Promising role of curcumin against viral diseases emphasizing COVID-19 management: A review on the mechanistic insights with reference to host-pathogen interaction and immunomodulation

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ABSTRACT

Curcumin has already acknowledged immense interest from both medical and scientific research because of its multifaceted activity. To date, the promising effects of curcumin were perceived against numerous inflammatory diseases. Besides, curcumin's role as a medicine has been studied in many virus infections like influenza, HIV, etc. There is a need to analyze the cellular mechanisms of curcumin including host-pathogen interaction and immunomodulatory effects, to explore the role of curcumin against COVID-19. With this background, our study suggests that curcumin can prevent COVID-19 infections by inhibiting the pathogen entry, viral genome replication and steps in the endosomal pathway along with inhibition of T-cell signalling by impairing the autophagy-mediated antigen-presenting pathway. This review explicit the possible mechanisms behind curcumin-induced cellular immunity and a therapeutic dosage of curcumin suggesting a preventive strategy against COVID-19.

1. Background

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also known as Diferuloylmethane, is a polyphenol product derived from the rhizomes of plant turmeric and other *Curcuma* sp. (Fig. 1). Historically, curcumin, in the form of turmeric, is generally used for flavouring additives and food preservatives in Asiatic countries due to its anti-fungal and anti-oxidant property. The popular use of curcumin in research is mainly due to its pleiotropic properties including anti-inflammatory, anti-oxidant and anti-carcinogenic activities (Ahmad et al., 2020). Curcumin can inhibit the inflammatory mediators, oxidation processes, and oxidative stress thereby acts as an anti-inflammatory agent against many diseases (Wal et al., 2019). Praditya et al. (2019b) have shown curcumin as an anti-bacterial agent against several strains of *Staphylococcus*, *Streptococcus*, *Helicobacter* and *Pseudomonas* mainly by growth inhibition. They also reported the anti-fungal property of curcumin. Different studies identified the efficacy of curcumin against Human immunodeficiency virus (HIV), Herpes simplex virus (HSV), Hepatitis viruses etc. (Praditya et al., 2019a; Prasad & Tyagi, 2015; Vitali et al., 2020). Although there are some controversies, the majority of the studies support the potential role of curcumin in inhibiting viral replication and growth inhibition (Mathew & Hsu, 2018). Apart from

these, long-term intake of curcumin can improve systolic blood pressure (Hadi et al., 2019), control obesity (Jarząb & Kukula-Koch, 2019), Type 2 Diabetes Mellitus (Pivari et al., 2019). Also, curcumin often acts as a cardio-protective, nephroprotective, anti-neoplastic, hepato-protective and anti-rheumatic compound (Pivari et al., 2019). In the present pandemic scenario, it would be of utmost importance to understand the effectiveness of this popular spice against *SARS-CoV-2* (the causative microorganism of COVID-19) by extrapolating computational predictions and already published literature. The hallmark of the present review is to scrutinize the mechanistic insight of this traditional ethnomedicine curcumin concerning viral lifecycle within the host cell and immune-modulation within the cell.

2. Methodology

A systematic literature review was conducted considering published literature from 2010 to 2021. A number of search engines like Pubmed, Google scholars, Dimensions and their cross-references were thoroughly studied. In the 'Dimensions' platform, 1606 articles were available with the phrase 'Curcumin and SARS-CoV-2', followed by 1216, 811 and 569 articles were available with the phrase 'Curcumin and COVID-19', 'Clinical trial of curcumin against COVID-19' and 'Immunomodulatory

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effect of curcumin against SARS-CoV-2′. Using VOSviewer software, a total of 4202 articles were exported and analysed the terms of co-occurrence (Supplementary Fig. 1). The result identified the novel areas to explore further. Considering the keywords "COVID-19", "viral infection mechanism", "viral lifecycle", "immune pathogenicity", "curcumin", "antiviral mechanism", etc., 205 published articles have been retrieved. Among them, the articles written in English, accessible full paper and relevance with the theme of the review, a total of 123 articles were finally selected for this comprehensive review.

3. COVID-19 – A briefing of pathophysiology

The preliminary symptoms like cough and cold along with fever in COVID-19, gradually develop into further complications like severe pneumonia, coagulopathy and acute respiratory distress syndrome (ARDS). Accumulating information suggest that *SARS-CoV-2* principally targets the cells which overexpress angiotensin-converting enzyme 2 (*ACE2*) and such target cells are airway epithelial cells, alveolar epithelial cells, vascular endothelial cells and macrophages in the lung. In general, men are more susceptible to COVID 19 and it has been linked with higher *ACE2* expression in them compared to women (Jin et al., 2020; Sharma et al., 2020; Tay et al., 2020). In addition to this, the risk of COVID 19 infections among children (Kelvin & Halperin, 2020) intrigued the need for host-pathogen interaction study in further detail.

The transmission of *SARS-CoV-2* occurs via respiratory aerosols and binds to the nasal epithelial cells in the upper respiratory tract resulting in severe pneumonia-like symptoms. Subsequent migration towards the lower respiratory tract causes damage in alveolar cells leading to the development of ARDS (Parasher, 2020). Also, COVID-19-associated coagulopathy (CAC) presents many similarities with those of sepsis-induced coagulopathy (SIC)/disseminated intravascular coagulation (DIC), haemophagocytic syndrome (HPS)/haemophagocytic lympho-histiocytosis (HLH), antiphospholipid syndrome (APS), and thrombotic microangiopathy (TMA) (Iba et al., 2020). DIC like massive intravascular clot formation is frequently observed among severely ill COVID patients (Iba et al., 2020). Cytokine storm has been strongly associated with COVID-19 so far. Discharge of proinflammatory cytokines (*IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF- α, TGF β*, etc.) and chemokines (*CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10*, etc.) from immune effector cells lead to such lethal uncontrolled systemic inflammatory response (Mehta et al., 2020). Although negligible changes in prothrombin time and platelet count were observed initially, unlike SIC/DIC, CAC displays

increased D-dimer and fibrinogen levels. Venous thromboembolism and arterial thrombosis are more frequent in CAC (Iba et al., 2020; Iba et al., 2020). Interestingly, secondary HLH is associated with COVID-19 disease severity and is characterized by the profound release of several cytokines and chemokines, including interleukin IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemo-attractant protein (MCP) 1, macrophage inflammatory protein (MIP) 1-α, and tumour necrosis factor (TNF)-α. Nonetheless, while neutrophil, monocyte, high-sensitivity C-reactive protein (Hs-CRP), procalcitonin were increased, the amount of eosinophil, lymphocyte numbers, lymphocyte-immune subsets, IgM, and C3 are found to be decreased significantly in COVID-19 patients (Li et al., 2020; Mehta et al., 2020).

