International Journal of Design & Nature and Ecodynamics
Vol. 17, No. 6, December, 2022, pp. 957-965
Journal homepage: http://iieta.org/journals/ijdne

# Review on Curcumin Compounds in Turmeric Plants for the Treatment of COVID-19

Rizal Irfandi[1*], Muhammad Ilham[2], Erwing[2], Ruslang[3], Muhammad Arafah[1], Andi Badli Rompegading[1], Suriati Eka Putri[4], Suriana Dwi Sartika[5], Siti Fauziah[6], Ayu Safitri Agustina[7], Hairil Akbar[8], Ahmad Fudholi[9,10]

[1] Department of Biology Education, Faculty of Teacher Training and Education, Universitas Puangrimaggalatung, Sengkang 90915, Indonesia
[2] Department of Biology Education, Faculty of Teacher Training and Education, Universitas Muhammadiyah Bone, Bone 92714, Indonesia
[3] Department of Nursing, Faculty of Nursing and Midwifery, Universitas Puangrimaggalatung, Sengkang 90915, Indonesia
[4] Department of Chemistry, Faculty of Mathematics and Natural Science, Universitas Negeri Makassar, Makassar, Jalan Daeng Tata Raya Makassar 90244, Indonesia
[5] Department of Internal Medicine Faculty of Medicine, Universitas Bosowa, Makassar 90244, Indonesia
[6] Department of Industrial Engineering, Universitas Muhammadiyah Luwuk, Banggai 94711, Indonesia
[7] Department of Chemistry, Faculty of Science, Universitas Muhammadiyah Bulukumba, Jl. Ir. Soekarno No. 9, Ujung Bulu, Bulukumba, Sulawesi Selatan 92513, Indonesia
[8] Graha Medika Institute of Health and Technology, Kotamobagu 9571, Indonesia
[9] Solar Energy Research Institute, Universiti Kebangsaan Malaysia, Bangi, Selangor 43600, Malaysia
[10] Research Center for Energy Conversion and Conservation, National Research and Innovation Agency (BRIN), Serpong 15314, Indonesia

Corresponding Author Email: rizalirfandi043@gmail.com

https://doi.org/10.18280/ijdne.170618

**Received:** 11 July 2022
**Accepted:** 6 October 2022

***Keywords:***
*COVID-19, curcumin compounds, turmeric plants*

**ABSTRACT**

Coronavirus Disease (COVID-19) is an infectious disease that has a high fatality rate and is spreading quickly throughout the world. The WHO claims that SARS-CoV-2, a brand-new coronavirus strain, is to blame for this outbreak (Severe Acute Respiratory Syndrome Corona Virus-2) and that COVID-19 must be treated with both conventional medical therapy and a combination of modern medicine. The technique of this study, a review of the literature, focused on numerous investigations looking at the potential of curcumin molecules from turmeric to cure the COVID-19 disease. Primary data for scientific papers is gathered from national and international journals through searches on electronic search engines like Google Scholar, Sciencedirect, or PubMed and selected publications are assessed, evaluated, and interpreted by authors. Turmeric contains substances that are immune system boosters, anti-inflammatory, antitumor, antiviral, and antioxidants. Curcumin may prevent a number of viral infections, according to evidence. In vitro testing has shown that the SARS-CoV virus is resistant to curcumin's antiviral properties. It's possible that curcumin can halt viral replication. Curcumin has the potential to treat COVID-19 effectively. Curcumin has antiviral activity that can fight the SARS-CoV-two virus. Treatment with curcumin can change the virus top protein structure, preventing the virus from entering the body and from budding. Future study on the use of curcumin as SARS-Cov-2 virus inhibitory agent is necessary in order to employ it as a novel and long-lasting therapy option for Covid-19 patients.

## 1. INTRODUCTION

Coronavirus Disease (COVID-19) is an infectious disease that has a high fatality rate and is spreading quickly throughout the world. Acute respiratory distress syndrome, pneumonia, and other serious illnesses, as well as asymptomatic upper respiratory tract infections, are possible COVID-19 clinical symptoms [1-3]. According to the WHO, SARS-CoV-2, a new strain of the coronavirus, is to blame for this outbreak (Severe Acute Respiratory Syndrome Corona Virus-2) [4]. According to sources, this disease first appeared in China's Wuhan region at the end of 2019 and has since spread to almost every country in the world, including Indonesia [5-8]. Based on the Autoregressive vector model, it estimates the number of cases and deaths of COVID-19. These estimates reveal an increasing number of infections and deaths from COVI-19 [9]. According to research and an evolutionary study, SARS-CoV-2 is believed to have bats as its primary natural host and that it might be transferred from bats to people via an unnamed intermediate host (zoonotic). It is now known that this virus attaches to the receptor Angiotensin Converting Enzyme 2 (ACE2) to infect individuals [8-11]. S (spike) protein helps the corona virus attach to ACE2 in human host cells so that it can begin its life cycle with the aid of Main Protease (MPro) in its replication process [12]. The Chinese authorities verified that this virus can spread from person to person in January 2020. Airborne droplets from coughing, sneezing, and touch can spread this illness [13]. Since the corona virus can occasionally evolve inside of people and become extremely contagious, it has a respectable capacity for survival in dry

environments [14]. A virus belonging to the genus Betacoronavirus is SARS-CoV-2. At first, four strains of this genus were recognized: HKU1, MERS-CoV, OC43, and SARS-CoV. Despite the fact that SARS-CoV-2 is the fifth strain of this species to be identified as having the ability to cause pneumonia [15]. The SARS-CoV-2 virus has an envelope and is a member of the Coronaviridae family. This envelope shape in viruses is crucial for some phases of the viral life cycle [16]. According to a genomic analysis, the Middle East Respiratory Syndrome Coronavirus and SARSCoV-2 are similar to the previous Corona viruses (MERS-CoV) [17]. Chloroquine and hydro chloroquine can stop viruses from entering host cells by lowering host receptor activity, protein rearrangement processes, and the acidity of the host cell environment. These substances also strengthen the immune system by enhancing cytokine production [18]. Through suppression of 3-chymotrypsin-like protease (3CLpro), an enzyme involved in virus growth, an antiviral that the FDA has licensed for use to treat HIV displays in vitro action against the Corona virus [19]. A recent in vitro study found that favipiravir and remdesivir dramatically reduced SARS-CoV-2 infection in healthy Vero E6 cells [20]. Many of these antiviral medications, including hydroxychloroquine, have reportedly been tested on SARS-CoV-2 patients, according to recent studies [21]. Ribavirin, Lopinavir, and Ritonavir [22], Remdesivir [23] and Tocilizumab [24]. In general, hydroxychloroquine is preferred over chloroquine because it has less tendency to produce cardiotoxicity [25]. In the early period of the COVID-19 pandemic, several studies showed that concomitant use of hydroxychloroquine and azithromycin could lead to a marked decrease in viral load [26]. However, based on evaluations of previous studies it is estimated that the likelihood of adverse cardiac events associated with this drug is estimated. So that the search for and development of new drugs in the treatment of COVID-19 continues [27]. Symptoms of this virus in patients often include a dry cough, sore throat, fever, and shortness of breath [28]. It takes a long time to produce a vaccine to treat illness due to the virus's capacity for mutation [29]. The Ministry of Health claims that since the virus self-medicates, individuals with robust immune systems can recover from this viral infection without the need for special care [30]. The immune system protects the body from infections brought on by bacteria, viruses, and parasites as well as other foreign substances [31]. Because of this, maintaining a robust immune system at this time is crucial for preventing viral infections in the body [32]. Maintaining the consumption of nutrients in food, especially those containing vitamins, minerals, and antioxidants, is one of the ways to increase immunity (immune system). Minerals can function as coenzymes, cofactors, and antioxidants that boost the immune system, while vitamins aid in the body's efficient metabolism and easy absorption of nutrients [33]. Needed vitamins, minerals, and antioxidants can be received through food made from either plants or animals. In the current scenario, traditional medical therapy and a combination of modern medicine are required for the treatment of COVID-19. Compared to therapies that simply employ modern medication, the use of herbal medicines can speed up the course of treatment [34]. Due to the risks and adverse effects of utilizing synthetic chemical pharmaceuticals, plants are now the primary source of medicines in the health sector. The need for herbal medications that permit the production of local medicinal plants is rising on a global scale [35]. There is mounting evidence that herbal substances have antiviral properties [36]. The bioactive component of turmeric is called curcumin [37] are effective illustrations of phytochemicals with many mechanisms of action. Curcumin has been approved by the US Food and Drug Administration (FDA). Curcumin has been shown to have curative and preventative properties against a number of diseases, including cancer, inflammatory diseases, neurological disorders, cardiovascular issues, lung issues, and metabolic disorders, in more than 300 clinical investigations [38]. In the therapy of COVID-19, curcumin may function as a potential inhibitor of the virus-host interaction (receptor protein-ACE2) at the point of human entrance as well as an attenuator by altering the pro-inflammatory effect of the Angiotensin II-AT1 receptor signaling pathway [39].

