Antiviral and immunomodulatory activity of curcumin: A case for prophylactic therapy for COVID-19

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ABSTRACT

Coronavirus disease-19 (COVID-19), a devastating respiratory illness caused by SARS-associated coronavirus-2 (SARS-CoV-2), has already affected over 64 million people and caused 1.48 million deaths, just 12 months from the first diagnosis. COVID-19 patients develop serious complications, including severe pneumonia, acute respiratory distress syndrome (ARDS), and multiorgan failure due to exaggerated host immune response following infection. Currently, drugs that were effective against SARS-CoV are being repurposed for SARS-CoV-2. During this public health emergency, food nutraceuticals could be promising prophylactic therapeutics for COVID-19. Curcumin, a bioactive compound in turmeric, exerts diverse pharmacological activities and is widely used in foods and traditional medicines. This review presents several lines of evidence, which suggest curcumin as a promising prophylactic, therapeutic candidate for COVID-19. First, curcumin exerts antiviral activity against many types of enveloped viruses, including SARS-CoV-2, by multiple mechanisms: direct interaction with viral membrane proteins; disruption of the viral envelope; inhibition of viral proteases; induce host antiviral responses. Second, curcumin protects from lethal pneumonia and ARDS via targeting NF-κB, inflammasome, IL-6 trans signal, and HMGB1 pathways. Third, curcumin is safe and well-tolerated in both healthy and diseased human subjects. In conclusion, accumulated evidence indicates that curcumin may be a potential prophylactic therapeutic for COVID-19 in the clinic and public health settings.

1. Introduction

Coronavirus disease-19 (COVID-19) is a dreadful respiratory illness caused by a newly discovered coronaviruses (CoV) strain known as SARS-CoV-2. SARS-CoV-2 much resembles SARS-associated coronavirus (SARS-CoV) that caused the SARS pandemic in 2003. It was first detected in Wuhan city, Hubei province, China, in December 2019, and as of Dec 02, 2020, over 64 million people are diagnosed with COVID-19, with around 1.48 deaths reported across the world (Source: Johns Hopkins University). WHO has declared COVID-19 as a global pandemic, and the prediction is that the number of deaths due to COVID-19 will further worsen in the coming months (Abais et al., 2015; Wu et al., 2020b). In most cases, COVID-19 patients exhibit fever, dry cough, dyspnoea, fatigue, and myalgia (Chen et al., 2020c; Huang et al., 2020; Wu et al., 2020a). However, in severe cases, COVID-19 patients develop fatal complications such as severe pneumonia, acute respiratory distress syndrome (ARDS), septic shock, arrhythmia, and acute cardiac injury (Wang et al., 2020). Other than the management with ventilator support and other supportive care, there are no effective treatments available for COVID-19. Therefore, there is an urgent need for the discovery and development of therapeutics for COVID-19. The discovery and development of an effective therapeutic agent against SARS-CoV-2 is a time-consuming process. Alternatively, repurposing of already-licensed pharmaceuticals may provide a faster path for developing effective therapeutics for COVID-19. First, effective drugs against SARS-CoV were tested against SARS-CoV-2 in the laboratory and...
clinical settings, and the results were very encouraging. These studies prompted WHO to initiate a large global mega trial called ‘SOLIDARITY’ for testing four therapeutics for COVID-19: i) remdesivir, an inhibitor of RNA-dependent RNA Polymerase; ii) antimalarial drugs chloroquine and hydroxychloroquine; iii) anti-retroviral drugs, lopinavir-ritonavir that are HIV protease inhibitors, and iv) immunomodulatory agent, interferon-beta. Additionally, vaccine trials (Amanat and Krammer, 2020) and convalescent plasma therapy (Bloch et al., 2020; Shen et al., 2020) for SARS-CoV-2 are also under investigation; the outcomes are very promising. So far, some vaccination trials for COVID-19 have shown to be safe and effective in inducing robust humoral and cellular responses in the participants (Jackson et al., 2020; Ramsamy et al., 2020; Walsh et al., 2020). Although it is good news, it is likely to take many months to vaccinate the entire global population.

Along with repurposing approved drugs, scientists are also actively seeking safe, natural products with antiviral pharmacological activity as potential prophylactic therapeutics for COVID-19. Turmeric (Curcuma longa) is a perennial herbaceous, rhizomatous plant of the ginger family Zingiberaceae. It is widely used in Ayurveda, Siddha, and traditional Chinese medicines for its medicinal properties such as anti-inflammatory, analgesic, antimicrobial, antiproliferative, and anti-inflammatory activity (Aggarwal and Sung, 2009; Karimi et al., 2019; Padmanaban and Rangarajan, 2016; Patel et al., 2020). Turmeric is also the most popular spice across the globe, especially in India. Turmeric’s medicinal properties are very promising. So far, some vaccination trials for COVID-19 patients were fever, dry cough, myalgia, fatigue, and dyspnoea. The average time period from onset of symptoms to hospital admission was 7 days, and all patients with COVID-19 were associated with mild-to severe-pneumonia (Huang et al., 2020). The systemic inflammation, as indicated by plasma levels of multiple interleukins including IL2, IL7, IL6, IL10, GCSF, IP10, MCP1, MIP1A, and TNFs, was elevated in COVID-19 patients as compared to healthy subjects, which further increased in ICU admitted patients (Chen et al., 2020a; Huang et al., 2020). Also, ICU admitted COVID-19 patients showed a immunosuppressive phenotype characterized by severe lymphopenia and lower IFN-gamma levels (Chen et al., 2020a). Few COVID-19 patients in ICU also developed secondary infections. Histopathological analysis showed typical ARDS features, including an influx of mononuclear cells, including monocytes and lymphocytes, into air spaces, bilateral diffuse alveolar damage, and desquamation of alveolar epithelial cells, and hyaline membrane formation (Xu et al., 2020). The mortality was mainly due to respiratory failure caused by ARDS and multiorgan failure (Du et al., 2020; Huang et al., 2020).

