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POTENTIAL ROLE OF CURCUMIN AS A TREATMENT OPTION FOR COVID-19: A REVIEW

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ABSTRACT

Severe Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes CoV disease 2019 (COVID-19) which is presently a pandemic declared by world health organization. Treatment modalities for this disease are being explored. Curcumin the phytoconstituent of Curcuma longa, can be a potential treatment for COVID-19 because various findings suggest its therapeutic properties like antioxidant, antiemetic, antifatigue effects which can potentially manage symptoms and signs of COVID-19, also it has antiviral properties such as impeding the viral binding to host cell as well as replication. It has restrictive actions on viral protease as well and having inhibitory actions on pro-inflammatory cytokine molecules.Thus, it alleviates symptoms due to inflammation such as fibrosis and edema in pulmonary region. Broncho dilatory effects of curcumin as well as suppression of cough via acting on bradykinin thus curcumin can alleviate symptoms such as cough in COVID-19 sufferers. Curcumin also has preventive actionson Cardiovascular and renal damage due to COVID-19. All these potential activities suggest the possible use of curcumin in management of COVID-19. Clinical studies should be considered to explore the same. In this review we highlight the potential therapeutic effects of curcumin against COVID-19.

Keywords: COVID-19, Curcumin, Treatment modalities, Antiviral, cytokine

INTRODUCTION

In 1917-1918 when there was Spanish flu outbreak, this was observed that mortality just was not related to aged people with feeble immunity but also associated with those who were young with regular immunity, in critical cases the virus brings about the overactive immunity response, which leads to generation of different inflammation elements which leads to, injury to respiratory parts especially lungs, illustrates acute respiratory distress syndrome (ARDS) which in turn leads to elevated death rate (Ziteng Liu & Ying, 2020). In epidemics like severe acute respiratory syndrome coronavirus (SARS-CoV)and middle east respiratory syndrome (MERS-CoV), extremely infectious influenza viruses as well as novel CoV 2019 (nCoV19) similar detrimental impact because of excessive immune response (Channappanavar & Perlman, 2017; K. J. Huang *et al.,* 2005; Kalil & Thomas, 2019; X. Yao *et al.,* 2020). In Wuhan, China on December 2019 for the first-time nCoV19 was discovered which was later on announced a pandemic by world health organization. Generally it is a respiratory disease, which also acts on other organ systems like cardiovascular system, kidneys as well as nervous system (Roberts *et al.,* 2020). COVID-19 is 96.5% alike to bat coronavirus RaTG13, which means bats might be the host of the virus and recognized to be passed on via close proximity and air droplets (Babaei *et al.,* 2020; Guo *et al.,* 2020). Almost all droplets commonly drops at range of few meters thus chances of spreading are less if distance is two or more than two meters (Kumari *et al.,* 2020). All around the world, proper treatment regimens for SARS-CoV-2 are being explored, various drugs have been repurposed and are proposed for management of COVID-19 (Wu *et al.,* 2020). Various review reports advises about possible effectiveness of biological compounds found in plants which can act opposite to COVID-19 (Mani *et al.,* 2020; McKee *et al.,* 2020). Biological compounds found in plants found to be efficacious in past outbreak.Biologically active constituents can possibly act as candidates for management of COVID-19, respiratory disorders like various sicknesses are effectively acted upon by turmeric like plant components (Barnard & Kumaki, 2011; Buhrmann *et al.,* 2020; Kunnumakkara *et al.,* 2017; Soni, Shukla, *et al.,* 2020; Vishvakarma, 2014; Y. Xu & Liu, 2017). Curcumin is the considerable constituent of turmeric which has shown protective and corrective properties for wider number of ailments (Soni, Mehta, *et al.,* 2020).

CURCUMIN: Curcumin is present in rhizome part of Curcuma longa, is a water repelling polyphenolic compound having small molar mass (368.37). In 1910 it was defined in chemical way, as the major main component, and two-eight percent of turmeric is curcumin (Akbar *et al.,* 2018; Sharma *et al.,* 2005; Soleimani *et al.,* 2018). As a seasoning curcumin is utilized and for other intents like makeup and pharmaceutical related products (Hosseini & Hosseinzadeh, 2018).

