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Potential role of Curcumin against viral infections with a view on structure and pathogenesis of COVID-19

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ABSTRACT

A novel Coronavirus disease 2019 (nCOVID-19) is an enveloped, positive sense, single stranded RNA viruses of zoonotic origin caused by Severe acute respiratory syndrome coronavirus, currently responsible for pandemic health crisis. Due to increasing mortality rate there is an immediate need to develop possible treatments and understand the mechanism through which virus can cause complications in human body. The review intended to provide link between natural product as treatment and COVID-19 disease. Therefore, this review summarizes the structure, pathogenesis as well as understanding the various role of curcumin as a treatment option for COVID-19 which includes: targeting viral entry to host cells, targeting viral replication, anti-viral, anti-inflammatory and anti-oxidant. Hence, curcumin can be a potential treatment option for COVID-19 patients and this review also suggest that more clinical research and development is needed in order to prepare a new drug for emerging SARS-CoV-2.

Keywords: COVID-19, angiotensin-converting enzyme II (ACE2), Curcumin

1. Introduction

It was just the beginning of the Year 2020; the world is running smoothly in a fast-paced life, suddenly the virus with a crown spike named "Coronavirus" strike all over the world and everything come to a standstill. On 11th March, 2020 the World Health Organization (WHO) declared coronavirus as Pandemic disease due to its high mortality rate worldwide. The ongoing pandemic, officially named as novel coronavirus disease 2019 (nCOVID-19) by WHO. COVID-19 caused by Severe acute respiratory syndrome coronavirus (SARS-CoV-2) belong the genus β-coronavirus, enveloped, positive-sense, single-stranded RNA genome ranging from 26-32 kilobases. SARS-CoV-2 has four structural protein – Envelope

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I, Membrane (M), Spike (S) and Nucleocapsid (N) protein. These four proteins are essential for virion assembly and infection of coronavirus [1]. Due to its high fatality rate, COVID-19 can infect various animal and humans ranging from asymptomatic clinical feature to multi-organ failure and therefore said to be zoonotic pathogens. In present there are no effective treatment available for the COVID-19 disease and it has become emergency to develop therapeutic for COVID-19, although many reports claim that some of the previously drugs used for the treatment of SARS- CoV and MERS-CoV such as remdesviri, lopinavir, ritonavir, interferon beta-1b, and ribavirin were effective for the treatment of patients with COVID-19 infections [2] and currently many researches are going on for treating and managing COVID-19 infections. From many researches, there is an evidence plant derived medicines is a promising tool against various viral infections. According to WHO report 80% of the human in developing countries depends on traditional plants for health requirements. Considering low toxicity screening of plant derived medicine like curcumin can be employed to target COVID-19. Additionally, numerous researches evidenced that antiviral property of curcumin which could be a potential treatment for COVID-19 [3]. Curcumin is a well-known bioactive ingredient extracted from roots of rhizome plant Curcuma longa, commonly known as turmeric (Haldi in Hindi) exhibit many pharmacological activities including antioxidant, anti-microbial, anti-proliferative, anti-inflammatory, neuroprotective and cardioprotective properties. [4]. and over 300 clinical trial approved by US Food and Drug Administration (FDA) as a treatment for these many diseases [3]. By combining all the hypothesis, this review suggest that curcumin could be a potential treatment for COVID-19 and which can be confirmed by future clinical trials in order to develop a new drug using curcumin with more efficacy and less side-effects.

2. Structure of COVID-19 (SARS-CoV-2)

SARS-CoV-2 is an enveloped positive-sense, single-stranded RNA viruses (ssRNA) from the family of Coronaviridae and belong to genus β-coronavirus of zoonotic origin which was discovered in Wuhan City, Hubei Province, China in December 2019. SARS-CoV-2 has four main structural protein – Envelope (E), Membrane (M), Spike (S) and Nucleocapsid (N) protein (Figure. 1). E protein is a transmembrane protein (~8–12 kDa), play a vital role in the assembly and the release of viruses. M protein (~25–30 kDa) promotes 2 different conformations allows the curvature of the membrane to bind the nucleocapsid and function is to give virus its shape. S protein (trimetric S glycoprotein) a class I fusion protein is divided into two domains: the receptor binding (S1 domain) and cell fusion (S2 domain) which is activated by human proteases and cleaved at S1/S2 containing receptor binding domain (RBD) and at S2 portion responsible for virus-cell membrane fusion and N protein bound the nucleic acid material of the virus (RNA binding protein), form nucleocapsid with high affinity for viral RNA which leads to structural changes. The virus also has hemagglutination-esterase (HE) dimer shows esterase activity to facilitate viral S protein cell entry and viral spread [5].

