ACADEMIA | Letters

Curcumin as a potential target for COVID19: A Concept Letter

Pathirage Kamal Perera, University of Colombo, Sri Lanka
Adrian Cuda Banda Meedeniya , Griffith Health, Griffith University Brisbane, Australia

---

Clinically, COVID-19 disease is variable, ranging from asymptomatic infection to multi-organ failure and death. At the onset of the pandemic in early 2020, approx. 80% of people infected with SARS CoV-2, did not develop symptoms; approx. 13% developed severe disease needing respiratory support and approx. 7% requiring intensive care, with clinical presentation including acute respiratory disease syndrome, sepsis, and multi-organ failure. Infection and illness were largely restricted to the adult population, with notable disease heterogeneity (Zhang et al 2020). The current disease etiology and epidemiology are markedly altered, largely driven by novel viral mutations.

The WHO recommended treatment for COVID19 disease

Efficacy in early clinical trials with Tocilizumab (Actemra), a monoclonal antibody-based therapy acting on the TNFα mediated response by targeting IL-6, has been demonstrated in COVID-19 patients in Italy and in China (National Health Commission). Reduced pro-inflammatory cytokines and chemokines were associated with a favorable prognosis [Thevarajan et al 2020]. Anti-inflammatory medication to block the cytokine response produces a significant reduction of morbidity & mortality.

Successful treatment with Methylprednisolone (40 mg twice daily, intravenously) was demonstrated in two subjects with severe COVID-19 disease in March 2020 (Dai et al 2020). Subsequently, low-dose dexamethasone treatment was given to 2104 randomized patients

Corresponding Author: Pathirage Kamal Perera, drpkamal@gmail.com
Citation: Perera, P.K., Meedeniya , A.C.B. (2021). Curcumin as a potential target for COVID19: A Concept Letter. *Academia Letters*, Article 3484. https://doi.org/10.20935/AL3484.

at 6 mg once per day patient, in 175+ NHS hospitals in the UK. "Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021)" (Horby et al 2020). Dexamethasone reduces the risk of death among patients with severe respiratory complications (Horby et al 2020, Aguas et al 2021).

Following its global utility in severe COVID-19 disease treatment, a strong recommendation for systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours) for 7 to 10 days in patients with severe and critical COVID-19 is recommended (Corticosteroids for COVID-19, WHO Living Guidance September 2020; COVID-19 Clinical Management, WHO Living Guidance January 2021). Blocking the cytokine storm is globally accepted as a therapeutic strategy for severe COVID-19. There is no recommended prophylactic strategy for early COVID-19 disease, towards preventing disease progression.

Potential for early intervention using traditional anti-viral and anti-inflammatory treatments

The WHO International Expert Meeting on traditional medicines on the SARS outbreak, 2003, positioned traditional herbal treatments as effective alternative strategies for improving patient outcomes [Feldmann et al 2020]. Multiple COVID-19 treatment clinical trials testing traditional medicines are underway - http://www.chictr.org.cn/abouten.aspx.

Curcumin (diferuloylmethane),a bioactive phytochemical in turmeric

Turmeric (Curcuma longa) is used extensively in traditional medicines, including the treatment of inflammatory diseases (Dahanayake 2019, Bhaishajya Chikitsa). Many studies have reported the inhibition of inflammatory pathways in several physiological systems by Curcumin (Figure 1), a secondary metabolite in turmeric. The primary bioactive molecule in turmeric, Curcumin has clear scientific experimental data, demonstrating its ability to modulate multiple signaling pathways [Hatcher 2008, Prasad et al 2011, Niranjan et al 2008].