Curcumin has various therapeutic and pharmacological actions for instance, anti-inflammatory activities (K. Cheng *et al.,* 2018), actions against malignancy, activities against viruses as well as bacteria, anti-oxidant properties (Fan *et al.,* 2015; Zhu *et al.,* 2017; Zorofchian Moghadamtousi *et al.,* 2014). Some clinical study results report that curcumin has these properties because of immune-modulation and few preclinical findings show that curcumin leads to restriction of pro-inflammatory cytokines activated because of viruses (Dai *et al.,* 2018; Praditya *et al.,* 2019; Richart *et al.,* 2018; Vitali *et al.,* 2020). Curcumin also has actions to cope up fatigue as well as properties against fibrosis and edema, all these properties can be utilized efficaciously to cope up with COVID-19 (Babaei *et al.,* 2020). Table 1 represents the structure of curcumin and lists its potential therapeutic effects against COVID-19.

ANTIVIRAL EFFECTS OF CURCUMIN: Curcumin has the restrictive ability for viruses, as found in various findings, and anti-viral actions are noticed for viruses such as respiratory syncytial, herpes simplex as well as parainfluenza type three viruses. A Study reported that precisely curcumin interact with proteins like protein kinase and DNA polymerase, additionally curcumin adjusts intercellular signaling, that are important for proper reproduction of virus, for instance impoverishment of nuclear factor-kB (NF-kB) communication (Zahedipour *et al.,* 2020). Curcumin hampers the duplication of virus, by hindering important phases of reproduction of virus inclusive of genomic duplication and linkage of viruses(Kwang *et al.,* 2006; D. Mathew & Hsu, 2018; Praditya *et al.,* 2019; Puar *et al.,* 2018). Curcumin has lipid loving structure, that's why it gets into lipid two layered structure, and interrupts the membrane, by making it lesser dense and reducing elastic moduli which in turn effects adherence of virus (Hung *et al.,* 2008).

As per a study curcumin was reported to constrain the respiratory syndrome (SARS) virus from getting linked to the host cell, also restricted the virus from reproducing inside the epithelial cells of nasal region (Yang *et al.,* 2017). Further information advises that by interrupting virus envelope's fluidness, curcumin restricts the porcine reproductive RS virus linkage to host cell (Du *et al.,* 2017).

Various distinctive categories of influenza viruses like H1N1, H2N2, H5N1 have been responsible for various epidemics and curcumin has found to have good attaching inclination towards glycoprotein of influenza virus, hemagglutinin that causes attachment of virus to host cell (Kannan & Kolandaivel, 2017). Also, curcumin has actions against SARS-CoV. As per a study on two twenty-one components of plants it was found that, 20 μm curcumin displayed considerable restrictive actions Vero E6 cell based cytopathic assay. It was showed that curcumin has some actions against SARS-CoV reproduction, also the restrictive actionson SARS-CoV protease, which is required for duplication of SARS-CoV, this shows curcumin can be possible treatment option for SARS-CoV (Wen *et al.,* 2007).

Possible Activities of Curcumin against Viral Reproduction: Viruses do not have ample enzymes required for its duplication, by utilizing the systems of cell the viruses do the required processes as well as its production, so all the critical steps involved in reproduction of virus like adhesion, binding etc. can be ideal targets for anti-viral agents. Curcumin is acknowledged to have activities restrictive activities against attachment of virus and also harming the factors needed for duplication (D. Mathew & Hsu, 2018).

Attachment of virus to host cell: Curcumin weakens the infectiousness of some viruses such as herpes virus, if it gets added upon cells prior to or after the infection (T.-Y. Chen *et al.,* 2013). Assessment of effect of curcumin on accession of virus to host cell is studied and it was observed that curcumin, changes the structural features of the proteins available on the externality of viruses and restricts access of virus to cell. Furthermore, curcumin being positively charged, shows electrostatic interaction with porcine epidemic diarrhea virus and contesting with it to attach with cell (Ting *et al.,* 2018). By the use of molecular docking, Utomo *et al.,* found that various components including curcumin can attach to target receptors for instance, to SARS-CoV protease receptors which are thought to be involved in viralinfection, in contrast to drugs or ligands as standard, thus curcumin can attach to target receptors (Yudi Utomo & Meiyanto, 2020).

