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Full length article

Curcumin, a traditional spice component, can hold the promise against COVID-19?

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ABSTRACT

The severity of the recent pandemic and the absence of any specific medication impelled the identification of existing drugs with potential in the treatment of Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Curcumin, known for its pharmacological abilities especially as an anti-inflammatory agent, can be hypothesized as a potential candidate in the therapeutic regimen. COVID-19 has an assorted range of pathophysiological consequences, including pulmonary damage, elevated inflammatory response, coagulopathy, and multi-organ damage. This review summarizes the several evidences for the pharmacological benefits of curcumin in COVID-19-associated clinical manifestations. Curcumin can be appraised to hinder cellular entry, replication of SARS-CoV-2, and to prevent and repair COVID-19-associated damage of pneumocytes, renal cells, cardiomyocytes, hematopoietic stem cells, etc. The modulation and protective effect of curcumin on cytokine storm-related disorders are also discussed. Collectively, this review provides grounds for its clinical evaluation in the therapeutic management of SARS-CoV-2 infection.

1. Introduction

An outburst of Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infection causes COVID-19 pandemic; with millions of cases and approximately 540 thousands of deaths (WHO, 2020). Prophylactic and therapeutic measures are not yet available against COVID-19 (Scavone et al., 2020). Prompted responses throughout the world have been initiated to identify the therapeutic molecule against SARS-CoV-2; large number of drugs have been suggested for repurposing against COVID-19 (Wu et al., 2020). Several reviews have suggested a potential role of phytochemicals in the fight against SARS-CoV-2 infection and the onset of COVID-19 (Mani et al., 2020; McKee et al., 2020). Phytochemicals have been proven effective against previous episodes of virus outbreaks in the last two decades (Barnard and Kumaki, 2011; Kunnumakkara et al., 2017; Xu and Liu, 2017). Bioactive ingredients may offer potential candidates for the prevention and treatment of COVID-19. Turmeric is one of such plant products that provide benefits in a variety of medical ailments including respiratory infections (Barnard and Kumaki, 2011; Buhrmann et al., 2020; Kunnumakkara et al., 2019; Soni et al., 2020; Vishvakarma, 2014; Xu and Liu, 2017). A major bioactive component of turmeric, curcumin has been shown to confer curative and preventive effects in the diverse forms of pathology and disorders, infections, and malignancies (Barnard and Kumaki, 2011; Kunnumakkara et al., 2019; Soni et al., 2020; Vishvakarma, 2014; Xu and Liu, 2017).

Various demographic factors, including dietary habits, have been linked with low COVID-19 case fatality rate observed in South-East Asia and East-Mediterranean (WHO, 2020). Turmeric is an integral part of

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spices used in food preparations in the South-East Asia and East-Mediterranean region of the globe. Immunity raised through nutritional supplementation has been recommended worldwide in the battle against COVID-19 and curcumin can be suggested to play a vital role in protective immunity.

Studies indicate the potential benefits of curcumin against respiratory viral infections (Avasarala et al., 2013; Barnard and Kumaki, 2011; Xu and Liu, 2017). Curcumin can effectively inhibit the viral enzyme of SARS-coronavirus (Barnard and Kumaki, 2011; Wen et al., 2007). Recent *in-silico* predictions suggest a stable interaction between curcumin and SARS-CoV-2 enzymes (Chen et al., 2020; Enmozhi et al., 2020; Huynh et al., 2020; Kandeel and Al-Nazawi, 2020). Regulations of coronavirus-infection-associated responses by curcumin is also suggested (Chen et al., 2020). Moreover, curcumin has been shown to modulate various pathophysiological consequences of SARS-CoV-2 infection (Akinyemi et al., 2015; Almatroodi et al., 2020; Dai et al., 2018; Hongtao et al., 2018; Kunnumakkara et al., 2017; Pang et al., 2015; Praditya et al., 2019; Titto et al., 2020; Vishvakarma, 2014). Nevertheless, the entry of SARS-CoV-2 into host cells is also predicted to be hindered by curcumin through direct interaction with viral ligands/target cell receptors (Kandeel and Al-Nazawi, 2020; Maurya et al., 2020). Moreover, the inhibition of Trans-membrane Serine Protease 2 (TMPRSS2) by curcumin has been reported (Katta et al., 2019), which is a priming enzyme for SARS-CoV-2 cellular entry (Hoffmann et al., 2020). Lung inflammation, a key manifestation of COVID-19 (Vardhana and Wolchok, 2020; Zhai et al., 2020), can be alleviated by curcumin (Dai et al., 2018). The potential role of curcumin in the treatment of COVID-19 has been suggested (Zahedipour et al., 2020), however, this review will highlight the promising targets of curcumin in pathological manifestations of SARS-CoV-2 infection, which can be exploited in preclinical and clinical investigations. To the best of review literature to date, there is no laboratory or clinical investigation which confirms the potential of curcumin against SARS-CoV-2. However, inhibitory effects against other related coronaviruses and respiratory viral infections promise the potential of curcumin against COVID-19. This is also be aided by shreds of evidences for the ameliorating effect of curcumin against COVID-19 associated clinical manifestations. Nevertheless, in silico investigations indicating efficient binding with critical proteins and enzymes of SARS-CoV-2 also hold the promise of curcumin.

2. SARS-CoV-2, COVID-19 and curcumin

A variety of beneficial effects of curcumin has been reviewed (Kunnumakkara et al., 2017; Praditya et al., 2019; Vishvakarma, 2014; Zahedipour et al., 2020) including antitumor, antihypertensive and antiviral activities. The antiviral activities of curcumin have been observed against a variety of viruses, including hepatitis viruses, Zika virus, Chikungunya virus, human immunodeficiency virus, human papillomavirus, herpes simplex virus-2 as well as respiratory influenza virus (Praditya et al., 2019). Previously, curcumin has been shown to hinder the replication of SARS-coronavirus as well (Wen et al., 2007). The genomic similarity of SARS-CoV-2 with SARS-coronavirus (>80%) and Middle East respiratory syndrome-coronavirus (Lu et al., 2020) collectively suggest the likelihood of effectiveness of curcumin against COVID-19. Established experimental evidences of the potential of curcumin in the therapeutic as well as the prophylactic management of respiratory infections and pathophysiology recommend its implementation in COVID-19. Recent experimental evidence from *in-silico* investigations predicted direct binding of curcumin with receptor/ligands mediating entry of the virus into host cells as well modulation of associated inflammatory events (Chen et al., 2020; Kandeel and Al-Nazawi, 2020; Maurya et al., 2020). The previously known ability of