Antioxidant: Cells contain a spectrum of antioxidant enzymes and small antioxidant molecules as antioxidant defenses which act to decrease cellular oxidative damage. Curcumin scavenges reactive free radicals which cause peroxidation of cell membranes. Whilst most antioxidants contain a functional phenolic or di-ketone group, Curcumin contains multiple functional antioxidant groups, including a β di-keto group, and phenyl rings with varying hy-

Corresponding Author: Pathirage Kamal Perera, drpkamal@gmail.com
Citation: Perera, P.K., Meedeniya , A.C.B. (2021). Curcumin as a potential target for COVID19: A Concept Letter. *Academia Letters*, Article 3484. https://doi.org/10.20935/AL3484.

droxyl and methoxy substituents (Jovanovic et al 1999, Wright 2002). Furthermore, some breakdown products of Curcumin are antioxidants, e.g. ferulic acid and vanillin. Besides direct benefits of antioxidants in disease pathogenesis during infection, reduced cell death and the resultant reduction of immune activation impacts disease progression.

Anti-inflammatory: The anti-inflammatory activity of Curcumin is proposed to equal the non-steroidal and steroidal drugs including indomethacin, phenylbutazone and dexamethasone, the latter drugs with side effects restricting their use. The anti-inflammatory properties of Curcumin are mediated via inhibition of cyclooxygenase-2 (COX-2) and suppression of prostaglandins (PGs) synthesis, lipoxygenase (LOX), inducible nitric oxide synthase (iNOS) induction, and the inhibition of cytokine production e.g. interferon-γ and tumor necrosis factor (TNF), and transcription factors NF-κB, and AP-1 (Brouet et al 1995, Chan et al 1998, Menon and Sudheer 2016, Venugopal et al 2007). Modulation by Curcumin of the TNF-α mediated inflammatory response was clearly demonstrated in both experimental models and in humans, via inhibition of NF-kβ activation and through modulation of the NF-kβ signal transduction cascade [Singh 1995, Avasarala et al 2013, Menon and Sudheer 2016].

The exposure of most cells to stimuli such as bacterial of viral proteins cause the rapid phosphorylation of Ikβ and its dissociation from NF- kβ allowing translocation of the activated free dimer to the nucleus, where it induces transcription of a variety of genes encoding cytokines, cell adhesion molecules, growth factors, and others. Curcumin inhibits the activation of NF- kβ via blocking IKB kinase. Curcumin also inhibits inflammation by suppression of TNF-mediated activation of NF-kβ (Shishodia et al 2005, Avasarala et al 2013).

Curcumin is a potent inhibitor of the cytokine-mediated immune response. In metabolic syndrome patients, a significant reduction in serum TNF-α, IL-6, TGF-β, MCP-1, and CRP was shown on treatment (500mg curcumin + 5mg piperine), compared to placebo (Ganjali et al 2014). Its mechanism of immune modulation is robustly demonstrated in the scientific literature: "Activation of Transcription Factor NF-kβ is suppressed by Curcumin", in The Journal of Biological Chemistry (IF 4.1), a 800+ citation, publication [Singh and Aggarwal 1995]. The use of Curcumin in immune modulation is argued in "Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers" published in the British Journal of Pharmacology (IF 6.5) [Aggarwal et al 2013].

Curcumin blocks the cytokine-mediated immune response in the lungs

The efficacy of Curcumin in controlling lung inflammation was reviewed in "Curcumin use in pulmonary diseases" in 2017, with over 85 citations [Lellia et al 2017]. Peter Sordilo

Corresponding Author: Pathirage Kamal Perera, drpkamal@gmail.com
Citation: Perera, P.K., Meedeniya , A.C.B. (2021). Curcumin as a potential target for COVID19: A Concept Letter. *Academia Letters*, Article 3484. https://doi.org/10.20935/AL3484.

in "Curcumin Suppression of Cytokine Release and Cytokine Storm. A Potential Therapy for Patients with Ebola and Other Severe Viral Infections" in 2015, reviewed Curcumin as a therapeutic for the cytokine storm [Sordillo et al 2015]. Dr. Sordilo discussed the use of Curcumin-based therapies for the treatment of COVID-19 in an ongoing Phase 2 clinical trial (Peter Sordilo, pers. com.).

