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Paradigm of Well-Orchestrated Pharmacokinetic Properties of Curcuminoids Relative to Conventional Drugs for the Inactivation of SARS-CoV-2 Receptors: An In Silico Approach

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Abstract: To cure SARS-CoV-2 infection, the repurposing of conventional antiviral drugs is currently advocated by researchers, though their action is not very effective. The present study, based on in silico methods, was intended to increase the therapeutic potential of conventional drugs: hydroxychloroquine (HCQ), favipiravir (FAV), and remdesivir (REM) by using curcuminoids like curcumin (CUR), bisdemethoxycurcumin (BDMC), and demethoxycurcumin (DMC) as adjunct drugs against SARS-CoV-2 receptor proteins, namely main protease (Mpro) and the S1 receptor-binding domain (RBD). The curcuminoids exhibited similar pharmacokinetic properties to the conventional drugs. The webserver (ANCHOR) predicted greater protein stability for both receptors with a disordered score (<0.5). The molecular docking study showed that the binding energy was highest (−27.47 kcal/mol) for BDMC toward Mpro receptors, while the binding energy of CUR (−20.47 kcal/mol) and DMC (−20.58 kcal/mol) was lower than that of HCQ (−24.58 kcal/mol), FAV (−22.87 kcal/mol), and REM (−23.48 kcal/mol). In the case of S1-RBD, CUR had the highest binding energy (−38.84 kcal/mol) and the lowest was in FAV (−23.77 kcal/mol), whereas HCQ (−35.87 kcal/mol) and REM (−38.44 kcal/mol) had greater binding energy than BDMC (−28.07 kcal/mol) and DMC (−30.29 kcal/mol). Hence, this study envisages that these curcuminoids could be employed in combination therapy with conventional drugs to disrupt the stability of SARS-CoV-2 receptor proteins.

Keywords: SARS-CoV-2; main protease; S1 receptor-binding domain; curcuminoids; conventional drugs; pharmacokinetic properties; ANCHOR; molecular docking

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1. Introduction

The outbreak of evolving COVID-19 disease began in late December 2019 in Wuhan, China, by the unusual coronavirus (SARS-CoV-2) and speedily spread within China and beyond [1]. The World Health Organization (WHO) declared the COVID-19 epidemic as a pandemic on 12 March 2020 [2]. To date, three major pathogenic human coronaviruses (CoVs) have been recognized, such as the Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), and a 2019 novel coronavirus (2019nCoV) [3]. SARS-CoV-2 is extremely fatal for human life, as identified by WHO [4].

A coronavirus has four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins [4,5]. The S protein is mainly involved in viral adherence,

integration, and entry, and thus it is considered a target for exploring new drugs [6,7]. The S protein provides a means of entry into host cells for the virus, which first attaches to the host receptor via the receptor-binding domain (RBD) of the S1 subunit and then to host membranes by the S2 subunit [8,9]. SARS-CoV-2 recognizes angiotensin-converting enzyme 2 (ACE2) as its receptor for binding to the S-protein [10,11]. It has earlier been elucidated that the RBD protein binds strongly to human ACE2 and bat ACE2 receptors. In addition, alterations in the RBD protein hinder the binding of SARS-CoV-2 to their respective ACE2 receptor in cells, explaining how this protein could play a role as an inhibitor of the attachment of SARS-CoV-2 [12].

Another important drug target of coronaviruses is the main protease (Mpro) [13]. Similar to papain-like protease(s), the Mpro needs the polyproteins that are translated from the viral RNA for its processing [14]. The Mpro has at least 11 cleavage sites for the large polyprotein 1ab (replicase 1ab), with the recognition sequence of LeuGln↓(Ser,Ala,Gly) (↓ indicates the cleavage site). Inactivation of Mpro will lead to inhibition of the viral replication.

Drug repurposing and the exploration of natural molecules can be an efficient approach to respond instantly to emerging infectious diseases because the synthesis of new drug generally takes more than 10 years [15]. FDA (Food and Drug Administration, Silver Spring, MD, USA)-approved drugs contribute safe alternative options only when at least moderate antiviral activity can be obtained. To date, several drugs have been tested in clinical trials against COVID-19 disease, such as hydroxychloroquine (HCQ), favipiravir (FAV), and remdesivir (REM) [15].