4. Deciphering the mechanisms of COVID-19 infection

Several viral proteins encoded by the viral genome play a pivotal role in the viral lifecycle as well as immune evasion within the host cell (Astuti & Ysrafil, 2020; V'kovski et al., 2020). Viral invasion impairs the innate immune system and thus are more prone to viral infection. The mechanism of viral replication and disease progression has been schematically shown (Fig. 2) and highlighted the major viral proteins in Table 1.

4.1. Virus lifecycle within the host cell

Like other viral infection, the lifecycle of *SARS-CoV-2* involves four major steps i.e. viral entry by attachment and fusion into a host cell, endocytosis of the virus, genome expansion and virion release.

4.1.1. Viral attachment

Attachment is the initial event that brings viruses to the cell membrane surface of the target cell through a receptor. Several studies have already established the importance of host cell receptors in viral infections, for example, hemagglutinin (HA) of *Influenza virus* binds with sialic acid (Samji, 2009), Human Immune deficiency Virus (*HIV*) binds to CD4 receptor (Wilen et al., 2012). Globally, a variety of studies have already confirmed that the S protein of the β-Coronavirus is a significant determinant of virus entry into host cells (Ou et al., 2020). Previous studies have shown that envelope spike glycoprotein of *SARS-CoV* binds to CD209L (a C-type lectin) and angiotensin-converting enzyme 2 (*ACE2*) whereas *MARS-CoV* binds to Dipeptidyl peptidase 4 (*DPP4*, also
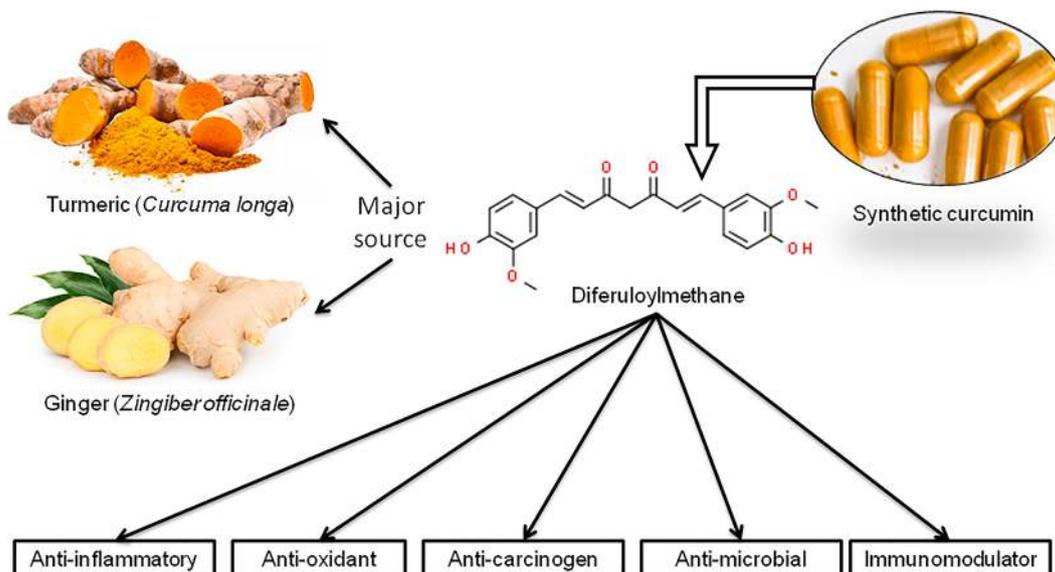

Fig. 1. Curcumin: Major sources, chemical structure and its medicinal properties.
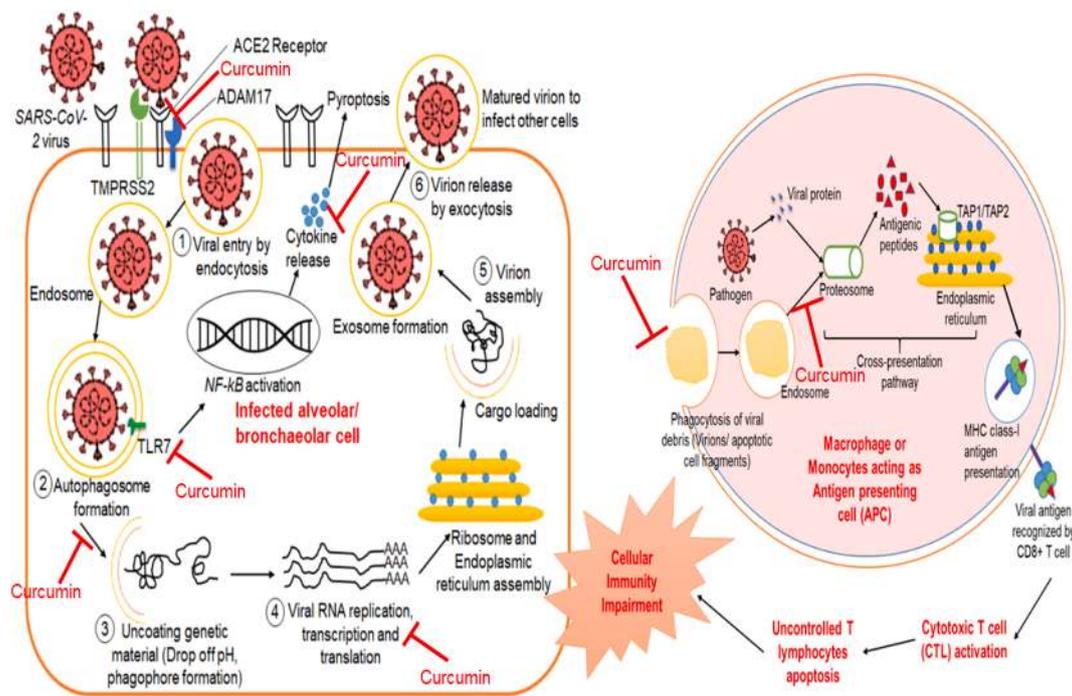
Fig. 2. Potential therapeutic targets of curcumin against *SARS-CoV-2* suggesting its role in COVID-19 management.

known as *CD26*). Similar to *SARS-CoV*, *SARS-CoV-2* also uses the angiotensin-converting enzyme 2 (*ACE2*) as a cellular receptor to penetrate the host system (Li et al., 2020).

For an enveloped virus, delivery of the viral genome requires membrane fusion reaction between the lipid bilayer of the virus and a host target cell membrane (Doms, 2016). In *SARS-COV-2*, this membrane fusion process is initiated by serine protease 2 (*TMPRSS2*) which activate the spike protein (S) through specific cleavage (Heurich et al., 2014; Hirano & Murakami, 2020; Hoffmann et al., 2020). The binding of this spike protein to the receptor triggers the *ADAM17*-mediated proteolytic "shedding" of *ACE2* at the ectodomain site for the promotion of viral uptake into the cell (Ciaglia et al., 2020; Scialo et al., 2020). Therefore, *TMPRSS2* and *ADAM17* both augment the viral entry into host cells and follow the clathrin-dependent and –independent endosomal pathway (Li et al., 2020).