Antimicrobial: Turmeric has wide anti-microbial properties including anti-bacterial, anti-fungal, anti-protozoan, and anti-viral activity [Zorofchian et al 2014]. C. longa rhizome extract has antifungal activity with greater efficacy than conventional antifungal medications such as fluconazole [Martins et al 2009]. Turmeric at low doses (0.8 and 1.0g/L) has inhibitory activity against a range of fungal species [Zorofchian et al 2014], whilst clinical studies have shown safety and tolerance of high doses of turmeric (12 g/day). Potent antibacterial activity via multiple mechanisms of action has been demonstrated against a variety of pathogenic and non-pathogenic bacteria including Staph. aureus, S. epidermis, E. coli, and P. aeruginosa. [Zorofchian et al 2014]. Tumeric and its derivative Curcumin has a wide range of activity against viruses, as previously discussed [Zorofchian et al 2014]. Its multiple antiviral actions include the inhibition of viral gene expression through competitive inhibition of nucleotide synthetic enzymes, the inhibition of viral proteases, and through reducing the infectivity of viral particles within the respiratory system [Zorofchian et al 2014, Mathew et al 2018]. Further, the prophylactic action of turmeric against Zika and chikungunya viruses have been demonstrated to be mediated through inhibition of viral binding to host cells [Mathew et al 2018, Mounce et al 2017, Chen et al 2010]. Molecular docking studies in-silico on SAR CoV-2 showed significant binding and neutralization by Curcumin of the active site of SARS CoV-2 main protease, which demonstrated the ability of Curcumin to neutralize the virus (Rajagopal et al 2020).

Multipotency

Multi-targeted interventions are strongly recommended as therapies for COVID-19, especially treatment combinations using anti-virals and immune-suppressants [Gaborit et al 2020]. The efficacy of turmeric as an anti-inflammatory and as an anti-viral medicine is of especial application in its proposed treatment for COVID-19. As pleaded by the authors in "Lancet; Correspondence", in April 2020, to capitalize on potential synergies or additive effects using "multi-targeted interventions for severe COVID-19" [Gaborit et al 2020], we will trial a combination of anti-viral and immuno-modulatory traditional medicine treatments as COVID-19 therapy. We will use a traditional medicine treatment comprised of a combination of medicinal (anti-viral and anti-inflammatory) phytochemicals, showing synergistic and additive therapeutic

Corresponding Author: Pathirage Kamal Perera, drpkamal@gmail.com
Citation: Perera, P.K., Meedeniya , A.C.B. (2021). Curcumin as a potential target for COVID19: A Concept Letter. *Academia Letters*, Article 3484. https://doi.org/10.20935/AL3484.

effects, towards improving disease prognosis, typifying the traditional medical approach.

The traditional medicine- Turmeric

The recent scientific evidence on the efficacy of Curcumin/Turmeric as an antioxidant, its regulation of inflammation, its antimicrobial actions, supports many centuries of documented clinical use of turmeric in traditional medicinal preparations [Hatcher et al 2008, Prasad et al 2011]. Turmeric has a long history in traditional medicine, together with a spectrum of uses in cultural practices, including its use as an ingredient (spice) in foods, ranging from the middle-east, south Asia to far-east Asia [Hatcher 2008, Prasad et al 2011, Niranjan et al 2008]. Most turmeric-based traditional treatments are inexpensive and readily accessed [Hewlings 2017].

Turmeric/Curcumin use is recommended in the treatment of COVID19

Together with community use, several clinical trials in India are testing turmeric as a treatment for COVID-19 disease. A formulation containing curcumin, Vitamin C, and Zinc in a randomized comparative clinical study, monitoring clinical indicators and inflammatory markers including, Interleukin-6, D-dimer, Ferritin and C Reactive Protein, in COVID-19 positive patients, showed curcumin Tablets were well tolerated without any side effects in any of the patients, with a significant improvement in disease prognosis (Dound et al 2021). A turmeric-based herbal formulation with p. longum, p. nigrum and other herbal medicines is been trialed in 130 patients with COVID 19, from the health care sector (Marda and Chaudhari 2020). Similarly in Iran, Mahsa et al are conducting a double-blinded, placebo-controlled clinical trial on the effects of curcumin-piperine co-supplementation on clinical signs, duration, severity, and inflammatory factors in COVID-19 patients (Mahsa et al 2020).