Hydroxychloroquine (HCQ) hinders receptor binding and membrane fusion, two crucial processes involved in cell entry by coronaviruses. HCQ exhibits an antiviral impact during pre- and post-infection by altering the glycosylation of ACE2 and inhibiting the virus fusion with the host cell. The modified terminal glycosylation of ACE2 may decrease the binding efficiency between ACE2 on host cells and the spike protein. The integration of the virus with the receptors of cells is hindered, and hence the infection can be controlled at an initial stage. Since HCQ moves into a cell, it is resisted in organelles at low pH such as endosomes, Golgi vesicles, and lysosomes. The virus uses endosomes for the entry process into cells; increasing the pH of endosomes via hydroxychloroquine produces a negative impact on the fusion step of the virus with the endosome [16]. Lysosomal proteases stimulate the fusion process between the host and viral membranes by cleaving spike proteins [17]. The increasing pH level in lysosomes inhibits the protease activity and, ultimately, the fusion process is suppressed [18]. It has been shown that the spread of SARS-CoV was controlled in cells treated with hydroxychloroquine prior to or after infection, suggesting both the prophylactic and therapeutic importance of HCQ in combating SARS-CoV. Therefore, it has been envisaged that HCQ could also be beneficial against SARS-CoV-2 [19,20]. HCQ can alter the activity of S1-RBD of SARS-CoV-2 involving in the binding process with ACE2 of host cells. Therefore, it has been envisaged that HCQ could also be beneficial against SARS-CoV-2 by targeting Mpro.

Favipiravir (FAV) is an efficient inhibitor of the influenza virus RNA polymerase, and it also works against all subtypes and strains of influenza viruses. FAV also has antiviral properties against other RNA viruses [21]. The active form of FAV is favipiravir-RTP (favipiravir ribofuranosyl-5′-triphosphate), which is obtained by intracellular phosphoribosylation, and this is identified as a substrate by RdRp and blocks the RNA polymerase activity [21]. Recently, it has been shown that FAV elicited better therapeutic responses in COVID-19 disease [22]. It is also expected that the FAV could be efficient in perturbing the activity of S1-RBD and Mpro of SARS-CoV-2.

Remdesivir (REM) is an also novel antiviral drug used to cure Ebola virus disease and Marburg virus infections. REM is the prodrug of a nucleotide analog that is metabolized to an analog of adenosine triphosphate intracellularly, which blocks the activity of viral RNA polymerases. REM has a wide range of activity against various virus families such as filoviruses (e.g., Ebola) and coronaviruses. The intravenous administered remdesivir

revealed a significant improvement in the first COVID-19 case in US, and a trial was started immediately afterward to understand the efficacy and safety of REM in patients of COVID-19 [23]. Whether REM can alter the activity of S1-RBD and Mpro of SARS-CoV-2 in the treatment of COVID-19 patients is a matter for further study.

Since time immemorial, turmeric (*Curcuma longa*) has been used as a spice, preservative, and coloring agent, although it plays a vital role in medicinal and pharmacological applications. It contains various medicinal properties like anti-inflammatory, antiviral, antibacterial, antioxidant, nematocidal, antiparasitic, and anticarcinogenic activities. Turmeric also inhibits the ROS (reactive oxygen species)-producing enzymes cyclooxygenase and lipoxygenase that suppress the activity of COX-I and COXII enzymes involved in the inflammatory reaction. Turmeric has 3–6% polyphenolic components, collectively known as curcuminoids that are a mixture of curcumin (CUR), bisdemethoxycurcumin (BDMC), and demethoxycurcumin (DMC). It has been observed that these curcuminoids are mainly involved in several biological activities [24]. It is generally recognized as safe (GRAS) by the Food and Drug Administration (FDA), and a maximum dose of turmeric of up to 12 g/day was harmless for human consumption during clinical trials without producing any adverse impact [25]. Thus, curcuminoids could be used in the treatment of COVID-19 patients after examination of their antiviral properties against SARS-CoV-2.

Among all curcuminoids, only curcumin had been used widely to explore its antiviral properties in different viruses e.g., parainfluenza virus type 3, feline infectious peritonitis virus, flock house virus, and respiratory syncytial virus [26]. Previously, it has been described that if curcumin is applied to cells prior to or upon infection, it impedes the infection steps of enveloped viruses, e.g., poxvirus, flavivirus, herpesvirus, and orthomyxovirus, although the plaque-formation ability of nonenveloped enteroviruses like 71 (EV71) is not changed [27]. However, curcumin disturbs the functional efficiency of viral envelope proteins like the hemagglutinin–neuraminidase protein of the Newcastle disease virus and the hemagglutinin protein of IAV [27]. Similarly, a study showed that curcumin inhibits infections by two arthropod-borne viruses, zika and chikungunya virus, by impeding the binding methods of these viruses to the host cell [28]. Several studies showed that other components (BDMC and DMC) of curcuminoids exhibit similar therapeutic properties like curcumin. Therefore, the present study focused on a novel idea for combination therapy by investigating the inhibitory potential of curcuminoids—BDMC, DMC, and CUR—along with selected conventional antiviral drugs (HCQ, FAV, and REM) targeting the Mpro and S1-RBD proteins of SARS-CoV-2.