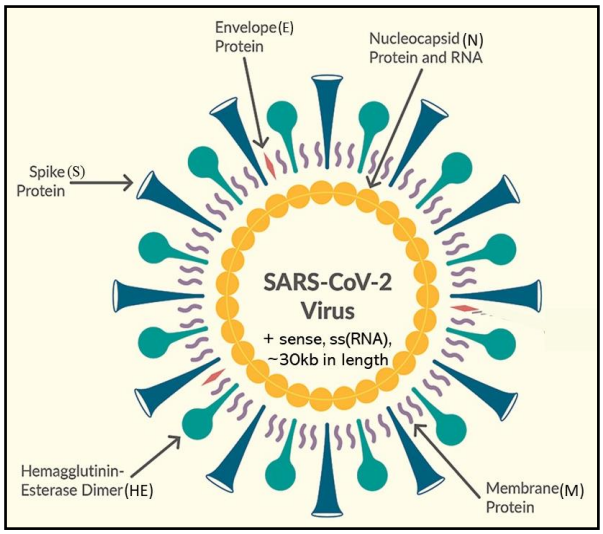

Figure 1. Represent the structure of SARS-CoV-2 (COVID-19) consist of four different proteins: Spike (S), Envelope (E), Membrane (M) and Nucleocapsid (N) proteins with genome positive sense, single stranded RNA and hemagglutination-esterase (HE)

3. Pathogenesis of COVID-19

In this review paper, previously emerged coronavirus SARS-CoV pathogenesis is compared in order to understand the pathogenesis of COVID-19. The highly transmissible pathogenic viruses are emerged in human at the beginning of the 21st century is Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) According to WHO, patients infected with COVID-19 show clinical manifestations including fever, non-productive cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia, which are found similar to the symptoms of SARS-CoV infections [6]. Hence, although the pathogenesis of COVID-19 is not understood clearly, the similar mechanisms of SARS-CoV can still help us to give a lot of information on the pathogenesis of SARS-CoV-2 infection.

3.1. Virus entry and replication

SARS-CoV-2 is an enveloped, positive-sense, single- stranded RNA virus from the family of Coronaviridae and belong to genus β-coronavirus. The major entry of SARS-CoV-2 into the host cell happens in respiratory tract and transmitted via respiratory droplets through coughing/sneezing and/or direct contact with infected individual. The major protein that represent the largest structures of the virus are spike(S) glycoproteins [1] which is divided into two domains: the receptor binding (S1 domain) and cell fusion (S2 domain) is essential for the attachment, fusion and entry of virus. *(Mohammad Ridwane. M. et al)* Using HeLa cells expressing or not expressing angiotensin-converting enzyme II (ACE2) proteins from humans, used as the cell receptor for SARS-CoV entry, it was revealed that SARS-CoV-2 was able to gain entry only in the cells expressing ACE2, suggesting that ACE2 is a cell receptor used by the virus. Structural and biophysical analysis showed that SARS-CoV-2 has 10 to 20 times higher affinity as compared to SARS-CoV, towards ACE2 [7]. ACE2 is majorly expressed in nasal mucosa, bronchus, oesophagus, heart, kidney, lung, bladder and ileum and these human organs are all vulnerable to SARS-CoV-2 [8]. ACE2 receptor binds to the viral (S) protein by direct membrane fusion between the virus and plasma membrane [9]. The S protein is cleaved into two subunits, S1 and S2, by an extracellular protease, where S1 binds to ACE2 and S2 is further cleaved and activated by the host surface-associated transmembrane protease serine protease type II (TMPRSS2). Together these result into entry of virus through the endocytic pathway to human host.

After the entry of virus into human host viral RNA released into the cytoplasm, SARS-CoV-2 hijacked the host machinery for the translation of open reading frame 1a (ORF1a) and ORF1ab which produces two polyproteins pp 1a and pp 1ab, cleaved by viral proteases to yield 16 non-structural proteins. After this RNA replicase transcriptase complex is formed which uses rough endoplasmic reticulum (ER) derived membrane for the synthesis of (-) RNAs copies of the genome that support as a template for full length (+) RNA genomes. Further transcription process leads to formation of sub-genomic RNAs, including structural and accessory proteins [1]. The newly formed polyproteins and structural proteins are inserted into endoplasmic reticulum through the Golgi apparatus [8], after which new virions assemble in budding Golgi vesicles and the mature SARS-CoV-2 virions are exocytose and released from the host cell into the surrounding environment to repeat the infection cycle [10].

