Homology Modeling and Molecular Docking Approach for Curcumin as a Potential Treatment for Novel SARS-COV-2 Targets

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Abstract

The emergence of SARS-CoV-2 causing COVID-19 led to a global health crisis, prompting extensive research into diagnostic methods and potential treatments. Various approaches, including molecular techniques and thermal scanning, have been employed for accurate identification of COVID-19 cases. However, no authorized drug or vaccine for SARS-CoV-2 has been approved, prompting investigations into alternative treatment options. Curcumin, a natural compound with diverse pharmacological effects, shows promise as an antiviral agent. Molecular docking studies reveal its ability to bind to the spike proteins of SARS-CoV-2 and SARS-CoV, suggesting potential therapeutic implications. In this comprehensive review, we explore the intricate structure of SARS-CoV-2, its transmission routes, primary symptoms, and the role of curcumin as a potential treatment targeting the viral spike proteins. Despite ongoing challenges, ongoing research and advancements offer hope for effectively combating COVID-19.

Keywords: SARS-CoV-2, COVID-19, coronavirus, curcumin, Structure analysis,molecular docking, spike protein, viral structure, antiviral agent, diagnostic methods, therapeutic approaches.

1. Introduction

In December 2019, the Chinese Health Authority officially informed the World Health Organization (WHO) regarding a series of pneumonia cases of undetermined cause within Wuhan City, situated in Hubei Province, China. Following thorough swab tests conducted on patients' throats, a previously unidentified coronavirus was detected and initially designated as Coronavirus-2019 by the WHO [1]. The Coronavirus Study Group rebranded this infectious pathogen as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), while the World Health Organization (WHO) designated the resulting illness as coronavirus disease 2019 (COVID-19). This disease is caused by the aforementioned infection and exhibits a noteworthy mortality rate [2].Across China, a total of 9,720 individuals fell ill, with 213 fatalities reported. Additionally, 106 cases emerged in 19 distinct countries [3].

Essentially, the coronavirus belongs to a group of positive, single-stranded RNA viruses characterized by a diverse array of enveloped particles. Its surface is adorned with spike-like protrusions that resemble a crown when observed through an electron microscope, hence the name "coronavirus [4].

The primary symptoms of COVID-19 encompassed fever, weakness, and cough, exhibiting resemblances to those observed in patients affected by SARS-CoV and MER [5]. Belonging to the subfamily Orthocoronavirinae in the family Coronaviridae and falling under the order Nidovirales, this pathogen is part of the Coronavirinae subfamily, which is divided into four genera. Among these genera, α- and β-coronaviruses are the ones classified as capable of infecting Homo sapiens [6].Uniquely found in animals, gamma coronavirus and delta-coronavirus represent distinct groups. Gamma-coronavirus includes viruses that infect whales and birds, while delta-coronavirus is comprised of infections isolated from pigs and birds [7].Drawing upon comprehensive phylogenetic analysis of the viral genome, the ailment exhibits a robust association with a cluster of SARS-like beta-coronaviruses recently detected in Chinese bat populations[8]. Through meticulous sequencing and developmental inquiries, bats are postulated as the probable natural reservoir for this virus[9, 10]. Given the unavailability of the exact bats from Wuhan's market, researchers explored receptor comparisons among diverse species, proposing alternative intermediate hosts like turtles, pangolins, and snakes [11, 12].