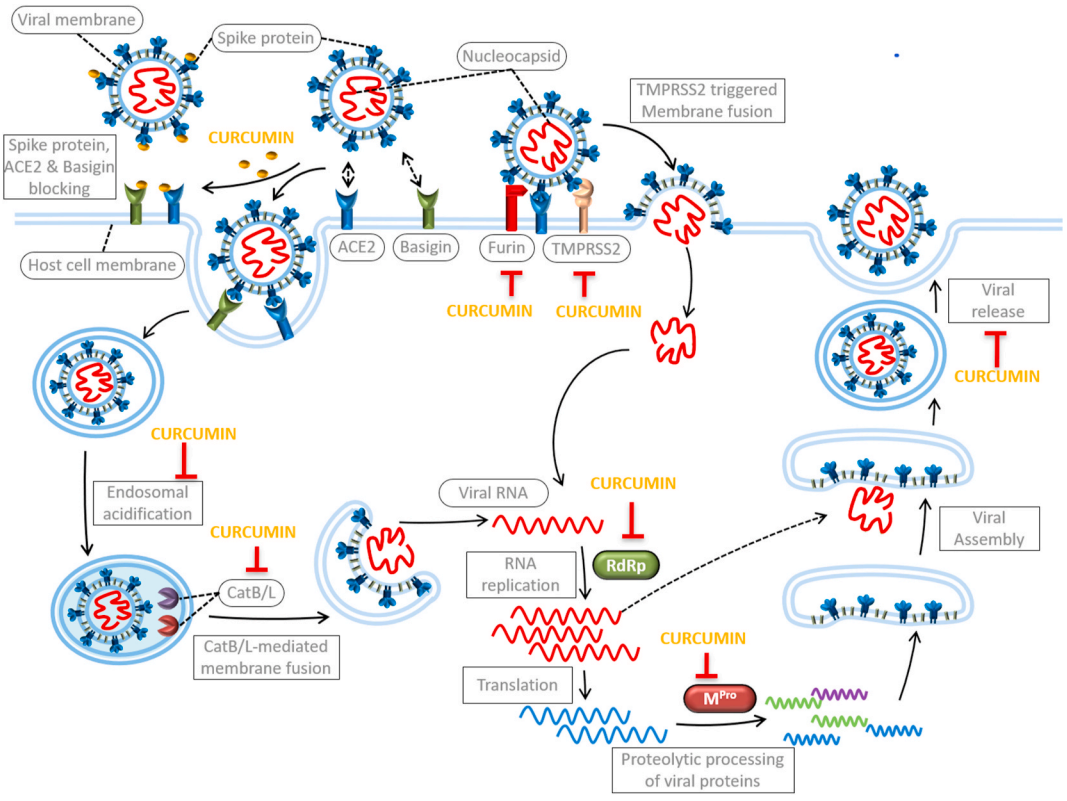

Fig. 1. Potential Targets of Curcumin in cellular entry and replication of SARAS-CoV-2.
Curcumin can block the spike protein, ACE2, basigin, TMPRSS2, Furin, CatB/L, and inhibits endosomal acidification in order to prevent the cellular entry of SSARS-CoV-2. Curcumin may hinder the replication of SARS-CoV-2 through inhibition of RNA-dependent RNA polymerase (RdRp), Main Protease (M^{Pro}) and its release from infected cells.

curcumin ability to modulate cellular and physiological consequences (Barnard and Kumaki, 2011; Kunnumakkara et al., 2017; Praditya et al., 2019; Wen et al., 2007) associated with SARS-CoV-2 infection along with recent *in-silico* predictions (Chen et al., 2020; Kandeel and Al-Nazawi, 2020; Maurya et al., 2020) further support its potential.

2.1. SARS-CoV-2 cellular entry and curcumin

Angiotensin-converting enzyme 2 (ACE2) serves as the doorstep for coronaviruses including SARS-CoV-2. This host cell surface molecule has been confirmed to serve as a docking port for viral spike protein (Hoffmann et al., 2020). Spike protein has two structural subunits which have an essential role in the recognition of target cells followed by viral entry. The viral envelope distal receptor binding subunit S1 of spike protein through its receptor-binding domain interacts with ACE2 on the target cell (Hoffmann et al., 2020; Shang et al., 2020). Curcumin has been predicted to interact and block the S1 subunit of SARS-CoV-2 (Maurya et al., 2020). Blocking of receptor-binding domain of spike protein will prevent the recognition of the target cell and subsequent cellular entry of viral particles. Nevertheless, predictive binding curcumin with ACE2 has been demonstrated (Maurya et al., 2020). Various amino acid residues of ACE2 have been identified (Ala 348, Asn 394, Glu 402, His 378, His 401, and Tyr385) from the active site of interaction with curcumin (Maurya et al., 2020). The ability to block interacting partners (ACE2 and spike protein) indicates the potential of curcumin in the prevention of SARS-CoV-2 entry to cells. Further, curcumin has been demonstrated to diminish the expression of TMPRSS-2 (Katta et al., 2019). TMPRSS-2 is one of the major activating proteases of the host cells for entry of SARS-Cov-2 (Hoffmann et al., 2020). The cleavage, of the S2 subunit of spike protein mediated by TMPRSS-2, serves as perquisite step for the release of viral content in host cells (Hoffmann et al., 2020; Shang et al., 2020). Endosomal cysteine proteases cathepsin B and L (CatB/L) also prime the viral particle release from endosome to the cytosol of a cell (Hoffmann et al., 2020; Shang et al., 2020). Modulation of CatB/L has been demonstrated by curcumin in disease models including pulmonary fibrosis (Ahlame et al., 2019; Ravish and Raghav, 2014). Further, the preactivation of SARS-CoV-2 spike protein by proprotein convertase furin has been reported (Shang et al., 2020). Unlike SARS-CoV, preactivation by proprotein convertase furin makes SARS-CoV-2 entry relatively less dependent on priming by TMPRSS2 and Cat B/L (Shang et al., 2020). Furin-mediated preactivation can be hypothesized as one of the major culprit underlying aggressive spread of infection. The study of Zhu et al. (2013) has demonstrated that furin activity can be affected by curcumin. Curcumin can inhibit the maturation of proprotein zymogen and consequent activity of furin (Zhu et al., 2013). Taken together, the direct interaction with proteins involved in the recognition and anchoring, i.e. spike protein and ACE2, along with modulation of expression as well as activity of key enzymes (TMPRSS2, Cat B/L, furin) mediating fusion of membranes and viral entry into the target cell by curcumin have been reported.