The consequences of SARS-CoV-2 antigens that they are presented to host Antigen presenting cells (APC), due to which dysregulation of ACE-2 in patients infected with COVID-19 disease showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines (Figure. 2).

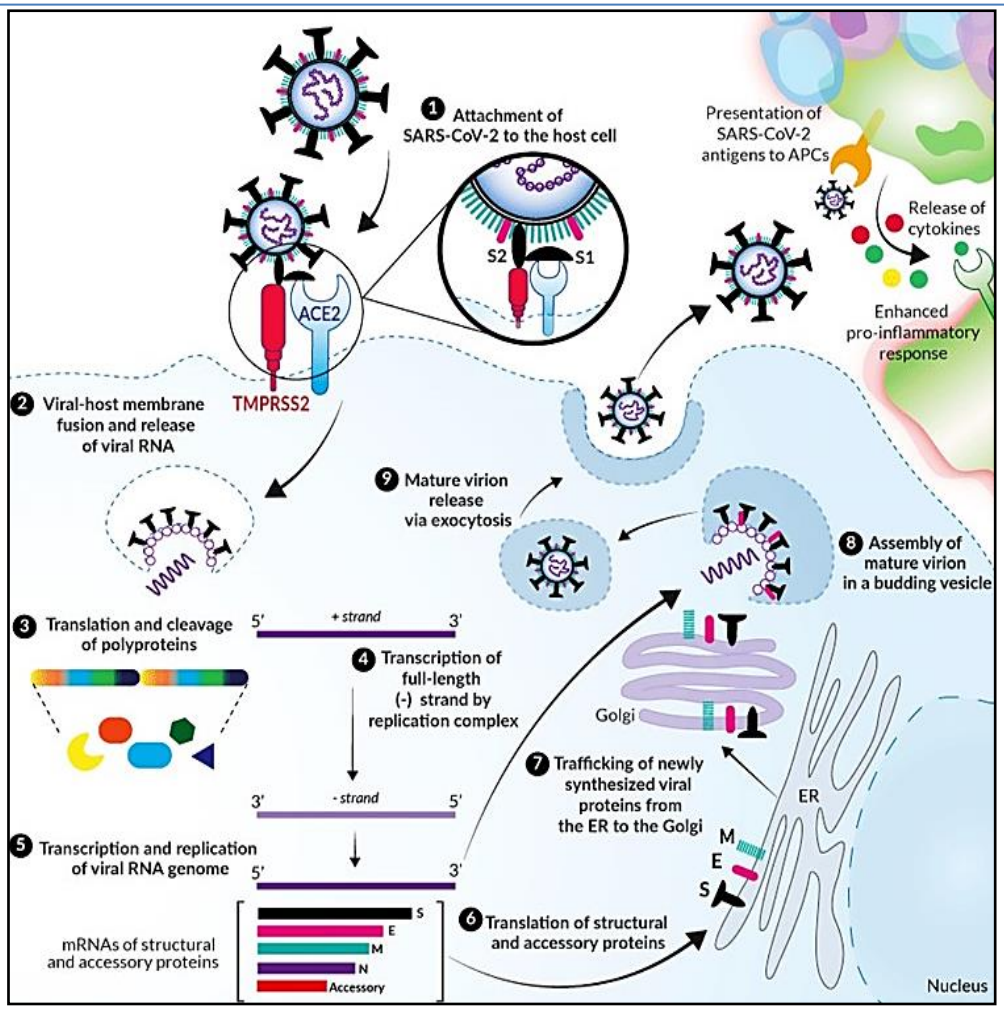

Figure 2. The illustration showing steps for entry and replication cycle of SARS-CoV-2; virus gain entry by binding the angiotensin-converting enzyme 2 (ACE2) receptor and cleavage by the serine protease TMPRSS2 (in red) to allow fusion with the host membrane. Once inside the cytoplasm, SARS-CoV-2 hijack the host machinery to transcribe, replicate and translate its RNA genome and structural proteins after which new virions assemble in budding Golgi vesicles and the mature SARS-CoV-2 virions are exocytose and released from the host cell into the surrounding environment to repeat the infection cycle.(*Source: www.invivogen.com)*

The main target of SARS-CoV-2 is the respiratory system due to which this virus cause infections in most of the individuals, combined with the incidence of acute cardiac injury. Most of the COVID-19 infections are due to respiratory failure triggered by a hyper-immune response called the "Cytokine storm". One study confirmed that SARS-CoV-2 cause infections similar as the SARS-CoV by blocking the host immune response which leads to disturbs the host antiviral defence mechanism.