3. Antiviral effects of curcumin against enveloped viruses including SARS-CoV-2

A large body of evidence has documented curcumin's direct antiviral activity against several enveloped viruses (Praditya et al., 2019), including SARS-CoV (Table 1). Wen et al. (2007) used cytopathic effects of SARS-CoV in Vero 6 cells as a cell-based assay to screen phytochemicals against SARS-CoV. They reported that curcumin (at 20 μM and 40μM) showed significant anti-SARS-CoV activity. The same study reported that curcumin inhibits SARS-CoV 3CL protease activity, which is vital for viral replication. Few studies have utilized computational modelling tools and predicted that curcumin interacts with S protein and ACE2 protein and potentially intervenes in viral entry into lung cells (Pandey et al., 2020). Based on these pleiotropic effects of curcumin, it is postulated that curcumin may directly intervene SARS-CoV-2 entry and or replication and prevent infection (Son et al., 2020). 4-octyl-itaconate, a pharmacological agonist of transcription factor NRF2 was reported to repress SARS-CoV-2 replication in lung cells by an independent interferon mechanism (Olagnier et al., 2020). Furthermore, the same study revealed that the activation of the NRF2 pathway by another structurally dissimilar agonist dimethyl fumarate inhibited SARS-CoV-2 replication, suggesting that NRF2 agonists are potential drug candidates for represing SARS-CoV-2 replication (Olagnier et al., 2020). We (Pandey et al., 2011; Thimmulappa et al., 2008) and others (Fattori et al., 2015; Jiménez-Osorio et al., 2016; Li et al., 2016) have previously reported that curcumin is a promising NRF2 agonist, and administration of curcumin activates NRF2 pathway in lungs of mice (Garg et al., 2008; Shen et al., 2015; Thimmulappa et al., 2008). So, it is conceivable that curcumin may also exert antiviral activity against SARS-COV-2 by activating the NRF2 pathway.

A recent study employed genome-wide screening using CRISPR-Cas9 and discovered HMGB1 as an important pro-viral host factor in determining SARS-CoV-2 infection (Wei et al., 2020). HMGB1 is a non-histone nuclear protein that binds with DNA and regulates transcription (Harris et al., 2012). However, under stress conditions such as viral infection, the
| S.No | Virus Name       | Human Disease | Study Design (dose) | Mode of Action                                                                 |
|------|-----------------|---------------|--------------------|--------------------------------------------------------------------------------|
| 1    | SARS-CoV        | Severe acute respiratory syndrome | In vitro         | Inhibit SARS-CoV 3CL protease (Wen et al., 2007)                                |
| 2    | SARS-CoV        | Respiratory illness  | In vitro         | Disrupt virus envelope; Inhibits hemagglutinin activity; NF-κB signaling       |
| 3    | Respiratory syncytial virus | Respiratory illness | In vitro         | Inhibit viral replication and budding (Obata et al., 2013)                    |
| 4    | Japanese encephalitis virus | Cold sores    | In vitro         | Not Reported                                                                  |
| 5    | Japanese encephalitis virus | Cold sores    | In vitro         | Inhibit viral replication and budding (Obata et al., 2013)                    |
| 6    | HIV             | AIDS, Liver disease | In vitro         | Inhibit HIV replication & HIV integrase                                          |
| 7    | Zika            | Zika Fever, Dengue fever | In vitro         | Inhibit viral binding to host cell                                             |
| 8    | Chikungunya virus | Chikungunya fever | In vitro         | Inhibit viral binding to host cell                                             |
| 9    | Dengue virus    | Dengue fever   | In vitro         | Disrupt viral envelope                                                         |

Curcumin was also effective against the respiratory virus, influenza A virus (IAV), and respiratory syncytial virus (RSV), which are the common causal agents of acute respiratory infections in the community (Chen et al., 2013; Dai et al., 2018; Ou et al., 2013). Curcumin inhibits IAV hemagglutinin's binding, a homotrimeric membrane glycoprotein, with host cell receptors (Ou et al., 2013). Curcumin also impairs the replication and budding of RSV in human nasal epithelial cells by inhibiting NF-κB and cyclooxygenase 2 signaling, implicated in RSV replication and budding (Obata et al., 2013). Mounce et al. (2017), reported antiviral effects of curcumin against the Zika and Chikungunya virus. The investigators demonstrated that curcumin or its derivatives attenuated the Zika and Chikungunya virus's infectivity by modifying its surface proteins, which resulted in blockage of its binding and entry into the host cells (Mounce et al., 2017). Curcumin and its analogs were also effective in inhibiting HIV replication by targeting HIV protease (Sui et al., 1993), HIV integrase (Mazumder et al., 1995; Vajragupta et al., 2005), and HIV tat protein (Ali and Banerjea, 2016). Anggakusumma et al. (Anggakusumma et al., 2014) studied the antiviral effects of curcumin against the hepatitis C virus. They observed that curcumin impaired virus binding and fusion with cell membranes by affecting the viral envelope's fluidity. Zen et al. (Chen et al., 2013) assessed whether curcumin's broad-spectrum antiviral activity is mediated by disruption of the enveloped virus's membrane structure. To address this, the authors evaluated the antiviral activity of curcumin against IAV, and other RNA enveloped virus (New castle disease virus, Dengue virus, Japanese encephalitis virus), and DNA enveloped (PRV swine herpes virus, vaccinia virus) in Vero cells. The authors observed that the curcumin effectively inhibited plaque formation when the virus was in-direct contact with the agent (during pre-and co-treatment experimental regimen); however, its antiviral activity was lost when Vero cells were treated post-infection. Furthermore, curcumin was ineffective against the non-enveloped virus, enterovirus 71. The authors concluded that curcumin's intrinsic ability to disrupt the membrane integrity of enveloped viruses was the common mechanism for inhibiting the viral infectivity (Chen et al., 2013).