2. Results and Discussion

Because of the higher infectious rate of SARS-CoV-2, affecting almost all countries, therapeutic alternatives are needed to overcome the health issues related to COVID-19. Mpro plays a crucial function in coronavirus replication. This enzyme is involved in the cleavage of the polyprotein, forming active proteins that will be packed into the virion. The molecular study of SARSCoV-2 proteases demonstrated that this virus protease has greater homology with the SARS-CoV protease [29]. The coronaviral surface spike protein S is a type I transmembrane glycoprotein that enables the initial host attachment via the cell surface receptor ACE2, and eventually membrane fusion is accomplished for cell entry [30,31]. Hence the S protein has been identified as a novel targeting candidate for both vaccine synthesis and immunotherapy [30]. Currently, the repurposing of FDA-approved drugs like hydroxychloroquine (HCQ), favipiravir (FAV), and remdesivir (REM) are being used to treat COVID-19 patients, and researchers are also giving attention to exploring the therapeutic efficiency of natural compounds like turmeric in curing SARS-CoV-2 infection.

2.1. Study of Pharmacokinetic Properties of the Ligands by a Predictive Model

The ADMET properties of all the selected compounds have been analyzed by using the admetSAR database. The ADMET profiles have some parameters to understand the drug-like properties of molecules e.g., Caco-2 cell permeability, AMES toxicity, carcinogenicity, and rat acute toxicity LD50, as mentioned in Table 1. All the selected components reveal permeability for Caco-2 cells and, in the case of AMES toxicity, all compounds have been observed to be nontoxic, except for HCQ.

Table 1. ADMET analysis of turmeric components and antiviral drugs.

Compounds	Caco-2 Permeability	AMES Toxicity	Carcinogens	Rat Acute Toxicity LD50 (mol/kg)
HCQ	Caco2-	AMES toxic	Non-carcinogens	2.6348
FAV	Caco2-	Non-AMES toxic	Non-carcinogens	2.1259
REM	Caco2-	Non-AMES toxic	Non-carcinogens	2.7169
CUR	Caco2+	Non-AMES toxic	Non-carcinogens	2.5468
BDMC	Caco2+	Non-AMES toxic	Non-carcinogens	2.2754
DMC	Caco2+	Non-AMES toxic	Non-carcinogens	2.2792

The carcinogenicity model suggested noncarcinogenic properties for all the compounds. The rat acute toxicity LD50 of all molecules was determined to be between 2.1259 and 2.7169 mol/kg. These outcomes strongly provide evidence of the potential of the selected compounds to act as a lead drug [32]. Hence, the ADMET analysis demonstrates that curcuminoids fulfill all the parameters of drug-like properties.

Figure 1 shows the BOILED-Egg construction to evaluate the passive gastrointestinal absorption (HIA) and brain penetration (BBB) of the selected compounds in the WLOGP-versus-TPSA referential. The white part represents a greater probability of passive absorption by the gastrointestinal tract, and the yellow region (yolk) indicates a high probability of brain penetration. However, it is a very simple concept based on two physicochemical descriptors only: (i) WLOGP for lipophilicity and (ii) TPSA for apparent polarity [33]. In this study, it has been observed that all the selected molecules except for REM, a conventional drug, followed the rule of the BOILED-Egg model for the prediction of absorption possibility. Here, the BOILED-Egg construction indicates that HCQ and BDMC have a high probability for both gastrointestinal absorption and brain penetration, whereas CUR, DMC, and FAV have more probability for only gastrointestinal absorption. The BOILED-Egg construction indicates that curcuminoids could be absorbed in the human body, thus increasing their therapeutic potential.

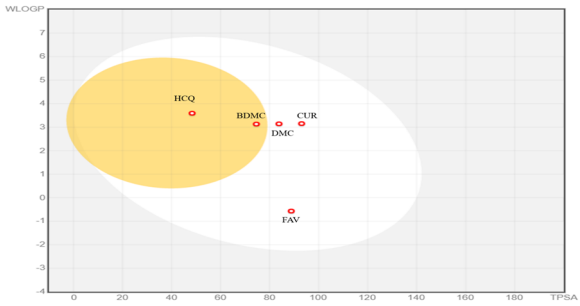

Figure 1. Assessment of the passive gastrointestinal absorption (HIA) and brain penetration (BBB) function of curcuminoids and antiviral drugs in the WLOGP-versus-TPSA referential by using the BIOLED-Egg construction.

Ligand-based target classes for the antiviral drugs were predicted by using a web tool, SwissTargetPrediction, as shown in Figure 2 [34].