The mechanism by which SARS-CoV-2 cause immune storm in an individual by entering inside the cell by interacting with the angiotensin-converting enzyme-2 (ACE2) receptors of the host cell which causes downregulation of ACE2 receptor, which ultimately disturbs the renin angiotensin pathway and causes angiotensin II generation. This angiotensin II generation then causes vascular damage, cell damage, inflammation and leads to acute respiratory distress syndrome (ARDS). The viral genome inside cell activates various proinflammatory signalling pathways [11] , which significantly produced a range of cytokines and chemokines such as Interleukin 1 beta (IL1-β), interleukin-1 receptor antagonist (IL1RA), interleukin 7 (IL7), IL8, IL9, IL10, interferon gamma (IFNγ), induced protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory proteins 1 alpha (MIP1α), MIP1β, Platelet Derived Growth Factor Subunit B (PDGFB), tumor necrosis factor (TNFα), and Vascular Endothelial Growth Factor A (VEGFA). In some cases, due to release of these cytokines' high levels of pro-inflammatory cytokines including IL2, IL7, IL10, IP10, MCP1, MIP1α, and TNFα are also increases in the infected patients [6].

4. Possible action of Curcumin for COVID-19 infections

This paper reviewed the possible role of curcumin in COVID-19 conditions with supporting evidence from existing literature. From many research studies it is established that curcumin has potential activity as an antiviral agent against several viruses like Influenza Type A, Hepatitis A, Zika, HIV, etc. Curcumin act as anti-viral agent by various mode of actions which includes: inhibition of viral entry into cells, suppression of viral replication, stimulation of interferons (IFNs) and other cytokines, and inhibition of viral protein expression. Many In-silico studies have also released that curcumin binds directly with the receptor-binding domain of the viral spike protein (involved in host cell binding) and the related host cell receptor, angiotensin-converting enzyme-2 (serves as a medium of viral entry), of SARS-CoV-2 virus. In addition, curcumin inhibits the release of cytokines like IL-1β, IL-6, IL8, TNFα, MCP-1, etc. Moreover, curcumin also exhibit blood coagulation property by inhibiting cyclooxygenase pathway and blocking calcium channel, hence curcumin can be an effective agent against SARS-CoV-2 infection with a disseminated intravascular coagulopathy pathological condition [12] caused by direct or indirect effect of the virus on coagulation pathways causing systemic thrombosis or by elevated proinflammatory cytokines (IL-6, IL-1, and TNF-α), leading to microvasculature damage and endothelial dysfunction in the lungs, causing haemostasis and pulmonary thrombi [13].

4.1 Curcumin as an Antiviral Agent- Inhibition of Viral attachment/penetration

The antiviral activities of curcumin were observed from many evidences against vesicular stomatitis virus, parainfluenza virus type 3, vesicular stomatitis virus, flock house virus, herpes simplex virus, and respiratory syncytial virus. Curcumin can block the entry and budding of the virus by altering the structure of the surface protein in viruses [6]. Recently, a molecular docking analysis through in silico computational study Jena et al. revealed that curcumin have dual binding affinity directly with the S protein and ACE-2 receptor binding domain of the SARS-CoV-2 virus [14]. ACE-2 is the receptor that binds with SARS-CoV-2 spike glycoprotein which promote the fusion of membrane and viral infection occurs through endocytosis. Therefore, spike glycoprotein is a potential candidate for drug targeting to inhibit the entry of virus. Binding of curcumin to receptor-binding domain (RBD) site of viral S protein and also to the viral attachment sites of ACE-2 receptor, revealed that curcumin can act as potential inhibitory agent for the entry of SARS-CoV2 viral protein (Figure. 3). This in silico docking studies showed that curcumin may effectively prevent the SARS-CoV2 entry into the host cell [4].