Emerging evidence suggests that antiretroviral drug lopinavir-ritonavir, a protease inhibitor exerts antiviral activity against SARS-CoV-2 (Choy et al., 2020). Unfortunately, combination lopinavir-ritonavir in COVID-19 patients showed no clinical benefits (Cao et al., 2020); however, the results of other on-going trials with lopinavir-ritonavir awaited. Hoffmann et al. (2020) reported that camostat mesylate, an inhibitor of serine protease TMPRSS2, effectively blocked the entry of SARS-CoV-2. Lopinavir/ritonavir (Chu et al., 2004; Yao et al., 2020) and camostat mesylate were also effective against SARS-associated coronavirus (Zhou et al., 2020). In vitro studies have demonstrated the potency of curcumin to function as an HIV protease inhibitor (Sui et al., 1993).

In summary, curcumin exerts antiviral activity against the enveloped virus by multiple mechanisms such as direct interaction with viral...
membrane proteins, disruption of the viral envelope, inhibition of viral proteases, and modulating host factors NF-κB, NRF2 and or HMGB1 pathways. Given that in vitro studies have confirmed the antiviral activity of curcumin against SARS-CoV, it is tempting to speculate that curcumin may also attenuate SARS-CoV-2 infectivity by mechanisms as summarized above.

4. Immunomodulatory activity of curcumin suppress cytokine release syndrome and mitigates progression to ARDS

The death of severely ill COVID-19 patients is associated with respiratory failure and or multiorgan failure caused by ARDS and septic shock. ARDS and or sepsis's pathogenesis involves an early hyperactivated inflammatory response characterized by a "cytokine storm" (Chen et al., 2020a, 2020c). A positive association between cytokine release syndrome (CRS) and the severity of illness and mortality among COVID-19 patients is reported by many studies (Tang et al., 2020). Immuno- modulatory drugs are likely to effectively mitigate ARDS progression or sepsis by dampening early inflammatory response following infectious insults (Tang et al., 2020; Yadav et al., 2017). A recently concluded clinical trial found that dexamethasone, a widely used immuno- modulatory drug, effectively improved the survival of severely ill hospitalized COVID-19 patients compared to placebo (Horby et al., 2020; Tomazini et al., 2020). This finding has renewed the interest in finding safer and more effective immunomodulatory therapeutics to treat COVID-19. Analysis of lung transcriptome and the circulatory inflammatory cytokines profiles of COVID-19 patients indicated that NF-κB, inflammatory IL-6 trans-signaling, and HMGB1 signaling may be driving the CRS (El-Hachem et al., 2020; Lee et al., 2020). We present several lines of evidence to illustrate how pleiotropic effects of curcumin could dampen CRS and mitigate the progression to ARDS and or sepsis in COVID-19 patients.

Curcumin administration via oral route alleviated reovirus 1L-induced-ARDS in mice that recapitulate the clinical features of ARDS (Avasarala et al., 2013). The same study reported that curcumin lowered interleukins levels such as IL6, MCP1, and IFN gamma by abrogating NF-κB activation in the lungs (Avasarala et al., 2013). In most cases, the clinical course of respiratory viral infection is exacerbated by secondary bacterial infections. Curcumin also effectively protects against lethal bacterial pneumonia (Zhang et al., 2019). Direct delivery of water-soluble curcumin into the lungs of mice infected with Klebsiella pneumoniae dramatically improved the survival and reduced lung and blood bacteremia compared to the vehicle-treated group. The improved survival of the infected mice treated with curcumin was associated with significantly reduced levels of inflammatory mediators (IL1β, TNFα, IL6, KC) in bronchoalveolar lavage fluid, lung tissue, and serum as well as diminished oxidative tissue injury as compared to vehicle treatment (Zhang et al., 2019). Most studies have revealed that curcumin alleviates viral-induced pulmonary inflammation by abrogating the activation of NF-κB signalling (Zhang et al., 2019) potentially by inhibiting upstream IKKβ kinase activity (Jobin et al., 1999; Kim et al., 2011; Xu and Liu, 2017).

Cytokines, especially IL1β and IL6, were markedly elevated in severely ill COVID patients admitted to intensive care units compared to stable COVID-19 patients (Conti et al., 2020; McElvaney et al., 2020). These observations have implicated inflammasome activation in driving CRS (Cauchois et al., 2020; Lee et al., 2020). Several studies have found the potency of curcumin to block inflammasome activation through Nod-like receptor family, pyrin domain-containing 3 (NLRP3), and inhibit secretion of mature IL-1β (Yin et al., 2018b) and abrogate pulmonary inflammation (Liu et al., 2018; Zhang et al., 2019).

