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ANTIVIRAL ACTIONS OF CURCUMIN ON ACE2 RECEPTOR, AN EFFICIENT DRUG CANDIDATE AGAINST SARS-CoV-2

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REVIEW ARTICLE

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Abstract

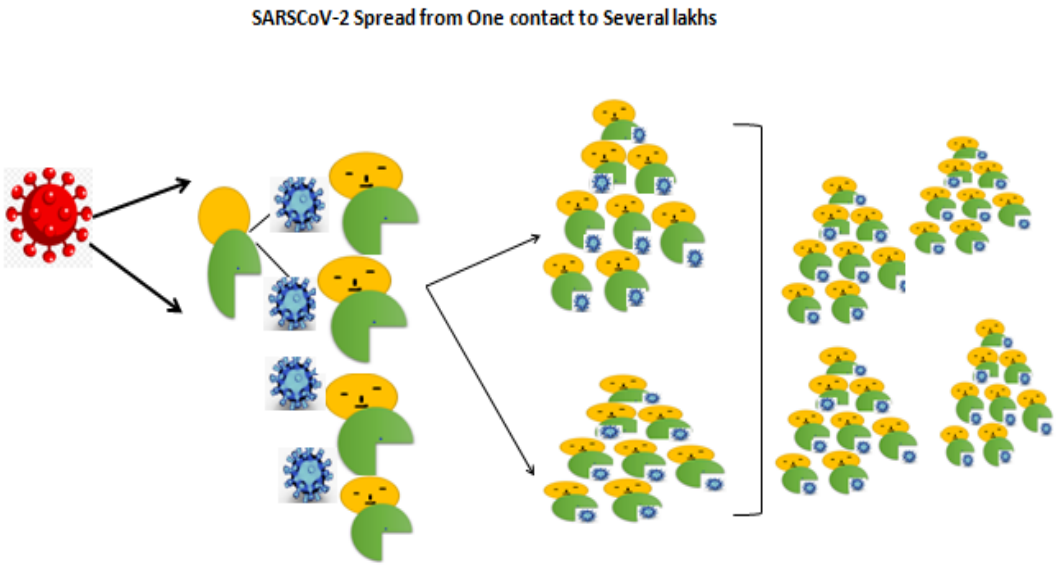
The world is currently confronted with one of the most severe global pandemics, which was triggered by the SARS-CoV-2 virus. This sudden and unexpected global outbreak turned into a question of our safe existence on Earth and places everyone's lives in danger. This pandemic is characterized by rapid spread, a lack of specific diagnosis, and a shortage of specific medication. Although, many drugs are recommended to patients, and some investigations are still under clinical trials. Nonetheless, researchers and scientists are utmost endeavoring to discover a particular drug against this virus. In our current review article, we have encapsulated the pathophysiology, clinical aspects, and present therapeutic regime of COVID-19. In addition, we have explained the ethnobotanical effects of curcumin and its mode of actions against SARS-CoV-2. Taking all of this into account, current researchers are primarily interested in natural bioactive compounds with anti-viral, anti-fungal, anti-bacterial and anti-inflammatory properties. In this review, we are mainly focusing on curcumin, a basic bioactive compound, a natural phenolic compound, a nutraceutical that is abundantly found in *Curcuma longa L.* (turmeric). Therefore, it could be a better candidate for inclusion as therapeutic regimen. Our main focus centered on its mechanism of action and how it caused inhibitory activity on Toll-like receptors, NF-κB, bradykinin, chemokines and inflammatory cytokines. Several literature reports provide evidence that curcumin could have a potential role in treatment of COVID-19. Thus, acts as an effective drug candidate against COVID-19 and further research studies need to be carried on computational biology before formulating it as a drug compound.

INTRODUCTION

SARS-CoV-2 is a novel respiratory disease that was transmitted from Wuhan, China, towards the end of December-2019. It was recognized and acknowledged as a novel coronavirus and was further termed as severe acute coronavirus 2 (SARS-CoV-2).Nevertheless, World Health Organization (WHO) alarmed the whole world about this pandemic outburst, which ultimately led to pneumonia [1-2]. They are encased by positive-stranded RNA viruses integrated to the family of Coronaviridae viruses, these can infect different hosts, including humans and other vertebrates, of several species through the intermediate hosts [3].Some of these family strains like HCoV-OC43, HCoV-HKU1, HCoV-229E, & HCoV-NL63 show minor gasping ailments, while other viruses like severe acute respiratory syndrome CoV (SARS-CoV) & the Middle East Respiratory Syndrome CoV (MERS–CoV) are capable of causing serious diseases [4-5].