4.1.2. Endocytosis of the virus

Following attachment and receptor clustering, many viruses are endocytosed and transported to endosomes where the low pH induces alterations in structural proteins of the virus that facilitate membrane fusion by protonating acidic residues. Generally, endocytic pathways include clathrin-mediated endocytosis, caveolae, macropinocytosis, and novel clathrin- and caveolae-independent pathways (Wang et al., 2008). In the case of *SARS-CoV-2*, clathrin-mediated endocytosis occurs in nasal epithelial cells because of the abundance of GTPase, dynamin whereas clathrin-independent endocytosis occurs in pneumocytes. However, due to comparatively higher expression of C-terminal binding protein (CtBP) 1 & 2 and P21-activated kinase 1, macropinocytosis also occurs in pneumocytes (Glebov, 2020). The virus-containing vacuoles undergo acidification, maturation and fusion with late endosomes or lysosomes. In the case of *Influenza A virus*, neuraminidase (NA) binds to lysosome-associate membrane proteins (LAMPs) and ruptures the membrane of the autophagosomes by deglycosylation (Ju et al., 2015).

Likewise in *SARS-CoV-2* infection, the ACE2-Spike protein complex is cleaved by cathepsin L protease within the autophagosomes leading to the fusion of viral and host cell membrane (Blaess et al., 2020). The acidic environment initiates conformational modifications in the viral capsid resulting in exposure of hydrophobic domains within the

endosomal membrane and forming a protein pore through which the viral genome can exit and enter the cytoplasm (Doms, 2016; Yamauchi & Helenius, 2013). In this regards, nonstructural viral proteins like (NSP2, NSP3, NSP4 and NSP6) play a crucial role in virus escaping through pore formation in late endosome (discussed in Table 1).

4.1.3. Viral genome expansion

The literature review suggests that RNA-dependent RNA polymerase (RdRp) plays an important role in the replication process of RNA viruses like *SARS-CoV-2* (Mathew & Hsu, 2018). After escaping from the autophagolysosome, genomic RNA undergoes an immediate translation. To avoid host detection, several non-structural proteins form a replication-transcription complex (RTC) as well as viral replication organelles like perinuclear double-membrane vesicles, convoluted membranes and small open double-membrane spherules (V'kovski et al., 2020). Two overlapping open reading frame (*ORF1a* and *ORF1b*) translated into the viral enzymes 3C-like protease (3CLpro) and papain-like protease (PLpro), help in viral replication via proteolytic cleavage. Another segment of RNA encodes structural proteins of the virus, such as the spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins (Chen et al., 2020; Oyanguren et al., 2020; Shereen et al., 2020). Translated structural proteins translocate into endoplasmic reticulum (ER) membranes and transport through the ER-to-Golgi intermediate compartment (ERGIC). Freshly formed genomic RNA undergoes N-encapsidation, resulting in budding into the lumen of secretory vesicular compartments (V'kovski et al., 2020; Zhang et al., 2020).

4.1.4. Virion release

Pathogen-associated molecular patterns (PAMPs) of the evolutionarily conserved microbes can be recognized by pattern recognition receptors (PRRs). Interestingly both *SARS-CoV* and *MERS-CoV* can induce the production of double-membrane vesicles that lack PRRs and then replicate in these vesicles, thereby avoiding the host detection of their dsRNA (Li et al., 2020). In this regards, viral single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA) are recognized by extracellular as well as endosomal Toll-like receptors (TLRs) and stimulate downstream signalling cascades (Vabret et al., 2020). It has been found that *TLR-7* plays a crucial role in *SARS-CoV-2* genome recognition and

Table 1

Description of the viral proteins encoded by *SARS-CoV-2* genome highlighting their role in the viral lifecycle and immune pathogenicity.

Viral proteins		Characteristics	Molecular functions	References
Structural protein	Spike-like surface glycoprotein	MW ~ 150 kDa; 1273 amino acids; Rich in glutamine, asparagine, leucine, phenylalanine and serine amino acids	S_1 subunit facilitates *hACE2*-mediated virus attachment; S_2 subunit promotes membrane fusion process into the host cell; help in promoting adhesion of infected cells with adjacent non-infected cells	Astuti & Ysrafil, 2020; Bianchi et al., 2020; Chen et al., 2020; Satarker & Nampoothiri, 2020
	Envelope glycoprotein	MW ~ 8–12 kDa; 76–109 amino acids; Contains N Terminal Domain (NTD) and hydrophilic C Terminal Domain (CTD)	Forms viriporins which is required for virion assembly and release	
	Membrane glycoprotein	220–260 amino acids; Contains hydrophilic C terminal and amphipathic N terminal	Determine the shape of the virus envelope; helps to stabilize nucleocapsids and promotes completion of viral assembly by stabilizing N protein-RNA complex, inside the internal virion	
	Nucleocapsid protein	Composed of a serine-rich linker region between NTD and CTD	NTD forms orthorhombic crystals and binds to the viral genome; linker region regulate self- functioning; CTD promotes nucleocapsid formation; promotes the activation of *COX-2* leading to inflammation in the lungs; inhibits *IFN-1* causing restrictions in immune responses	
Non-structural proteins		NSP1 (Leader protein)	Inhibit host mRNA translation, antagonize IFN signalling and induce inflammatory cytokines and chemokines	Astuti & Ysrafil, 2020; Min et al., 2020; Samaddar et al., 2020; Yoshimoto, 2020; Zhang et al., 2020
		NSP2	Binding to prohibitin-1 (*PHB1*) and prohibitin-2 (*PHB2*) leads to disruption of the host cell environment	
		NSP3	Encode papain-like protease (PLpro) that helps to cleave the site between NSP2 and NSP3 and release essential viral proteins for viral activity	
		NSP4 (Transmembrane domain 2)	Interacting with NSP3 causes rearrangement of the host cell membrane	
		NSP5	Encode chymotrypsin-like protease (3CLpro/Mpro) that cleaves at 11 different sites to produce mature and intermediate viral polyproteins	
		NSP6 (Putative Transmembrane domain)	Restricting autophagolysosome development cause hindrance of autophagosomes from transporting viral components for degradation in lysosomes	
		NSP7 (Peptide cofactor)	Forms a complex NSP8 and NSP12 to yield RNA polymerase activity	
		NSP8 (Peptide cofactor)	Forms hexadecameric complex of RNA polymerase	
		NSP9	Encode RNA-binding protein phosphatase that helps in viral genome replication and transcription	
		NSP10	Interacting with NSP14 and NSP16 to stimulate SAM-dependent methyltransferase activity and 2′-*O*-Ribosemethyltransferase activity respectively	
		NSP11	Unknown activity yet	
		NSP12 (RdRP)	Encodes RNA-dependent RNA polymerase that replicates viral RNA	
		NSP13 (Helicase)	Unwinds duplex RNA; elicits 5′-triphosphatase activity to introduce a 5′-terminal cap of mRNA	
		NSP14 (N7-methyltransferase)	Proofreading of viral genome by endonuclease and methyltransferase activity	
		NSP15 (Endoribonuclease)	Cleaves RNA at 3′-uridylates to form a 2′-3′ cyclic phosphodiester product that protects viral RNA from host recognition and inhibit innate response	
		NSP16 (2′-*O*-Ribosemethyltransferase)	Methylate 2′-hydroxyadenine using SAM as methyl pool thereby avoid MDA5 recognition of viral RNA and inhibit innate immunity regulation	