In early 2020 a critically ill patient was given oral turmeric and black seed oil for four days (but not given Remdesivir, Tocilizumab or Dexamethasone) and showed resolution of airspace disease throughout the lungs (Ali 2020), with full recovery. With Turmeric used in traditional medicine as an immune modulator and an anti-microbial, the development of a turmeric-based therapy for COVID-19 is rationalized [Hatcher et al 2008, Avasarala et al 2013].

Corresponding Author: Pathirage Kamal Perera, drpkamal@gmail.com
Citation: Perera, P.K., Meedeniya , A.C.B. (2021). Curcumin as a potential target for COVID19: A Concept Letter. *Academia Letters*, Article 3484. https://doi.org/10.20935/AL3484.

Conclusion

Therefore, we strongly hypothesize that the herbal antivirals Curcumin/Turmeric will reduce the viral load and modulate the cytokine-mediated inflammatory pathway involving IL-6, TNFα / NF-kβ, thereby suppressing the "cytokine storm", significantly reducing morbidity and mortality, in COVID 19. Further, we recommend well design clinical trials to support this concept.

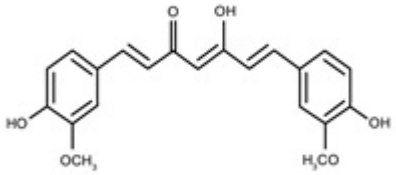

Figure 1. Curcumin (diferuloylmethane low molecular-weight polyphenol [C21H20O6], chemically characterized in 1910, it is orally bioavailable and non-adverse to humans)

Corresponding Author: Pathirage Kamal Perera, drpkamal@gmail.com
Citation: Perera, P.K., Meedeniya , A.C.B. (2021). Curcumin as a potential target for COVID19: A Concept Letter. *Academia Letters*, Article 3484. https://doi.org/10.20935/AL3484.

References

Aguas, R., et al, CoMo Consortium (2021) Potential health and economic impacts of dexamethasone treatment for patients with COVID-19. Nature Communications V 12, 915.

Aggarwal, B.B., Gupta, S.C., Sung B. (2013) Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. British Journal of Pharmacology.169(8):1672-92. (237 citations)

Ali, M (2020) COVID-19 ventilator dependent respiratory failure successfully treated with antiinflammatory botanicals. Chest, Annual Meeting. October 18-21, 2020. DOI: https://doi.org/10.1016/j.chest.2020.09.065

Avasarala S., Zhang F., Liu G, Wang R, London S D., London L (2013) Curcumin Modulates the Inflammatory Response and Inhibits Subsequent Fibrosis in a Mouse Model of Viral induced Acute Respiratory Distress Syndrome. PLoS ONE 8(2): e57285. Bhaishajya Ratnavali Udarda Sheetapitta Kotha Chikitsa 55/13-17.

Brouet I., H. Ohshima (1995) Curcumin , an anti-tumor promoter and anti-inflammatory agent, inhibit induction of nitric oxide synthase in activated macrophages. Biochem Biophys Res Commun 206, 533–540.

Chan, M. M., Huang, H. I., Fenton, M. R., Fong, D., (1998) In vivo inhibition of nitric oxide synthase gene expression by Curcumin , a cancer preventive natural product with anti-inflammatory properties. Biochem Pharmacol 55, 1955–1962.

Chen DY, Shien JH, Tiley L, Chiou SS, Wang SY (2010). Curcumin inhibits influenza virus infection and haemagglutination activity. 119, Food Chemistry 4, pp 1346-1351.

Dai Jinghong, Xiong Yali, Li Hui, Qian Yajun, Xu Ying, Xu Qingqing, Yan Xin & Tang Jian (2020) Corticosteroid treatment in severe COVID-19 pneumonia: two cases and literature review. Clinical Rheumatology 39:2031–2037.