Acidification of endosome, containing internalized SARS-CoV-2, requires for its maturation which triggers the activation of endosomal proteinases including CatB/L (Sun et al., 2020). This will kick off the fusion of viral and endosomal membranes to release viral RNA and prompt its replication. Inhibition of endosomal acidification has been proposed as a strategy for treatment (Sun et al., 2020). The vacuolar-ATPase (V-ATPase) load the H^+ in cellular vesicles from cytosol and curcumin can inhibit the expression of V-ATPase (Vishvakarma et al., 2011). Moreover, trimmed down acid production by curcumin-treated cells has been demonstrated (Soni et al., 2020; Vishvakarma et al., 2011). Therefore, curcumin can be hypothesized to restrict viral entry into cytosol even after the interaction of spike protein-ACE2. Possible targets of curcumin involved in the cellular entry of SARS-CoV-2 are given in Fig. 1. This corollary suggests the potential of curcumin in the prevention of SARS-CoV-2 cellular entry and hence can protect from the onset of COVID-19.

Interestingly, the novel route for viral entry of SRAS-CoV-2 to the target cell has been proposed through basigin (also known as CD147 or extracellular matrix metalloproteinase inducer: EMMPRIN) (Ulrich and Pillat, 2020). This alternative route may provide an opportunity to the viral particle to invade target cells under unavailability/blocking of ACE2, the preferred receptor of SARS-CoV-2 (Hoffmann et al., 2020; Shang et al., 2020). This will tear out the efficacy of ACE2 blockers. However, curcumin has been shown to inhibit the basigin (Cao et al., 2014). Targeting both the key receptors of SARS-CoV-2, i.e. ACE2 and basigin, provides a better chance of prevention of SARS-CoV-2 cellular entry by curcumin.

Curcumin has a high affinity with dipeptidyl peptidase 4 (DPP4) (Huang et al., 2019). A Variety of coronaviruses utilizes DDP4 as a receptor for internalization (Hirano and Murakami, 2020). Another putative receptor for coronaviruses entry is aminopeptidase N/CD13 (Hirano and Murakami, 2020) which serves as a potential target for various disorders. As confirmed by antibody competition assay and surface plasmon resonance analysis, curcumin can directly interact, both in vitro and in vivo, and irreversibly inhibits aminopeptidase N (Shim et al., 2003). Taken together, curcumin can be predicted to target most of the molecular participants involved in SARS-CoV-2 cellular entry and hence stands tall as a contender in COVID-19 treatment.

2.2. SARS-CoV-2 replication and curcumin

A large number of investigations are aimed to target key events and enzymes involved in viral replication of SARS-CoV-2. Foremost candidates in these targets are RNA-dependent RNA polymerase (RdRp) and main protease (M^{Pro}; also known as 3c-like proteinase). Various *in-silico* predictive and molecular simulation studies prompted the repurposing of known drugs in the treatment of COVID-19 (Kandeel and Al-Nazawi, 2020; Mani et al., 2020; Maurya et al., 2020; McKee et al., 2020; Zahedipour et al., 2020). Previous investigations suggest that effective phytochemicals interfering coronavirus replication majorly target SARS-CoV-2 M^{Pro}(Lin et al., 2014). Although, a large number of investigation reports in the form of preprints (at the time of writing this manuscript) are available, few peer-reviewed studies predict the direct binding of curcumin with SARS-CoV-2 M^{Pro} (Enmozhi et al., 2020; Huynh et al., 2020; Kandeel and Al-Nazawi, 2020). Moreover, a nice fit of curcumin inside the pocket of SARS-CoV-2 M^{Pro}has also been predicted (Huynh et al., 2020). Similarly, many preprint (not-peer reviewed) investigations suggest targeting of RdRp of SARS-CoV-2. Previously, Du et al. (2018) have observed the inhibition of coronavirus RNA replication. Although the Porcine epidemic diarrhea virus was applied as a model of coronavirus (Du et al., 2018), it suggests targeting of RdRp by curcumin. Moreover, curcumin was shown to prevent the release of viral particles from infected cells (Du et al., 2018). As discussed, curcumin can be predicted to have the ability to interact with RdRp and SARS-CoV-2 M^{Pro} and can prevent the viral budding from cells. Targets of curcumin in the replication of SARS-CoV-2 are depicted in Fig. 1. This collectively indicates that curcumin can interfere with the viral replication machinery of SARS-CoV-2 and thus have a promising chance of success in the therapeutic intervention of COVID-19.

2.3. COVID-19, renin-angiotensin system and curcumin

ACE2 of the target cell provides anchorage for the spike protein of SARS-CoV-2 which initiates the process of its cellular entry (Shang et al., 2020). ACE2 is an inactivator of angiotensin II (AngII) and expressed on the cell surface. Simultaneous endocytosis of ACE2 during SARS-coronaviruses, including SARS-CoV-2, cellular entry has been reported (Hoffmann et al., 2020; Zhu et al., 2013). This reduction of the cell surface level of ACE2 leads to the accumulation of AngII and the elevated amount of AngII has been linked with acute lung injury in COVID-19 (Hirano and Murakami, 2020; Hoffmann et al., 2020). The octapeptideAngII generated through catalytic cleavage of