Curcumin is an immunomodulatory substance that inhibits the replication and entry of the SARSCoV-2 virus into host cells as well as the pathophysiological symptoms of COVID-19. Curcumin has been shown to be effective against inflammatory conditions, coagulation issues, and respiratory ailments (including infections with influenza and other coronaviruses) in previous experimental studies. Due to curcumin's adaptable and promising therapeutic potential in COVID-19, curcumin clinical trials are essential [40, 41]. Curcumin can help strengthen the immune system's defenses against viruses by having specific antiviral capabilities against enveloped RNA viruses. The results of earlier investigations also showed that curcumin has a wide range of biological and pharmacological activities, ranging from antiviral to anti-inflammatory with no toxicity [42, 43].

The goal of this study was to perform a more thorough analysis into the potential of curcumin compounds from the turmeric plant to cure COVID-19, as a crucial foundation for the creation of COVID-19 medications.

## 2. METHODS

This study used a literature review as its method and concentrated on many studies concerning the possibility of curcumin compounds to treat COVID-19 illness. Primary data for scientific papers is gathered from national and international journals through searches on electronic search engines like Google Scholar, ScienceDirect, or PubMed. Selected publications are assessed, evaluated, and interpreted by authors. The author's viewpoint on the possibility of the curcumin components in turmeric as a COVID-19 treatment is reflected in this perspective.

## 3. THE SUBSTANCES FOUND IN TURMERIC

Turmeric contains substances that are immune system boosters, anti-inflammatory, antitumor, antiviral, and antioxidants [44]. An analysis of turmeric simplicial powder's chemical composition revealed that its primary components were curcuminoid chemicals, fatty oils, and essential oils. Chemical analyses of different turmeric simplicial revealed that the chemical composition of the turmeric plant was 60-70 percent curcuminoid chemicals, 4.2 to 14 percent essential oil, and 4.4 to 12.7 percent fatty oil [45-47]. Three curcuminoid chemicals make up the bulk of turmeric: Curcumin, also known as 1,7-bis(4-hydroxy-3-methoxyphenyl)- 1,6-heptadiene-3,6-dione, is a compound with a number of biological functions. 1-(4-hydroxy-3-methoxyphenyl) -7-(4-

hydroxyphenyl) 1,6-Heptadiene-3,5-dione and 1,7-bisdemethoxycurcumin (4-hydroxyphenyl) 1,6-Heptadiene-3,5-dione, also known as bisdemethoxy curcumin [48]. There are other chemicals, such as 4-(3-methoxy-4-hydroxyphenyl)-2-oxoenbutanyl 3-(3-methoxy- 4-hydroxyphenyl), that are derivatives. Called propenoate or 1,7-bis calebin A (4-hydroxy-3-methoxyphenyl) - \s1,4,6-heptatriene-3-one,1-hydroxy-1,7-bis(4hydroxyphenyl)-3-methoxyphenyl) the 3.5-dione of 1,7-bis-6 heptene (4-hydroxyphenyl) 1,7-bis (1-heptene-3,5-diones), 1,5-bis (1,4,6-heptatriene-3-ones), and 1,4-hydroxyphenyl (1,7) (4-hydroxy-3-methoxyphenyl) -1,4-pentadiene-3-on [49]. Curcuminone and dehydrocurdion were also found in the MeOH extract of the turmeric rhizome, in addition to curcuminoids (4S,5S) Some of the substances that are found in turmeric include curcumenol, isoprocurcumenol, zedoaronediol, procurcumenol, epiprocurcumenol, germacron-13-al, bisabola-3,10-diene-2-one, bisabola-3,10-diene, bisacumol, bisacurone, 4-hydroxy-bisabola-2,10-diene-9-one, and procurcuma [50]. The three distinct curcuminoid compounds are curcumin, demethoxycurcumin, and bisdemethoxycurcumin [51]. The IUPAC nomenclature for the chemical compound curcumin is 1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. Having anti-inflammatory, antioxidant, and anti-cancer characteristics, it is an amphipathic molecule. A lipophilic methine segment encircles the polar core of the segment. Curcumin's dicarbonyl group, which serves as both a phenylhydroxyl group and a methoxy group, encourages the insertion and acceptance of H-bonds [52]. Several viruses, including hepatitis, influenza, Zika, chikungunya, HIV, herpes, and human papillomavirus (HPV) viruses, are said to be susceptible to the antiviral activities of curcumin compounds [53, 54]. Without being resistant to curcumin, curcumin compounds can directly combat H6N1 and H1N1 virus infection by preventing viral attachment and decreasing hemagglutination [55]. Additionally, computational studies have shown through molecular simulations that curcumin can directly bind to the SARS-CoV-2 virus' ACE2 receptor and S protein, inhibiting the virus' ability to connect to human host cells [56]. Due to its high fat solubility, the antioxidant chemical curcumin reacts with lipid radicals on cell membranes to produce phenoxyl radicals [57].