clearance through exocytosis (Onofrio et al., 2020). Also, an *in-silico* experiment reported that extracellular *TLR-4* is most likely to be involved in recognizing molecular patterns from *SARS-CoV-2* (Choudhury & Mukherjee, 2020). However, the freshly formed envelope glycoproteins are inserted into the membrane of the endoplasmic reticulum or Golgi, and the Nucleocapsid is shaped by the combination of genomic RNA and Nucleocapsid protein. The virions germinate into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). Finally, the vesicles containing the virus particles fuse with the plasma membrane to release the virus through exocytosis and infect surrounding cells (Li et al., 2020; Shereen et al., 2020).

4.2. Cellular immunity against infection

A large group of scientists have tried to understand the immunological perspective of COVID-19. Usually soon after the virus enters into the host cell, the cellular immune response is initiated by PPRs recognition of PAMPs. This ligand binding activates several signalling pathways like NF-kB, IRF3 and AP-1 which synergistically stimulate IFN-1 production thereby limit virus entry as well as restrict viral replication (Taefehshokr et al., 2020). In a healthy individual, a well-coordinated immune response characterizes the first line of defence against viral infection, while on the contrary, extreme inflammatory innate response and dysregulated adaptive immune system ensue detrimental tissue damage at the systemic level (Catanzaro et al., 2020). Although coronaviruses have a preferential tropism for lung cells, it mostly impairs the innate immune machinery by directly infecting T cells (Wang et al., 2020). *SARS-CoV-2* targets multiple aspects of innate immunity like cytokine storm, impairing interferon signalling and suppression of antigen presentation on both MHC class I and II (Taefehshokr et al., 2020). At the same time, an accumulation of mononuclear cells in the lungs coupled with a low level of hyperactive T-cells in the peripheral blood indicates that T-cells are attracted away from blood towards the infected sites to control the viral infection (Li et al., 2020; Tay et al., 2020). Both B-cells and T-cells responses against *SARS-CoV-2,* are diagnosed in the blood around 7 days after the onset of symptoms.

In the lung/alveolar epithelial cells, *SARS-CoV-2* mainly deploy cellular immune responses and interfere with the IFN-signalling pathway with the membrane protein (M), Nucleocapsid protein (N) and non-structural proteins like NSP1, NSP3, PLpro acting as IFN antagonist (Taefehshokr et al., 2020; Tay et al., 2020). During infection, non-structural proteins of this virus protect themselves from recognition by PRRs and inhibit the transcription of interferons leading to modulate IFN response in plasmacytoid dendritic cells (pDC) and other immune cells. This alters the cytokine secretion profile of infected cells to enhance the recruitment of myeloid immune cells over NK cells, which in turn produce more cytokines, creating a cycle of inflammation that damages the lung (Taefehshokr et al., 2020). Apart from this interferon signalling, antigen presentation is an important antiviral mechanism that is being affected in the case of COVID-19. In this regards, Macrophages in the lung and upper respiratory tract act as sentinel cells and are among the first immune cells to encounter incoming virion whereas DCs are key players in antigen presentation, cytokine production, instructing specific T cell responses (Kumar et al., 2020; Li et al., 2020; Taefehshokr et al., 2020). Nonetheless, coronaviruses trigger different complement pathways producing C3a and C5a components which then combine with dysregulated neutrophilia, endothelial injury and hyper-coagulopathy seem to be entangled to drive the severity of COVID-19 (Java et al., 2020; Liu & Ying, 2020).

After an encounter with the infected cells, the viral antigen, through the endosomal cross-presentation pathway, will be presented to the antigen presentation cells (APC) and its antigenic peptides are accessible by major histocompatibility complex (MHC-I) or human leukocyte antigen (HLA) in humans thereby recognized by virus-specific cytotoxic T (CD8$^+$ T) lymphocytes. Antigen presentation subsequently stimulates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells (Li et al., 2020). In the case of a healthy immune system, T cells become activated when CD8$^+$ T cells recognize viral antigens by MHC-I molecules present on the infected cells. Then activated T cells undergo clonal expansion to proliferate into a large number of progeny T cells with identical receptors. This ultimately lyses the infected cells by inducing apoptosis and secrete pro-inflammatory cytokines (Gutierrez et al., 2020). As a result, uncontrolled apoptosis of T lymphocytes occurs with the release of pro-inflammatory cytokines leads to local tissue damage and impairment of the immune system.

5. Chemistry of curcumin

5.1. Sources & chemical composition

Curcumin is the main natural polyphenol found in turmeric (*Curcuma longa*) and other species of the *Zingiberaceae* family (Amalraj et al., 2017; Hewlings & Kalman, 2017). The powdered extracts of turmeric-dried roots may contain essential oils, proteins, fat, minerals, carbohydrates, moisture, and curcuminoids (Ahmad et al., 2020; Prasad et al., 2014). The aroma of this spice is principally derived from sesquiterpenes which is a mixture of α- and β-turmerones with aromatic turmerone (Amalraj et al., 2017). The polyphenols (curcuminoids) are a mixture of 71.5% curcumin, chemically a diferuloylmethane [1,7-bis(4-hydroxy-3-methoxy-phenyl)-hepta-1,6-diene-3,5-dione] mixed with its two derivatives, 19.4% demethoxycurcumin [4-hydroxycinnamoyl-(4-hydroxy-3-methoxycinnamoyl) methane] and 9.1% bisdemethoxycurcumin [bis-(4-hydroxy cinnamoyl) methane], defining the chemical formulae as $C_{21}H_{20}O_6$, $C_{20}H_{18}O_5$ and $C_{19}H_{16}O_4$ respectively (Amalraj et al., 2017; Gupta et al., 2013; Hewlings & Kalman, 2017; Prasad et al., 2014).