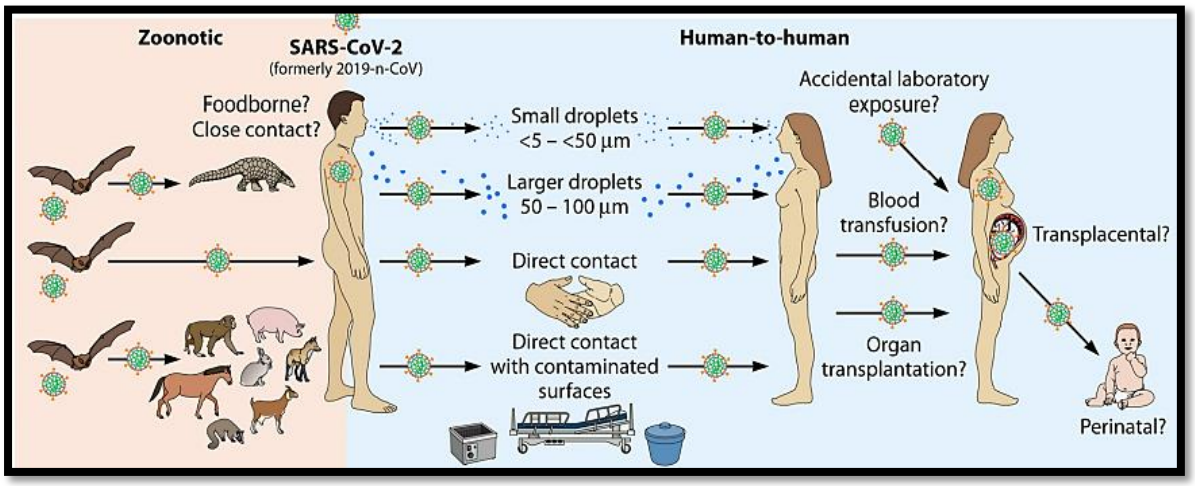

Figure 1: Transmission of infection from one person to another

Infiltrating the respiratory system via droplets, respiratory secretions, and saliva [13, 14], COVID-19 emerges as a highly transmissible and newly recognized respiratory illness. The Angiotensin-Converting Enzyme 2 receptor, abundantly distributed throughout the respiratory system and salivary gland epithelial cells, serves as an initial point of interest for SARS-CoV [15]. For a visual representation of the coronavirus transmission route, refer to figure 1 [16].

In this comprehensive review paper, we delve into various perspectives surrounding SARS-CoV-2, examining its intricacies in detail. Moreover, our focus centers on exploring the potential use of curcumin as a treatment for this viral infection, along with understanding its underlying mechanism of action. By combining scientific insights and emerging research, we

aim to shed light on the promising prospects of curcumin in combatting this global health challenge.

2. Structure of SARS-CoV-2:

Within coronaviruses lies a non-segmented, s-stranded, +vesense RNA genome spanning 30-kb, enclosed by a 5-cap and 3-poly (A) tail.Severe acute respiratory syndrome coronavirus 2, specifically, boasts a 29,891 basepair-long genome with a GC content of 38%.In their genomic composition, coronaviruses exhibit an envelope that surrounds a viral nucleocapsid, displaying a distinctive helical symmetry. Alongside the familiar genes, the genome also accommodates supplementary ones, including 3a/b, 4A/b, and the HE genes.Coronavirus harbors a positive-sense genome that serves as mRNA, and this genetic information is translated into a polyprotein called 1a/1ab (pp1a/1ab). The RTC (replication transcription complex) comprises Nsps (Non-structural proteins) and is formed within double membrane vesicles (DMV), utilizing the polyprotein gene. Subsequently, the RTC orchestrates the arrangement of Subgenomic RNA through a fascinating process known as discontinuous transcription[17, 18 and 19].