### 3.1 Antiviral using curcumin

Curcumin may prevent a number of viral infections, according to evidence. Dengue, Zika, and Chikungunya viruses as well as the influenza A virus (IAV) [58] are prevented from attaching to host cells by curcumin. Hepatitis C viral entrance is inhibited by curcumin (HCV) [59] human norovirus (HuNoV) [60] hemorrhagic septicemia (HSV) and bovine herpesvirus 1 (BHV-1). Curcumin also prevents the transcription of the respiratory syncytial virus (RSV) and the replication of viral genomes [61] and Japanese encephalitis virus (JEV) [62] and stop the Epstein-Barr virus from assembling and translating (EBV) [63] human cytomegalovirus (HCMV) [64] and human immunodeficiency virus (HIV) [65, 66]. Due to curcumin's antiviral effect, which inhibits HIV-1 integrase with an IC50 value of 40 M, derivative compounds of curcumin have been proposed as anti-AIDS drugs. According to data, curcumin may prevent the HIV-1 integrase protein from replicating [67]. Curcumin's capacity to interact with a variety of molecular sites and consequently set off cellular signaling pathways including death and inflammation leads to its pleiotropic effect on viruses. A number of proteins, including DNA polymerase, thioredoxin reductase, protein kinase (PK), tubulin, and lipoxygenase, are directly impacted by curcumin, according to earlier studies (LOX). Curcumin also alters intercellular signaling pathways, reducing NF-B and PI3K/Akt signaling, both of which are necessary for effective viral replication. Additionally, it disrupts key viral replication processes like viral attachment and genome replication, which slows viral growth. Additionally, it influences cellular alterations that are post-transcriptional and post-translational [68-71]. It has been shown that curcumin therapy changes the surface protein structure of the virus, blocking virus entry and virus budding. Curcumin also has an impact on membrane proteins through molecular docking with target receptors such the SARS-CoV-2 protease, spike glycoprotein-RBD, and PD-ACE2, which are thought to be more crucial in viral infection than ligands or drugs. Among these receptors are the SARS-CoV-2 protease, spike glycoprotein-RBD, and PD-ACE2. The references show that some compounds, including curcumin, can bind to particular receptors [72]. The entire set of enzymes required for viral replication is not present in viruses. Cellular machinery is used by viruses for their metabolism and reproductive operations. Antiviral drugs must prevent the virus from spreading while without damaging healthy cells. Potential treatment targets for viral replication include attachment, penetration, uncoating, genome replication, and gene expression. Curcumin has a number of recognized actions, including preventing viral infection by destroying viral components needed for viral replication and preventing viral penetration [73].

## 4. CURCUMIN'S ANTIVIRAL EFFECT AGAINST SARS-COV-2 BASED ON *IN SILICO* STUDIES

The immunological human host receptors for COVID-19 that are the subject of the current investigation are angiotensin-converting enzyme (ACE)-2, interleukin (IL)-1b, IL-6, tumor necrosis factor-alpha (TNF-a), and protease-activated receptor (TNF-a). In order to avoid viral contamination and manage excessive production of the early clinical response to COVID-19, PAR)-1 uses a derivative of curcumin. Infection will be reduced and a variety of problems brought on by this protein will be screened for in COVID-19 patients by targeting this host protein, using an *in silico* methodology to demonstrate. Eleven of the twenty curcumin analogues that were docked against five different human host receptor targets interacted more favorably at the active site. The COVID-19 human host binding target (ACE-2) for the virus works well with its clinical inflammatory receptors (IL-1b, IL-6, TNF-a, and PAR-1), which have a kcal/mol range of 5.0 to 8.3. Out of all the tested curcumin analog target complexes, hydrazinocurcumin demonstrated the strongest binding affinity for the target proteins ACE-2 and PAR-1, with docking values of 8.3 and 6.9 kcal/mol, respectively. Hydrazinocurcumin showed three hydrogen bonding interactions at the amino acid residues (his195, gln102, and trp566) in the ACE-2 binding pocket. While Lys158 and His255 interact with the target protein molecule PAR-1 in different ways—with Lys158 forming double hydrogen bonds and His255 interacting with PAR-1 through single hydrogen and covalent bonds—hydrazinocurcumin interacts with Lys158. The least-affinity binding of the final five chosen

curcumin derivatives to the chosen host protein was revealed by density functional theory (DFT) research [74].

Overall, curcumin may be useful in the management of viral epidemics like COVID-19 and other enveloped viral diseases. There is space for improvement in antiviral strategies since viruses can interact with their cellular receptors, allowing them to enter cells and proliferate in intricate ways. Here, we discuss how curcumin and its derivatives, which are components of turmeric, can suppress enveloped viruses. It works to prevent the virus from adhering to the cell surface. The coronavirus is susceptible to curcumin, just as many other enclosed viruses. The discovery of the mechanism by which curcumin inhibits the coronavirus has reached its zenith [75].

Based on its projected binding site's predicted minimum binding energy to the chosen protein target. The 11 chosen ligands had outstanding pharmacokinetic qualities according to the ADME component analysis. All 11 of the chosen curcumin derivatives have favorable ADME characteristics, making them excellent candidates for antiviral medications that block viral reproduction and life cycles [76]. With Caco-2 permeability ranging from 18.89 to 33.62 nm/s and good HIA in the range of 83.96 to 99.43 percent, eleven ligands were tested. The substances examined for bioavailability had solubilities in pure water and buffers that were, respectively, between 2.74 and 45612.4 mg/l and 0.3502 and 85.1844 mg/L. The chemical demonstrated very good blood-brain barrier penetration values of 0.0913-2.9443 and very good plasma protein binding values of 88.03-99.41 percent. Accordingly, curcumin hydrazino ligand (CID 135,494.223) had the highest scores for blood-brain barrier penetration, plasma protein binding, and MDCK cell permeability, with scores of 104.49 nm/s, 99.4196 percent, and 2.9443, respectively. The four cytochrome P450 enzymes were not inhibited by any of the five enzymes tested, with the exception of the CYP 2C9 inhibitor, which plays a role in the drug's xenobiotic mechanism. The skin permeability score of the bisdemethoxy curcumin ligand (CID5315472) is 2.1161 logkp cm/hour, while its solubility in pure water is 85.1844 mg/L [77].

Di-O-acetyl demethoxy curcumin's greatest binding affinity to the COVID-19 host protein target was shown by the DFT inquiry results, which also showed a lower energy gap of 0.0411, as well as less hardness (0.0205) and more softness (48.6026). Similar to this, didemethyl curcumin and O-demethyl demethoxy curcumin, the next two molecules in the ranking, showed less energy gaps (0.0455 and 0.0457) and more softness (43.9560 and 43.7541, respectively). DFT research is another option to diO-acetyl demethoxy curcumin. When compared to the other curcumin derivatives looked at, the smallest of the five investigated compounds, hydrazinocurcumin, showed the strongest docking binding affinity with COVID-19 host protein targets and the best ADME characteristics. It also had the highest softness score of 17.2920. The *in silico* screening of the DFT calculations was done here to better support the highest ligand-binding affinities and highest docking scores with host protein targets, which are essential for viral reproduction and growth mechanisms. An very helpful quantitative metric for the biological activity of any chemical substance is the computation of boundary orbital energies using the HOMO-LUMO orbital energy. This method is practical and semi-empirical in nature. Higher docking scores for compounds with target proteins are caused by the functional orbitals of the ligand molecules, which may be demonstrated and visualized more clearly by using HOMO-LUMO orbital energies [78].

Through the creation of six hydrogen bonds, curcumin exhibits a significant affinity for interacting with glycoprotein S in silico. In comparison to the control substances napamostat and hydroxychloroquine, curcumin performed better. Curcumin also exhibits strong affinity for ACE2. The docking outcomes also demonstrate that curcumin forms two hydrogen bonds and interacts with the protein's active site. Curcumin also shown more affinity for ACE2 than do control substances like captopril and hydroxychloroquine. In order to promote viral fusion and internalization via the ACE2 receptor, the SARS-CoV-2 glycoprotein interacts with the host cell. Therefore, the probable targets for the treatment of COVID-19 are ACE2 and glycoprotein S [79].