A Middle East Respiratory Syndrome coronavirus (MERS-CoV) was discovered ten years after SARS-CoV, which is another extremely deadly coronavirus in the Middle East. The SARS coronavirus (SARS-CoV) binds to angiotensin-converting enzyme 2 (ACE2) as a receptor and predominantly infest the bronchial cells that areciliated along with type II pneumocytes.In contrast, MERS-CoV utilizes DPP4 as a receptor (DPP4 is also known as the CD26) and spreads to unciliated bronchial epithelial cells along with type II pneumocytes. [6-9].

Finally, in the sequel of corona viruses, origination of SARS-CoV-2 was in Wuhan territory, China. However, first reported infection was connected with animal market and then human-to-human transmission [10].Based on a variety of studies,COVID-19 is identified as an air-borne infection and is spread via respiratory droplets and close contact between individuals (Figure 1). A recent investigation found that SARS-CoV-2 and SARS-CoV gene sequence homologies were matched by 79.5% and 50% with the Middle-East respiratory syndrome coronavirus (MERS-CoV) [11].



The structural RNA genome of SARS-CoV-2 includes RNA-dependent RNA (RdRp) polymerase for multiplication, with various proteins like hemagglutinin-esterase (HE), spike (S), envelope (E), membrane (M), and proteins of the nucleocapsid (N). The spike (S) protein is the fundamental and most essential protein to assist host receptor fixation to ACE2. While E, S, and M are proteins incorporated into the endoplasmic (ER) membrane and transported to the ER– Golgi intermediate section (ERGIC). Spike protein is our major concern here because it is the most and important primary protein in SARS-CoV-2 pathogenesis [12]. Nonetheless, communication occurring between the corona virus spike (S) protein with receptor is the major influencer for such virions attachment on to human cells [13]. Various peptidases have been well illustrated as SARSCoV-2 cellular receptors, including Aminopeptidase N (APN) as the receptor for alpha Corona virus, angiotensin-converting enzyme 2 (ACE2) as the receptor for SARS-CoV-2 and dipeptidyl-peptidase 4 (DPP4) as the receptor for MERS-CoV [14]. Thus, spike (S) protein is regarded as major receptor and compounds which are able to Inhibit binding of S protein binding to receptor is primary strategy for refraining and treating the malady.

Nevertheless, provided insights into the viral transmission and treatment targets for SARS-CoV-2. Interestingly we come across that SARS-CoV-2 utilizes the same entrance of SARS-CoV receptor that is ACE2 and S Protein Priming Serine Protease (TMPRSS2). A TMPRSS2 inhibitor that has been approved for clinical use may provide an alternative therapy. Therefore, our findings show substantial parallels between SARS-CoV-2 & SARS-CoV maladies and indicate a possible antiviral response target. On this note, the most common and easiest way to stop SARS-CoV-2 is to mask/inhibit the virus' spike protein binding site to ACE-2's receptor-binding domain (RBD) with bioactive agents like curcumin which has revealed its antiviral activity.

CURRENT APPROACHES FOR PREVENTING TRANSMISSION

Taking all extremities into consideration and the emergency created by the epidemic led to the empirical use of broad-spectrum antibiotics and antiviral medicines, some patients with diseases in multiple countries were treating with clinically authorized medications and even some were not approved. Putting this aside, currently four distinct fundamental techniques are being followed by many countries to cure and manage the pandemic disease caused by SARS-COV-2.

They are of:

1. Inhibition of cellular viral entrance and its reproduction Processes
2. Direct antiviral actions
3. Enhancement of host immune response
4. Strictly adhere to lockdown measures and also bring awareness among people about sanitation and physical distancing. There are currently no specialized antiviral medicines that targeted SARS-CoV-2.