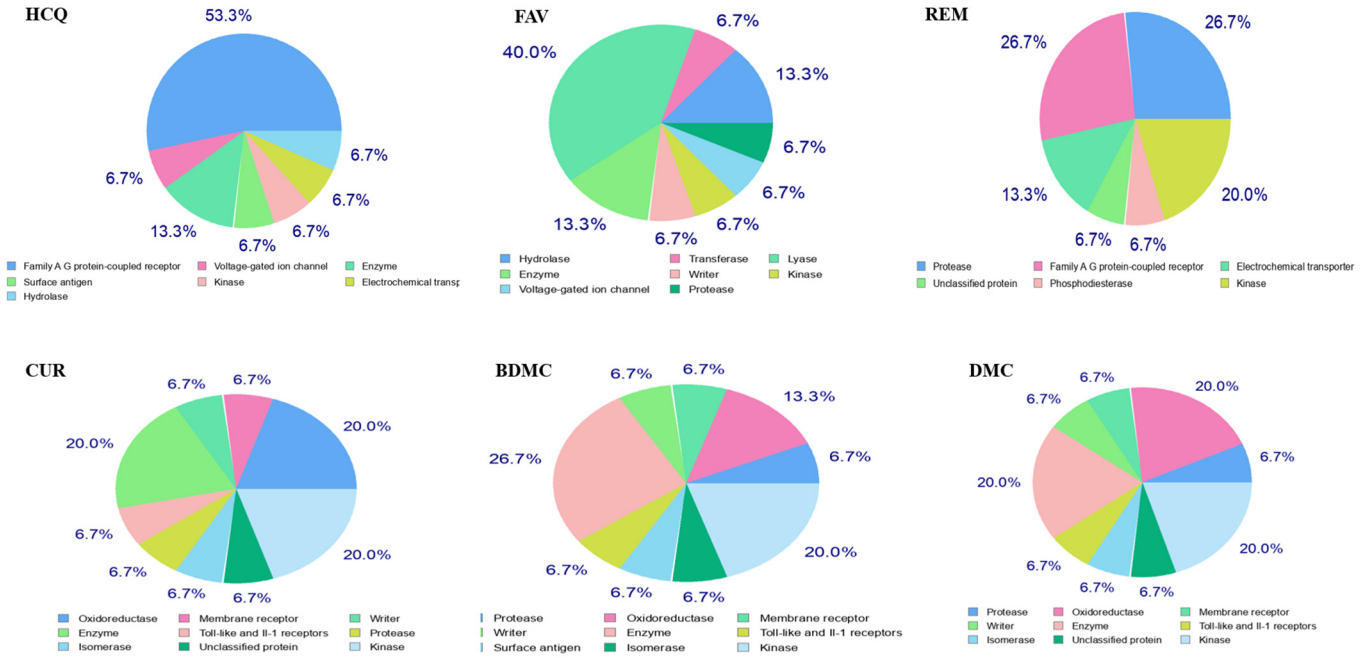

Figure 2. Prediction of target class by the SwissTargetPrediction web server for turmeric components and antiviral drugs: HCQ, FAV, REM, CUR, BDMC, and DMC.

Some common target sites (enzyme, surface antigen, kinase, writer, protease, and unclassified protein) have been described for conventional drugs as well as for curcuminoids. It has been observed that the kinase is a target site for all antiviral conventional drugs (HCQ, FAV and REM) and curcuminoids (CUR, BDMC, and DMC). Except for REM, all molecules target the enzyme, whereas only two molecules, HCQ and BDMC, have a surface antigen as a target site. Curcuminoids (CUR, BDMC, and DMC) are similar to the conventional drug FAV in reference to Histone acetyltransferase (writer); in the case of the protease site, all the molecules have the possibility to integrate with it. Nuclear-factor erythroid 2-related factor 2 (unclassified protein) has been explored as a target site for CUR and DMC, similar to REM.

Interestingly, like curcuminoids (CUR, BDMC, and DMC), the selected conventional drugs do not have the possibility to bind with oxidoreductase, membrane receptors, Toll-like and IL-1 receptors, and isomerases, indicating that the curcuminoids have more target classes in comparison with HCQ, FAV, and REM. Hence, the above parameters (ADMET, physicochemical properties and target class) reveal that the curcuminoids possess all the pharmacokinetic properties that are required for them to be developed as a new drug [34].

2.2. Determination of Protein Stability

Several proteins have naturally disordered regions (IDRs), which are functional polypeptide parts that achieve a larger flexible conformational ensemble despite a single, familiar structure. Disorder prediction methods can differentiate between ordered and disordered parts from the amino acid sequence and have contributed essential data for identifying the various properties of intrinsically disordered proteins by aiding the description of individual instances and large-scale measurement of these protein regions. One well-known approach, IUPred, provides a novel method for the determination of protein disorder by following an energy assessment method that uses the fundamental variances between the biophysical properties of ordered and disordered sites [35]. The ANCHOR method, based on the energy assessment method, is also employed to explore the disordered tendency and binding potential of protein parts.

The diagram found from the web server (https://iupred2a.elte.hu; accessed on 25 June 2023) (Figure 3) upon submission of FASTA files of the protein receptors gained a

score of less than 0.5 for all residues of Mpro (Figure 3a) and S1-RBD (Figure 3b), which suggested that the integrity of residues in SARS-CoV-2 protein receptors is extremely high [36]. Hence, individual drugs like HCQ might not have the potential to block the activity of Mpro and S1-RBD.