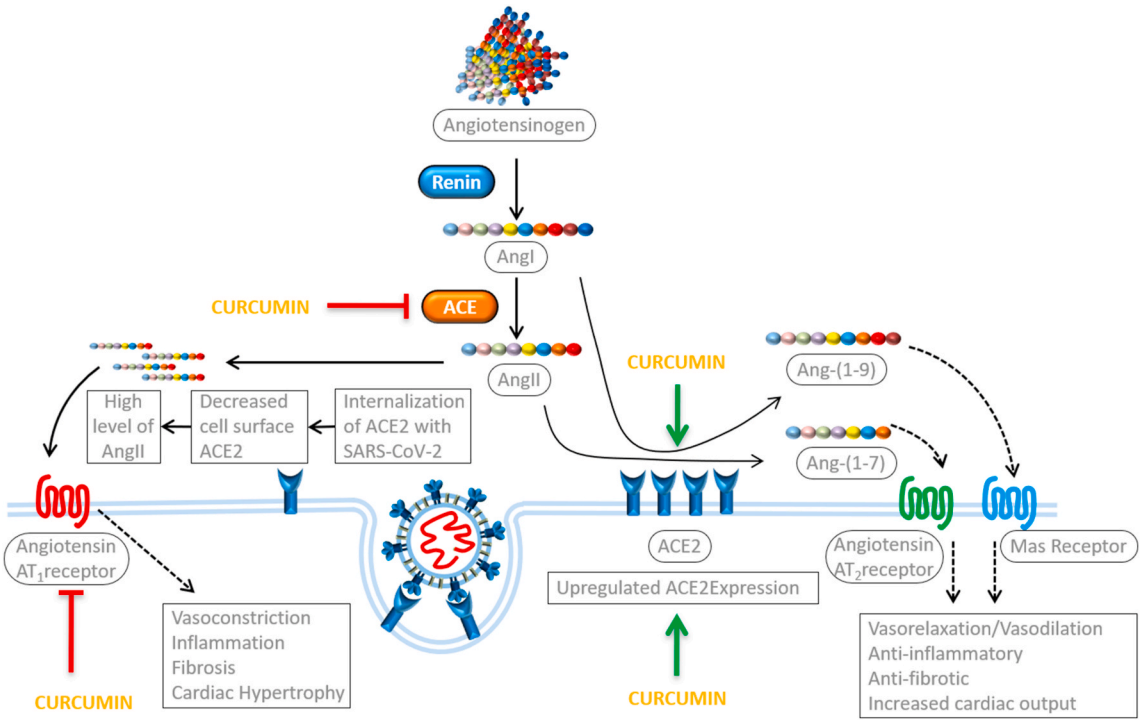

Fig. 2. Modulation of Renin-Angiotensin System (RAS) by curcumin.
Curcumin-mediated inhibition of ACE can decline the formation of AngII. Inactivation of AngII may be accelerated by curcumin-driven enhanced expression of ACE2. Curcumin can prevent the detrimental effects of AngII through the downregulation angiotensin AT_1 receptor. Stimulation of angiotensin AT_2 receptor and Mas receptor by Ang-(1–7) and Ang-(1–9), ACE2 catalyzed cleavage products of AngII and AngI, respectively, will also negate the effect of AngII.

decapeptideangiotensin (AngI; also known as proangiotensin) by Angiotensin-converting enzyme 1 (ACE1 or simply ACE) (D'Ardes et al., 2020). Angiotensinogen, a functionally active 452 amino acid proteins, secreted by the liver is a precursor of AngI. The first ten amino acids of Angiotensinogen produce AngI after proteolytic cleavage by renin. Thus, this renin-angiotensin system has a crucial role to play in the manifestation of COVID-19 (D'Ardes et al., 2020). Moreover, AngII acts as a vasoconstrictor and leads to hypertension and stimulation of inflammatory response. Curcumin can modulate the expression level of AngII and prevent fibrosis (Pang et al., 2015). Further modulation of the ACE2 level by curcumin has been reported (Katta et al., 2019; Pang et al., 2015). Improvement of ACE2 expression by curcumin can induce the inactivation of AngII and thus prevent the elevated AngII level-triggered cellular signaling, subsequent damage, and pathological consequences. Interestingly, the elevated level of ACE2 expression by curcumin can be suspected of increased susceptibility towards SARS-CoV-2 cellular entry. However, the use of ACE modulators yet not been linked with increased susceptibility for acquiring SARS-CoV-2 infection of mortality. Further, curcumin inhibits the ACE1 expression in hypertensive rats (Akinyemi et al., 2015). The inhibition of ACE1 can avoid the formation of excessive AngII and prevent the onset of pathological consequences of SARS-CoV-2 infection.

The elevated level of AngII subsequently stimulates the angiotensin AT_1 receptor. Detrimental effects triggered by angiotensin AT_1 receptor stimulation include vasoconstriction, inflammatory response, fibrosis, and altered redox balance, leading to the development of acute respiratory distress syndrome (ARDS), major clinical manifestations of COVID-19 (D'Ardes et al., 2020). Curcumin can downregulate the expression of angiotensin AT_1 receptor on various types of cells (Pang et al., 2015; Yao et al., 2016), and subsequently exerts antihypertensive effect (Yao et al., 2016). Two different receptors for angiotensin (angiotensin AT_1 receptor and angiotensin AT_2 receptor) promulgate contrasting effects after stimulation by AngII(D'Ardes et al., 2020). Stimulation of angiotensin AT_2 receptor can exercise protective and regenerative consequences, including anti-inflammatory response, the release of vasodilators, and reverses fibrosis (Rodrigues Prestes et al., 2017). Tilted expression of receptors towards angiotensin AT_2 receptor after curcumin treatment has been reported in the murine model of fibrosis (Pang et al., 2015). Further, curcumin-mediated upregulation of ACE2 expression (Katta et al., 2019; Pang et al., 2015) can elicit the conversion of AngII to angiotensin-(1–7) [Ang-(1–7)]. Ang-(1–7) stimulates the Mas receptor and can negate the effect of AngII- angiotensin AT_1 receptor signaling similar to the activation of angiotensin AT_2 receptor (D'Ardes et al., 2020; Rodrigues Prestes et al., 2017). Affecting renin-angiotensin system by curcumin through modulation of its elements, including ACE1, ACE2, AngII and angiotensin AT_1/AT_2 receptor (Fig. 2.) may improve the hypertensive and inflammatory responses in COVID-19 patients and thus prevent the cellular as well tissue damage and disease progression.

2.4. *Curcumin and cellular signaling in COVID-19*

Stimulation of angiotensin AT_1 receptor by AngII and subsequent thrust to signaling provide a foundation for pathological consequences of SARS-CoV-2 infection (Hirano and Murakami, 2020). Angiotensin AT_1 receptor, through coupled G-protein, activates NADPH oxidase, which in turn activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Activation of NF-κB and its nuclear translocation elicit the expression of inflammatory mediators (Sun, 2017). The regulatory aptitude of curcumin in NF-κB activation and prospective use in inflammatory disorders, including lung pathology is established (Lelli et al., 2017). Among the pleiotropic effects of curcumin, inhibition of transcription factor NF-κB has been primarily linked with its therapeutic consequences (Buhrmann et al., 2020; Kunnumakkara et al., 2019; Lelli et al., 2017; Vishvakarma, 2014). Inhibition of NF-κB by curcumin has been shown to protect cellular damage as well as the onset of the carcinogenic event (Kunnumakkara et al., 2017, 2019; Vishvakarma, 2014) along with anti-infective properties (Buhrmann et al.,