Replication of virus: One of the approach to restrict the virus is by, utilization of compounds which can prohibit the duplication of the virus (Yang *et al.,* 2017). In a study conducted by Ting et al in which porcine epidemic diarrhea virus was utilized as a coronavirus model, it was showed that curcumin can possibly prohibit the duplication of porcine epidemic diarrhea virus (PEDV), plaque was decreased along with viral titers, that demonstrates activities of curcumin against duplication phases of PEDV (Ting *et al.,* 2018).

Restrictive actions against viral protease: Various protease inhibiting agents, have been formed to hinder the growth of viruses such as SARS, MERS,and HIV, because protease is required by virus to split up the proteins of the host cell, for instance beta CoV (**β**CoV) splits up the protein components of host cell by application of protease (Zumla *et al.,* 2016). For management of COVID-19 several protease inhibiting agents, for instance HIV drug lopinavir has been proven(Harrison, 2020; Senathilake *et al.,* 2020). By molecular docking, Khaerunnisa *et al.,* investigated numerous compounds found in plants, including curcumin to have promising effects to restrict the SARS-CoV-2main protease and can act as possible curative agent (Khaerunnisa *et al.,* 2020). Figure 1 represents possible therapeutic effects of curcumin on COVID-19.

INHIBITORYACTIONSONINFLAMMATION: Various in-vitro and in-vivo studies have shown that, along with compounds similar to it curcumin found to restrict the formation and letting out of cytokines like interleukin-6 (IL-6) and IL-1 (Avasarala *et al.,* 2013; Dai *et al.,* 2018; Mozaffarian *et al.,* 2011; B. Zhang *et al.,* 2019; Y. Zhang *et al.,* 2015). In mice with klebsiella stimulated serious pneumonia, cytokines were drastically reduced by respiratory administration of solubilized curcumin (B. Zhang *et al.,* 2019). Furthermore, other mediators of inflammation such as Monocyte Chemoattractant Protein-1(MCP-1) which manages the immune response and also, advances fibrosis in lungs (Dai *et al.,* 2018). The method by which curcumin adjusts the inflammatory response, has been examined and it involves varying signal pathways such NF-kB path (Cohen *et al.,* 2009; Han *et al.,* 2018; Salminen *et al.,* 2011). Through various modes curcumin manages signals of NF-kB pathway. In sufferers of malignancy of neck and head region, curcumin found to decrease the actions ofinhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ), as noticed in saliva sampling related to decrease in expressing of IL-8 (Kim *et al.,* 2011). Additional mediators such as cyclooxygenase-2 (COX-2) is also found to be managed by curcumin and it is a crucial enzyme needed for production of prostaglandin (Khan & Khan, 2018).

In the chronic obstructive pulmonary disease (COPD) animal study model, curcumin reported to interrupt the formation of COX-2 (Yuan *et al.,* 2018). Curcumin not only restricts the inflammatory cytokines, but also manages and adjusts the anti-inflammatory molecules in a positive mannerspecifically IL-10. Numerous studies show that curcumin and its analogs elevates formation and actions (Chai *et al.,* 2020; L. Chen *et al.,* 2018; Larmonier *et al.,* 2008; Mollazadeh *et al.,* 2019). IL-10 negatively regulates inflammation reactions, and decreases the IL-6 etc. by working on the inflammation monocytes and thus, injury of the tissues as a consequence of inflammatory response (Bamboat *et al.,* 2010).

Possible effects of curcumin in management of respiratory fibrosis & edema associated with inflammation

Inflammatory cytokines, can be triggered by CoVs. These viruses, stimulates cytokine storm, which in turn leads to injury to organs. CoVs, trigger the cells involved in immune system to release cytokines to vascular endothelial cells of pulmonary region (Jiang *et al.,* 2020).