By interfering with SARS-CoV-2 attachment and internalization in different organs, including the liver, mobile diovascular system, and kidneys, curcumin may have protective effects against COVID-19 infection. Inflammation, apoptosis, RNA replication, and other cellular signaling pathways may all be modified by it, along with IFN and other cytokines and RNA replication and apoptosis. When COVID-19 infection is severe, curcumin may also decrease the pathways linked to pulmonary edema and fibrosis, which may be easier to detect. Given that disseminated intravascular coagulopathy can be associated with SARS-CoV-2 coronavirus infection and that curcumin has blood anticoagulation properties (by inhibiting platelet aggregation, the COX pathway, and blocking calcium signaling), curcumin can be suggested as a potent treatment for this pathological condition [80]. In addition, curcumin may help COVID-19 patients manage their myalgia and fatigue [81].

40 patients with mild COVID-19 who were admitted to an infectious disease ward and 40 patients with severe COVID-19 who were admitted to the critical care unit at the same hospital were randomly assigned to receive nanocurcumin (160 mg/day, for 21 days) or a placebo. 40 comparable healthy controls were additionally selected. Th17 cells and Th17 cell-associated cytokine levels in mild and severe COVID-19 patients receiving nanocurcumin significantly decreased as compared to the placebo group and their baseline levels. It's crucial to remember that these factors were significantly more common in COVID-19 patients than in the control group [82].

In order to evaluate the efficacy of nanocurcumin, this study team also conducted an additional open-label, non-randomized clinical trial on COVID-19 patients who were hospitalized with mild-to-moderate disease. Most symptoms vanished significantly more quickly in patients receiving Sinacurcumin soft gel at the same dosage as in this experiment than in the control group [83].

In a different study, the natural phenol curcumin and the cysteine protease bromelain both had significant immunomodulatory effects that interfered with key stages in the pathogenesis of COVID-19. Bromelain is a cysteine protease derived from pineapple stems. Transcription factor inhibition and proinflammatory mediator downregulation are two of its anti-inflammatory effects. In addition, bromelain hydrolyzes bradykinin, inhibits cyclooxygenase, modifies prostaglandins and thromboxane, influences inflammation and coagulation, and inhibits cyclooxygenase. It's interesting to note that while recent experimental investigations have demonstrated that bromelain can also suppress the virus, curcumin has been shown *in silico* studies to impede both viral entrance into cells and replication of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). get in the cell. In instance, after being administered orally, curcumin is

significantly more readily absorbed when bromelain is present. This is the first study that, to our knowledge, discusses the significance of bromelain and, more importantly, the potential preventative value of the synergistic impact of bromelain and curcumin against severe COVID-19 [73].

This review provides some support for the idea that curcumin represents a promising COVID-19 therapy and prevention candidate. Direct interaction with viral membrane proteins, rupturing of the viral envelope, inhibition of viral proteases, and production of a host antiviral response are the first mechanisms by which curcumin exhibits antiviral activity against several types of enveloped viruses, including SARS-CoV-2. Curcumin also prevents deadly pneumonia and ARDS by focusing on NF-B, the inflammasome, IL-6 signal trans, and the HMGB1 pathway. Third, giving curcumin to healthy or ill humans results in no negative side effects. As a result, mounting data support curcumin as a potential COVID-19 prevention strategy in both clinical and public health settings.

## 5. CURCUMIN PREVENTS VIRUSES FROM ENTERING CELLS

Curcumin is a natural polyphenol that can inhibit viral replication at doses of 3–10 M, however it has been shown to be ineffective against the SARS-CoV virus in vitro [84]. The effectiveness of curcumin against the SARS-CoV-2 binding protein and its cellular receptors was assessed by the researchers using an *in silico* predictive model based on their findings about antiviral activity. Via the ACE2 receptor, the SARSCoV2 S glycoprotein interacts with the host cell to promote viral fusion and internalization. As a result, ACE2 and glycoprotein S are possible targets for COVID-19 treatment. Curcumin has a strong affinity to interact with glycoprotein S through the creation of six hydrogen bonds, according to *in silico* study. In comparison to the control substances napamostat and hydroxychloroquine, curcumin performed better in this trial. Curcumin also has affinity for ACE2. The docking outcomes demonstrate that curcumin not only creates two hydrogen bonds but also interacts with the protein's active site. Similar to how captopril and hydroxychloroquine, which were used as controls, curcumin had greater affinity for ACE2 [85]. SARSCoV-2 entrance from spike protein is facilitated by transmembrane protease serine 2 (TMPRSS2) [86]. Curcumin and TMPRSS2 created an H-bond and four hydrophobic interactions, according to an *in silico* research that focused on TMPRSS2 [87]. These results confirm that curcumin treatment decreased the expression of TMPRSS2 in prostate cancer cells, as shown in an in vitro investigation [88, 89]. Since it is necessary for viral maturation and replication, the SARS-CoV-2 primary protease (Mpro) is a potential target for SARS-CoV-2 treatment. RNA-dependent RNA polymerase (RdRp, Nsp12) and helicase (Nsp13), two proteins matured by Mpro, are dependent on Mpro cleavage [90]. Mpro inhibition stops the spread of the virus, making substances that inhibit Mpro potential targets for COVID-19 treatment [91]. An *in silico* docking analysis of a variety of molecules, including medicines already used to treat COVID-19, was carried out to evaluate their propensity to bind to Mpro. In this investigation, two compounds with strong affinity for Mpro were used as controls: N3 and O6K [92].

## 6. CURCUMIN STOPS THE REPLICATION OF VIRUSES

In order to ascertain the impact of curcumin on viral replication, the study assessed the quantity of spike protein present in Vero E6 cell cultures infected with the SARS-CoV. The results show that curcumin prevents the reproduction of the SARS-CoV with an EC50 value greater than 10 M [93]. Effects of curcumin on the production of negative strand RNA using PEDV as a model coronavirus. They demonstrated how curcumin could stop PEDV from reproducing. After being treated to curcumin, plaque decreases. Curcumin may be able to stop viral replication, as evidenced by the drop in viral titer and plaque count [94-97].

## 7. AUTHOR'S VIEW

We see that the potential active compounds contained in the turmeric herbal plant in the form of curcumin have the potential to have an effect in handling COVID-19. The description of the potential of curcumin compounds as contained in the research above uses some of the latest references, so it is hoped that herbal plants can be a natural treatment solution to overcome the current epidemic of the virus, so that the potential of this plant can be further developed and become an alternative treatment for COVID-19 quality for the future. Finally, our research showed that curcumin has potential for immunomodulatory and anti-cytokine therapy against COVID-19 and can be an alternative choice of COVID-19 drug and a promising drug of choice for the treatment of COVID-19, but additional experimental trials in vitro, in vivo, and clinical evaluation are required for commercialization as a COVID-19 drug.