Currently use of hydroxychloroquine and its derivatives for treatment of SARS-CoV-2 were on upsurge. Derivatives of hydorxychloroquine and its related homologous bioactive agents like Quensyl™, Plaquenil™, Hydroquin™, Dolquine™, and Quinoric™ have been utilized from ages for the malarial therapy [15]. At present several clinical trials were being carried out on not only chloroquine but on various other ethno-botanical agents for its efficacy and wide-spectrum antiviral potentiality [16, 17]. However, Chloroquine phosphate displayed to refrain terminal phosphorylation of ACE2. On the other hand, hydroxychloroquine increases the pH in endosomes which include refraining of virus entry inside cell [18, 19]. Similarly, curcumin also possess bioactive agents which has been depicted in various literature reports. Until the exact drug candidate is released for mitigation of pandemic virus, several measures such as washing hands to wearing mask and boosting immunity need to be followed [20].

PHARMACEUTICAL AGENTS AGAINST COVID-19

In the face of the urgently needed treatment of these patients, researchers are trying to re-purpose medicines that are already authorized for other diseases and have taken all acceptable safety profiles, instead of taking several months to years to create and test molecules from scratch. These alternative medicines that are already approved for a variety of human ailments might perform antiviral action in a variety of ways, including preventing viral entry, inhibiting viral enzymes, targeting a host component required for replication, and precluding virus particle formation. In particular, several antivirals and antimalarials have shown potential treatment capabilities and reduced COVID-19 hazards (Table 1) [21]. To date, COVID-19 has not been treated with absolute treatments, but preventative and helpful therapy is used to limit additional problems and organ damage.

CURRENTLY AVAILABLE CHEMOTHERAPEUTIC AGENTS AGAINST VIRUS

Nevertheless, COVID-19 infections in humans are linked not only with numerous pulmonary or respiratory problems but risk associated to several other organs, including the renal, heart, and liver, which can lead to their metabolic impairment and possible precise medication is necessary for treatment of the present pandemic condition [30].

Many medication options are provided without precise specificity to enhance effectiveness in Covid-19 therapy. (Shown in Figure 3).

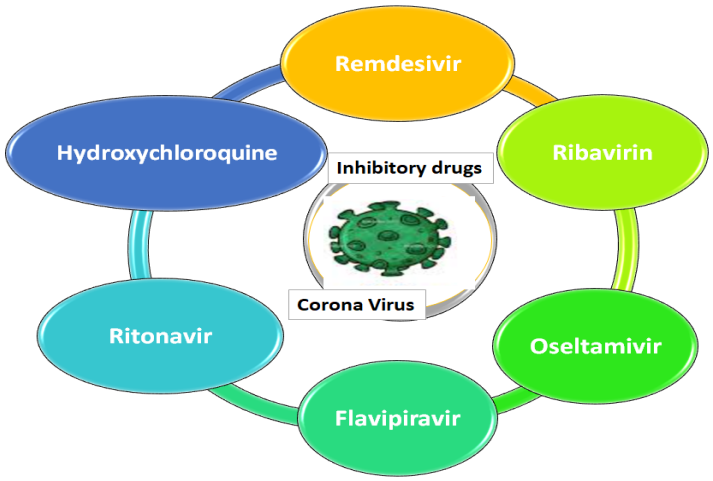
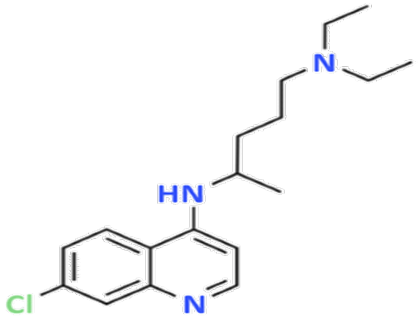
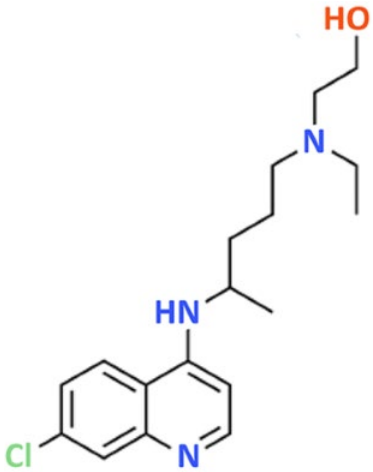
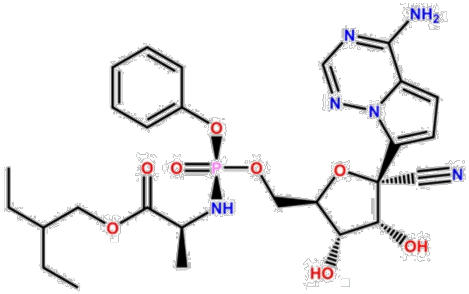
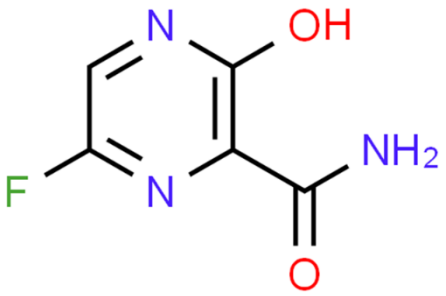
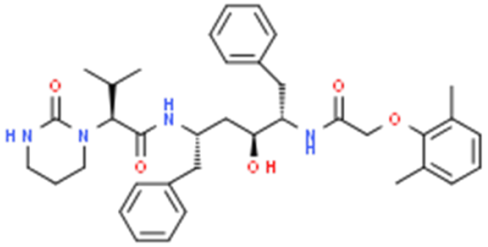
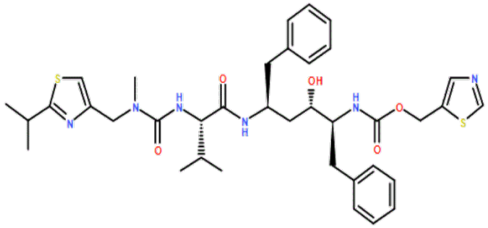
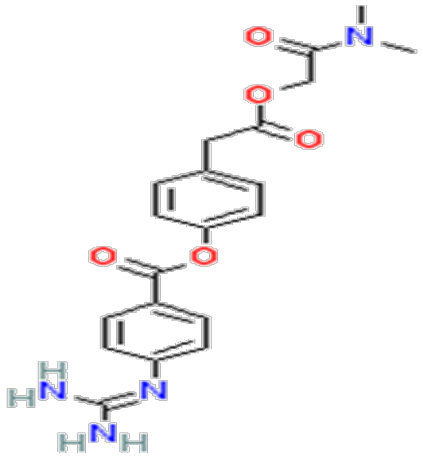
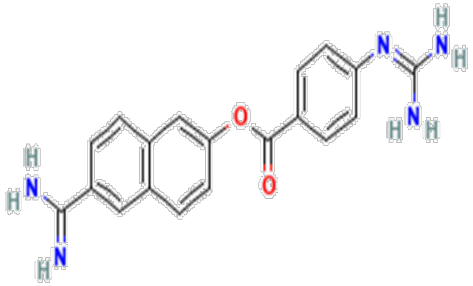