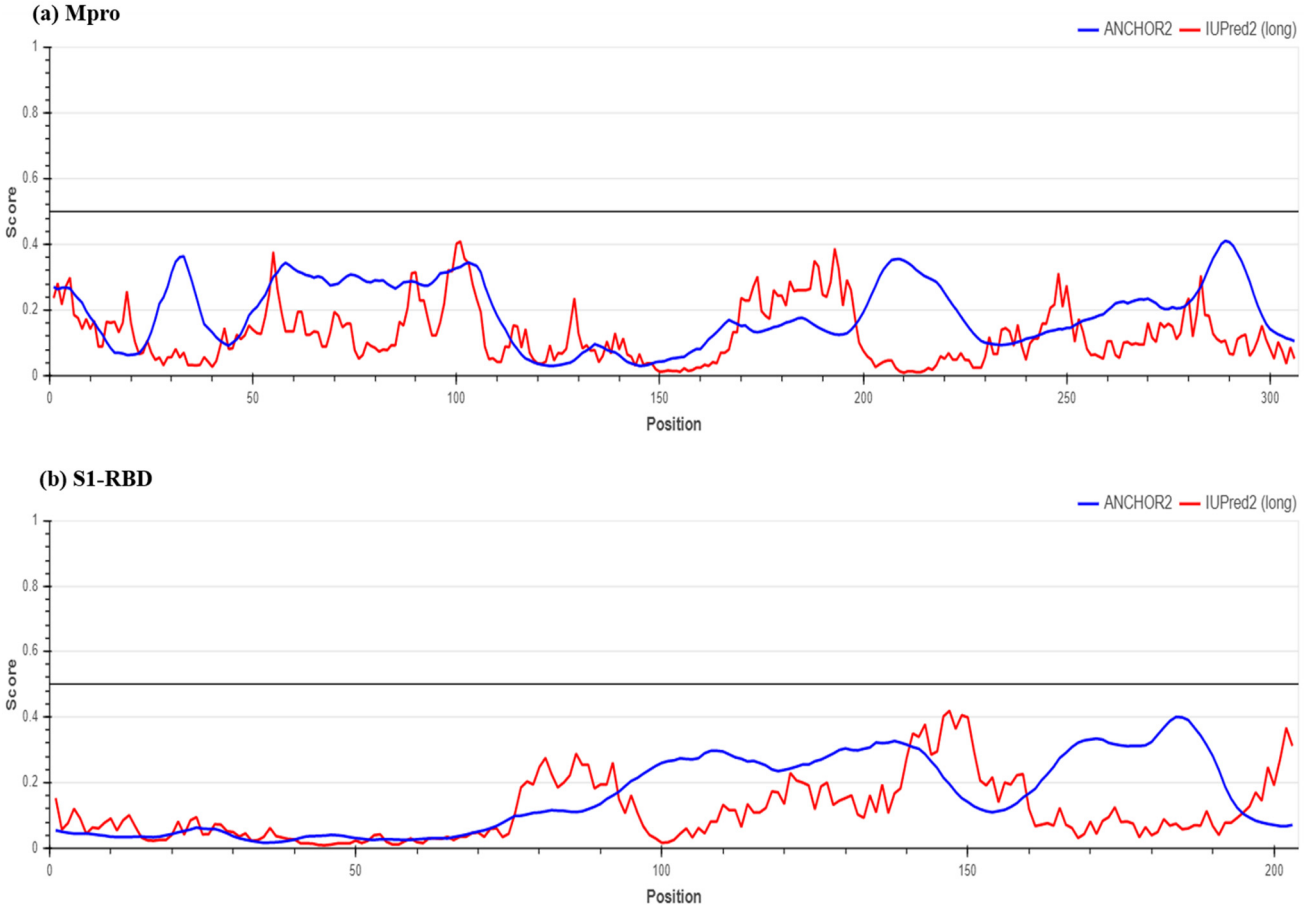

Figure 3. Determination of protein disorder employing the IUPred web server for receptors of SARS-CoV-2. (**a**) Mpro, (**b**) S1-RBD.

2.3. Interaction of Ligands with Receptors of SARS-CoV-2

Molecular docking plays a crucial role in determining the binding potential of molecules to an active site of the target receptor protein [37]. Figure 4 shows the interactive efficiency of conventional antiviral drugs (HCQ, FAV, and REM) and curcuminoids (CUR, BDMC, and DMC) with the Mpro and S1-RBD proteins of SARS-CoV-2 in the form of 3D and 2D structures of each complex (Figure 4).