Pulmonary fibrosis: In about 32% COVID-19 suffering individuals, pulmonary fibrosis (PF) is the consequence, associated ARDS (Rodríguez-Morales *et al.,* 2020). Proinflammatory cytokines are secreted, when there is ARDS due to infection of nCoV19 in the respiratory region. There is production of IL-1β, when nCoV19 binds to toll like receptor and there is generation of pro-IL-1β which converts to IL-1β upon splitting up by caspase-1, this IL-1β is responsible for PF(Conti *et al.,* 2020). Curcumin constricts the expressing of cytokines to prohibit the cell inflammation response via NF-kB path and fibrosis around the regeneration stage of infection through weakening transforming growth factor-β (TGF-β) in ARDS stimulated mouse model (Avasarala *et al.,* 2013).Moreover curcumin has been found to decrease the collagen in fibrotic study model, stimulated by bleomycin etc. (B. Chen *et al.,* 2008; Cutroneo *et al.,* 2007; Tourkina *et al.,* 2004; Venkatesan, 1999; Venkatesan & Chandrakasan, 1995; M. Xu *et al.,* 2007).

Pulmonary oedema: In tissue level examination, of few COVID-19 suffering individuals, pulmonary oedema (PO) was observed as well as fibrinoid containing inflammation clusters(Tian *et al.,* 2020). As an outcome of aggregation of liquid inside lungs, PO occurs (Bärtsch *et al.,* 2005; Maggiorini, 2006). Protein of SARS-CoV envelope, activates protein kinase C, as an outcome of that there is decreased action of Na+ channels at exterior of epithelial cells of pulmonary region which in turn leads to PO(DeDiego *et al.,* 2014). Preventive utilization of curcumin reduced inflammation, which decreased the inflow of liquid to lung region of rats as per latest findings. This was because of reduction in cytokines and alteration of NF-kB path which leads to decrease in cell attaching molecules and by making steady thehypoxia-inducible factor 1-alpha which furthermore, reduces the pulmonary oedema(M *et al.,* 2020; T. Mathew & SKS, 2015; Sagi *et al.,* 2014).

ANTIEMETIC EFFECT: As Herbaceous medication, since old times the turmeric is utilized to manage vomiting in regions of Asia(Zhijun Liu *et al.,* 2018). Curcumin alleviated appetition in rats with chemotherapy persuaded by fluorouracil(Q. Yao *et al.,* 2013). So, there is possibility of curcumin being efficacious in treating vomiting due to COVID-19.

ANTIFATIGUE EFFECT: As per a study on mice, when curcumin was given via oral route, it alleviated the fatigue, and physical function was also bettered(W. C. Huang *et al.,* 2015). In a randomized double blinded study, when curcumin was given to people involved in study it decreased the work-linked anxiety and lethargy (Sudheeran *et al.,* 2016). In healthy males, delayed onset muscle soreness was decreased, which was due to intense exercise(Nicol *et al.,* 2015). In case of myalgia related encephalomyelitis curcumin was quoted to be a new curative modality (Morris *et al.,* 2019). By barring NF-κ Bcurcumin restricts the retrograde response which in turn leads to prohibition of sepsis stimulated muscle wasting (Alamdari *et al.,* 2009). In aged healthy population, curcumin obviated muscle loss, better physical capabilities as well as deferred the initiation of sarcopenia (Ledda *et al.,* 2019). Curcumin can be utilized to manage fatigue like signs in COVID-19 as per these findings.

ANTIOXIDANT EFFECT: Critical COVID-19 suffering individuals may experience pneumonia which in turn leads to low levels of oxygen in the blood which interrupts cellular metabolism, and decreases the supplying of energy, which leads to elevation in fermentation in absence of oxygen then there is excessive metabolic acid, and oxygen free radicals generates which damages the phospholipid bilayer, of the membrane of the cell (B. Li *et al.,* 2020).Thus, an agent with antioxidant actions can be utilized to manage such cases. Curcumin, has found to be potent antioxidant agent, in various studies(Abrahams *et al.,* 2019; Farzaei *et al.,* 2018; Mary *et al.,* 2018; Trujillo *et al.,* 2013). Curcumin precisely cleans out the reactive oxygen species being a potent antioxidant agent (Ziteng Liu & Ying, 2020). Curcumin showed to act against the possible actions of reactive oxygen species, on expressing inflammation cytokines, by decreasing the Thioredoxin interacting protein (TIP)(Ren *et al.,* 2019). Curcumin found to decline the concentration of Malondialdehyde and xanthine oxidase as well total anti-oxidative capacity was improved in lung damage stimulated by ventilator (Wang *et al.,* 2018).