## 8. CONCLUSION AND RECOMMENDATION

Curcumin has potential importance in the treatment of COVID-19 viral infection. Curcumin in ADME component analysis showed excellent pharmacokinetic properties. We saw the influence of curcumin derivative structure in its cytotoxic activity against the COVID-19 virus. Structure Treatment with curcumin can change the structure of the top protein of the virus, preventing the virus from entering the body and sprouting. By modifying the characteristics of the host lipid bilayer with the help of target receptors such as the SARS-CoV-2 protease using molecular docking, curcumin impacts membrane proteins. The findings imply that some substances, such as curcumin, can bind to target receptors. Future studies on the use of curcumin as an inhibitory agent of the SARS-Cov-2 virus are needed to use it as a new and long-lasting therapeutic option for COVID-19 patients. Molecular simulations have shown that curcumin can bind exclusively to the S protein based on the SARS-CoV-two virus and the ACE2 receptor, which would prevent the virus from attaching to human host cells. Curcumin has antiviral activity that can fight various types of viruses, especially the SARS-CoV-two virus. Treatment with curcumin can change the structure of the top protein of the virus, preventing the virus from entering the body and sprouting. By modifying the characteristics of the host lipid bilayer with the help of target receptors such as the SARS-CoV-2 protease using molecular docking, curcumin impacts membrane proteins. The findings imply that some

substances, such as curcumin, can bind to target receptors. Future studies on the use of curcumin as an inhibitory agent of the SARS-Cov-2 virus are needed to use it as a new and long-lasting therapeutic option for COVID-19 patients. Future studies on the use of curcumin as an inhibitory agent of the SARS-Cov-2 virus are needed to use it as a new and long-lasting therapeutic option for COVID-19 patients.

## REFERENCES


[1] Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger N., Herrler, T., Erichsen, S., Schiergens, T., Herrler, G., Wu, N., Nitsche, A. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell, 181(2): 271-280. https://doi.org/10.1016/j.cell.2020.02.052

[2] Aini, N., Modjo, R., Lestari, F. (2022). Hospital preparedness in facing COVID-19 pandemic: A systematic literature review. International Journal of Design & Nature and Ecodynamics, 17(2): 311-317. https://doi.org/10.18280/ijdne.170219.

[3] Adedotun, A. F. (2022). Hybrid neural network prediction for time series analysis of COVID-19 cases in Nigeria. J. Intell Manag. Decis., 1(1): 46-55. https://doi.org/10.56578/jimd010106.

[4] Lai, C.C., Shih, T.P., Ko, W.C., Tang, H.J. Hsueh, P.R. (2020). Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) and Corona Virus Disease-2019 (COVID-19): The epidemic and the challenges. International Journal of Antimicrobial Agents, 55: 1-9. https://doi.org/10.1016/j.ijantimicag.2020.105924

[5] Sanders, J.M, Monogue, M.L, Jodlowski, T.Z. (2020). Pharmacological treatments for coronavirus disease 2019 (COVID-19): A review. JAMA, https://doi.org/10.1001/jama.2020.6019

[6] Shereen, M.A., Khan, S., Kazmi, A., Bashir, N. and Siddique, R. (2020). COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. Journal of Advanced Research, 24: 91-98. https://doi.org/10.1016/j.jare.2020.03.005

[7] Obat, B.P. (2020). Pedoman penggunaan herbal dan suplemen kesehatan dalam menghadapi COVID-19 di Indonesia. Jakarta: BPOM RI.

[8] Okafor, S.O., Ugwu, C.I., Nkwede, J.O., Onah, S., Amadi, G., Udenze, C., Chuke, N. (2022). COVID-19 public health and social measures in Southeast Nigeria and its implication to public health management and sustainability. Oppor Chall. Sustain., 1(1): 61-75. https://doi.org/10.56578/ocs010107

[9] Onuche, O.G, Funmi, A.A, Ayodeji, O.O. (2021). Vector Autoregressive Modeling of COVID-19 Incidence Rate in Nigeria. International Journal of Design & Nature and Ecodynamics, 16(6): 665-669. https://doi.org/10.18280/ijdne.160607

[10] Liu, F., Xu, A., Zhang, Y., Xuan, W., Yan, T., Pan, K., Zhang, J. (2020). Patients of COVID-19 may benefit from sustained lopinavir-combined regimen and the increase of eosinophil may predict the outcome of COVID-19 progression. International Journal of Infectious Diseases, 95: 183-191. https://doi.org/10.1016/j.ijid.2020.03.013

[11] Guo, Y.R., Cao, Q.D., Hong, Z.S., Tan, Y.Y., Chen, S.D., Jin, H.J., Tan, K.S., Wang, D.Y., Yan, Y. (2020). The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) Outbreak-an Update on The Status. Military Medical Research, 7(1): 1-10. https://doi.org/10.1186/s40779-020-00240-0

[12] Fauzi, T.M. (2021). Kajian curcumin pada kunyit dan temulawak dalam penyembuhan penyakit coronavirus diseases 2019 (COVID-19). Majalah Ilmiah Methoda, 11(2): 138-144. https://doi.org/10.46880/methoda.Vol11No2.pp138-144

[13] WHO, W. (2020). Novel Coronavirus (2019-nCoV) Situation Report—1. WHO.

[14] Rahmawati, E.N., Teruna, H.Y., Zhamri, A. (2018). Sintesis dan uji toksisitas senyawa analog kurkumin 3,5-bis((e)-metoksi benziliden)-1-(fenilsulfonil)-piperidin-4-on. Jurnal Sain Dan Kesehatan, 9(1): 151-158. https://doi.org/10.37859/jp.v9i1.1074

[15] Ahkam, A.H., Hermanto, F.E., Alamsyah, A., Aliyyah, I.H., Fatchiyah, F. (2020). Virtual prediction of antiviral potential of ginger (Zingiber officinale) bioac-tive compounds against spike and MPro of SARSCoV2. Journal of Biological Researches, 25(2): 52-57. https://doi.org/10.23869/50

[16] Li, C., Zhao, W., He, C., Wu, D., Yue, Y., Chen, Y. (2020). COVID-19 prevention and control strategies for psychiatric hospitals. Psychiatry Research, 289: 112935. https://doi.org/10.1016/j.psychres.2020.112935

[17] Burhan, E. (2020). Coronavirus yang meresahkan dunia. Journal of the Indonesian Medical Association, 70(2): 1-3.

[18] Yu, W.B., Tang, G.D., Zhang, L., Corlett, R.T. (2020). Decoding the evolution and transmissions of the novel pneumonia coronavirus (SARS-CoV-2/HCoV-19) using whole genomic data. Zoological Research, 41(3): 247-257. https://doi.org/10.24272/j.issn.2095-8137.2020.022

[19] Schoeman, D., Fielding, B.C. (2019). Coronavirus envelope protein: current knowledge. Virology journal, 16(1): 1-22. https://doi.org/10.1186/s12985-019-1182-0

[20] Islam, M.T., Sarkar, C., El-Kersh, D.M. (2020). Natural products and their derivatives against coronavirus: A review of the non-clinical and pre-clinical data. Phytotherapy Research, 34(10): 2471-2492. https://doi.org/10.1002/ptr.6700

[21] Zhou, D., Dai, S.M., Tong, Q. (2020). COVID-19: A recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. Journal of Antimicrobial Chemotherapy, 75(7): 1667-1670. https://doi.org/10.1093/jac/dkaa114

[22] Wilde, A., Jochmans, D., Posthuma, C. (2014). Screening of an FDA-Approved Compound Library Identifies Four Small-Molecule Inhibitors of Middle East Respiratory Syndrome Coronavirus Replication in Cell Culture. Antimicrobial Agents and Chemotherapy, 58: 4875-4884. https://doi.org/10.1128/AAC.03011-14

[23] Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research, 30(3): 269-271. https://doi.org/10.1038/s41422-020-0282-0

[24] Mahevas, M., Tran, V.T., Roumier, M. (2020). Clinical efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: Observational comparative study using routine care data, BMJ, 369.