Figure 4a represents the binding of conventional antiviral drugs and curcuminoids with the Mpro receptor of SARS-CoV-2. The Mpro has three domains: domains I (residues 8–101), II (residues 102–194), and III (residues 201–303) [38]. The molecular study shows that conventional drugs (HCQ, FAV, and REM) interact with residues of domain I and III, whereas curcuminoids (CUR, BDMC, and DMC) attach to domains I and II. Such outcomes suggest that curcuminoids may be able to inhibit the activity of Mpro enzymes in SARS-CoV-2. HCQ formed hydrophobic interactions with Mpro via residues PRO9 and MET6 and suggested weak interactions of HCQ due to the non-involvement of the H-bond. The complex of FAV–Mpro involved MET6, VAL303, and RAG298, in which atoms (N and O) of VAL303 interacted with the single N6 atom of the RAV ligand through a H-bond while other residues formed Pi–alkyl interactions. The antiviral drug REM revealed the interactive residues (SER46, THR45, THR25, and THR24) involved in making a complex with the Mpro receptor, in which H-bond interactions were involved in the attachment of a

single atom (N) of SER46 with two atoms (N11 and O2) as well as of a single atom (OG1) of THR25 with three atoms (N3, O4, and O3) of REM. In contrast to conventional drugs, a sole atom (C26) of curcumin formed a H-bond interaction with two atoms OG1 (THR25) and an O atom (THR24) of Mpro (Figure 2a). The other interaction was hydrophilic, with residue GLN189 (NE2). The residues (SER1, MET6, and PRO9) of Mpro participated in binding with BDMC, in which SER1 (N) formed a Pi–cation and other residues interacted by Pi–alkyl formation. In the case of DMC interaction, only a single residue (ASN142) complexed with Mpro by Pi–donor hydrogen bonding. Such complexation of conventional drugs and curcuminoids indicated that the natural compound curcuminoids are also capable of deforming the structural stability of Mpro. Generally, the COVID-19 main protease regulates the replication process in SARS-CoV-2 [14], which can be suppressed by curcuminoids, as described in a report in which a curcumin component perturbed the function of the protease by direct intermolecular interactions [39]. It has also been reported that curcumin has biocidal activity on several pathogenic microbes (Tarık et al., 2020) [40].

The residues of S1-RBD interacted with the conventional drugs and curcuminoid as shown in Figure 4b. S1-RBD has binding sites between residues 331–526 that aids it to bind to ACE2 [41]. In this study, the conventional drugs (HCQ, FAV, and REM) bound between residues 330–495, while the curcuminoids (CUR, BDMC, and DMC) formed complexes between residues 333–439 of S1-RBD, indicating that, like conventional drugs, curcuminoids could also hinder the attachment of SARS-CoV-2 with the ACE2 receptor of host cells. The atoms C (ASN330), O (ALA331), and NH1 (complex of ARG495 and PHE334) had strong binding capacity, with the single atom CL1 of HCQ forming three H-bonds, while the atoms O (ASN357) and OG1 (THR259) attached to the C20 atom of HCQ by making a Pi-bond. The C8 atom of HCQ also interacted with SER358 via a Pi-bond. The participation of H-bonds and Pi-bonds in forming complexes showed that HCQ is more efficient at stabilizing the structural integrity of the RBD protein. The ligand FAV formed a 3D complex by interacting with active residues (TYR438, THR332, LYS333, and ASN437) of the RBD receptor, in which atoms of TYR438 (OH) and THR332 (O) formed H-bonds with N5 and N6 of FAV, respectively. Also, LYS333 and ASN437 of RBD were involved in forming Pi–donor hydrogen bonds with FAV atoms, and a Pi–lone pair interaction was observed with TYR 438. Only two residues (THR332 and TYR356) of the RBD protein were bound to the REM ligand, where a H-bond interaction was observed for THR332 (O) with an atom (O3) of REM. In the case of curcuminoid interactions, curcumin also has an effective interaction potential with S1-RBD, while ILE428 (O) of S1-RBD formed a H-bond with atom C26 of curcumin. The ND1 atom (ASN437) participated to form a complex with S1-RBD via carbon–hydrogen bonding, while TYR438 and LYS333 formed a hydrophobic complex with curcumin. The molecule BDMC attached to many residues (LYS439, SER336, ASN435, ILE428, and ASP429) of the RBD receptors. The formed RBD–BDMC complex had observed H-bond interactions between ILE428 (O) and SER336 (OG) with atoms O3 and O2 of BDMC, respectively; other carbon–hydrogen bond interactions were also involved between residues ASN435 and ASP429, and the Pi–cation in LYS439 was involved with BDMC. The receptor RBD formed a complex with DMC through residue (LYS439, LYS333, and ILE428) interactions, in which carbon–hydrogen bonding was involved in LYS333 (CE) and ILE428 (O) with O3 and C25 of the DMC molecule, respectively. However, residue LYS439 of RBD interacted with DMC by forming a Pi–cation interaction. The interaction efficiency of curcuminoid with S1-RBD showed that the curcuminoid can perturb the attachment of SARS-CoV-2 with the host surface. The attachment of virus to the host cell membrane is the initial stage of viral infection. Previously, it was described that if curcumin is applied to cells prior to or after infection, it inhibits the series of infections from enveloped viruses [42]. It has also been explained that curcuminoids like curcumin inhibit arthropod-borne viruses, such as zika and chikungunya virus infections, by perturbing the binding step of viruses on the host-cell surface [43]. The application of curcuminoid at certain doses and times revealed its antiviral efficiency, for example, against viral entry, rather than against RNA replication [44].