5.2. Pharmacokinetic property

Curcumin can be delivered by oral intake, subcutaneous, intraperitoneal, intravenous injection, topical and nasal treatment (Prasad et al., 2014). However, pieces of the literature suggest that curcumin has poor absorption, biodistribution, metabolism, and bioavailability despite having vast pharmacological significance (Dei Cas & Ghidoni, 2019; Prasad et al., 2014). After oral intake, curcumin gets metabolized within the liver through extensive phase I and II biotransformation with the help of gut microbiota (Dei Cas & Ghidoni, 2019). In phase I reaction, double bonds of curcumin is reduced by alcohol dehydrogenase into dihydro-curcumin, tetrahydro-curcumin, hexahydro-curcumin, and octahydro-curcumin (Dei Cas & Ghidoni, 2019; Nelson et al., 2017). Later in phase II reaction, curcumin and its phase I metabolites are rapidly conjugated with glucuronic acid by UGTs (Uridine 5′-diphospho-glucuronosyltransferases) and sulfate by SULTs (Sulfotransferases) at the phenol position (Dei Cas & Ghidoni, 2019).

6. Major targets of curcumin against COVID-19

Based on the above-explained mechanisms of infection pathogenesis, two major targets can be considered for the therapeutic approach - one is the lifecycle of the virus within the host cell and another part is the ability of the innate immune system to defend against infection.

6.1. Targeting virus lifecycle within the host cell

Combating viral infection, viral entry and its replication within the host cell are the most important events and have always been a challenge. While non-enveloped viruses (e.g. *Adenovirus, Poliovirus, Rotavirus, Hepatitis A virus, Coxsackievirus*) can directly or indirectly penetrate the plasma membrane, an enveloped virus (e.g. *Hepatitis C virus, Rubella virus, HIV, Ebola virus, Influenza virus, Coronavirus*, etc.) requires the fusion of the viral envelope with a cellular membrane (Thorley et al., 2010).

6.1.1. Inhibition of viral attachment with the host cell

Evidences suggest the mechanism behind curcumin-induced inhibition of enveloped virus entry into a host cell. Several *in vitro* experiments have been conducted to explore the role of curcumin and its analogues on viral entry inhibition (Anggakusuma et al., 2014; Mathew & Hsu, 2018). For instance, membrane fluidity experiments indicate that curcumin impairs both viral binding and fusion in the case of *HCV* and thus inhibit cell-to-cell transmission independent of the viral genotype (Anggakusuma et al., 2014). Also, curcumin has a direct effect on viral particle infectivity redirected by the inhibition of haemagglutination in *H1N1* as well as in *H6N1* subtype and treatment with 30 μM curcumin reduced more than 90% virus yield (Praditya et al., 2019a). Consistently, both the zika and chikungunya virus was responded to 5 μM curcumin without effecting the cellular viability. In a dose- and time-dependent manner, curcumin can reduce the infectivity of the enveloped viruses without disturbing the integrity of the viral RNA (Mounce et al., 2017).

Recently literature revealed that curcumin holds the better binding capability to the *ACE2* receptors and may hinder the entry of the COVID-19 virus (Zahedipour et al., 2020). *In-vivo* studies revealed that curcumin derivatives at a comparatively low dose can decrease the level of *Ang II* thereby upregulate *ACE2* protein (Pang et al., 2015; Xu et al., 2018). Also, scientists have tried to explore the viral entry inhibition efficiency of curcumin using an *insilico* simulation study. It has been found that curcumin can bind to the human ACE2 and receptor-binding domain of the viral S-protein with a binding energy of −7.8 Kcal/mol and −7.9 Kcal/mol respectively (Jena, 2019). Later, it has been found that keto and enol form of curcumin interacts (binding energy −20.753 Kcal/mol and −16.08067 Kcal/mol respectively) with the key residues (Q493, N501, Y505, Y489 and Q498) of the receptor-binding motif (RBM) in the spike glycoprotein (Shanmugarajan et al., 2020). Also, curcumin may play important role in *ADAM17* inhibition (Borah et al., 2016). Recently curcumin possesses a strong binding affinity (19.86 kJ/mol) with *TMPRSS2* (Motohashi et al., 2020).

6.1.2. Inhibition of endocytic pathway within the host cell

To date, no shreds of evidence were reported on the direct effect of curcumin on the viral genome released into the host cell. But there is plenty of literature that supported the impact of curcumin on lysosomal function (Rainey et al., 2020; Zhang et al., 2016). Studies found that curcumin induces endoplasmic reticulum stress which cause an unfolded protein response and Ca^{2+} release thereby enhances apoptosis through destabilizing the mitochondrial compartment in the cancerous cell (Moustapha et al., 2015; Oyanguren et al., 2020). Besides this, lysosomal membrane permeabilization is involved in curcumin-induced programmed cell death in the lung cancer cell, where curcumin pre-treatment causes lysosome rupture and subsequent release of several lysosomal proteins and this cytosolic relocation of lysosomal proteins leads to cellular apoptosis (Chen et al., 2012). But apoptosis seems to be a "devil" in the case of cytopathic virus like *SARS-CoV-2* because this phenomenon causes extreme inflammation leading to vascular leakage (Tay et al., 2020). In the non-cancerous cell, curcumin can stabilize the pathogen containing vacuolar membrane and prevents the escape of cytosolic pathogens, thereby inhibit the fusion with lysosomes (Marathe et al., 2012). Emerging evidence indicates the function of curcumin may vary depending on the cellular environment. In the case of COVID-19, curcumin may block autophagosomes-lysosome fusion by stabilizing pathogen containing vacuole and restrict genome replication.

6.1.3. Inhibition of viral genome expansion into host cell

Previous literature suggested that curcumin plays important role in hindering viral genome expansion through several mechanisms either within virus particle or host cells. For instance, curcumin was found to have an inhibitory effect against the Hepatitis B virus (*HBV*). It has been observed that *PGC1-α*, co-activator of *HBV* transcription, was down-regulated by curcumin treatment (Mouler Rechtman et al., 2010). On the other hand, curcumin downregulates *HCV* gene expression via suppression of the *Akt-SREBP-1* activation (Kim et al., 2010). However, curcumin can potentially inhibit *HBV* gene replication *via* down-regulation of covalently closed circular DNA-bound histone acetylation (Wei et al., 2017). A comprehensive analysis suggested that curcumin inhibits *HIV-1* and *HIV-2* proteases at concentration IC_{50} 100 μM and 250 μM respectively by substrate binding activity while *HIV-1* integrase was inhibited at concentration IC_{50} 40 μM. In addition to this, curcumin also hinders transcription elongation by inhibiting the *Tat* protein of *HIV-1* (Ali & Banerjea, 2016; Kumari et al., 2015; Prasad & Tyagi, 2015). Recently an *insilico* analysis revealed that curcumin has a potential binding affinity with Ebola viral protein through which viral entry and replication might be inhibited (Noor et al., 2018).

Recently some molecular docking studies reported that curcumin can possess an inhibitory effect on viral protein translation by binding with the active sites of $3CL^{Pro}$/chymotrypsin-like protease (NSP3) and PL^{Pro}/papain-like protease (NSP5) (Das et al., 2020; Linda Laksmiani et al., 2020).