A growing body of evidence suggests that a higher circulatory IL6 level is predictive of severity of illness and mortality in COVID-19 patients (Nasonov and Samsonov, 2020), and abrogating IL6 signalling by JAK inhibitors is advocated to be an additional way to mitigate the progression to ARDS in COVID-19 patients (Nasonov and Samsonov, 2020). Although the direct role of IL6 per se in acute lung injury is conflicting, IL6 is implicated in-hyperactivation of immune responses; vascular dysfunction leading to multiorgan failure; fibrotic responses by trans-signalling mechanisms in which the complex of IL6 with soluble IL6 receptor (sIL-6R) promote pro-inflammatory cytokine expression in T helper (Th1) cells, monocytes and stromal cells (fibroblasts and endothelial cells) via activation of downstream JAK/STAT3 signaling (Barthausen et al., 2011; Scheller et al., 2014). Selective blockade of IL6 trans-signaling pathway in macrophages dampened inflammatory cytokine secretion and protected from polymicrobial sepsis in mouse models (Barthausen et al., 2011). CRS also mediates endothelial injury and increases the risk for coagulopathy in COVID-19 patients, further worsening the prognosis. Hospitalized COVID-19 patients are associated with elevated levels of plasminogen activator inhibitor-1 (PAI-1). Kang et al. (2020), reported that IL-6 trans-signaling plays a crucial role in endothelial dysfunction during microbial infection resulting in secretion of PAI-1, promoting thrombosis. The same researchers showed blockade of IL-6 trans-signaling by Tolcilizumab decreased endothelial dysfunction and circulatory levels of PAI-1 in COVID-19 patients. Curcumin effectively blocked IL6 trans-signaling (Sharit et al., 2003; Hahn et al., 2018; Weissenberger et al., 2010) and inhibited the progression of inflammatory diseases (Zhao et al., 2016; Zhu et al., 2017). Curcumin is also reported to exert anticoagulant activity by reducing TNF alpha-induced endothelial tissue factor (Pendurthi et al., 1997) and by directly inhibiting thrombin activity (Kim et al., 2012). Chen et al. reported that curcumin administration significantly reduced plasma fibrinogen and fibrin deposition in kidney in rat model of LPS-induced endotoxemia (Bierhaus et al., 1997).

Circulatory levels of HMGB1 positively correlate with severe illness in COVID-19 patients (Chen et al., 2020b). Extracellular HMGB1 functions as an inflammatory cytokine and plays a crucial role in the pathogenesis of acute lung injury and/or ARDS (Andersson et al., 2020) by upregulating inflammation. In mouse models, curcumin administration down-regulated HMGB1 expression and attenuated LPS-induced acute lung injury (Cheng et al., 2018). Moreover, curcumin supplementation also protected from HMGB1 mediated vascular injury and hepatitis (Wang et al., 2012) in mouse models.

Besides inhibiting proinflammatory signals, curcumin also upregulates anti-inflammatory responses. Curcumin administration alleviated acute lung injury induced in cecal ligation and puncture-induced sepsis model, and it was accompanied by elevated numbers of regulatory T cells (FOXP3+ T-reg) and M2 Macrophages (Chai et al., 2020). T-reg and M2 macrophages suppress activated immune cells (CD4+, CD8+ T cells) via TGF-β and IL-10 secretion and facilitate inflammation resolution (Chai et al., 2020). In vitro studies revealed that curcumin enhanced the differentiation of T-reg cells and the polarization of M2 macrophages (Chai et al., 2020). These findings suggest that curcumin treatment may improve the resolution of pulmonary inflammation and tissue repair by increasing T-reg and M2 macrophages. In the later stages of COVID-19, some severely ill patients develop myelosuppression characterized by a lower number of blood neutrophils and monocytes, which increases the risk for secondary infections (Liao et al., 2020). Curcumin has been shown to potentiate myelopoiesis in mouse models, although the underlying mechanisms are not clear (Vishvakarma et al., 2012). Few studies have also revealed that curcumin mediates immunomodulatory activity by affecting other molecular targets such as NADPH oxidase, and NRF2. Besides direct antioxidant activity, curcumin dampens reactive oxygen species (ROS) generation by inhibiting NADPH oxidase activity (Moghadam et al., 2015; Huang et al., 2015). ROS generated by NADPH oxidase activity is implicated in over-activation of the innate immune response, inflammation, tissue injury, and death during sepsis (Bernard et al., 2014; Kong et al., 2010). Curcumin also activates transcription factor NRF2, a master regulator of cellular antioxidant defenses, including heme oxygenase-1 and GSH-biosynthesizing enzymes (Dai et al., 2018; Pandey et al., 2011). Activation of the NRF2 pathway is shown to mitigate oxidative tissue injury in the lungs (Banga et al., 2004; Thimmulappa et al., 2006a), inhibits pulmonary inflammation.
In an RCT, Campbell et al. (2019) reported inhibiting cytokine response syndrome and oxidative stress and thus mitigating the progression to pneumonia and or ARDS following SARS-CoV-2 infection. Curcumin mediates immunomodulatory responses by positively regulating NRF2 and repressing ACE2 expression by negatively regulating HMGB1. Curcumin mediates immunomodulatory responses by disrupting the viral envelope, S protein and or ACE2, which prevents the entry of the virus into the cells. Curcumin induces antiviral responses by positively regulating NRF2 and repressing ACE2 expression by negatively regulating HMGB1. Curcumin mediates immunomodulatory responses by inhibiting cytokine response syndrome and oxidative stress and thus mitigating the progression to pneumonia and or ARDS following SARS-CoV-2 infection. (Harvey et al., 2011), protects from an acute lung injury, ARDS, and or sepsis (Cuadrado et al., 2019; Kong et al., 2011; Thimmulappa et al., 2006a, 2006b, 2007; Yamamoto et al., 2018).

As illustrated in Figure 1, a large body of evidence provides a strong rationale that curcumin supplementation could alleviate cytokine release syndrome, oxidative stress, apoptosis, and ensuing tissue injury following viral infection; thus, it could be a promising therapeutic for COVID-19.