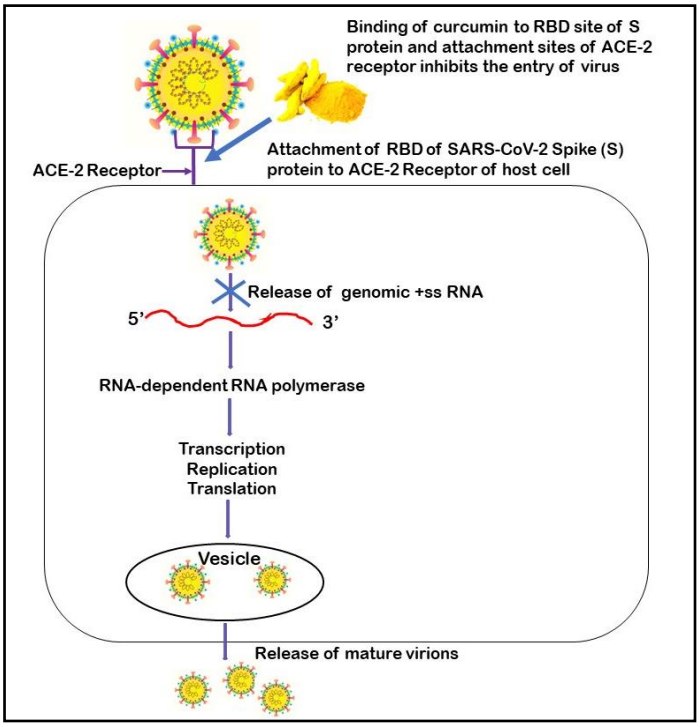

Figure 3. Represent the action of curcumin as anti-viral by preventing the viral entry and attachment of SARS-CoV-2 with the angiotensin-converting enzyme 2 (ACE2) receptor.

4.2 Curcumin Inhibits Inflammatory Reaction

Various inflammatory cytokines reaction can induce into pulmonary vascular endothelial cells by Coronavirus which result in various organ damage by stimulating the immune cells. Many in vivo and in vitro studies showed that curcumin can inhibit the production and release of pro-inflammatory response, such as IL-1, IL-6, IL-8, TNF-α. Curcumin also decreases expression of many other inflammatory mediators, including MCP1, MIPI1, growth regulated oncogene alpha (GROα), GROβ, IP10, stromal cell derived factor 1 (SDF1), matrix metalloproteinase-2 (MMP-2), IFN-γ, and MMP-9, which regulate the activity of immune cells and inflammatory responses and promote fibrosis in the lung after infection.

Anti-inflammatory activity of curcumin involves various signalling pathways, from which nuclear factor kappa B (NF-kB) plays a vital role in managing numerous inflammatory responses through multiple mechanisms (Figure. 4):

1. Curcumin inhibits activation of IKKβ which helps to decrease the expression of IL-8, TNF-α, and IFN-γ.

2. Curcumin inhibits the degradation of phosphorylation of IkB serine 32 to block the cytokine-mediated NF-kB activation and thus suppress the pro-inflammatory gene expression.

3. Curcumin inhibits the NF-kB signalling in order to initiate AMPK signalling pathway.

4. Curcumin target p65 to disturb the NF-kB pathway in the cytosol of macrophages and increase nucleus where it forms complex with the NF-kB, eventually there is an upregulation in transcription of pro-inflammatory cytokines [15].

These multi-mechanism mode of action of curcumin as anti-inflammatory can be used for the treatment of many inflammation infections reported in COVID-19 patients includes: pulmonary inflammation, pulmonary fibrosis and pulmonary edema.