6.2. Role of curcumin in immunomodulation

Apart from targeting the viral lifecycle, the immune system plays an important role against infection. The role of curcumin as an immune-modulator against a plethora of viral and bacterial infection has been extensively studied (Lai et al., 2020; Mathew & Hsu, 2018; Sordillo & Helson, 2015). Several mechanisms of cellular immunity against pathogen have been observed.

6.2.1. Autophagy and apoptosis

Autophagy and apoptosis are two major interconnected host cell responses to viral infection. Autophagy is a catabolic process that degrades and recycles cytosolic materials while apoptosis is a highly regulated form of cell death in which the cell contains the necessary information to die on its own (Mehrbod et al., 2019). Earlier kinds of the literature confirmed that curcumin can induce G2/M cell cycle arrest,

autophagy, stimulate apoptosis, and interrupt molecular signalling (Rainey et al., 2020). Several *in-vitro* studies also confirmed that curcumin causes apoptosis by blocking the PI3K-Akt pathway (Kuttikrishnan et al., 2019), by inhibiting the NF-kB activation in tumour cells and releasing cytochrome *c* (Araveti & Srivastava, 2019).

Interestingly, these two processes play a negative role in viral infection. For example, autophagy stimulates the replication of *Influenza A virus* (Wang et al., 2018), *HIV-1* and HIV disease progression (Killian, 2012). Also, autophagy is involved in antigen preparation and presentation (Crotzer & Blum, 2009) which produce viral antigen on the cell surface and eventually triggers T-cell mediated signalling pathway. Therefore, inhibition of normal autophagy and apoptosis can be the target to combat viral infection. In this favour, curcumin potentially inhibits cellular apoptosis and autophagy by inhibiting caspase-3 activation (Li et al., 2017), inducing the expression of *Bcl-2* and inhibiting the expression levels of *Bax, beclin-1, BNIP3* and *SIRT1* thereby show a protective effect against hypoxia/reoxygenation (HUANG et al., 2015), uncontrolled tissue damage (Zhao et al., 2017).

6.2.2. TLRs activation

Activation of Toll-like receptors (TLRs) play a pivotal role in the activation of innate immune response and inflammation. It has been found that curcumin can inhibit extracellular *TLR2, TLR4* and intracellular *TLR9* (Boozari et al., 2019). Curcumin attenuates activation of *TLR4* acting directly on the receptor or by its downstream pathway and thus suppress the release of cytokines and chemokines (Panaro et al., 2020). In the case of *Influenza A virus*, curcumin can inhibit virus-induced activation of *TLR2* and *TLR4* thereby block the *NF-kB* signalling pathway (Dai et al., 2018). A mouse model experiment revealed that post-infection intravenous treatment of 200 mg/kg of body weight can significantly reduce pro-inflammatory cytokines level and augment anti-inflammatory cytokines by inhibiting TLR2, TLR4 and TLR9 (Abo-Zaid et al., 2020). However, another study suggested that curcumin may play an inhibitory role against the activation of *TLR7* (Lai et al., 2017) thereby reducing the production of INF-α and TNF-α. In this regards, curcumin can inhibit ROS generation by increasing glutathione (GSH) activity as well as modulating several signalling pathways like PPARγ, JNK, NF-kB and Nrf2 (Kim et al., 2020; Liu & Ying, 2020).

6.2.3. T-cell Regulation

Regulation of T-cell is one of the most important mechanisms in cellular immunity, which can be modulated by curcumin and its derivatives (Bhattacharyya et al., 2010; Chai et al., 2020; Kliem et al., 2012). Curcumin thwarts T cell-activation-induced Ca^{2+} mobilization with IC_{50} of 12.5 μM and thereby impedes Nuclear Factor of Activated T Cells (NFAT) activation and NFAT-regulated cytokine expression (Kliem et al., 2012). Besides this, curcumin abolishes CD2/CD3/CD28-initiated T-helper cell activation by constraining cell proliferation, differentiation and cytokine production. Also, a spontaneous decline of CD69 expression and upregulation of CCR7, L-selectin, and TGF-β1 was observed (Kim et al., 2013). This may lead to inhibit the suppressive activity of T-regulatory cells (Bhattacharyya et al., 2010). A more recent study revealed that curcumin can ease the grade of severity of ALI/ARDS and unrestrained inflammation by promoting the delineation of immature $CD4^+$ T cells to $CD4^+$ $CD25^+$ $FOXP3^+$ Treg (T-regulatory) cells (Chai et al., 2020).

6.2.4. Cytokine regulation

Viral infection is mostly resulted in a discrepancy in pro-and anti-inflammatory cytokines as a part of innate immunity activation to eliminate viruses. A large number of evidence suggest that curcumin potentially regulate cytokine release (Bereswill et al., 2010; Mathew & Hsu, 2018; Sordillo & Helson, 2015). Curcumin inhibited the production of IL-8, MIP-1α, MCP-1, IL-1β, and TNF-α by PMA- or LPS-stimulated monocytes and alveolar macrophages in a concentration- and a time-dependent manner (Mathew & Hsu, 2018) while an integrated

analysis revealed that five asymmetric mono-carbonyl analogues of curcumin can hinder the release of TNF-α and IL-6 in a dose-dependent pattern (Liang et al., 2014). It has been shown that curcumin significantly increases the level of anti-inflammatory cytokine IL-10 and decrease pro-inflammatory cytokine expression in the mouse intestine (Bereswill et al., 2010). Another study found that IL-10 concentrations were significantly increased in curcumin-treated (average concentration of 200 mg/kg) hepatic cirrhosis mouse when compared to the non-treated group (Abo-Zaid et al., 2020). Decreased serum level of TNF-α and IL-6 was also found in rat with acute renal injury after treatment of curcumin at a concentration of 100 μg/g body weight (Zhu et al., 2017). A structure–activity relationship coupled with a molecular docking study showed that most of the curcumin derivatives effectively inhibit *H1N1* neuraminidase activity. Along with this, significant attenuation of pro-inflammatory cytokines (*TNF-α, IL-6* and *IFN-γ*) levels was observed in mice after curcumin treatment (Lai et al., 2020). Even so, a recent study on the mouse with an acute lung infection (ALI/ARDS) suggested that *IL-17A, MPO-producing neutrophils* decreased after pretreatment with 50 μL of curcumin at a concentration of 20 mg/mL (Chai et al., 2020). Also, curcumin-stabilized silver nanoparticles (Cur-AgNP) significantly reduced HIV replication within the host cell by inhibition of pro-inflammatory cytokines level (Sharma et al., 2017). However, a mouse model study revealed that curcumin potentially decreases the systematic as well as local myocardial expression of pro-inflammatory cytokines (*TNF- α, IL-6, IL-1β*) resulting in inhibition of NF-kB activation in *Coxsackievirus* infection (Song et al., 2013). In contrast to this, a reduction of only local tissue inflammation was found in case of *HSV-2* infection resulting decrease the risk of HIV acquisition in the female genital tract of women (Vitali et al., 2020). Furthermore, Sordillo & Helson (2015) also showed a number of evidences regarding the action of curcumin against cytokine storm. They found that curcumin can effectively block the release of pro-inflammatory cytokines and thereby can be suggested as useful for treatment of Ebola patients.