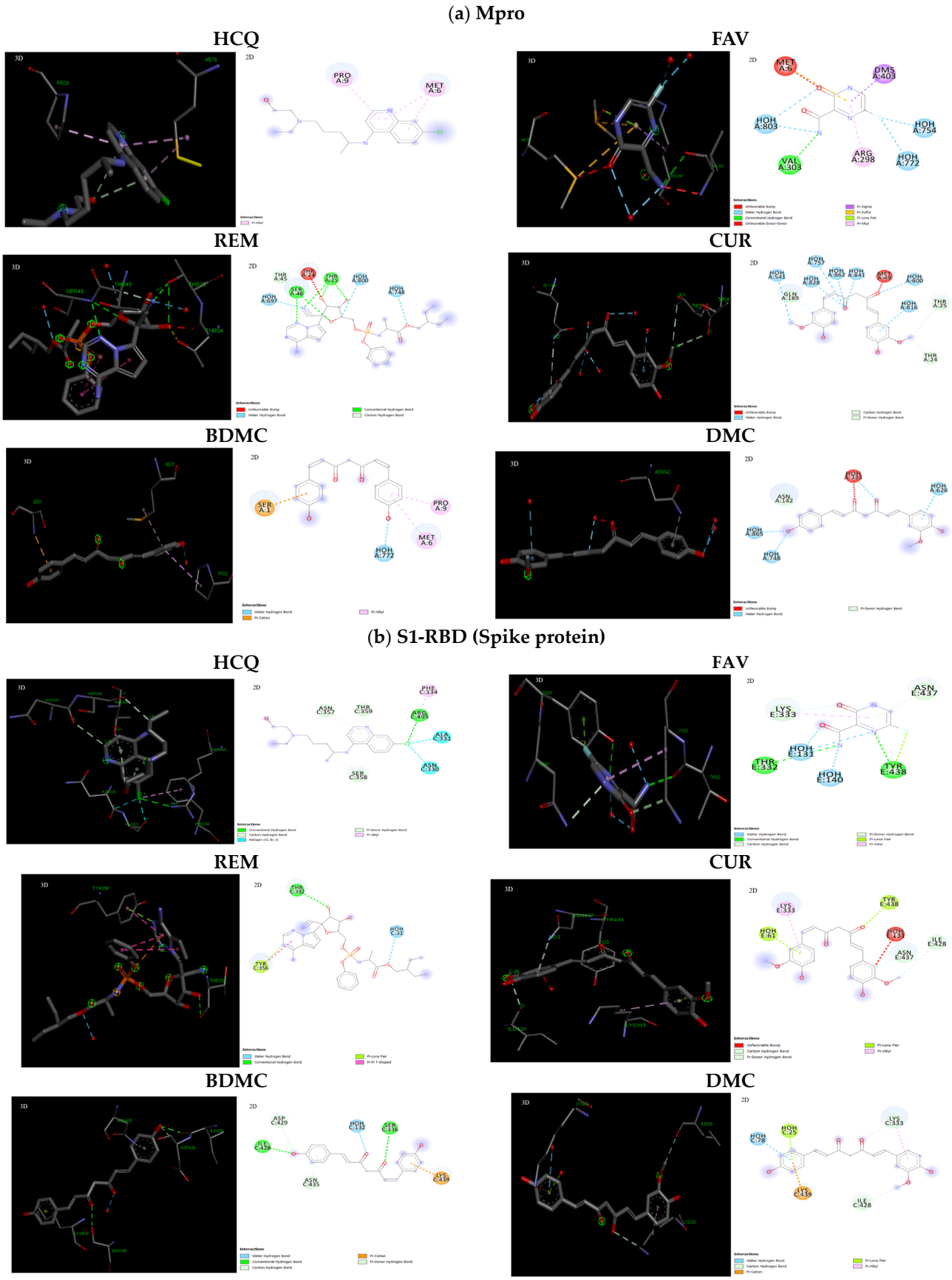

Figure 4. Visualization of structural insights into the interaction of turmeric compounds and conventional antiviral drugs with (**a**) Mpro and (**b**) S1-RBD of SARS-CoV-2.

The global energy of interacting compounds is based on their binding free energy, and a greater negative value depicts a higher binding possibility [42], as shown in Table 2.

Table 2. The calculated binding energy of compounds after interacting with active sites of receptor proteins (Mpro and S1-RBD) of SARS-CoV-2.