Dound Yogesh, Mandlik Sagar, Suryavanshi Shrikant, Dound Bhushan (2021) Eficacy and Tolerability of Curmune Formulation in the Management of COVID-19: A Randomised Comparative Clinical Study. Indian Practitioner 74(3):20-26.

Farzaneh S, Mohamadian RN, Mahsa K, Naeima E, Hossein BM(2018). Curcumin affects tracheal responsiveness and lung pathology in asthmatic rats. Pharmacological Reports 70 981–987.

Corresponding Author: Pathirage Kamal Perera, drpkamal@gmail.com
Citation: Perera, P.K., Meedeniya , A.C.B. (2021). Curcumin as a potential target for COVID19: A Concept Letter. *Academia Letters*, Article 3484. https://doi.org/10.20935/AL3484.

Feldmann Marc, Maini Ravinder N, Woody James N, et al (2020) Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed Vol 395 May 2, 2020.

Gaborit B, Bergmann J, Mussini C, Arribas J, Behrens G, Walmsley S, Pozniak A, Raffi F, (2020) Plea for multitargeted interventions for severe COVID-19 Correspondence, Lancet April 20.

Ganjali S, Sahebkar A, Mahdipour E, et al. (2014) Investigation of the effects of curcumin on serum cytokines in obese individuals: A randomized controlled trial. Sci World J 2014: 898361. doi: 10.1155/2014/898361

Hatcher, H., Planalp, R., Cho, J. et al. (2008) Curcumin : From ancient medicine to current clinical trials. Cell. Mol. Life Sci. 65, 1631–1652.

Hewlings S., Kalman, D. (2017) Curcumin : A Review of Its' Effects on Human Health Foods 2017, 6, 92; doi:10.3390/foods6100092

Horby et al (2020) Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. Oxford University News Release. June 2020

Jovanovic S. V., Steenken S., Boone C. W., Simic M. G. (1999) H-atom transfer is a preferred antioxidant mechanism of Curcumin . J Am Chem Soc 121, 9677–968.

Lellia D., Sahebkar A., Johnston T., Pedone P. C. (2017) Curcumin use in pulmonary diseases: State of the art and future perspectives. Pharmacological Research (115) pp 133-148. (85 citations)

Litwinienko G., Ingold K. U. (2004) Abnormal solvent effect on hydrogen atom abstraction: Resolution of the Curcumin antioxidant controversy. The role of sequential proton loss electron transfer. J Org Chem 64, 5888–5896.

Mahsa M, Mohammad B,; Amirhossein S,; Davood S,; Hossein RH, Bijan I,; Gholamreza A,. (2020) Effects of curcumin-piperine co-supplementation on clinical signs, duration, severity, and inflammatory factors in patients with COVID-19: a structured summary of a study protocol for a randomised controlled trial. Trials; 21(1): 1027, 2020 Dec 17.

Marda, G and Chaudhari, M (2020) Randomized Clinical Trial of Ayurveda Spice Mix Tablet for the Prevention of SARSCoV-2 Infection (COVID-19) in Healthcare Personnel/High-Risk patients. Randomized, Parallel Group, Active Controlled Trial; CTRI/2020/07/026674.

Corresponding Author: Pathirage Kamal Perera, drpkamal@gmail.com
Citation: Perera, P.K., Meedeniya , A.C.B. (2021). Curcumin as a potential target for COVID19: A Concept Letter. *Academia Letters*, Article 3484. https://doi.org/10.20935/AL3484.

Martins, C., Da Silva, D., Neres, A., et al., [2009] "Curcumin as a promising antifungal of clinical interest," Journal of Antimicrobial Chemotherapy, vol. 63 2, pp. 337–339.

Mathew, D., Li Hsu, W. Antiviral potential of Curcumin (2018) Journal of Functional Foods. 40, pp 692-699.

Menon, V. P., Sudheer, A. R., (2016) Antioxidant and anti-inflammatory properties of Curcumin . In. The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease. Eds. Bharat B. Aggarwal, Young-Joon Surh, Shishir Shishodia. Series- Advances in experimental medicine and biology, Springer. ISBN-13:978-0-387-46400-8.