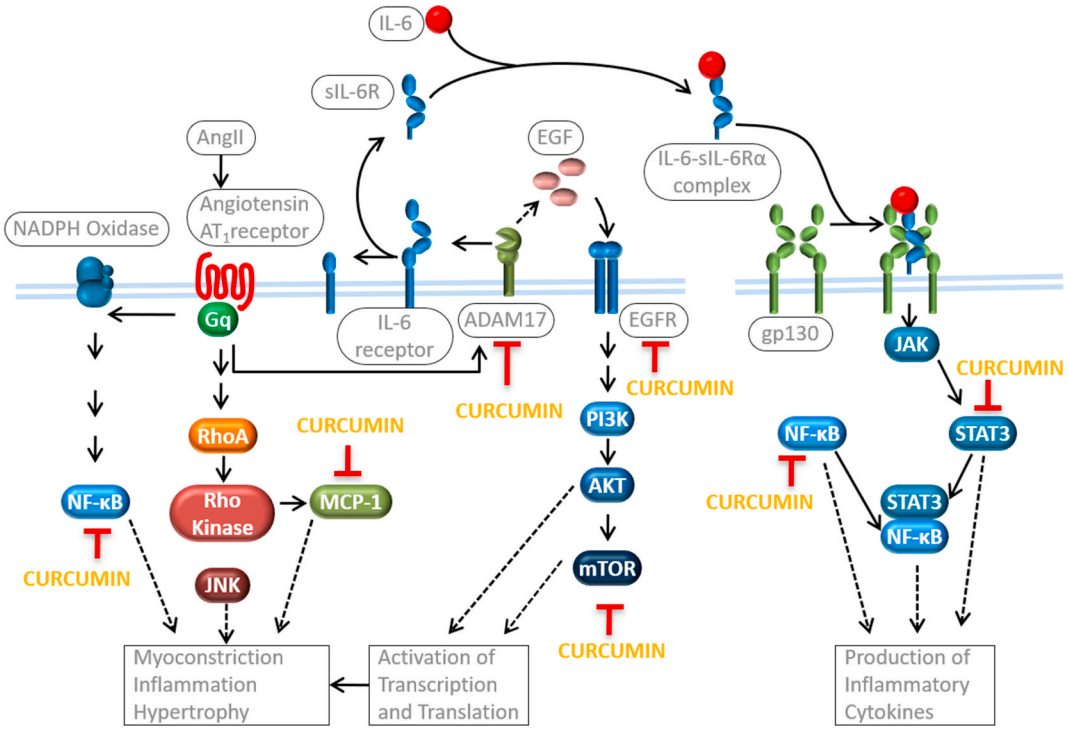

Fig. 3. Promising targets of curcumin in cell signaling in COVID-19.
Inhibition of AngII-stimulated angiotensin AT1 receptor signaling in COVID-19 by curcumin will hamper the activation of NF-κB and MCP-1. Curcumin will also inhibit the ADAM17 and prevent the formation of IL-6-sIL-6R complex and EGF. Enhanced degradation of EGFR and inhibition of mTOR by curcumin will also prevent ill effects in COVID-19. Inhibition of STAT3 by curcumin will also avoid the production of inflammatory cytokines.

2020; Kunnumakkara et al., 2019; Xu and Liu, 2017). Curcumin has been shown to attenuate the Influenza virus-induced lung inflammation through inhibition of NF-κB signaling (Xu and Liu, 2017). Moreover, the induction of NF-κB in airway epithelium was found to increase lung inflammation and associated damage in a murine model (Sheller et al., 2009). Curcumin-mediated inhibition of NF-κB and prevention of subsequent molecular cascade can be hypothesized as a protective measure in COVID-19. Angiotensin AT_1 receptor signaling also activates RhoA/Rho-kinase and induces monocyte chemoattractant protein-1 (MCP-1) (Mattson and Maudsley, 2009) which, like NF-κB, also promotes inflammation. Anti-inflammatory effects of curcumin have been shown to encompass the inhibition of MCP-1 (Kunnumakkara et al., 2017).

Angiotensin AT_1 receptor engagement with AngII also triggers the activation of a disintegrin and metalloproteinase 17 (ADAM17) through the elevated cytosolic level of Ca^{2+} (Mattson and Maudsley, 2009). ADAM17 activation provides ligand availability for epidermal growth factor receptor (EGFR), and process the soluble form of the interleukin (IL)-6 receptor α subunit (sIL-6R) and tumor necrosis factor-α (TNF-α). EGFR signaling mediates activation of phosphatidylinositol 3-kinase (PI3K), and Akt kinases (Mattson and Maudsley, 2009). Curcumin has been shown to modulate the ADAM17 activity through miR145 (Yu et al., 2013). Curcumin-mediated inhibition of ADAM17 may be hypothesized to avert the associated consequences in COVID-19 including EGFR-mediated signaling. Moreover, curcumin can induce the degradation of EGFR in lung cells through its phosphorylation (Lee et al., 2011). In addition to the inhibitory activity on ADAM17, degradation of EGFR induced by curcumin can ascertain to ward off their terminal consequences in SARS-CoV-2 infection. The decline in the generation of sIL-6R and TNF-α owing to the inhibition of ADAM17 by curcumin can be sought to prevent the local as well as systemic upregulation of inflammatory cytokine. Therefore, curcumin can be proposed as a promising candidate for the prevention of ill effects associated with SARS-CoV-2 infection. George et al. (2020) have reviewed the potential role of mammalian target of rapamycin (mTOR) in clinical manifestation of COVID-19 and advocated that its inhibitor can be repurposed for treatment of COVID-19 (George et al., 2020). Pulmonary fibrosis is one of the consequences of SARS-CoV-2 infection and mTOR has been suggested as an emerging target (George et al., 2020). Curcumin has been reviewed as an inhibitor of mTOR (Kotha and Luthria, 2019), and thus repurposing of this golden spice component will provide health benefits to COVID-19 patients. mTOR has also been implicated in age-related disorders, including inflamm-aging. Moreover, the poor outcomes of COVID-19 observed in patients with preexisting medical conditions and old age. Curcumin-mediated inhibition of mTOR can also improve the prognosis in old age patients infected with SARS-CoV-2.

In a variety of IL-6R α subunit negative cells, including fibroblast, epithelial and endothelial cells, signal transducer and activator of transcription 3 (STAT3) activation through gp130 is mediated by IL-6-sIL-6R complex (Hirano and Murakami, 2020). Inhibition of ADAM17 by curcumin (Yu et al., 2013) can diminish the processing of sIL-6R and thus may prevent the activation of STAT3 in these cells. Further cells of the immune system display membrane-bound IL-6 receptor, which activates Janus tyrosine kinase (JAKs) and STAT3. The pleiotropic effect of this activation includes activation of acquired as well as innate immune cells leading to the excessive release of cytokine termed as a cytokine release syndrome. Nevertheless, blocking STAT3 activation through small-molecule inhibitors has been hypothesized to prevent cytokine storm and potentiate the effect of viral replication inhibitors like remdesivir (Bosch-Barrera et al., 2020). This dual targeting of STAT3 and viral replication has been under clinical trial (Bosch-Barrera et al., 2020). Moreover, STAT3 inhibition by curcumin has been reported in varied forms of cells (Kunnumakkara et al., 2017; Soni et al., 2020). STAT3 inhibition by curcumin has been suggested to improve the sensitivity of target cells towards chemotherapeutic drugs (Soni et al., 2020). Potential targets of curcumin in COVID-19 associated cell signaling are depicted in Fig. 3. Thus the use of curcumin in the therapeutic regimen against COVID-19 may provide direct benefit as well as