5. Safety profile, bioavailability, and clinical efficacy of curcumin

In ayurvedic medicine, turmeric has been employed to cure a broad spectrum of common ailments, and similar usage has been noted in Chinese traditional medicine. Clinical trial in asthmatics using turmeric extract was associated with better disease control than placebo (Manarin et al., 2019). Because of its diverse pharmacological activities and FDA approval as "Generally Recognized As Safe," curcumin has been evaluated to treat various human diseases in over 100 clinical trials (www.clinicaltrial.gov). We have summarized the selected clinical trials conducted in the last 10 yr in Table 2, and these human trials were conducted both in healthy subjects and diseased patients. Almost all the clinical trials have revealed that curcumin supplementation is safe and well-tolerated even at doses as high as 8 g/day. There is significant accumulated evidence suggesting curcumin or curcumin containing nutraceuticals mitigate various human diseases by exerting anti-oxidant and anti-inflammatory actions. Randomized clinical trials (RCT) have shown that curcumin, when supplemented as adjunctive therapy maintained and or induced remission in ulcerative colitis patients (Coelho et al., 2020). Hanai et al. (2006) reported that curcumin supplementation (two doses of 1g/day) for six months as an adjunct therapy in patients with stable ulcerative colitis was well tolerated and significantly protected from remission and improved the quality of life as compared to placebo. Lang et al. (2015) conducted a multicentre RCT in patients with mild to moderate ulcerative colitis. They observed that patients receiving curcumin (3g/day) and mesalamine showed significant clinical remission compared to the placebo plus mesalamine group. In an RCT, Campbell et al. (2019) reported beneficial effects of curcumin in young adults with high-risk for cardiovascular diseases (body mass index >30). Curcumin supplementation (500 mg/day) for 12 weeks significantly reduced serum levels of homocysteine and concomitantly increased HDL-cholesterol (HDL-C) levels, however, there was no improvement in blood pressure as compared to placebo (Campbell et al., 2019). Panahi et al. (2015) compared lipid profiles in patients with metabolic syndrome at baseline and eight weeks after curcuminoids supplementation (1g/day). When compared to baseline, curcuminoid supplementation for eight weeks significantly increased HDL-C as well as reduced serum levels of LDL-C, total cholesterol, triglycerides, and lipoprotein(a) (Panahi et al., 2015). Nanoformulation of curcumin was also evaluated in patients with rheumatoid arthritis. Administration of curcumin nanomicelle (40mg, 3 times/day) to rheumatoid arthritis patients for 12 weeks reduced the clinical disease score (tender joint count and swollen joint count) compared to baseline. In another RCT, Amalraj et al. (2017) also reported that supplementation of highly bioavailable curcumin formulation reduced the clinical symptoms in patients with rheumatoid arthritis as compared to placebo. Furthermore, supplementation of curcumin at high doses showed clinical improvement in gastrointestinal disorders, namely in gall-bladder, gastric ulceration, irritable bowel disease, tropical pancreatitis, and biliary motility (reviewed in Gupta et al., 2013).

Except for a few trials demonstrating clinical benefits, most curcumin trials showed no significant clinical benefits (White et al., 2019). Inadequate clinical efficacy of curcumin is attributed to poor bioavailability at the target site due to low absorption, instability at physiological pH, rapid hepatic metabolism, and systemic clearance (Liu et al., 2016). Upon oral consumption, a large portion of the ingested curcumin is excreted in feces, and the intestines absorb a relatively smaller amount. The absorbed curcumin is rapidly metabolized by the liver yielding an aqueous-soluble moiety eliminated by the kidney (Pan et al., 1999) and therefore, plasma levels of curcumin remains below detection limits. In contrast, the plasma levels of curcumin metabolite, curcumin-O-glucuronide were detected by 30 min after curcumin intake by healthy human subjects and reached to a maximum concentration of 29 ng/ml by 2.57h (Cheng et al., 2019). Although curcumin levels of
Table 2. Completed clinical trials of curcumin in healthy and diseased subjects with various disorders.