Table 1: List of most commonly used pharmaceutical candidates in the treatment of covid-19

Pharmaceutical agents	Mechanism of action	Target site	Infections that are generally used for	General structure	Reference
Chloroquine (CQ)	Therapy with chloroquine phosphate is advanced approach to mitigate the exacerbation of pneumonia, enhancing the lung imaging, encouraging the inhibition of COVID-19 disease	Lungs	Malaria, Arthritis, Lupus, SARS-CoV, MERS-CoV		[22]
Hydroxychloroquine (HCQ)	An intracellular trafficking and virus fusion can be disrupted by a lysosome-tropic base. Cytokines in the serum might also be reduced. Generally chloroquine is sensitive to malaria but hydroxychloroquine is utilized for treatment of rheumatoid arthritis, heart problems and therapy for other disease conditions	Endosomal acidification	SARS-CoV, MERS-CoV, SARS-CoV-2		[23]
Remdesivir	Terminates the non-obligate chain	RNA-dependent RNA polymerase (RdRp)	Ebola, SARS-CoV-2		[24]

Favipiravir	Inhibits RNA-dependent RNA polymerase (RdRp)	RNA-dependent RNA polymerase (RdRp)	Influenza, yellow fever, chikungunya, norovirus, enterovirus SARS-CoV-2		[25]
Protease inhibitors: Lopinavir-Ritonavir	Hindrance of 3-chymotrypsin which resembles the protease enzyme, which plays a crucial part in essential structural protein reproduction and synthesis	3Chymotrypsin Like protease	HIV, SARS-CoV-2	Lopinavir  Ritonavir 	[26]
Tocilizumab	Interferes with the IL-6 membrane binding site of the receptor (IL-6R), thereby blocking the assembling of the activated complex with the transmembrane protein.	IL-6 receptor	Rheumatoid arthritis, systemic juvenile idiopathic arthritis.	----	[27]