[25] Hung, I.F.N., Lung, K.C., Tso, E.Y.K., Liu, R., Chung, T.W.H., Chu, M.Y., Yuen, K.Y. (2020). Triple

combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: An open-label, randomised, phase 2 trial. The Lancet, 395(10238): 1695-1704. https://doi.org/10.1016/S0140-6736(20)31042-4

[26] Wang, Y., Zhang, D., Du, G. (2020b). Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. Lancet, 395: 1569-1578. https://doi.org/10.1016/S0140-6736(20)31022-9

[27] Xu, X., Han, M., Li, T., Sun, W., Wang, D., Fu, B., Wei, H. (2020). Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences, 117(20): 10970-10975. https://doi.org/10.1073/pnas.2005615117

[28] Rawaf, S., Al-Saffar, M., Quezada-Yamamoto, H., Alshaikh, M., Pelly, M., Rawaf, D. (2020). Chloroquine and hydroxychloroquine effectiveness in human subjects during coronavirus: A systematic review. medRxiv, 11. https://doi.org/10.1101/2020.05.07.20094326

[29] Roshanravan, N., Seif, F., Ostadrahimi, A., Pouraghaei, M., Ghaffari, S. (2020). Targeting cytokine storm to manage patients with COVID-19: A mini-review. Arch Med Res., 51(7): 608-612. https://doi.org/10.1016/j.arcmed.2020.06.012

[30] Kavous, S., Morteza, G., Amir, G., Faezeh, H., Maryam, S., Hassan, S. (2021). An umbrella review of clinical efficacy and adverse cardiac events associated with hydroxychloroquine or chloroquine with or without azithromycin in patients with COVID-19. Anesth Pain Med., 11(4): e115827. https://doi.org/10.5812/aapm.115827

[31] Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., Iosifidis, C., Agha, R. (2020). World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). International Journal of Surgery, 76: 71-76. https://doi.org/10.1016/j.ijsu.2020.02.034

[32] Supriyatna, A., Ida Kinasih, I., Adisty, V., Mohamad, J. (2020). Evolusi SARS-CoV-2 dalam perspektif wahyu memandu ilmu (WMI). LP2M UIN Sunan Gunung Djati, Bandung.

[33] Syahrir, A., Rahem, A., Prayoga, A. (2020). Religiositas mahasiswa farmasi uin malang selama pandemi COVID-19. Journal of Halal Product and Research, 3(1): 25-34.

[34] Aripin, I. (2019). Pendidikan nilai pada materi konsep sistem imun. Bio Educatio:(The Journal of Science and Biology Education), 4(1): 1-11.

[35] Susilo, A., Rumende, C.M., Pitoyo, C.W., Santoso, W.D., Yulianti, M., Herikurniawan, H., Sinto, R., Singh, G., Nainggolan, L., Nelwan, E.J., Chen, L.K. (2020). Coronavirus disease 2019: tinjauan literatur terkini. Jurnal Penyakit Dalam Indonesia, 7(1): 45-67. http://dx.doi.org/10.7454/jpdi.v7i1.415

[36] Siswanto, B., and Ernawati, F. (2013). Peran beberapa zat gizi mikro dalam sistem imunitas. Gizi Indonesia, 36(1): 57-64.

[37] Le, Q., Lay, H. (2020). Whether Herbal Medicines Play an Important Role in the COVID-19 Therapeutics and Boosting Immune as One of the Preventive Solutions: A Science Opinion. Journal of Ayurvedic Herb Med, 6(1): 1-3.

[38] Oladunmoye, M.K., Kehinde, F.Y. (2011). Ethnobotanical survey of medicinal plants used in treating viral infections among Yoruba tribe of South Western Nigeria. African Journal of Microbiology Research, 5(19): 2991-3004. https://doi.org/10.5897/AJMR10.004

[39] Praditya, D., Kirchhoff, L., Brüning, J., Rachmawati, H., Steinmann, J., Steinmann, E. (2019). Anti-infective properties of the golden spice curcumin. Frontiers in microbiology, 10: 912. https://doi.org/10.3389/fmicb.2019.00912

[40] Abdollahi, E., Momtazi, A.A., Johnston, T.P., Sahebkar, A. (2018). Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: A nature-made jack-of-alltrades. Journal of Cellular Physiology, 233(2): 830-848. https://doi.org/10.1002/jcp.25778

[41] Jager, R., Lowery, R.P., Calvanese, A.V., Joy, J.M., Purpura, M., Wilson, J.M. (2014). Comparative absorption of curcumin formulations. Nutrition Journal, 13(1): 1-8. https://doi.org/10.1186/1475-2891-13-11

[42] Manoharan, Y., Haridas, V., Vasanthakumar, K.C., Muthu, S., Thavoorullah, F.F., Shetty, P. (2020). Curcumin: a wonder drug as a preventive measure for COVID19 management. Indian Journal of Clinical Biochemistry, 35(3): 373-375. https://doi.org/10.1007/s12291-020-00902-9

[43] Hooper, P.L. (2020). COVID-19 and heme oxygenase: Novel insight into the disease and potential therapies. Cell Stress & Chaperones, 25(5): 707-710. https://doi.org/10.1007/s12192-020-01126-9

[44] Soni, V.K., Mehta, A., Ratre, Y.K., Tiwari, A.K., Amit, A., Singh, R.P., Sonkar, S.C., Chaturvedi, N., Shukla, D., Vishvakarma, N.K. (2020). Curcumin, a traditional spice component, can hold the promise against COVID-19. European Journal of Pharmacology, 886: 173551. https://doi.org/10.1016/j.ejphar.2020.173551

[45] Praditya, D., Kirchhoff, L., Bruning, J., Rachmawati, H., Steinmann, J., Steinmann, E. (2019). Anti-infective properties of the golden spice curcumin. Frontiers in Microbiology, 10: 912.

[46] Zahedipour, F., Hosseini, S. A., Sathyapalan, T., Majeed, M., Jamialahmadi, T., Al-Rasadi, K., Banach, M., Sahebkar, A. (2020). Potential effects of curcumin in the treatment of COVID-19 infection. Phytotherapy Research, 34(11): 2911-2920. https://doi.org/10.1002/ptr.6738

[47] Qaiser, D., Srivastava, A., Qaiser, A. (2018). Anticancer herbs for improving the quality of life. International Annals of Science, 5(1): 1-11. https://doi.org/10.21467/ias.5.1.1-11

[48] Simanjuntak, P. (2012). Studi Kimia dan Farmakologi Tanaman Kunyit (Curcuma longa L) Sebagai Tumbuhan Obat Serbaguna. Agrium: Jurnal Ilmu Pertanian, 17(2): 103-107. http://dx.doi.org/10.30596%2Fagrium.v17i2.306

[49] Galen, E., Van., Kroes, B., Garcia-Llorente, G. (2018). Assessment report on Curcuma longa L. rhizome-EMA/HMPC/749518/2016. European Medicines Agency Committee on Herbal Medicinal Products (HMPC): 1-34.