| Sl. No | Disease condition | Dose | Sample size | Study design; study Duration | Study Outcome | Reference |
|--------|-------------------|------|-------------|-------------------------------|---------------|-----------|
| 1      | Rheumatoid arthritis | 1.2 g/day | N = 18; double blind, cross over study; 15 days | Significant improvement in pain and physical function scores | S. D. Desdhar et al., Preliminary study on antirheumatic activity of curcumin ( diferuloylmethane). Indian J Med Res 71, 632-634 (1980). |
| 2      | Osteoarthritis (Knee) | 1.5 g/day | N = 367; Randomized, multicenter study; 30 days | No significant Changes | V. Kopninatraikul et al., Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. Clin Interv Aging 9, 451–458 (2014). |
| 3      | Osteoarthritis (Knee) | 0.5 g twice per day | N = 120, Randomized, Single blind, multicenter study; 42 days | Significant improvement in pain and physical function scores | K. Maidhi et al., Safety and efficacy of Curcuma longa extract in the treatment of painful knee osteoarthritis: a randomized placebo-controlled trial. Inflammopharmacology 21, 129–136 (2013). |
| 4      | Osteoarthritis (Knee) | 0.5 g twice per day | N = 40, Randomized, double-blind placebo-controlled parallel trial; 42 days | Significant improvement in pain and physical function scores | Y. Panahi et al., Curcuminoid treatment for knee osteoarthritis: a randomized double-blind placebo-controlled trial. Phytother Res 28, 1625–1631 (2014). |
| 5      | Metabolic disorders | 0.5 g twice per day | N = 117; Randomized controlled trial; 56 days | Significant decrease in inflammatory cytokines (MCP-1, TGF-β, IL-6 and TNF-α) | Y. Panahi et al., Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: A randomized controlled trial and an updated meta-analysis. Clin Nutr 34, 1101–1108 (2015). |
| 6      | Psoriasis | 2g/day | N = 63, Randomized, double-blind, placebo-controlled; 84 days | Reduction in PASI Score (erythema, scaling and induration of lesions) and serum IL-22 titer | E. Antiga et al., Oral Curcumin (Meriva) Is Effective as an Adjuvant Treatment and Is Able to Reduce IL-22 Serum Levels in Patients with Psoriasis Vulgaris. Biomed Res Int 2015, 286364 (2015). |
| 7      | Scalp Psoriasis | Turmeric tonic, twice per day | N = 40, Randomized, <1-Soft-enter Run-en- > double-blind, placebo-controlled; 63 days | Reduction in PASI Score (erythema, scaling and induration of lesions) and improvement | P. Babraun et al., Turmeric tonic as a treatment in scalp psoriasis: A randomized placebo-control clinical trial. J Cosmet Dermatol 17, 461–466 (2018). |
| 8      | Radiation dermatitis | 6g/day | N = 30; Randomized, double-blind, placebo-controlled; Until completion of radiotherapy | Reduction of Radiation dermatitis severity scores | J. L. Ryan et al., Curcumin for radiation dermatitis: a randomized, double-blind, placebo-controlled clinical trial of thirty breast cancer patients. Radiat Res 180, 34–43 (2013). |
| 9      | Healthy (Aged adults) | 1.5g/day BCM-95® CG (Biocurcumax™) | N = 160; Randomized, double-blind, placebo-controlled trial; 365 days | No significant differences in clinical parameters and cognitive measures | S. R. Rainey-Smith et al., Curcumin and cognition: a randomised, placebo-controlled, double-blind study of community-dwelling older adults. Br J Nutr 115, 2106–2113 (2016). |
| 10     | Healthy (Aged adults) | Longvida® Optimized Curcumin, in 1 month dose of 400 mg | N = 60; Randomized, double-blind, placebo-controlled Phase 3/4 trial; 30 days | Improvement of alertness and <1-Soft-enter Run-on- > contentedness; as well as decreases levels of LDL cholesterol | K. H. Cox et al., Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population. J Psychopharmacol 29, 642–651 (2015). |
| 11     | Alzheimer Disease | 0.09 g curcumin in theracurmin; twice per day | N = 46, Randomized, double-blind, Two groups; 540 days | Improvement in Buschke selective reminding test, visual memory and attention. | G. W. Small et al., Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial. Am J Geriatr Psychiatry 26, 266–277 (2018). |
| 12     | Anxiety and depression | 1g/day | N = 50, Randomized, double-blind blind, placebo-controlled study; 56 days | Significant decrease Inventory of Depressive Symptomatology score | A. L. Lopresti et al., Curcumin and major depression: a randomised, double-blind, placebo-controlled trial investigating the potential of peripheral biomarkers to predict treatment response and antidepressant mechanisms of change. Eur Neuropsychopharmacol 25, 38–50 (2015). |
| 13     | Anxiety and depression | 1g/day | N = 56, Randomized, double-blind, placebo-controlled study; 56 days | Significant decrease Inventory of Depressive Symptomatology score | A. L. Lopresti et al., Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study. J Affect Disord 167, 368–375 (2014). |
| Sl. No | Disease condition                  | Dose            | Sample size; Study design; study Duration | Study Outcome                                                                                          | Reference                                                                                             |
|-------|-----------------------------------|-----------------|--------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| 14    | Anxiety and depression            | 1g/day          | N = 108; Randomized, double-blind, placebo-controlled study; 42 days | Significant decrease in antidepressent behavioral response, along with decrease in inflammatory cytokines in the plasma | J. J. Yu et al., Chronic Supplementation of Curcumin Enhances the Efficacy of Antidepressants in Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. J Clin Psychopharmacol 35, 406–410 (2015). |
| 15    | Anxiety and depression            | 1g/day (C3 Complex formula) | N = 30; Double blind, cross over trial; 30 days | Significant decrease Beck Anxiety Inventory scale                                                      | H. Esmaily et al., An investigation of the effects of curcumin on anxiety and depression in obese individuals: A randomized controlled trial. Chin J Integr Med 21, 332–338 (2015). |
| 16    | Anxiety and depression            | 0.5 g/day       | N = 40; Randomized, double-blind, placebo-controlled study; 35 days | Reduction in rapid depressive symptoms reduction                                                   | J. Bergman et al., Curcumin as an add-on to antidepressive treatment: a randomized, double-blind, placebo-controlled, pilot clinical study. Clin Neuropsycharmacol 36, 73–77 (2013). |
| 17    | Anxiety and depression            | 1 g/day         | N = 60; Randomized controlled trial; 42 days | Reduction in Hamilton depression rating scale                                                        | J. Sammakhan et al., Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial. Phytother Res 28, 579–585 (2014). |
| 18    | Cardiovascular disorder           | 0.2 g/day       | N = 70; Randomized, double-blind, placebo-controlled study; 28 days | Reduction in total cholesterol                                                                    | J. J. A. Ferguson et al., Curcumin potentiates cholesterol-lowering effects of phytosterols in hypercholesterolaemic individuals. A randomised controlled trial. Metabolism 82, 22–35 (2018). |
| 19    | Cardiovascular disorder           | 0.5 g/day (C3 complex capsules) | N = 30; Randomized, double-blind, cross over study; 30 days | Reduction in pro-oxidant-anti-oxidant balance and serum Triglycerol                                | A. Sahebkar et al., Curcuminoids modulate pro-oxidant-antioxidant balance but not the immune response to heat shock protein 27 and oxidized LDL in obese individuals. Phytother Res 27, 1883–1888 (2013). |