BRONCHODILATION EFFECT: Considerably curcumin restricts the narrowing of air passage as well as hyper-reacting to histamine stimulated by ovalbumin in guinea pigs (Ram *et al.,* 2003). In study model of mouse with asthma, curcumin found to restrict the broncho narrowing considerably (Subhashini *et al.,* 2013). As per a study, in which curcumin was administered versus regular treatment regimen to asthma patients and it was found that, there was considerable betterment in forced expiratory volume in group with curcumin administered rather than regular therapy. Curcumin is advised to be utilized as an additional therapy for bronchial asthma condition(Abidi *et al.,* 2014).

Restriction of Cough by Bradykinin Inhibition: In the inflammation affairs, bradykinin (BK) seems to be a crucial part for instance in chronic or acute inflammation related disorders like asthma etc. (Broadley *et al.,* 2010; Hewitt *et al.,* 2016). In such sicknesses BK seems to be stimulating cough, also with those patients which are administered with angiotensin converting enzyme (ACE) inhibitors (Hewitt *et al.,* 2016; Katsumata *et al.,* 1991). Curcumin prohibits activated protein-1BK stimulated IL-6 expressing in air passage smooth muscle cells is restricted by curcumin through this restriction(Chien Da Huang *et al.,* 2003; Singh & Aggarwal, 1995). Curcumin reported to have greater inclination towards(BK1) receptor with restrictive activity rather than BK2 receptor (Yimam *et al.,* 2016). BK triggers B2 receptor which leads to activation of COX and 12-lipoxygenase (LOX) metabolic reaction intermediates. Furthermore these compounds stimulate the transient receptor potential channel, subfamily channels, as a consequence of that there is elevation of cough and air passage hindrance (Al-Shamlan & El-Hashim, 2019). Curcumin has restrictive actions on COX-2 and 5-LOX (Babaei *et al.,* 2020). Thus, curcumin suppresses bradykinin and decreases cough.

EFFECT ON INTERFERONS: Interferons act crucially in protection against CoV infections. Interferon inducing may be impeded by CoVs. Furthermore, there is inhibition of Signal transducer and activator of transcription 1 (STAT1) which is crucial protein in the inflammation-caused by interferons(Kindler *et al.,* 2016). Every kind of interferon acts in prevention of viral infections (Samuel, 2001). Higher death rates in elderly people is because of the greater threshold of interferon lead immune response (Shahabi Nezhad *et al.,* 2020). To effectively decrease the death rate, triggering the innate immunity response at initial phases of the infection to induce interferons. Accomplishment of this can be done, by giving those compounds which can elevate the production of interferons (Kumaki *et al.,* 2017; Zhao *et al.,* 2012). In regard to varying viral diseases, curcumin found to have actions on interferons as per various findings (Jasso-Miranda *et al.,* 2019; Mounce *et al.,* 2017).