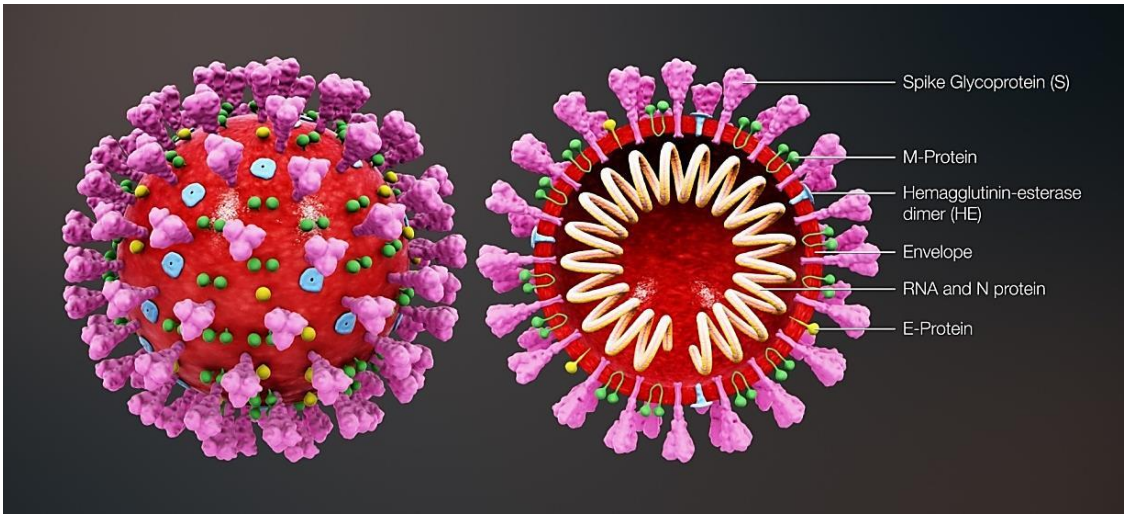

Figure 2: Structure of SARS-CoV-2

Structural Proteins:

The major structural proteins of the virus encompass spike proteins, nucleocapsid proteins, envelope proteins, and membrane proteins. These essential components are all encoded at the 3" end of the viral genome [20].The spike protein, a versatile class I viral transmembrane protein, boasts an array of diverse functions. With its amino acid count ranging from 1,160 to 1,400 [21], it acquires a crown-like appearance as it assumes a prominent position on the surface of the virion.Intricate interactions between infectious virion particles and various host cell receptors enable cellular entry, facilitated by the S protein [22]. These S proteins exhibit a two-domain structure, consisting of a substantial ectodomain and a smaller endodomain.Within the ectodomain, two subsets, S1 and S2, are distinguished, showcasing a strikingly similar domain arrangement among all Coronavirus S proteins. While the S1 subunit plays a crucial role in binding to the host's receptors, the other subunit contributes to the process of membrane fusion [23, 24].The S-protein has the capability to establish connections with the ACE2 receptor located on the surface of the host's cells [25].The protein

M plays a crucial role in mediating the majority of protein-protein interactions required for coronavirus assembly. When proteins M and E are co-expressed, they give rise to virus-like particles (VLPs), forming the distinctive coronavirus envelopes. The protein M consists of three transmembrane domains, featuring a small amino terminus on the external side and a longcarboxy terminus on the internal side [26].The monomeric form of M exhibits a molecular mass spanning from 25 to 30 kDa. The interior or intracellular membrane of the cytoplasm houses a significant portion of this molecule, comprising both the minuscule N-terminal and C-terminal endodomains [27].Within the realm of critical structural proteins, the enigmatic E protein holds a distinct position, being the smallest with a size spanning 8-12 kDa [28]. Despite their relative scarcity in the virion, these proteins function as viroporins, acting as ion channels and contributing to a multitude of tasks encompassing virus assembly, pathogenesis, and release [29, 30].Embedded within helical nucleocapsids, the N protein serves as a nucleocapsid protein, boasting two well-preserved domains, NTD and CTD, each endowed with specific roles. While both NTD and CTD can bind to RNA in vitro, they employ distinct binding mechanisms. This versatile protein carries out a myriad of functions, including facilitating complex formation during viral assembly, enabling interactions with the M protein, and enhancing the efficiency of virus transcription[31, 32].

Non- Structural Proteins:

Coronaviruses boast the largest genome, spanning 30 kb, encompassing a diverse array of structural, accessory genes, extensive replicase, and other nonstructural proteins (Nsps) [33]. The virus genome's ORF1a/b segment is responsible for encoding two polyproteins, pp1a (Nsp1-11) and pp1ab (Nsp1-16), collectively comprising two-thirds of the genome [34]. The cleavage of the ORF1ab gene results in the synthesis of 16 nonstructural proteins, leading to the expression of polypeptides [35].The repertoire of these proteins encompasses a diverse set of functions: NSP3 and NSP5 take on proteolytic roles, skillfully orchestrating proteases. Nsp13, Nsp14, Nsp15, and Nsp16 showcase their enzymatic prowess, actively participating in intricate viral RNA post-translational modifications, with a primary focus on the elusive 5′-capping, thereby orchestrating an artful evasion of the host's innate immune system. Within this intricate viral orchestra, NSP12 assumes a pivotal role, meticulously conducting RNA replication with utmost precision and finesse. Furthermore, NSP5 exhibits its captivating ADP-ribose phosphatase activity, an essential component for impeccable posttranslational modifications, while NSP14 and NSP15 skillfully wield their impressive exoribonuclease and endoribonuclease activities, respectively, contributing to the symphony of viral mastery [36]. The orchestration of their nonstructural proteins (NSPs) involves meticulous cleavage maneuvers executed by specific proteases. Nsp3, the papain-like protease, adeptly severs NSPs 1 to 3, while the indomitable 3CLPro, also known as the 3-chymotrypsinlike proteinase, skillfully executes its cutting prowess, precisely removing the C-terminus from Nsp4 to Nsp16 [37].

3. Current Medication:

Extensive scrutiny by esteemed authorities such as the World Health Organization, the Food and Drug Administration, and the Centers for Disease Control and Prevention reveals a disheartening reality - the quest for an effective drug, therapy, or vaccine to combat the

relentless SARS-CoV-2 infection remains unfulfilled, with no authorized solution at present. Nonetheless, amidst this ongoing battle, certain medications have emerged in the armamentarium used to confront COVID-19 in afflicted individuals. Among these are Remdesivir, Chloroquine, Hydroxychloroquine, and others, which stand as valiant contenders in the ongoing struggle against the formidable adversary that is SARS-CoV-2 [38].Among its illustrious achievements, Remdesivir (RDV) has showcased its antiviral prowess against formidable viruses like SARS-CoV and MERS-CoV [39]. As a potent RNA polymerase inhibitor, this analogue nucleotide has demonstrated its mettle, effectively thwarting viral replication. Amidst the arduous battle against the COVID-19 pandemic, Remdesivir has earned the coveted approval of the Food and Drug Administration for treatment, receiving authorization for approximately 250 infected patients. Its remarkable impact became evident when administered to three patients in the United States, leading to significant symptom improvement without substantial side effects. This astonishing breakthrough further underscored Remdesivir's efficacy in substantially reducing the mortality rate, with an impressive 64 percent of cases exhibiting noticeable improvement [40].The therapeutic armamentarium has been bolstered with the administration of chloroquine to afflicted individuals. Distinguished by its longstanding authorization by the FDA for the treatment of malaria, arthritis, and lupus, chloroquine has garnered significant attention in Covid-19 treatment [41].

4. Curcumin as a Treatment for SARS-COV-2 Targets:

Curcumin, an inherent phytochemical derived from Curcuma longa, emerges as a formidable natural compound, showcasing an impressive array of pharmacological attributes encompassing antioxidant, anti-inflammatory, anti-cancer, and anti-viral effects [42, 43]. The captivating allure of curcumin and its derivatives, with roots steeped in a history of traditional medicinal interest, has spurred intensive exploration through both in vitro and in vivo studies. This dynamic compound has entwined its essence with over 100 cellular targets, ranging from cytokines and proteins to transcription factors and receptors, establishing an intricate network of potential therapeutic engagements.Prior investigations have shed light on the latent promise of curcumin as an agent in combating Influenza A virus infection, a profound impact attributed to its ability to finely regulate the immune response, thereby mitigating damage to lung tissue. Furthermore, curcumin has been unveiled to wield anti-neuraminidase (NA) activity, serving as a potential inhibitor for the influenza virus NA protein. Buoyed by these insights, curcumin and its derivatives emerged as viable contenders, subject to docking analyses onto the spike proteins of SARS-CoV and SARS-CoV-2 [44, 45]. This intricate endeavor sought to unveil the underlying binding interactions, ultimately unraveling the tantalizing prospect of curcumin as a potential therapeutic measure against viral infections.