| 20    | Metabolic syndrome                | 1.89 g/day      | N = 65; Randomized, double-blind study; 84 days | Reduction in low density lipoprotein cholesterol and triglycerol and triglycerol/high density lipoprotein cholesterol ratio | Y. S. Yang et al., Lipid-lowering effects of curcumin in patients with metabolic syndrome: a randomised, double-blind, placebo-controlled trial. Phytother Res 28, 1770–1777 (2014). |
| 21    | Metabolic syndrome                | 2.4 g/day and 1.5 g/day | N = 250; Randomized, double-blind, placebo-controlled study; 56 days | Improved Body Mass Index, body fat and waste circumference                                             | F. Amin et al., Clinical efficacy of the co-administration of Turmeric and Black seeds (Kalongi) in metabolic syndrome - a double blind randomized controlled trial - TAK-MetS trial. Complement Ther Med 23, 165–174 (2015). |
| 22    | Inflammatory Bowel Disease         | 3 g/day         | N = 50; Randomized, double-blind, placebo-controlled study; 30 days | Improvement in clinical symptoms                                                                 | A. Long et al., Curcumin in Combination With Mesalamine Induces Remission in Patients With Mild-to-Moderate Ulcerative Colitis in a Randomized Controlled Trial. Clin Gastroenterol Hepatol 13, 1444–1449.e1441 (2015). |
| 23    | Hepatoprotective effects          | 0.237 g/day     | N = 60; Randomized, double-blind, placebo-controlled study; 84 days | Reduction in alanine aminotransferase, Aspartate amino-transferase levels                           | S. W. Kim et al., The effectiveness of fermented turmeric powder in subjects with elevated alanine transaminase levels: a randomized controlled study. BMC Complement Altern Med 13, 58 (2013). |
| 24    | non-alcoholic fatty liver disease  | 0.07 g/day      | N = 80; Randomized, double-blind, placebo-controlled study; 56 days | Reduction in weight and body mass index and improvement liver ultrasonographic findings            | S. Rahmani et al., Treatment of Non-alcoholic Fatty Liver Disease with Curcumin: A Randomized Placebo-controlled Trial. Phytother Res 30, 1540–1548 (2016). |
| 25    | Chronic kidney disorder           | 0.32 g/day      | N = 101, Randomized, double-blind, placebo-controlled study; 56 days | Reduction in lipid peroxidation and increase in antioxidant activity                               | A. S. Jiménez-Osorio et al., The Effect of Dietary Supplementation With Curcumin on Redox Status and Nrf2 Activation in Patients With Nondiabetic or Diabetic Proteinuric Chronic Kidney Disease: A Pilot Study. J Ren Nutr 26, 237–244 (2016). |
| Sl. No | Disease condition | Dose | Sample size; Study design; study Duration | Study Outcome | Reference |
|--------|-------------------|------|------------------------------------------|---------------|-----------|
| 26     | Chronic prostatitis/Chronic pelvic pain syndrome | 0.2 g | N = 60; Randomized, single-blind, placebo-controlled study; Phase II; 30 days | Improvement in chronic Chronic Prostatitis Symptom Index | G. Morgia et al., A phase II, randomized, single-blind, placebo-controlled clinical trial on the efficacy of Curcumin and Calendula suppositories for the treatment of patients with chronic prostatitis/chronic pelvic pain syndrome type III. Arch Ital Urol Androl 89, 110–113 (2017). |
| 27     | Type II Diabetis Mellitus | 0.3 g/day | N = 100; Randomized double-blind, placebo-controlled study; 84 days | Reduction in fasting blood glucose and free fatty acid levels | L. X. Na et al., Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial. Mol Nutr Food Res 57, 1569–1577 (2013). |
| 28     | Type II Diabetis Mellitus | 2 g/day | N = 60, Open label randomized clinical study; 28 days | Decrease in fasting blood glucose, low density lipoprotein cholestrol and anti-inflammatory molecule hs C-reactive protein | N. Maiti et al., Efficacy of Turmeric as Adjuvant Therapy in Type 2 Diabetic Patients. Indian J Clin Biochem 30, 180–186 (2015). |
| 29     | Type II Diabetis Mellitus | 0.08 g/day (nano-formulation) | N = 70, Randomized double blind, placebo control add-on clinical study; 90 days | Reduction in fast blood glucose, triglycerol, glycated hemoglobin a1c, and body mass index | H. R. Rahimi et al., The effect of nano-curcumin on HbA1c, fasting blood glucose, and lipid profile in diabetic subjects: a randomized clinical trial. Avicenna J Phytopharm 6, 567–577 (2016). |
| 30     | Type II Diabetis Mellitus | 0.45 g/day | N = 8, Open-label, randomized control study; 11 days | Decrease in glucose, low density lipoprotein cholestrol, very low density lipoprotein cholestrol and triglycerol | P. Neerati et al., Evaluation of the effect of curcumin capsules on glyburide therapy in patients with type-2 diabetes mellitus. Phytother Res 28, 1796–1800 (2014). |
| 31     | Obesity (female) | 2.8 g/day | N = 62, Randomized, doubled-blind, placebo-controlled, crossover study; 70 days | No significant changes in clinical parameters | F. Di Pietro et al., Potential role of bioavailable curcumin in weight loss and omental adipose tissue decrease: preliminary data of a randomized, controlled trial in overweight people with metabolic syndrome. Preliminary study. Eur Rev Med Pharmacol Sci 19, 4195–4202 (2015). |
| 32     | Obesity | 1 g/day | N = 30, Randomized, doubled-blind, cross over study; 28 days | Reduction in inflammatory cytokines, and vascular endothelial growth factor | S. Ganjali et al., Investigation of the effects of curcumin on serum cytokines in obese individuals: a randomized controlled trial. ScientificWorldJournal 2014, 898361 (2014). |
| 33     | Beta-thalassemia | 0.5 g/day | N = 60 | Reduction in oxidative stress, iron levels and increase in hemoglobin concentration and antioxidant level. | O. U. Yapanitch et al., Treatment of β-Thalassemia/ Hemoglobin E with Antioxidant Cocktails Results in Decreased Oxidative Stress, Increased Hemoglobin Concentration, and Improvement of the Hypercoagulable State. Oxid Med Cell Longev 2015, 537954 (2015). |
| 34     | Beta-thalassemia | 1 g/day | N = 68, Randomized, doubled-blind, controlled clinical study; 84 days | Reduction in total & direct bilirubin content. Increase in antioxidant activity, hemoglobin, ferritin, iron, and catalase activity. | E. Mohammadi et al., An investigation of the effects of curcumin on iron overload, hepcidin level, and liver function in β-thalassemia major patients: A double-blind randomized controlled clinical trial. Phytother Res 32, 1828–1835 (2018). |
| 35     | Breast Cancer (metastatic) | 0.5–8 g/day | N = 14, open-label, Phase I clinical trial; 7 days | Reduction in carcinoembryonic antigen tumor marker; Vascular endothelial growth factor showing anti-angiogenic effect | M. Bayer-Robert et al., Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. Cancer Biol Ther 9, 8–14 (2010). |
| 36     | Pancreatic cancer | 0.2–0.4 g/day | N = 16, Phase I clinical trial | Improved fatigue- and association with quality of life scores | M. Kanai et al., A phase I study investigating the safety and pharmacokinetics of highly bioavailable curcumin (Theracurmin) in cancer patients. Cancer Chemother Pharmacol 71, 1521–1530 (2013). |
were undetectable, plasma PK levels of curcumin-O-glucuronide corresponded with pharmacodynamic (PD) responses of curcumin such as increase in NRF2 regulated antioxidant gene expression and suppression of histone deacetylase (HDAC) 1, HDAC2, HDAC3 and HDAC4 in blood cells. The study underscored the potential role of curcumin metabolite in mediating the PD responses of curcumin. Intense research is being underway to improve curcumin's bioavailability by developing a formulation to increase its solubility, stability, and absorption (Jyoti et al., 2019; Liu et al., 2016). The formulations such as water-soluble curcumin, curcumin nanocarrier, and curcumin plus piperine have increased the bioavailability of curcumin and improved the clinical efficacy of curcumin.