6.2.5. Complement system

Curcumin significantly inhibit the classical pathway and zymosan-induced activation of the alternate pathway of the complement system in a dose-dependent manner (Kulkarni, 2005). In support of this, curcumin is also shown to decrease C3 activity with increase IgG and IgM, thereby trigger humoral immunity (Çiftçi, 2011).

7. Potential role of curcumin in COVID-19 management

Since mid-December of 2019, the pandemic COVID-19 has been spreading exponentially and shook the global health scenario. The symptoms of *SARS-CoV-2* infection develop ARDS by manifesting Acute Lung Infection (ALI) which was also found in previous infections like *SARS-CoV, MERS-CoV, H5N1, H7N9*. However, 'cytokine storm' is the common phenomenon that plays a crucial role in the development and progression of fatal pneumonia (Liu & Ying, 2020; Mehta et al., 2020). Hence, apart from the inhibition of viral entry into the host cell, targeting the regulation of the cytokine is one of the most important mechanisms of combating COVID-19 infection. Many studies have highlighted the usefulness of herbal medicines like Phytoextracts, fruit extracts, traditional spices, etc. in the improvement of severe illness. Curcumin is one of the extensively studied compounds that has already claimed for its benefits in human health and disease prevention. Supplementary Table 1 shows that curcumin can potentially block pathogen entry into host cell irrespective of the presence of envelope, along with inhibiting the viral genome expansion while it can also inhibit virion release mechanisms in some cases. Comparing with the available literature, it has been suggested that CoVs infection can be prevented by inhibition of viral entry, viral genome release and replication within the host cell. In addition to this, curcumin induced immunomodulation plays an important role in viral infection. The present review portraits the possible underlying molecular aspects of the disease and how curcumin can play role in the prophylaxis of COVID-19 (Fig. 2).

While discussing the role of curcumin on COVID-19 treatment, *insilico* studies play important role in understanding the possible mechanism. Recently multi-omics based study has identified curcumin as a candidate prophylactic agent (Barh et al., 2020). Curcumin possesses the binding efficiency to the RBD of the viral spike protein as well as human ACE2 causing the blockage of ACE2 receptor resulting in inhibition of the viral attachment with the host cell (Jena, 2019; Shanmugarajan et al., 2020). Also, curcumin potentially binds to TMPRSS2 and ADAM17 leading to mispriming of the S-protein of the virus and hACE2 (Borah et al., 2016; Motohashi et al., 2020). This possibly inhibits the membrane fusion process of viral entry into the lung/alveolar epithelial cells. In addition to this, curcumin can potentially increase soluble ACE2 protein which may competitively bind with *SARS-CoV-2* not only to neutralize the virus but also rescue cellular ACE2 activity which negatively regulates the renin-angiotensin system (RAS) to protect the lung from injury (Zhang et al., 2020). Not only entry inhibition, but curcumin can also impair the endosome-lysosomal fusion process by endosomal membrane stabilization (Marathe et al., 2012) and lysosomal membrane permeabilization (Chen et al., 2012) that eventually blocks the viral genome released into the host cell and prevent replication. *Insilico* simulation suggests the binding efficiency of curcumin with the NSP3 and NSP5 may affect the RdRP activity of viral genome replication and DMV formation (Astuti & Ysrafil, 2020; Das et al., 2020; Linda Laksmiani et al., 2020; Soni et al., 2020). Also, impairment of the PLpro activity eventually protects the host cell environment by blocking NSP2 function and prevents the endosomal escape of essential non-structural proteins (Astuti & Ysrafil, 2020; Yoshimoto, 2020). Hence, it can be proposed that curcumin may inhibit several stages of the viral lifecycle within the host cell.

Earlier pieces of literature have already established the fact that curcumin acts as an immunomodulatory agent against viral infections and other inflammatory diseases. It was found that curcumin binds to a series of enzymes (carbonyl reductase, glutathione-S-transferase, glyoxalase, etc.) involved in reactive oxygen species (ROS) metabolic pathway and upregulate their expression (Larasati et al., 2018). In oxidative stress condition, curcumin decreased malondialdehyde and nitric oxide levels by increasing thiol, superoxide dismutase, and catalase levels (Memarzia et al., 2021). In the case of COVID-19, curcumin-induced inhibition of the autophagolysosome fusion may disturb MHC class-II antigen preparation and processing in the infected alveolar/lung epithelial cells. Thus, $CD4^+$ T cells cannot be recognized by the APC (dendritic cell) thereby become unsuccessful to differentiate into T-helper cell. This inactivation of T cells is one of the primary mechanism behind the inhibition of pro-inflammatory cytokines release. Apart from this, curcumin interferes with TLRs leading to the NF-kB signalling pathway (Kim et al., 2020; Liu & Ying, 2020). This also activates IFN-1 signalling cascades that restricts viral genome replication and viral entry into the T cells. Overall, curcumin pro-inflammatory cytokine interleukin 4 (IL)-4, transforming growth factor-beta, IL-17, interferon-gamma levels, and type 1/type 2 helper cells (Th1)/(Th2) ratio in conditions with disturbance in the immune system (Memarzia et al., 2021). Recently an integrated *insilico* simulation study revealed that hydrazinocurcumin act as a warrior against COVID-19 by altering the cytokine regulation (H. Noor et al., 2021). The immunomodulatory role of curcumin against this infection understood so far, supports its potential prophylactic use, which either directly inactivates T-cell or regulate cytokine production.

The present review attempted to understand the molecular mechanism of COVID-19 pathogenesis. A comparative analysis has been performed (Table 2) considering several viral diseases and highlighted the dose-dependent response of curcumin in multiple test system (*in vitro*, *in vivo* and human population-based studies). It has been suggested that pre-treatment of curcumin may regulate lysosomal functions in a dose-dependent manner through ER/calcium/mitochondrial pathway (Rainey et al., 2020). While most of the studies showed that curcumin

Table 2

The dose-dependent response of curcumin in multiple test system (*in vitro*, *in vivo* and population based studies).