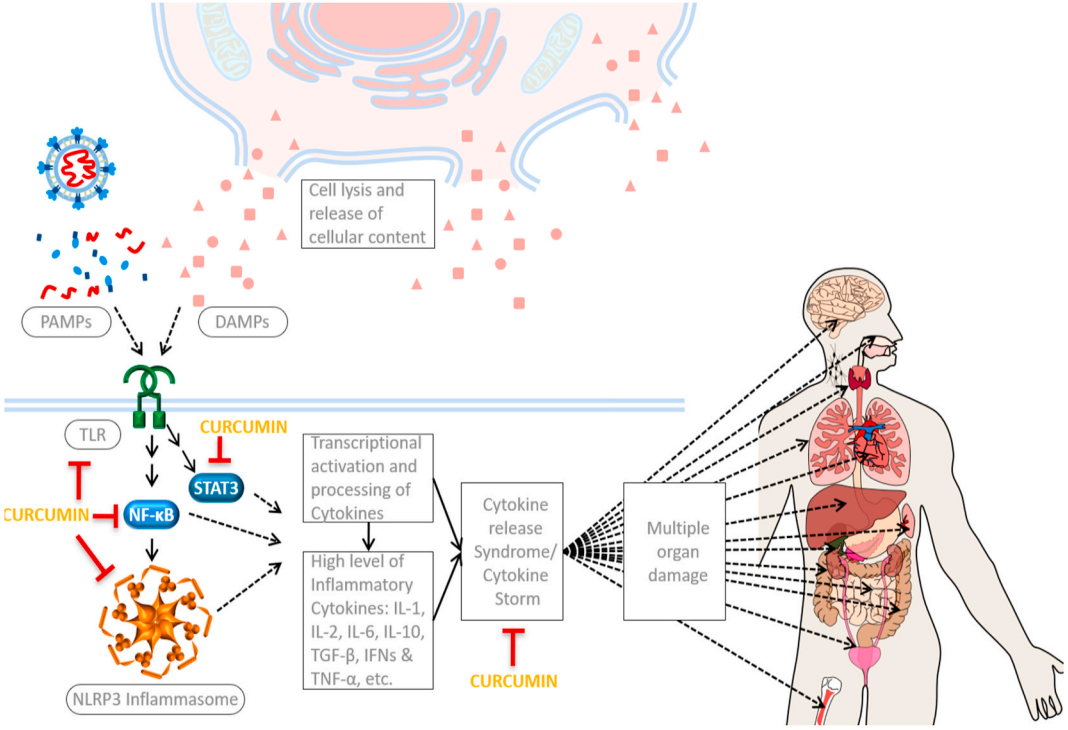

Fig. 4. Inhibition of cytokine storm by curcumin in COVID-19.
Viral components and cellular content released by infected cell lysis constitute PAMPs and DAMPs. PAMPs and DAMPs trigger TLR stimulation. Curcumin can inhibit TLR signaling and downstream activation of NF-κB, STAT3, and NLRP3 Inflammasome. This will prevent the production and elevated level of inflammatory cytokines, i.e. cytokine syndrome. This can avoid multiple organ damage in COVID-19.

its role as an adjunct may improve the efficacy of other antiviral medication.

2.5. COVID-19, cytokine storm and curcumin

Curcumin can be predicted to prevent as well as alleviate many pathological effects of SARS-CoV-2 infection. Immunomodulatory activities of curcumin are well established (Kunnumakkara et al., 2017, 2019; Vishvakarma, 2014; Xu and Liu, 2017; Zahedipour et al., 2020). Hyperactivation and immune cells, pro-inflammatory response, and anomalous release of cytokine, termed as cytokine release syndrome, play a foremost role in deteriorated outcomes in several viral diseases including COVID-19 (Hirano and Murakami, 2020; Sordillo and Helson, 2015). Such a plethora of cytokine in the systemic circulation is often referred to as cytokine storm (Hirano and Murakami, 2020; Sordillo and Helson, 2015). These elevations in cytokine levels have been linked as the culprit behind deterioration and multiple organ damage in COVID-19 (Vardhana and Wolchok, 2020).

Signaling sequences triggered by SARS-CoV-2 infection, consequent onset, and associated organ damage are illustrated in Figs. 3 and 4. SARS-CoV-2 infection to alveolar cells elicits the proinflammatory consequences (Hirano and Murakami, 2020; Vardhana and Wolchok, 2020). The lysis of pneumocyte during the initial phase of COVID-19 leads to the release of intracellular content, which serves as the damage associated molecular patterns (DAMPs) (Mason, 2020; Vardhana and Wolchok, 2020). DAMPS can also be contributed by proteins released after tissue injury in COVID-19 including heparin sulphate, fragments of hyaluronan, and heat shock proteins (Vardhana and Wolchok, 2020). Similarly, pathogen-associated molecular patterns (PAMPs) like viral proteins and RNAs also turn up in the arena of alveoli. Pattern recognition receptors can interact with DAMPs and PAMPs and trigger the innate immune response. Toll-like receptors (TLR) are major pattern recognition receptors held accountable for such activation in a variety of pathological conditions, including viral infections (Hirano and Murakami, 2020; Vardhana and Wolchok, 2020). Previous reports indicate the down-regulation of TLR by curcumin (Katta et al., 2019; Kunnumakkara et al., 2017; Vishvakarma, 2014). Activation of NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome through downstream signaling of TLR encourages the maturation and the release of proinflammatory cytokines. TLR also activate NF-κB which prompts the transcriptional activation of several cytokines, their receptors as well as NLRP3. Curcumin has the potential to diminish NF-κB activation (Kunnumakkara et al., 2017; Vishvakarma, 2014; Xu and Liu, 2017) as well as inhibit the NLRP3 inflammasome (Hassanzadeh et al., 2020).

The cytokines involved in cytokine storm include IL-1, IL-2, IL-6, IL-10, Transforming growth factor (TGF)-β, Interferons (IFN), and TNF-α. Expressions of IL-6 and TNF-α are majorly linked with COVID-19 associated ARDS and organ damage (Hirano and Murakami, 2020; Vardhana and Wolchok, 2020). Curcumin inhibits Influenza-A virus-induced production of IL-6 and TNF-α in host cells (Xu and Liu, 2017). The suppressive effect of curcumin on IFN-α was also demonstrated, and the inhibitory effect of curcumin on these inflammatory cytokines was linked with NF-κB inhibition (Xu and Liu, 2017). The inhibitory potential of curcumin on the production of inflammatory cytokines was reviewed and was hypothesized to ameliorate pulmonary fibrosis (Zahedipour et al., 2020). A systemic increase of inflammatory cytokines and cytokine storm put forward the playground for multiple organ damage and poor prognosis. Liu and Ying (2020) have reviewed the ability of curcumin in the suppression of cytokine storm and its potential in the treatment of viral disorders including coronaviruses (Liu and Ying, 2020). Collectively, the ability of curcumin to alter the inflammatory state through modulation of its regulatory elements can prevent the onset of cytokine storm. The inhibition of cytokine storm in SARS-CoV-2 infected patients can be of immense advantage in the prevention of progression of the disease.