Camostatmesilate	Hindrance of serine protease	TMPRSS2	SARS-CoV-2		[28]
Nafamostatmesilate	Arrests SARS-CoV-2, MERS-CoV by acting on different points of the viral cycle	Synthetic serine protease inhibitor	Pneumonia, SARS-CoV-2, MERS-CoV		[29]

COMMON ADVERSE CONSEQUENCES OF DRUGS

Importantly, treatment schemes that contain two or more drugs combined, such as Azithromycin along with CQ and HCQ may have serious adverse effects, including heart toxicity, such as the QT prolongation interval and sudden cardiac death produced by drugs [31].Furthermore, this research should address several concerns, such as medication dose, duration of therapy, specific parameters for treatment management/monitoring, high-risk populations, and serious side effects [32].

Some attempts were made to combine certain medications such instance triple combination of cepharanthine, selamectin and mefloquine hydrochloride used as prophylaxis against malaria but revealed to possess adverse effects [33-34]. Using more than one medication simultaneously might however, create significant adverse effects on individuals. The detection of medicine-drug interactions in the therapy of Covid-19 is thus very important. Multiple medication use significantly increases the adverse effects of drug employed, according to research. The likelihood of poly-pharmacy is typically increased in the elderly. Studies have shown that the negative effects on patients may also rise with the increase in the number of medications used [35]. Nevertheless, the adverse effects caused by most common drugs used for various other therapies including SARS-CoV-2 are depicted in (Table-2). These side effects are undoubtedly related to medication use, and they may vary depending on the average frequency and rate of the effect.

Table 2: List of most common Adverse Consequences of pharmaceuticals in Covid-19

Pharmaceutical candidate	Most common negative consequences	Reference
Chloroquine	Tracheitis, Primary biliary cirrhosis, Kidney damage, Anemia	[36]
Hydroxychloroquine	Cardiovascular collapse, Lyell, Thrombocytopenia	[37]
Favipiravir	Gout, Hyperuricemia, Kidney function impairment	[38]
Ribavirin	Dizziness, Neutropenia, Aspergillosis Thrombocytopenia	[39]
Lopinavir	Severe hyponatremia, Mild metabolic acidosis and hyperkalemia	[40]
Ritonavir	Cardiovascular collapse Dizziness, Renal tubular acidosis	[41]
Tocilizumab	Arterial hypertension, Hypercholesterolemia, Hypertriglyceridemia and Acute pancreatitis	[42]
Azithromycin	Bone marrow failure, Thrombocytopenia, Neutropenia	[43]

BIO-ACTIVE COMPOUNDS AS ANTI-VIRAL MEDICINES

By taking into account all the foregoing harmful implications, the popularity of alternative medicines and natural products as potential alternatives solution to this crisis has reinforced this interest. The characteristics of SARS-CoV, MERS-CoV, and other viral illnesses have already been investigated and may be examined using alternative natural bioactive compounds and it found a path to battle with COVID-19. Therefore, it is crucial that micronutrients and bioactive substances can be used to combat COVID-19. Phytochemicals are non-nutrient plant chemicals that can affect human health when consumed. Flavonoids, anthocyanins, carotenoids, polyphenols, and phytosterols are commonly recognized in dietetic supplements. Several have been shown to have essential human health functions as therapeutic agents [44].

Bio-active products play a possible function in combating with initiating COVID-19 infections with SARS-CoV-2. Curcumin, allicin, kaempferol, gingerol, silvestrol, herbaceous, epigallocatechin-gallate etc., are potential bioactive substances. Bioactive therapeutic candidates against COVID-19 may be isolated from different plants. They show promising effective hindrances against SARS, MERS, dengue virus, HSV, HPV, rabies virus, poxvirus, respiratory syncytial virus, and influenza-parainfluenza viruses. Medicinal plants could be a great source for the manufacturing of vaccines and therapies based on proteins and peptides.

CURCUMIN AS A TARGETED ANTIVIRAL THERAPEUTIC

Turmeric (*Curcuma Longa*) is a herbal, rhizomatous, perennial plant from the Zingiberaceae, a Ginger family. It is widely utilized for its therapeutic characteristics, such as antivirals, antifreeze, antimicrobials, and anti-proliferative activities and used as anti-inflammatory medicine in Ayurveda, Siddha, and traditional Chinese cultures. The therapeutic effects of turmeric are mainly attributed to the three principal curcuminoids. They are curcumin, demethoxycurcumin, and bisdemethoxycurcumin. The most abundant bioactive curcuminoid in turmeric is curcumin, whichis a hydrophobic polyphenolthat is also called diferuloylmethane. Curcumin controls the production of inflammatory enzymes, ciliates, adherence molecules, and cell surface protection by regulating the activation of

different transcription factors. It promotes various activities, including anti-inflammatory, anti-bacterial, antiviral, and immunomodulatory activities (Shown in Figure 4) [45].