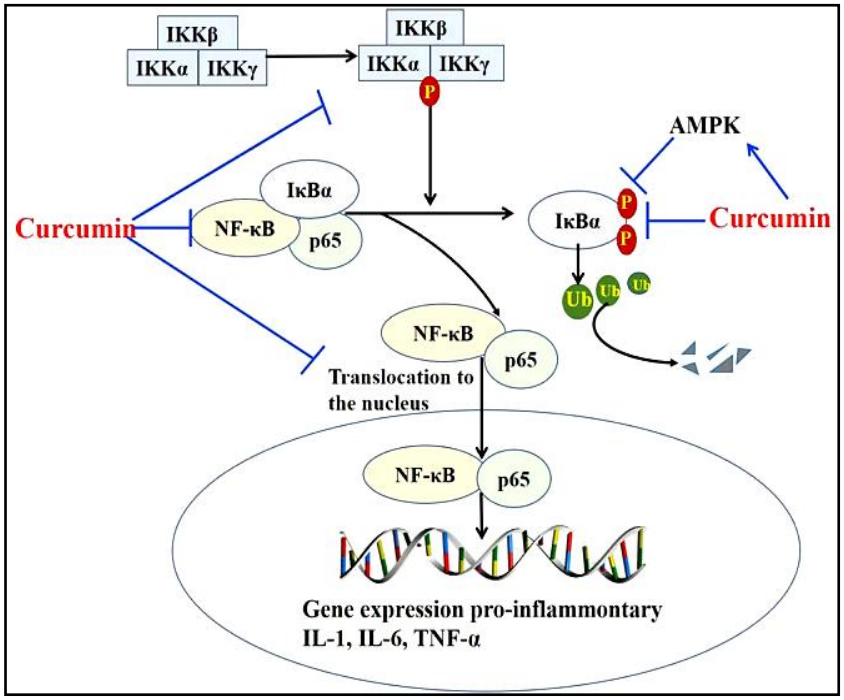

Figure 4. Represent possible inhibitory action of Curcumin for COVID-19 infection by inhibiting the formation of pro-inflammatory cytokines by targeting the NF-κB pathways.
Source: https://www.frontiersin.org/files/Articles/555562/fcell-08-00479-HTML/image_m/fcell-08-00479-g002.jpg

4.3 Curcumin inhibitory effect on Viral Protease

To manage COVID-19 infection the drugs that currently used are protease inhibitors. The main protease (Mpro) recognized as a promising target among Coronaviruses infections such as MERS-CoV and SARS-CoV. The Mpro cleave the essential structural proteins of the host cells during viral formation by processing viral polyproteins from viral RNA. Numerous phytochemical compounds such as curcumin that may have ability to inhibit the SARS-CoV-2 infection by molecular docking as curcumin showed relatively

low binding energies and constant inhibition, as well as curcumin have an inhibitory effect on COVID-19 Mpro and therefore curcumin could act as therapeutic agent [3].

4.4 Curcumin as inhibition of reactive oxygen species (ROS)

Oxidative stress is present in all the lung injuries including acute respiratory distress syndrome (ARDS) caused by CoVs leads to the initiation and maintenance of chronic low-grade inflammation. Curcumin has two active groups, one hydroxy hydrogen on the benzene ring that has an anti-oxidation effect and the other a β-diketone moiety. From In vitro experiments it has been shown that curcumin have potential to scavenges the superoxide anion radical and the OH^- produced by the Fenton reaction. Curcumin also inhibits the peroxidation of lecithin and DNA oxidative damage caused by ROS.

Mechanism underlying that curcumin have ability to scavenge ROS can be indirect via enzymatic regulation through electron transfer from various intracellular small oxidative molecules. Curcumin can upregulate the expression of superoxide dismutase 2 (SOD2), a key enzyme to convert O^{2-} to H_2O_2, which is then reduced to H_2O by glutathione (GSH) redox system and inhibits the generation of ROS. Additionally, curcumin reduced the influenza infection with influenza A virus and influenza pneumonia by activating nuclear factor erythroid 2-related factor 2 (Nrf2) signalling and inducing the generation of various antioxidants. Curcumin also inhibits influenza A virus by inducing activation of Toll like receptors 2/4 (TLR2/4), mitogen-activated protein kinase (MAPK), and NF-kB pathways which may suppress the inflammation and replication of influenza A virus. Therefore, curcumin could have antioxidant properties in the treatment of SARS-CoV-2 intervened lungs oxidative stress [3,14].

5. Conclusion and future scope

The goal of this paper was to review the multiple action of curcumin that could be beneficial for the treatment of COVID-19 patients and to understand the mechanism through which the SARS-CoV-2 causing complications in human body by comparing mode of action from previously emerged coronavirus MERS and SARS in order to develop better treatment options in this urgency of pandemic situation. It can be concluded that curcumin may have various beneficial effects on the COVID-19, due to its multi-mechanism ability of targeting viral entry to host cells, targeting viral replication and may act as effective inhibitory agent on NF-kB and various pro-inflammatory fatal cytokines storm which leads to multiple organs failures, and eventually death in serious cases of COVID-19. However, drug may be prepared from curcumin which have low toxicity and more efficacy can be useful of the COVID-19 patients. Future aspects can be that further clinical research and development studies are needed in order to prepare a new formulation using curcumin or it can be incorporate with other pharmaceutical drugs for better effect on COVID-19 patients.

6. Declarations

6.1 Acknowledgement

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6.2 Competing Interests

The authors declared that there is no conflict of interest exist in the publication.

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