2.6. Curcumin and cellular damage in COVID-19

SARS-CoV-2 primarily infects alveolar type II (ATII) cells, which serve as precursors for alveolar type I (ATI) cells (Mason, 2020). Alveolar ATI cells do the gaseous exchange during the function of breathing. Preferential infection of SARS-CoV-2 and their propagation in alveolar ATII cells followed the release of viral particles. This triggers the apoptotic death of the target cell and further infection to adjacent alveolar ATII cells. Death and insufficiency of alveolar ATII cells, to regenerate gas exchanging alveolar ATI cells, may trigger the secondary pathway of epithelial regeneration (Mason, 2020). Cumulative cell death along with inflammatory consequences manifests the diffuse alveolar damage, hyaline membrane rich in fibrin, and appearance of giant multinucleated cells. Repeated cycles of infection, cell death, and subsequent tissue damage contribute to the development of ARDS. The protection of alveolar ATII cells by curcumin has been shown in the inflammatory lung injury model (Almatroodi et al., 2020). Therefore, curcumin can be helpful in the protection of primary target cells of SARS-CoV-2 in alveoli. Alveolar ATII cells also secrete some glycoprotein and lipoprotein surfactants including palmitoylphosphatidylcholine which provide lubrication in the act of breathing. Curcumin-mediated protection of alveolar ATII cells may refrain the difficulty in the breathing, one of the primary symptoms of COVID-19. Moreover, the repair of alveolar ATII cells by curcumin can halt the progression of the disease. This may also reduce or prevent the necessity of ventilation in COVID-19. Further, curcumin refurbishes the barrier integrity of alveolar epithelium and promotes the clearance of alveolar fluid (Titto et al., 2020). This activity of curcumin can prevent the manifestation of pneumonia-like symptoms in the patients infected with SARS-CoV-2.

Curcumin can protect from the cardiovascular consequences of COVID-19. COVID-19 patients develop cardiovascular ailments owing to its systemic influence. Diminish ACE2 expression, either by viral endocytosis or inhibitor therapy, may have a detrimental effect on the cardiovascular system owing to the elevated level of AngII and angiotensin AT_1 receptor stimulation (Yamamoto et al., 2006). Curcumin can improve the ACE2 expression in the myocardial cells (Pang et al., 2015), and hence may protect from injurious effects of COVID-19 on cardiovascular tissues. Further curcumin attenuates the myocardial fibrosis through the modulation of AngII and angiotensin AT_1 receptor expression (Pang et al., 2015). Other clinical complications underlying injurious outcome of COVID-19 include disseminated intravascular coagulation (Horowitz and Freeman, 2020). Hemostasis and coagulation are centrally maintained by platelet function (Keihanian et al., 2018). Cardiovascular complications can be linked with platelet dysfunction (Keihanian et al., 2018; Tabeshpour et al., 2018) even in COVID-19 patients (Horowitz and Freeman, 2020). The positive activity of curcumin in fibrinolysis and anticoagulation (Keihanian et al., 2018) may prevent the onset of cardiovascular disorders. Sepsis-induced coagulopathy has been detected in few severe COVID-19 patients, especially those on ventilation. Anticoagulant and antiplatelet effects of curcumin (Keihanian et al., 2018; Tabeshpour et al., 2018) can be hypothesized to thwart such coagulopathy and associated clinical manifestations in COVID-19 patients.

Among many renal problems associated with COVID-19, renal fibrosis has been one of the most culprits, and the renal injury has been linked with a high mortality rate (Ronco et al., 2020). The potential role of curcumin in prevention of renal defects associated with COVID-19 has been discussed by Zahedipour et al. (2020). Curcumin can alleviate the renal fibrosis in ischemia-reperfusion through the modulation of the Akt signaling pathway (Hongtao et al., 2018).

The augmented level of myeloid-derived suppressor cells in the circulation with the severity of COVID-19 has been associated (Agrati et al., 2020). This indicates myelosuppression in SARS-CoV-2 infected patients, which prevents the appropriate maturation of the immune cells. Myeloid-derived suppressor cells (MDSC) are not the only consequence of refrained differentiation of hematopoietic stem cells (HSC), but it also plays a critical role in the suppression of immune response (Bergenfelz and Leandersson, 2020). The myelopotentiating effect of curcumin in the murine animal model with myelosuppression has been reported (Vishvakarma, 2014; Vishvakarma et al., 2012). Curcumin inhibits MDSC to display its therapeutic benefits including anti-inflammatory effects (Salminen et al., 2018). Elevated serum level of the lactate dehydrogenase (LDH) in the majority of COVID-19 patients has been linked with the severity of the disease and worse outcome (Henry et al., 2020). The elevated LDH level and consequent rise in the serum lactate can also be linked with the organ damage and immunospuppression (Vishvakarma, 2014). Curcumin has been shown to confer protection from ailing effects of the lactate (Soni et al., 2020) as well as guard against the induced immunospuppression (Vishvakarma, 2014; Vishvakarma et al., 2012).

Severity and vulnerability to the COVID-19 have been linked with a low level of hemeoxigenase 1 (HO-1) (Hooper, 2020). Its low level can also be linked with vascular damage associated with SARS-CoV-2 infection as HO-1 has a critical role in prevention of vascular inflammation and injury. The study Ke et al. (2020) has demonstrated that curcumin modulates HO-1 in the murine system. Moreover, through modulation of HO-1, curcumin has been shown to protect alveolar stem cells. Nevertheless, the HO-1 inducer ability of curcumin has been reviewed and advocated for its clinical trial in COVID-19 (Hooper, 2020). Collectively, abilities in the prevention of SARS-CoV-2-associated cellular and tissue damage along with amelioration of suppressive state on HO-1 expression and myelopoietic differentiation, curcumin stands as the front runner for inclusion in the therapeutic strategies for COVID-19.

3. Safety and limitations

Curcumin was found devoid of any significant toxicity in most of the preclinical as well as clinical investigations (Kunnumakkara et al., 2017; Kurien et al., 2011; Vishvakarma, 2014). Few investigations have reported the negative effects of curcumin. Most notably, Burgos-Morón et al. (2010) have presented an assemblage of deleterious effects of curcumin on various aspects, including DNA damage, induction of reactive oxygen species, and inhibition of drug-metabolizing enzymes. Further, inhibition of drug metabolizing enzymes, like glutathione-S-transferase and cytochrome P450, by curcumin was conjectured to the accumulation of simultaneously used other drugs and their toxicity (Burgos-Morón et al., 2010). However, a series of experiments conducted by Kurien et al. (2011), to address these concerns, indicated no direct DNA toxicity of curcumin at physiological concentration (Kurien et al., 2011).