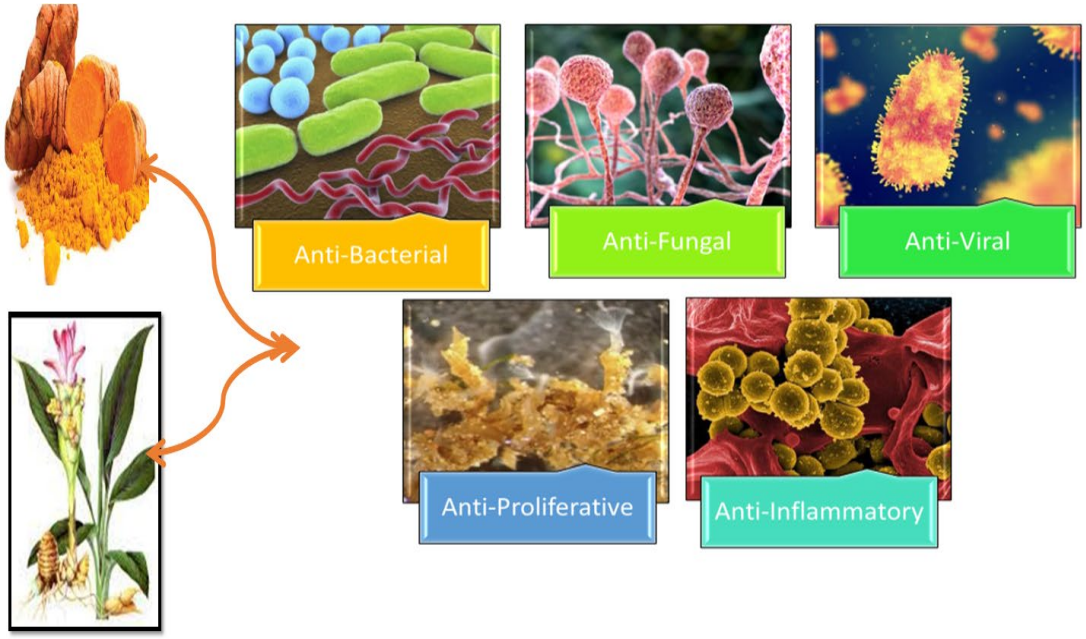


Figure 4: Potentials of Curcumin (bio-active Compound of turmeric which acts as Anti-bacterial, Anti-fungal, Anti-viral and Anti-inflammatory actions) (The Picture edited by the author himself)

Curcumin, a spice formerly confined to the kitchen but today its use in covid-19 inhibition is under clinical trials by many researchers. Curcumin may have a therapeutic role in diseases, such as familial adenomatous polyposis, bowel inflammation, ulcerative colitis, colon cancer, pancreatic cancer, hypercholesterolemia and atherosclerosis. Curcumin has been shown to have immunostimulatory, antioxidant, and anti-viral properties. Curcumin, has revealed antiviral activity which can be demonstrated via many methods, including blocking the entrance of the virus into cells, inhibiting virus encapsulation, and regulating multiple signaling pathways along with other viral replication activities. In several lung diseases, such as COPD, ARDS, pulmonary fibrosis, and asthma studies were also shown great protective effects by using curcumin. (Shown in Table 3) Curcumin is a strong antioxidant, so that it impacts through the neutralization of free radicals and through the improved synthesis of antioxidant enzymes that help to boost up the immunity [46].

