from camel milk, when used to encapsulate curcumin, improved the solubility of curcumin by 2500 times. The camel β-casein micelles interact with curcumin mainly via hydrophobic interaction, which leads to increased solubility of curcumin. Thus, Curcumin therapy shall be one of the best practices to be followed to boost immunity and maintain sound health during the Covid-19 pandemic era (Rattis *et al.*, 2021).

CONCLUSION

The distinct clinical manifestations of COVID-19 infection, secondary to virus-induced inflammatory tissue injury of the respiratory system, have been explored from various therapeutic perspectives. Scientific data have revealed that the mitigation of disease is possible via inhibition of inflammatory pathways that involve NF-κB and other pro-inflammatory cytokines. According to the Indian Ayurvedic system of medicine, Curcumin shall be a potential therapeutic agent in treating various respiratory diseases. Thus, curcumin is used as a potential candidate to treat COVID-19, while one of the authors tested Curcumin therapy for more than a year during a pandemic and experienced substantial relief from sore throat and inflammation, which not only boosted immunity and confidence in him. Further, nano-formulations of curcumin-casein have great value as a potent drug so that it can be used as adjuvant therapy for COVID-19 to improve immunity and boost the health of human beings.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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