6. Nanoformulation of curcumin for pulmonary delivery: an alternative delivery approach

Broad-spectrum antiviral activity and immunomodulatory activity provides a strong rationale for testing curcumin for COVID-19 treatment. However, low bioavailability is the major obstacle in attaining the therapeutic potential of oral curcumin. In contrast, pulmonary delivery of curcumin will overcome this limitation and offers several advantages: direct delivery of high concentration of curcumin to the site of infection; direct contact of curcumin with the virus SARS-CoV-2; direct deposition into lower airways and alveolar region; larger surface area for deposition and absorption; lower intra- and extracellular detoxification enzymatic activity in the pulmonary system (Borghardt et al., 2018). The nanotechnology-based formulation has dramatically eased drug delivery to the pulmonary system (Selvaraj et al., 2018; Smola et al., 2008). Scientists have developed curcumin encapsulated nano-carriers such as liposomes (De Leo et al., 2018), niosomes (Obied et al., 2019), lipid complexation (Gupta and Dixit, 2011), micro/nano-emulsions (Sood et al., 2014; Yu and Huang, 2012) and polymeric nanoparticles (Umerska et al., 2018). This nanof ormulated curcumin could be delivered in dry powder, nebulizer, solution, nasal spray or gel (Sood et al., 2014). Curcumin at physiological pH of 7.4 is unstable with a shelf life of 10 min, and the pH of the respiratory tract ranges from 7.2 to 7.4. The nanof ormulation of curcumin would be protected from exposure to alkaline pH and thereby improve curcumin's stability at the target site. Furthermore, nanof ormulations of curcumin could also be engineered for longer-retention, sustained release, and penetration across the mucus barrier (Sung et al., 2007). Clinical studies of liposomal curcumin, microparticle curcumin, and micelle curcumin by oral delivery have been found to be safe (Yallah et al., 2015) and shown to be effective in reducing markers of oxidative stress (Helli et al., 2021). Animal studies have shown that inhalable curcumin effectively mitigates lethal bacterial pneumonia (Zhang et al., 2020). FDA has already approved inhalable powder of antibiotic tobramycin, and the nebulized liposomal formulation of ciprofloxacin was found to effective in reducing Pseudomonas aeruginosa infection in a phase III clinical trials for non-CF bronchiectasis (Haworth et al., 2019).

In summary, accumulated evidence suggests that the pulmonary delivery of nanoformulated curcumin such as liposomal curcumin would help in deposition of curcumin in the lower airways at a higher concentration, which may inhibit SARS-CoV-2 infectivity and concomitantly mitigate pulmonary inflammation and the progression to ARDS.

7. Conclusions

There is an urgent need for therapeutics against COVID-19 outbreak. Besides vaccine trials, few therapeutics such as remdesivir and or interferon-beta based on prior knowledge of antiviral activity against SARS-CoV, are in clinical practice for the treatment of COVID-19. Recognizing the public health emergency, perhaps it is imperative to evaluate phytochemical curcumin for management or treatment of COVID-19 in a randomized clinical trial because i) it is relatively safe; ii) it shows broad-spectrum antiviral activity against enveloped viruses; iii) it may suppress SARS-CoV-2 infection by directly modifying spike protein and or ACE2 and inducing host antiviral responses by targeting NRF2 and HMGB1; iv) it exerts immunomodulatory activity by blocking NF-kB, inflammasome, HMGB1, and IL-6 driven inflammatory responses; v) it dampens ROS production by inhibiting NAPDH oxidase and alleviates oxidative tissue injury by increasing antioxidant defenses by modulating NRF2.

Declarations

Author contribution statement

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