In a recent pursuit of scientific inquiry, pioneering research endeavors embarked on a journey to investigate the profound impact of curcumin and its derivatives on viral proteins. A noteworthy study conducted in 2022 set forth on a virtual screening quest, meticulously exploring the interactions of curcumin and its analogs with the spike surface glycoproteins of both SARS-CoV-2 and SARS-CoV. Employing state-of-the-art Molecular docking simulations, these intrepid investigators delved into the binding preferences of the curcumin

derivatives within the active site of the receptor. The scope of their investigations spanned the flexible docking analyses, carefully orchestrating these investigations using the refined spike protein of SARS-CoV (6CRV) and the RBD domain of SARS-CoV-2 (6M0J) as the vantage points for exploration.Employing the intricate methodology of molecular docking, this empirical quest ventured to unveil the propensities of curcumin and its derivatives to bind with the spike proteins of two illustrious coronaviruses. With precision and meticulousness, the investigation saw the docking of curcumin and 24 of its derivatives onto 6CRV and 6M0J.Within the domain of 6CRV, the binding energies exhibited a range from −10.98 to −5.12 kcal/mol, while in the realm of 6M0J, they showcased a range from −10.01 to −5.33 kcal/mol.The profound exploration of the curcumin compounds unfurled a captivating tableau of interactions, as a majority of these compounds masterfully orchestrated hydrogen bonding with Arg99, Met144, and Lys198.All the compounds adroitly engaged in hydrophobic interactions, partaking in the delicate dance of π-π stacking, π-cation, and π-σ.The curcumin derivative that displayed the most compelling binding affinity proved to be Bis-demethoxycurcumin, showcasing resolute prowess as it confidently engaged with both 6CRV (ΔG = −10.98 kcal/mol) and 6M0J (ΔG = −10.01 kcal/mol).

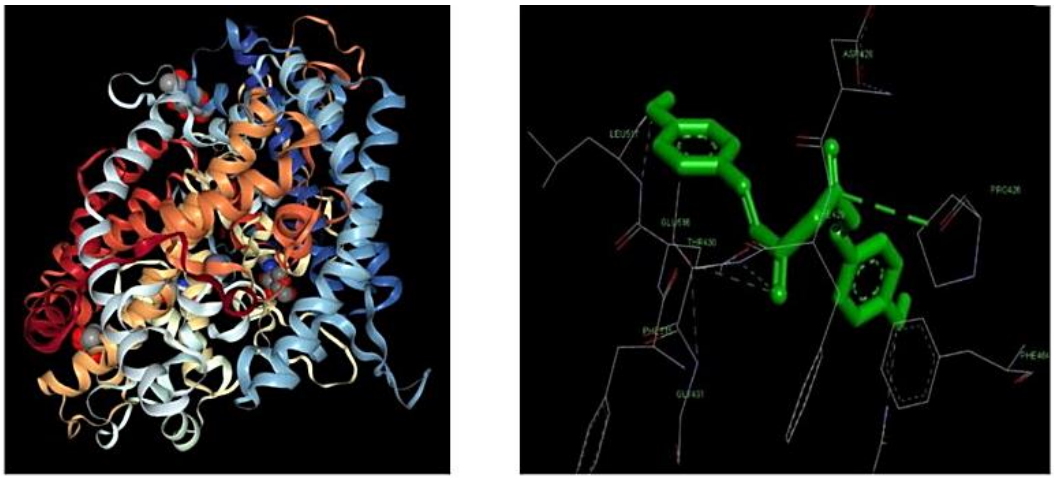

Figure 3: Bis-demethoxycurcumin with the SARS-CoV-2 spike protein

The researchers embarked on a comprehensive investigation, drawn to the multifaceted biological activities of Curcumin and its derivatives, which include antiviral properties. In this pursuit, they delved into the potential of curcumin and its derivatives to interact with the spike proteins of both SARS-CoV and SARS-CoV-2. Employing cutting-edge computational molecular docking methods, they explored the intricate binding interactions between these compounds and the RBD domain of the SARS-CoV-2 Spike protein and the SARS-CoV spike protein. The meticulous in-silico analyses, along with the use of the ADMET tool, yielded insightful predictions, with Bis-demethoxycurcumin, compound-4, and compound-2 emerging as the most promising candidates for efficacious binding with the spike proteins in in silico studies. These encouraging findings pave the way for further exploration, unveiling potential therapeutic avenues in the relentless battle against these enigmatic coronaviruses[46].