Table 3: Some viral diseases that are proven to be treated by curcumin activity

Name of the infection	Causative candidate	Action mechanism	Reference
Dengue fever	Dengue virus	Spoil viral envelope	[47]
Chikungunya fever	Chikungunya virus	Hinder virus binding to host cell	[48]
Zika Fever	Zika virus	Hinder virus binding to host cell	[49]
Liver disease	Hepatitis B & C virus	Downregulates PGC-1α, hinder RNA replication and viral assembly	[50]
AIDS	HIV	Hinder HIV integrases and proteases	[51]
Encephalitis	Japanese encephalitis virus	Spoilage of viral envelope	[52]
Cold sores	Type 1 Herpes simplex virus	----	[53]
Respiratory illness	Respiratory syncytial virus	Hinder viral replication and budding	[54]
Respiratory illness	Influenza A virus	Disrupts virus envelope and hinder haemagglutinin activity	[55]
Severe acute respiratory syndrome	SARS-CoV	Hinder SARS-CoV and 3 3CL (chymotrypsin-like) protease	[56]

MODE OF ACTION

Curcumin and its derivatives fight efficiently as it acts as an inhibitor for stopping the binding of SARS-COV-2 to angiotensin-converting enzyme-2 through significant binding with spike protein and its inhibition, inhibiting ACE2 receptor active site in the host cell and it can also rupture the viral envelope upon its binding. But, the doorway to most all corona viruses, including SARS-CoV-2, is angiotensin-converting enzyme 2 (ACE2). So here, we are mainly concentrated on the inhibition of S protein to ACE2 receptors of host cells by using curcumin [57].

Curcumin can able to interact with the spike protein of the virus immediately after recognizing its presence in host cells even before their attachment to host cells. The interaction between curcumin and the S1 subunit (again, be consistent with the term used) of SARS-CoV-2 was anticipated. Blocking the spike protein receptor-binding field will impede or block the target cell identification and the following virus particle cellular entrance. Various residues of ACE2 Amino acid have been detected at the active site of interaction with curcumin such as Ala 348, Asn 394, Glu 402, His 378, His 401, and Tyr385 depicted in literature reports [58]. SARS-CoV-2 binds to the host's ACE 2 receptor to immediately inhibit caspase-3, a unique cysteine protease, that is responsible for executing programmed death/ (apoptosis). Nonethelesss, $P^{53,}$ is also regarded as Guardian angel which is also a strong inhibitor on some viruses. So, host is incapable to recognize virus and virus can show its replicative stages and infect the host cells completely and activates cytokines and oxyradicals abundantly and leads to many further complications [59].

Several literature reports have displayed the inhibitory mode of action from plant based product curcumin which has shown viral-triggered pulmonary inflammation by nullifying the instigation of NF-κB signalling [60] potentially by inhibiting upstream IKKβ kinase actions. Now curcumin can immediately come into action and encounter these viral actions by inhibiting Bradykinin (BK) receptors in host as it can show dysregulated bradykinin (BK) signaling, which has been postulated as the cause of the cytokine storm. Nevertheless, abolishing IL6 signalling by JAK inhibitors is directed to be an additional manner to alleviate the progression to ARDS in COVID-19 patients [61]. As a basis for this idea, the down regulation of ACE2, the entrance protein of SARS-CoV-2, results in increased availability of BK and des-Arg9-BK, the active metabolite of BK in the host. Des-Arg9-BK levels are also elevated as a result of ACE2's decreased derivative activity due to its down regulation. BK inhibition can inhibit the rush of cytokines such as Interleukins-6, 8, 10, IL-β along with Tumor necrosis factor alpha (TNF-α) and the second important action of curcumin is the inhibition of NF-kβ along with oxyradicals, which can help in the inhibition of viral replication in host cells. By these actions, curcumin can efficiently block the spread of Covid-19 infection. (Shown in Figure 5).

Thus, curcumin can prevent SARS-CoV-2 entry into cells by inhibiting interaction partners (ACE2 and spike protein). Nevertheless, suppresses the pro-inflammatory signals and upregulates anti-inflammatory responses. Curcumin oral administration among in vitro models have shown alleviated acute lung injury triggered in cecal ligation and puncture-instigated sepsis which was associated by increased numbers of regulatory T cells (FOXP3þ T-reg) and M2 Macrophages [62]. However, regulation of T cell and M2 macrophages mitigate trigerred immune cells (CD4, CD8 cells) via TGF-β and IL-10 secretion and assist inflammation resolution. Furthermore, the expression of TMPRSS-2 has been reduced by curcumin. The cleavage of the S2 subunit of the TMPRSS-2-mediated spike protein is a necessary step towards the hindrance of viral ingredients in host cells.