[50] Qaiser, D., Srivastava, A., Qaiser, A. (2018). Anticancer herbs for improving the quality of life. International Annals of Science, 5(1): 1-11.

[51] Srinivasan, K.R. (1953). Composition of Curcuma longa. Journal of Pharm. Pharmacol., 5: 448.

[52] Park, S.Y., Kim, D.S. (2002). Discovery of natural

products from Curcuma l onga that protect cells from beta-amyloid insult: A drug discovery effort against Alzheimer's disease. Journal of natural products, 65(9): 1227-1231. https://doi.org/10.1021/np010039x

[53] Ohshiro, M., Kuroyanagi, M., Ueno, A. (1990). Structures of sesquiterpenes from Curcuma longa. Phytochemistry, 29(7): 2201-2205. https://doi.org/10.1016/0031-9422(90)83038-3

[54] Al-Doori, A., Ahmed, D., Kadhom, M., Yousif, E. (2021). Herbal medicine as an alternative method to treat and prevent COVID-19. Baghdad Journal of Biochemistry and Applied Biological Sciences, 2(1): 1-20. https://doi.org/10.47419/bjbabs.v2i01.25

[55] Gangal, N., Nagle, V., Pawar, Y., Dasgupta, S. (2020). Reconsidering traditional medicinal plants to combat COVID-19. AIJR Preprints, 34: 1-6.

[56] Das, M., Banerji, A., Cheemalapati, V.N., Hazra, J. (2020). Antiviral activity of indian medicinal plants: prventive measures for COVID-19. Journal of Global Biosciences, 9(5): 7307-7319.

[57] Chen, D.Y., Shien, J.H., Tiley, L., Chiou, S.S., Wang, S.Y., Chang, T.J., Lee, Y.J., Chan, K.W., Hsu, W.L. (2010). Curcumin inhibits influenza virus infection and haemagglutination activity. Food Chemistry, 119(4): 1346-1351. https://doi.org/10.1016/j.foodchem.2009.09.011

[58] Jena, A.B., Kanungo, N., Nayak, V., Chainy, G.B.N., Dandapat, J. (2021). Catechin and curcumin interact with corona (2019- nCoV/SARS-CoV2) viral S protein and ACE2 of human cell membrane: insights from computational study and implication for intervention. Sci Rep., 11(1): 2043.

[59] Sreejayan, N., Rao, M.N.A. (1994). Inhibition of radiation-induced lipid peroxidation by curcumin. Journal of Pharmacy and Pharmacology, 46(12): 1013-1016. https://doi.org/10.1016/S0378-5173(97)04900-4

[60] Chen, T.Y., Chen, D.Y., Wen, H.W., Ou, J.L., Chiou, S.S., Chen, J.M., Hsu, W.L. (2013). Inhibition of enveloped viruses infectivity by curcumin. PLoS One, 8(5): 62482. https://doi.org/10.1371/journal.pone.0062482

[61] Chen, B., Zhang, D.P., Gao, W. (2008). Effect of curcumin on the expression of collagen type I protein and transforming growth factor-beta1 mRNA in pulmonary fibrosis rats. Zhonghua lao dong wei sheng zhi ye bing za zhi= Zhonghua laodong weisheng zhiyebing zazhi= Chinese journal of industrial hygiene and occupational diseases, 26(5): 257-261.

[62] Yang, K.Y., Lin, L.C., Tseng, T.Y., Wang, S.C., Tsai, T.H. (2007). Oral bioavailability of curcumin in rat and the herbal analysis from Curcuma longa by LC-MS/MS. Journal of Chromatography. Analytical Technologies in the Biomedical and Life Sciences, 853(1-2): 183-189. https://doi.org/10.1016/j.jchromb.2007.03.010

[63] Obata, K., Kojima, T., Masaki, T., Okabayashi, T., Yokota, S., Hirakawa, S., Tanaka, S. (2013). Curcumin prevents replication of respiratory syncytial virus and the epithelial responses to it in human nasal epithelial cells. PLoS One, 8(9): e70225. https://doi.org/10.1371/journal.pone.0070225

[64] Iranshahi, M., Sahebkar, A., Takasaki, M., Konoshima, T., Tokuda, H. (2009). Cancer chemopreventive activity of the prenylated coumarin, umbelliprenin, in vivo. European Journal of Cancer Prevention, 18(5): 412-415. https://doi.org/10.1097/CEJ.0b013e32832c389e

[65] Hergenhahn, M., Soto, U., Weninger, A., Polack, A., Hsu, C.H., Cheng, A.L., Rösl, F. (2002). The chemopreventive compound curcumin is an efficient inhibitor of Epstein-Barr virus BZLF1 transcription in Raji DR-LUC cells. Mol Carcinog., 33(3): 137-45. https://doi.org/10.1002/mc.10029

[66] Lv, Y., An, Z., Chen, H., Wang, Z., Liu, L. (2014). Mechanism of curcumin resistance to human cytomegalovirus in HELF cells. BMC complementary and alternative medicine, 14(1): 1-7. https://doi.org/10.1186/1472-6882-14-284

[67] Kaur, I., Gupta, R.C., Puri, M. (2011). Ribosome inactivating proteins from plants inhibiting viruses. Virologica sinica, 26(6): 357-65. https://doi.org/10.1007/s12250-011-3223-8

[68] Ali, A., Banerjea, A.C. (2016). Curcumin inhibits HIV-1 by promoting Tat protein degradation. Scientific reports, 6(1): 1-9. https://doi.org/10.1038/srep27539

[69] Mazumder, A., Raghavan, K., Weinstein, J., Kohn, K.W., Pommier, Y. (1995). Inhibition of human immunodeficiency virus type-1 integrase by curcumin. Biochemical pharmacology, 49(8): 1165-1170. https://doi.org/10.1016/0006-2952(95)98514-A

[70] Ahn, K.S., Sethi, G., Jain, A.K., Jaiswal, A.K., Aggarwal, B.B. (2006). Genetic deletion of NAD(P)H: Quinone oxidoreductase 1 abrogates activation of nuclear factor-kappaB, IkappaBalpha kinase, c-Jun Nterminal kinase, Akt, p38, and p44/42 mitogenactivated protein kinases and potentiates apoptosis. The Journal of Biological Chemistry, 281(29): 19798-19808. https://doi.org/10.1074/jbc.M601162200

[71] Mathew, D., Hsu, W.L. (2018). Antiviral potential of curcumin. Journal of Functional Foods, 40: 692-699. https://doi.org/10.1016/j.jff.2017.12.017

[72] Praditya, D., Kirchhoff, L., Brüning, J., Rachmawati, H., Steinmann, J., Steinmann, E. (2019). Anti-infective properties of the golden spice curcumin. Frontiers in Microbiology, 10: 912.