5. Detection Methods:

The effective management of COVID-19 necessitates precise and accurate diagnostic methods. Various diagnostic approaches are employed, including molecular techniques, serology, and viral culture. To initiate the diagnostic process, patients typically undergo initial laboratory examinations, encompassing complete blood count, coagulation testing, and serum biochemistry assessments. Notably, laboratory findings have unveiled that SARS-CoV-2 predominantly targets lymphocytes, especially T cells, resulting in a significant reduction of total lymphocyte counts in the majority of patients. Such reductions in lymphocyte counts could potentially serve as a diagnostic indicator for SARS-CoV-2 infection and its severity [47]. Cutting-edge technologies like infrared sensors and thermal scanning play a pivotal role, particularly in the realm of pre-diagnosis screening. To facilitate this process, thermal cameras are strategically deployed to detect individuals with elevated body temperatures. These sophisticated cameras boast the capability to scan distances of up to 10 meters, ensuring comprehensive coverage. Originally confined to specific hospital entrances, this innovative approach has since extended to encompass various hospital departments. Functioning on the principles of infrared radiation detection, thermal cameras adeptly capture heat signatures and seamlessly translate them into visual images, enhancing the diagnostic capabilities and supporting efforts in early detection and surveillance [48].The Nucleic acid amplification test method stands as a robust diagnostic tool, skillfully employing nasal swabs or blood samples for analysis through real-time fluorescence polymerase chain reaction [49]. Recognizing the urgent need, regulatory bodies such as the US Food and Drug Administration (FDA) have granted emergency authorization for COVID-19 diagnostic kits founded on RT-PCR technology. Pioneering the way as the first commercial diagnostic kit, Cobas SARS-CoV-2 has set a high standard, catering to tests spanning from moderate to high complexity [50].Recognizing the limitations of the Nucleic acid amplification test, Chinese scientists have advocated for the utilization of CT imaging as an alternative diagnostic approach for COVID-19 [51]. This proposition finds support in a case study wherein a patient presented with a sore throat and exhaustion. Despite initial negative COVID-19 results from the Fluorescent Real Time Polymerase Chain Reaction test of sputum during the first six days of hospitalization, a subsequent chest CT scan revealed significant peripheral ground-glass opacities in both lungs, with greater involvement observed in the left upper lobe and liner segment of the left lung. The progression of ground-glass opacities in the lungs was evident three days after hospital admission, indicative of COVID-19 infection [52]. Amidst the pursuit of novel diagnostic and treatment strategies, the application of CRISPR/Cas13 technology emerges as an intriguing frontier, showcasing potential promise in the ongoing endeavors to combat COVID-19 [53].

6. Conclusion:

In conclusion, the emergence of SARS-CoV-2 as the cause of COVID-19 brought about an unprecedented global health crisis. Efforts to understand and combat the virus have been vast and comprehensive. Diagnostic methods, including molecular techniques, serology, and thermal scanning, have been employed to accurately identify and manage COVID-19 cases. However, the search for effective drugs and vaccines remains ongoing. In this pursuit, curcumin and its derivatives have shown potential as antiviral agents, with molecular docking

studies revealing their ability to bind to the spike proteins of SARS-CoV-2 and SARS-CoV. Bis-demethoxycurcumin, compound-4, and compound-2 demonstrated the most promising binding affinity. Further research in this direction holds promise in the fight against these enigmatic coronaviruses. As the world continues its relentless battle against COVID-19, ongoing investigations and advancements in diagnostic and therapeutic approaches offer hope for a brighter future in managing and controlling this global health challenge.

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