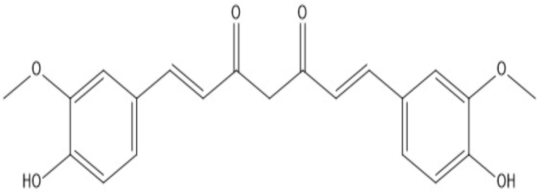
Curcumin in managing cardiovascular damage due to COVID-19: In developing Type-2 diabetes, hypertension as well as cardiovascular system (CVS), (ACE2) plays important role (Turner *et al.,* 2004). Infection of COVID-19 begins with attachment of the virus to the ACE2. nCoV19 leads to symptom of respiratory tract, and these signs are produced in patients which have CV disorders (CVD), because ACE-2 is more signified in patients having cardiovascular ailments. Because of the fact that ACE2 plays the role of receptor of nCoV19, there should be researches on actions of hypertension medications to treat COVID-19 (Zheng *et al.,* 2020). As per Pang et al, curcumin found to reducehypertension and treated cardiac fibrosis in rats by improving angiotensin II type II receptor and decreasing angiotensin II type I receptor and elevation of ACE2 in myocardial tissue (Pang *et al.,* 2015). Type 1 and type 2 helper T cells gets destabilized during SARS-CoV-2 infection which induces inflammation response, and thus CV signs arise in the sufferers of COVID-19 (Chaolin Huang *et al.,* 2020). In cardiac cells curcumin decreased the spread of immune cells execution of inflammation mediators (X. Li *et al.,* 2017).

Curcumin in managing kidney damage due to COVID-19: Occurrence of kidney disease (KD) is growing amongst COVID-19 patients, which can be consequence of two factors acting together, SARS-CoV-2 and inflammation response, acute or chronic renal damage sufferers have higher death rate (Y. Cheng *et al.,* 2020).In kidneys ACE2 is greatly revealed, and there can possibly be KD because of decrease in ACE2 and elevation in expressing of ACE (Ye *et al.,* 2004).

Sclerosis can advance if angiotensin II is decreased , this advises that ACE antagonists may have side effect in the treatment of COVID-19 (Ahmad *et al.,* 1997). As per Xu et al, curcumin can possibly increase the ACE2, as a consequence of that renal flow of blood rises, and possible anti-fibrotic actions on kidneys (X. Xu *et al.,* 2018); (Zeenathfar and Akhtar 2020). That's how curcumin can be considered to manage KD possibly in COVID-19.

CONCLUSION

In 2002, SARS-CoV firstly appeared and spread to 32 countries across the globe followed by MERS-CoV outbreak in 2012. The SARS-CoV-2 is just an alarm for the people to prepare themselves for the upcoming deadly diseases and pandemics.Although, no conclusive pharmacological treatment is available, different combinations of medications such as tocilizumab, hydroxychloroquine, remdesivir, lopinavir/ritonavir, and serum convalescence are to some degree hopeful. Since there is no definite therapeutic measure for CoV, aggressive strategies have been adopted to create an effective vaccine against the virus. Phytochemicals can have the potential to manage the symptoms of the disease, and may possibly tackle the disease. Curcumin may have the potential to tackle this disease, because it has findings in its favor explaining its anti-viral activities such as restriction of replication as well as restriction of adhesion of viruses to host cell, against CoV as well as other viruses. Other properties of curcumin such as anti-oxidant effect, anti-emetic effect, restrictive activities against inflammatory

Structure	Therapeutic effects
 (CURCUMIN STRUCTURE)	• Antiviral effect • Antiemetic effect • Antifatigue effect • Antioxidant effect • Bronchodilation effect • Cough suppression by acting on bradykinin • Inhibition of pro-inflammatory cytokines • Prevention of cardiovascular and renal damage in COVID-19

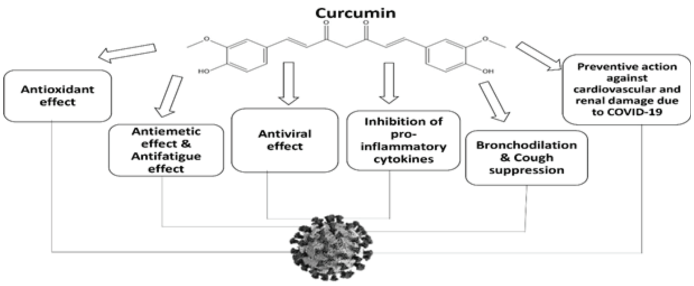


Figure 1: Represents the various possible effects of curcumin on COVID-19.

cytokines, and possible actions to prevent cardiovascular and renal damage due to COVID-19 makes curcumin the potential option for COVID-19 treatment. Clinical studies are required to explore the role of curcumin in management of COVID-19.

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