[73] Puar, Y.R., Shanmugam, M.K., Fan, L., Arfuso, F., Sethi, G., Tergaonkar, V. (2018). Evidence for the involvement of the master transcription factor NF-κB in cancer initiation and progression. Biomedicine, 6(3): 82. https://doi.org/10.3390/biomedicines6030082

[74] Utomo, R.Y., Meiyanto, E. (2020). Revealing the potency of citrus and galangal constituents to Halt SARS-CoV-2 infection. Preprints, 2020030214. https://doi.org/10.20944/preprints202003.0214.v1

[75] Wen, C.C., Kuo, Y.H., Jan, J.T., Liang, P.H., Wang, S.Y., Liu, H.G., Lee, S.S. (2007). Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. Journal of Medicinal Chemistry, 50(17): 4087-4095. https://doi.org/10.1021/jm070295s

[76] Maurya, V.K., Kumar, S., Prasad, A.K., Bhatt, M.L., Saxena S.K. (2020). Structure-based drug designing for potential antiviral activity of selected natural products from Ayurveda against SARS-CoV-2 spike glycoprotein and its cellular receptor. Virus Disease, 31(2): 179-193. https://doi.org/10.1007/s13337-020-00598-8

[77] Panagiotis, K., Irene, K., Styliani, K., Maria, D. (2020). The combination of bromelain and curcumin as an immune-boosting nutraceutical in the prevention of severe COVID-19. Metabolism Open, 8: 100066.

https://doi.org/10.1016/j.metop.2020.100066
[78] Manoharan, Y., Haridas, V., Vasanthakumar, K.C., Muthu, S., Thavoorullah, F.F., Shetty, P. (2020). Curcumin: A wonder drug as a preventive measure for COVID19 management. Indian Journal of Clinical Biochemistry, 35(3): 373-375. https://doi.org/10.1007/s12291-020-00902-9
[79] Magden, J., Kaariainen, L., Ahola, T. (2005). Inhibitors of virus replication: Recent developments and prospects. Applied Microbiology and Biotechnology, 66(6): 612-621. https://doi.org/10.1007/s00253-004-1783-3
[80] Rathinavel, T., Meganathan, B., Kumarasamy, S., Ammashi, S., Thangaswamy, S., Ragunathan, Y., Palanisamy, S. (2020). Potential COVID-19 drug from natural phenolic compounds through in silico virtual screening approach. Biointerface Res Appl Chem, 10161-10173.
[81] Malkhasian, A.Y., Howlin, B.J. (2016). Docking and DFT studies on ligand binding to Quercetin 2,3-dioxygenase. Journal of Biomolecular Structure & Dynamics, 34(11): 2453-2461. https://doi.org/10.1080/07391102.2015.1123190
[82] Maurya, V.K., Kumar, S., Prasad, A.K., Bhatt, M.L.B., Saxena, S.K. (2020). Structure-based Drug Designing for Potential Antiviral Activity of Selected Natural Products from Ayurveda against SARS-CoV-2 Spike Glycoprotein and its Cellular Receptor. VirusDis, 31: 179-193. https://doi.org/10.1007/s13337-020-00598-8
[83] Zahedipour, F., Hosseini, S.A., Sathyapalan, T., Majeed, M., Jamialahmadi, T., Al-Rasadi, K., Sahebkar, A. (2020). Potential effects of curcumin in the treatment of COVID-19 infection. Phytotherapy Research, 34(11): 2911-2920. https://doi.org/10.1002/ptr.6738
[84] Babaei, F., Nassiri-Asl, M., Hosseinzadeh, H. (2020). Curcumin (a constituent of turmeric): New treatment option against COVID-19. Food Science & Nutrition, 8(10): 5215-5227.
[85] Tahmasebi, S., El-Esawi, M.A., Mahmoud, Z.H., Timoshin, A., Valizadeh, H., Roshangar, L., Ahmadi, M. (2021). Immunomodulatory effects of Nanocurcumin on Th17 cell responses in mild and severe COVID-19 patients. Journal of Cellular Physiology, 236(7): 5325-5338. https://doi.org/10.1002/jcp.30233
[86] Saber-Moghaddam, N., Salari, S., Hejazi, S., Amini, M., Taherzadeh, Z., Eslami, S., Elyasi, S. (2021). Oral nano-curcumin formulation efficacy in management of mild to moderate hospitalized coronavirus disease-19 patients: An open label nonrandomized clinical trial. Phytotherapy research, 35(5): 2616-2623. https://doi.org/10.1002/ptr.7004
[87] Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T., Herrler, G., Wu N., Nitsche, A. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell, 181(2): 271-280. https://doi.org/10.1016/j.cell.2020.02.052
[88] Okazaki, K., Papagiannakopoulos, T., Motohashi, H. (2020). Metabolic features of cancer cells in NRF2 addiction status. Biophysical Reviews, 12(2): 435-441. https://doi.org/10.1007/s12551-020-00659-8
[89] Prevarskaya, N., Zhang, L., Barritt, G. (2007). TRP channels in cancer. Biochim Biophys Acta. 1772(8): 937-946. https://doi.org/10.1016/j.bbadis.2007.05.006
[90] Hu, Y., Dobi, A., Sreenath, T., Cook, C., Tadase, A.Y., Ravindranath, L., Srivastava, S. (2008). Delineation of TMPRSS2-ERG splice variants in prostate cancer. Clinical Cancer Research, 14(15): 4719-4725. https://doi.org/10.1158/1078-0432.CCR-08-0531
[91] Rut, W., Groborz, K., Zhang, L., Modrzycka, S., Poreba, M., Hilgenfeld, R., Drag, M. (2020). Profiling of flaviviral NS2B-NS3 protease specificity provides a structural basis for the development of selective chemical tools that differentiate Dengue from Zika and West Nile viruses. Antiviral Research, 175: 104731. https://doi.org/10.1016/j.antiviral.2020.104731
[92] Anand, P., Kunnumakkara, A.B., Newman, R.A., Aggarwal, B.B. (2007). Bioavailability of curcumin: Problems and promises. Molecular Pharmaceutics, 4(6): 807-818. https://doi.org/10.1021/mp700113r
[93] Luan, B., Huynh, T., Cheng, X., Lan, G., Wang, H.R. (2020). Targeting proteases for treating COVID-19. Journal of proteome research, 19(11): 4316-4326. https://doi.org/10.1021/acs.jproteome.0c00430
[94] Wen, C.C., Kuo, Y.H., Jan, J.T., Liang, P.H., Wang, S.Y., Liu, H.G. Lee, S.S. (2007). Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. Journal of Medicinal Chemistry, 50(17): 4087-4095. https://doi.org/10.1021/jm070295s
[95] Ting, D., Dong, N., Fang, L., Lu, J., Bi, J., Xiao, S., Han, H. (2018). Multisite inhibitors for enteric coronavirus: Antiviral cationic carbon dots based on curcumin. ACS Applied Nano Materials, 1(10): 5451-5459. https://doi.org/10.1021/acsanm.8b00779
[96] Sun, L., Xing, Y., Chen, X., Zheng, Y., Yang, Y., Nichols, D.B., Chen, Z. (2012). Coronavirus papain-like proteases negatively regulate antiviral innate immune response through disruption of STING-mediated signaling. PloS one, 7(2): e30802. https://doi.org/10.1371/journal.pone.0030802
[97] Zumla, A., Chan, J.F., Azhar, E.I., Hui, D.S., Yuen, K.Y. (2016). Coronaviruses—drug discovery and therapeutic options. Nature reviews Drug discovery, 15(5): 327-347. https://doi.org/10.1038/nrd.2015.37