Heart rate variability increased by curcumin was observed in the collagen-induced arthritic rat model (Dou et al., 2018). Cardiovascular complications and co-morbidities associated with COVID-19 contribute to the negative outcome of the treatment strategies (Horowitz and Freeman, 2020). However, the majority of investigations report no cardiac toxicity (Kunnumakkara et al., 2017, 2019), but also indicate cardioprotective effects of curcumin (Moulin et al., 2020; Pang et al., 2015). Deregulated surface expression of ACE2 and angiotensin receptors contribute to cardiac complications in COVID-19. Curcumin provides myocardial protection through modulation of ACE2 and angiotensin AT_1 and AT_2 receptor (Pang et al., 2015). Many approaches have been implemented to overcome a major obstacle in the clinical success of curcumin i.e., its bioavailability (Kunnumakkara et al., 2019). A novel water-soluble formulation of curcumin improved the ARDS manifestation and severity of pneumonia in the murine model (Zhang et al., 2019).

The beneficial effect of curcumin against SARS-CoV-2 has not yet been reported by any of the preclinical or clinical investigations. However, potential benefits, as envisaged in this review, are based on experimental pieces of evidences of curcumin against respiratory illnesses, other coronaviruses, and clinical manifestations associated with

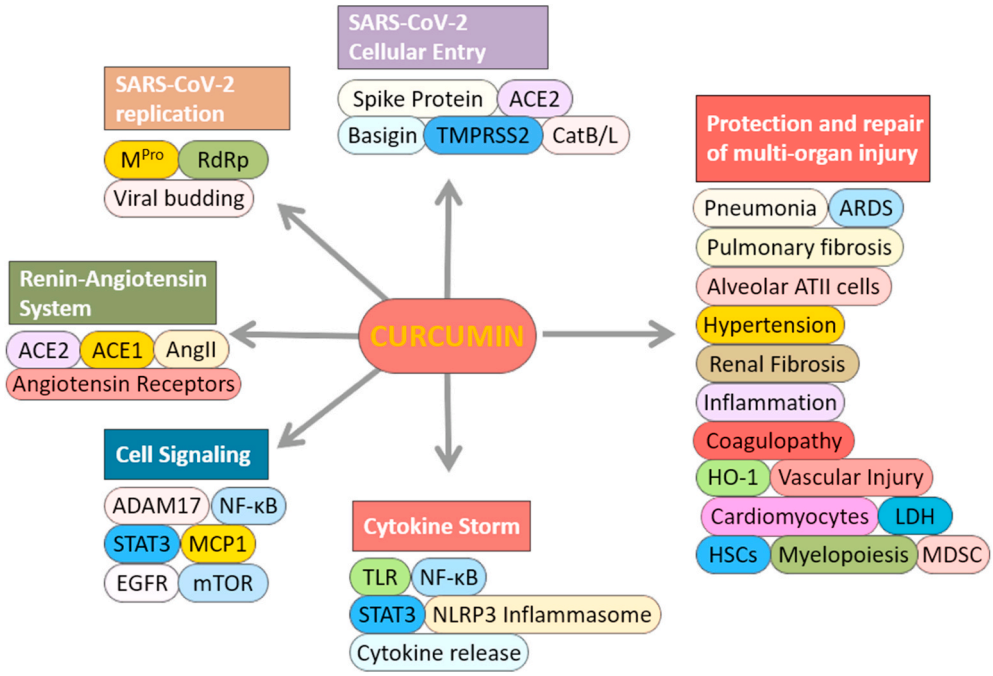

Fig. 5. Potential of curcumin in COVID-19.
Curcumin can affect various dimensions in COVID-19 including cellular entry and replication of SARS-CoV-2, Renin-Angiotensin system, cell signaling, and cytokine storm through their regulatory components. This will provide protection and repair of multi-organ injury.

COVID-19. Few in silico investigation have predicted the direct binding of curcumin with the surface proteins mediating cellular entry of virus and other enzymes essential for viral replications, like SARS-CoV-2 M^{Pro} and RdRp (Kandeel and Al-Nazawi, 2020; Maurya et al., 2020). Presented benefits of curcumin against SARS-CoV-2 are based on experimental investigations with similar clinical manifestations, infections with other coronaviruses or non-coronaviruses. Thus, therapeutic prospects of curcumin against COVID-19 presented here warrant an investigational endorsement against SARS-CoV-2.

4. Conclusion

Collectively, curcumin can modulate the events of SARS-CoV-2 cellular entry, their replication, and molecular cascade manifesting pathophysiological consequences of COVID-19. Potential targets of curcumin in components in COVID-19 are summarized in Fig. 5. Although, direct experimental (in vitro as well as in vivo) confirmation of the hypothesized benefits of curcumin against SARS-CoV-2 are absent, previous experimental evidences indicating its efficacy in respiratory ailments (including influenza and other coronavirus infections), inflammatory disorders, and coagulopathy, promotes its candidature as a drug in the treatment of COVID-19. Owing to probable and promising therapeutic potential in COVID-19, clinical trials of curcumin are insisted (Hooper, 2020; Horowitz and Freeman, 2020). Recent *in-silico* investigations, revealing its ability to interact with essential viral proteins, involved in entry and replication also put forward its potential. Its ability to protect and prevent cellular and organ damage along with improved differentiation of immune cells may provide health benefits to COVID-19 patients. Moreover, the potential to improve the activity of other drugs in antiviral settings endorses utilization of curcumin as an adjuvant with manifold benefits. This review of curcumin and its abilities motivates its clinical investigation as a therapeutic agent in the improvement of morbidity and mortality associated with SARS-CoV-2 infection.

CRediT authorship contribution statement

Vivek Kumar Soni: Conceptualization, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Arundhati Mehta:** Conceptualization, Investigation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Yashwant Kumar Ratre:** Writing - original draft, Formal analysis, Visualization. **Atul Kumar Tiwari:** Writing - original draft, Writing - review & editing, Formal analysis. **Ajay Amit:** Conceptualization, Writing - original draft, Writing - review & editing, Formal analysis. **Rajat Pratap Singh:** Conceptualization, Writing - original draft, Writing - review & editing, Formal analysis. **Subash Chandra Sonkar:** Writing - original draft, Writing - review & editing, Formal analysis, Visualization, Resources. **Navaneet Chaturvedi:** Writing - original draft, Writing - review & editing, Formal analysis, Visualization, Resources. **Dhananjay Shukla:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Resources, Supervision. **Naveen Kumar Vishvakarma:** Conceptualization, Formal analysis, Investigation, Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision.

Declaration of competing interest

The authors declare that there is no competing interest to disclose.

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