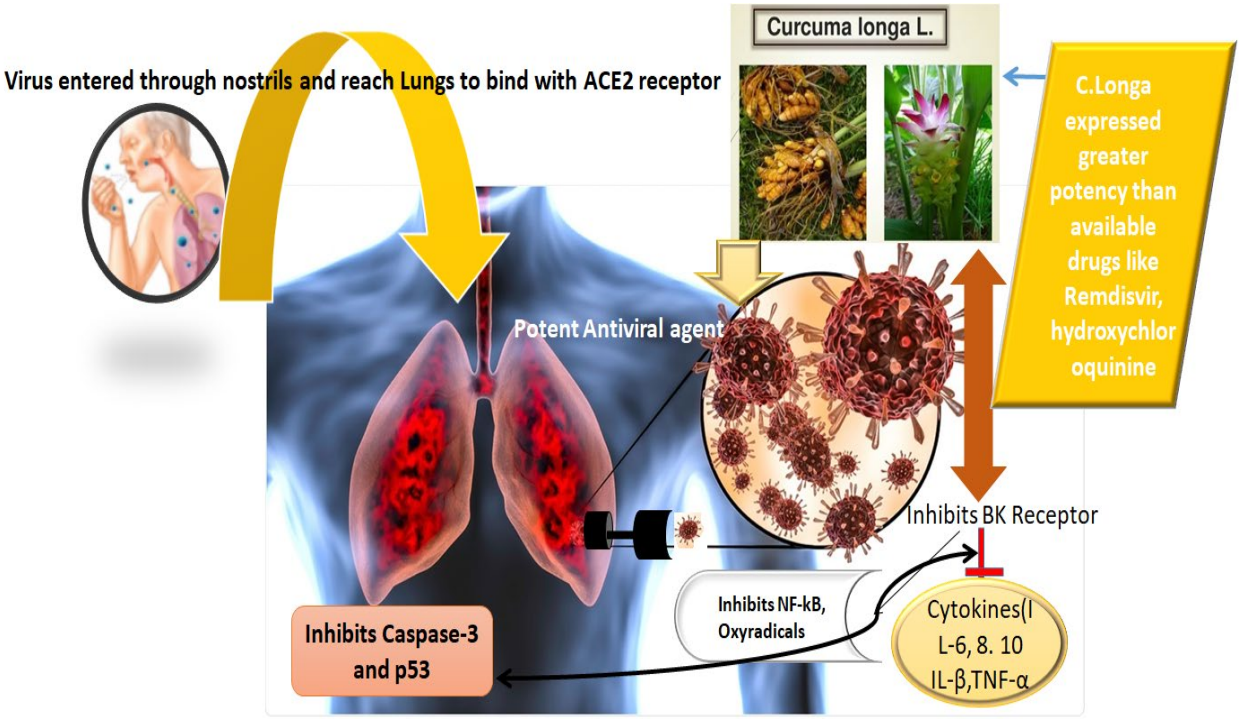


Figure 5: Mode of action of Curcumin against SARS-CoV2. (The viruses show aggression on alveolar epithelial cells and are differentiated by dendritic cells and macrophages, which later discharge cytokines and chemokines to help white blood cells in the blood reach the alveoli. Curcumin stops the production of pro-inflammatory cytokine by inhibiting the NF-kB pathway). (The figure is drawn by author herself)

CONCLUSION

The outburst of SARS-CoV-2 universally is regarded as a serious pandemic health issue. Moreover, RNA genome of SARS-CoV-2 has been recognized to be greatly homologous with other kinds of the corona viruses. Although, for the current catastrophe of pandemic SARS-CoV-2 maladies, remedial and precluding methods are correspondingly required to overwhelm the existing life-threatening maladies. Since natural products has abundance of ethno-botanical significance which have revealed to possess antiviral properties These, natural products such as Curcumin has potential bioactive compounds which has shown promising activity for the development of therapeutic drugs and can be effective against allied corona virus strains due to their analogous life cycles. There is a need to develop low molecular weight compounds obtained from curcumin which possess promising ligands to block or inhibit the replication of virus which is possible with support of AI assistance. However, natural products such as curcumin is a precise alternative as it shows many checkpoints not only binding to S protein and its hindrance but also shows wide range of molecular targets without showing any sort of adverse consequences. Therefore, there is a need for more research about molecular docking, development of computational AI has to be incorporated to enhance drug designation. Thus, our review article provides broad insights to all researchers to further go for clinical trials to find an effective candidate against SARSCoV-2.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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