Study system	Dose	Time of administration	Route of administration	Mechanism of action	References
***In vitro* study**					
Human Huh-7 cells	10–20 μM	Pre- transfection	NA	Activates lysosomal destabilization, induces apoptosis	Oyanguren et al., 2020
HeLa, BHK-21, and Vero-E6 cells	5 μM	Pre-transfection	NA	Reduce the infectivity of the Chikungunya and Zika viruses without disturbing the integrity of the viral RNA	Mounce et al., 2017
HepG2, HepG2.2.15 and HEK293 cells	50–150 μM	Pre-transfection	NA	Inhibits *HBV* transcription by downregulation of PGC1-α	Mouler Rechtman et al., 2010
Human Huh-7 cells	5–15 mM	Pre-transfection	NA	Inhibits *HCV* gene expression by suppressing *Akt-SREBP-1* activation	Kim et al., 2010
PBMC cell line	IC_{50} 100 μM	Post-transfection	NA	Attenuates viral replication by inhibiting *HIV-1* protease	Kumari et al., 2015; Prasad and Tyagi, 2015
	IC_{50} 250 μM	Post-transfection	NA	Attenuates viral replication by inhibiting *HIV-2* protease	
	IC_{50} 40 μM	Post-transfection	NA	Attenuates viral replication by inhibiting *HIV-1* integrase	
HEK-293 T cells	80 μM	Post-transfection	NA	Inhibits *HIV-1* virus transcription by promoting *Tat* protein degradation	Ali & Banerjea, 2016
HepG2.2.15 cells	20 μmol/L	Post-transfection	NA	Inhibits *HBV* gene replication *via* down-regulation of cccDNA-bound histone acetylation	Wei et al., 2017
PBMC cells	IC_{50} 12.5 μM	Post-transfection	NA	Inhibit T cell activation by blocking Ca^{2+} mobilization and NFAT activation	Kliem et al., 2012
PBMC cells	20 μg/ml	Post-transfection	NA	Decline of CD69 expression and upregulation of CCR7, L-selectin, TGF-β1; attenuates T cell activation	Kim et al., 2013
***In vivo* study**					
ALI/ARDS Mouse	50 μL (20 mg/ml)	Pre-infection	Intra-peritonial	IL-17A ↓, MPO-producing neutrophils ↓, NF-κB p65↓ in lungs, IL-10 ↑	Chai et al., 2020
Mice with liver injury	200 mg/kg body weight	Post- infection	Intra-venous	Reduce pro-inflammatory cytokines level and augment anti-inflammatory cytokines by inhibiting TLR2, TLR4 and TLR9	Abo-Zaid et al., 2020
H1N1 infected mouse	25 mg/kg body weight /day	Post-infection	Intra-peritonial	TNFα↓, IL-6↓, INF-γ↓	Lai et al., 2020
Rat with acute kidney injury	100 mg/kg body weight	Post-infection	Intra-peritonial	TNFα↓, IL-6↓	Zhu et al., 2017
Human population study					
Healthy male	500 mg/3days	Pre-exercise	Oral intake	IL-6↓	Sciberras et al., 2015
Osteoarthritis patients	80 mg daily	Intervention	Oral intake	Decrease the level of C-reactive protein (CRP), CD4 + and CD8 + T cells, Th17 cells and B cells frequency	Atabaki et al., 2020
COVID-19 patient	160 mg curcumin daily for 2 weeks	Intervention	Oral intake (nano-micelles)	IL-6↓, IL-1β↓	Hassaniazad et al., 2020; Saber-Moghaddam et al., 2021; Valizadeh et al., 2020
	1 g curcumin daily for 2 weeks	Intervention	Oral intake (Curcumin-piperine capsule)	Trial continue	Miryan et al., 2020

can inhibit viral transcription when treated after exposure, some studies indicate that it can regulate cytokine release in case of pre-exposure treatment. However, a major criticism of curcumin has been raised regarding its poor bioavailability. Though dose-escalating studies have indicated the safety of curcumin at doses as high as 12 g/day over 3 months (Gupta et al., 2013), curcumin possesses very poor bioavailability and often found in undetectable concentrations in blood and extra intestinal tissue due to its chemical instability, rapid metabolism, poor absorption and rapid systemic elimination (Dei Cas & Ghidoni, 2019; Lopresti, 2018; Prasad et al., 2014). Since most of the studies revealed the oral delivery of curcumin, it has been suggested that subcutaneous treatment of formulated curcumin provide effective and sustained tissue concentration (Prasad et al., 2014). In addition to this, it has been found that different novel delivery systems such as solid lipid particle, micellar system, or hydrophilic nanoparticles could increase curcumin concentration up to 15–20 fold (Dei Cas & Ghidoni, 2019).

Recent clinical trial showed that daily four times oral intake of 40 mg nanocurcumin in micelles formation for 2 weeks can significantly decrease IL-6 and IL-1β expression and secretion in COVID-19 patients (Hassaniazad et al., 2020; Saber-Moghaddam et al., 2021; Valizadeh et al., 2020). However, another trial of curcumin-piperine co-

supplementation against COVID-19 is still being continued (Miryan et al., 2020). Thimmulappa et al., (2021) suggested the nasal delivery of liposomal curcumin may inhibit *SARS-CoV-2* infectivity by deposition of curcumin in the lower airways at a higher concentration and consequently mitigate pulmonary inflammation and the progression to ARDS. In summary, accumulated evidences suggested that curcumin can be effective against *SARS-CoV-2* as supportive therapy. Table 2 provides a systemic representation of effective curcumin dose and hence can be utilized as a reference frame for validation in future.

8. Conclusion

While the entire world is putting efforts into the discovery of a vaccine against coronavirus infection, the antiviral potential of curcumin against *SARS-CoV-2* shows a promising role in COVID-19 management. Since ancient time, curcumin possesses a multifaceted role in several disease management. As an antiviral agent, existing literature suggested that targeting viral lifecycle and cellular responses are important strategies to combat viral infection. The present review emphasized the molecular mechanism of host-pathogen interaction and subsequent immune response in the host. In this background, curcumin

can potentially inhibit the SARS-CoV-2 entry within human mainly by blocking the ACE2 receptor, hinder viral genome replication by altering viral non-structural protein activity. Not only viral entry, curcumin indeed can prohibit 'cytokine storm'-induced multi-organ failure by constraining the inflammatory response and other cellular immune response. However, having such potency, it can be suggested that curcumin must be administered as solid lipid particle, micellar system, or hydrophilic nanoparticles due to its poor bioavailability. Hence, further studies warrant detailed dose–response analysis for validation in the large-scale human population.

Ethical statement

This material is the authors' own original work, which has not been previously published elsewhere.

The paper is not currently being considered for publication elsewhere.

The paper reflects the authors' own research and analysis in a truthful and complete manner.

The paper properly credits the meaningful contributions of co-authors and co-researchers.

The results are appropriately placed in the context of prior and existing research.

All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.

All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

Credit Author Statement

SD: Literature search, Manuscript writing, Figure and table preparing; PB: Supervision, Manuscript writing and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2021.104503.

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