Mounce BC, Cesaro T, Carrau L, Vallet T, Vignuzzi M., (2017) Curcumin inhibits Zika and chikungunya virus infection by inhibiting cell binding Antiviral Res. 142:148-157.

Niranjan, A., Prakash, D. (2008) Chemical constituents and biological activities of turmeric (Curcuma longa L.) A review. J Food Sci Technol., 45(2), 109–116.

Prasad, S, Aggarwal, B. (2011) Turmeric the golden spice, From Traditional Medicine to Modern Medicine, in Benzie IFF, Wachtel-Galor S, (eds.) Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition.

Rajagopal K, Varakumar P, Baliwada A and Byran G (2020) Activity of phytochemical constituents of Curcuma longa (turmeric) and Andrographis paniculata against coronavirus (COVID-19): an in silico approach. Future Journal of Pharmaceutical Sciences. 6:104.

Sanivarapu R, Vallabhaneni V, and Verma V, (2016) The Potential of Curcumin in Treatment of Spinal Cord Injury. Neurology Research International. Volume 2016, Article ID 9468193.

Shishodia, S., Amin, H. M., Lai, R., and Aggarwal, B. B., (2005) Curcumin (diferuloylmethane) inhibits constitutive NF-kappaB activation, induces G1/S arrest, suppresses proliferation, and induces apoptosis in mantle lymphoma. Biochem Pharmacol 70(5), 700–713.

Singh, S. and Aggarwal, B. B. (1995) Activation of Transcription Factor NF-kB Is Suppressed by Curcumin (Diferulolylmethane); The Journal of Biological Chemistry; 270 (42 / 20), 24995–000. (800+ citations)

Sordillo, Peter P., Helson, Lawrence (2015) Curcumin Suppression of Cytokine Release and

Corresponding Author: Pathirage Kamal Perera, drpkamal@gmail.com
Citation: Perera, P.K., Meedeniya , A.C.B. (2021). Curcumin as a potential target for COVID19: A Concept Letter. *Academia Letters*, Article 3484. https://doi.org/10.20935/AL3484.

Cytokine Storm. A Potential Therapy for Patients with Ebola and Other Severe Viral Infections. In Vivo 29: 1-4.

Thevarajan, I., Nguyen, T. H. O., Koutsakos, M, et al. (2020) Breadth of concomitant immune responses prior to patient recovery: a case report of nonsevere COVID-19. Nature Medicine 41591-020-0819-2.

Venugopal P. Menon, A., Sudheer, R., (2007) Modulation of transcription factors by Curcumin. In. The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease. Eds. Bharat B. Aggarwal, Young-Joon Surh, Shishir Shishodia. Series- Advances in experimental medicine and biology, Springer. ISBN-13:978-0-387-46400-8.

Wang Wei, Ye Linbai, Ye Li, et al (2007) Up-regulation of IL-6 and TNF-α induced by SARS-coronavirus spike protein in murine macrophages via NF-κB pathway. Virus Research, 128, (1–2), 1-8.

Wright J. S., Predicting the antioxidant activity of Curcumin and Curcumin oids (2002) J Mol Struct (Theochem) 591, 207–217.

Xu X, Han MA-O, Li T, et al (2020) Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A 1091-6490.

Zhang Y et al, (2020) The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19). The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. CCDC Weekly / Vol. 2 / No. 8.

Zorofchian, S., Damtousi, M., Kadir, H., Hassandarvish, P., (2014) A Review on Antibacterial, Antiviral, and Antifungal Activity of Curcumin In. Biologic Activity and Biotechnological Development of Natural Products, , Ed. J Carvalho BioMed Research International, Hindawi. https://doi.org/10.1155/2014/186864

Corresponding Author: Pathirage Kamal Perera, drpkamal@gmail.com
Citation: Perera, P.K., Meedeniya , A.C.B. (2021). Curcumin as a potential target for COVID19: A Concept Letter. *Academia Letters*, Article 3484. `https://doi.org/10.20935/AL3484`.