Compounds	Mpro (kcal/mol)	S1-RBD (kcal/mol)
HCQ	−24.58	−35.87
FAV	−22.87	−23.77
REM	−23.48	−38.44
CUR	−20.47	−38.84
BDMC	−27.47	−28.07
DMC	−20.58	−30.29

The obtained binding energy was highest (−27.47 kcal/mol) for the curcuminoid BDMC among all the selected molecules during their interaction with Mpro, whereas the binding energy for the other curcuminoids, CUR (−20.47 kcal/mol) and DMC (−20.58 kcal/mol), revealed lower energies than for all the conventional drugs: HCQ (−24.58 kcal/mol), FAV (−22.87 kcal/mol), and REM (−23.48 kcal/mol). In the case of S1-RBD complexation, the highest binding energy was exhibited in the curcuminoid CUR (−38.84 kcal/mol) and the lowest in the conventional antiviral drug FAV (−23.77 kcal/mol), whereas the other conventional drugs, HCQ (−35.87 kcal/mol) and REM (−38.44 kcal/mol), had higher binding energies than the curcuminoids BDMC (−28.07 kcal/mol) and DMC (−30.29 kcal/mol). It was also observed that the obtained binding energy for both groups of the selected molecules (conventional antiviral drugs and curcuminoids) had greater efficiency toward S1-RBD in disrupting its structural integrity. Also, these molecules inhibited the active site of the Mpro enzyme, which is involved in processing polyproteins in SARS-CoV-2.

Table 3 describes the different toxicity levels of curcumin and its derivatives against several RNA viruses like HIV, ZIKV, DENV, IAV, HRSV as well as SARS-CoV-2, which support the current findings. It has been revealed that curcumin and its derivatives inhibited the activity of the main protease in HIV, ZIKV, and SARS-CoV-2 (Table 3). As the molecular docking studies showed, curcumin and bisdemethoxycurcumin could block the enzymatic activity of Mpro with binding energies of −20.47 and −27.47 kcal/mol (Table 2), respectively. Curcumin and demethoxycurcumin could also inhibit the attachment of viruses like ZIKV and HRSV to the host membrane (Table 3) which was also observed in SARS-CoV-2 through the current interactive study. The binding energy for curcumin (−38.84 kcal/mol) and demethoxycurcumin (−30.29 kcal/mol) (Table 2) shows their efficiency in inactivating the S1-RBD protein during attachment to the host cell. Besides Mpro and S1-RBD, curcumin and its derivatives are also capable of targeting other virulent factors to inhibit viral infections like SARS-CoV-2, as seen in Table 3.

Based on their physicochemical properties and the molecular docking study of the selected molecules, it was noted that the antiviral potential of curcuminoid (CUR, BDMC, and DMC) against SARS-CoV-2 infection in targeting remarkable Mpro and S1-RBD receptor is promisingly comparable to conventional antiviral drugs (HCQ, FAV, and REM). The consequences of molecular docking suggest that the curcuminoids could be used as adjunct drugs along with conventional drugs for the inhibition of SARS-CoV-2 protein receptors involved in the development of the COVID-19 disease (Figure 5).

The pharmacokinetic paradigm of curcuminoids and their molecular interactions with SARS-CoV-2 receptor proteins have close resemblances to that of the conventional drugs. The present work presents an interesting clue to the use of curcuminoids, individually or as combination therapy, to degrade the virulent factors of deadly viruses which will be fascinating to researchers doing further research.

Table 3. Potential toxicity of curcumin and its derivatives against RNA viruses.

Viruses	Doses	Curcumin and Its Derivatives	Outcomes	Ref.
Human Immunodeficiency Virus (HIV)	20–120 μM	Curcumin	Inhibited HIV-1 protease	[45]
	0.7–12 μM	Synthetic curcumin analogue lacking the β-diketone moiety named as curcumin A	Lowered late viral genome-copy levels	[46]
Zika Virus (ZIKV)	10 μM–1 mM	Curcumin, bisdemethoxycurcumin, demethoxycurcumin	Inactivated virus or hindered cell attachment	[47]
Dengue virus (DENV)	36–66 μM	Curcumin, bisdemethoxycurcumin, acyclic and cyclohexanone analogues of curcumin	Inhibited the viral protease activity, downregulated acetyl-CoA carboxylase and fatty acid synthase	[48]
Influenza A Virus (IAV)	25–200 μM	Curcumin	Decreased IAV neuraminidase (NA) activity, inhibitor of the PI3K/Akt signalling pathway	[49]
Human Respiratory Syncytial Virus (HRSV)	5–15 μM	Curcumin-stabilized silver nanoparticles	Inhibited the viral G protein expression involved in viral attachment	[50]
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	>10 μM	Curcumin	Suppressed the main protease and inhibited the viral non-structural protein Nsp15	[51,52]

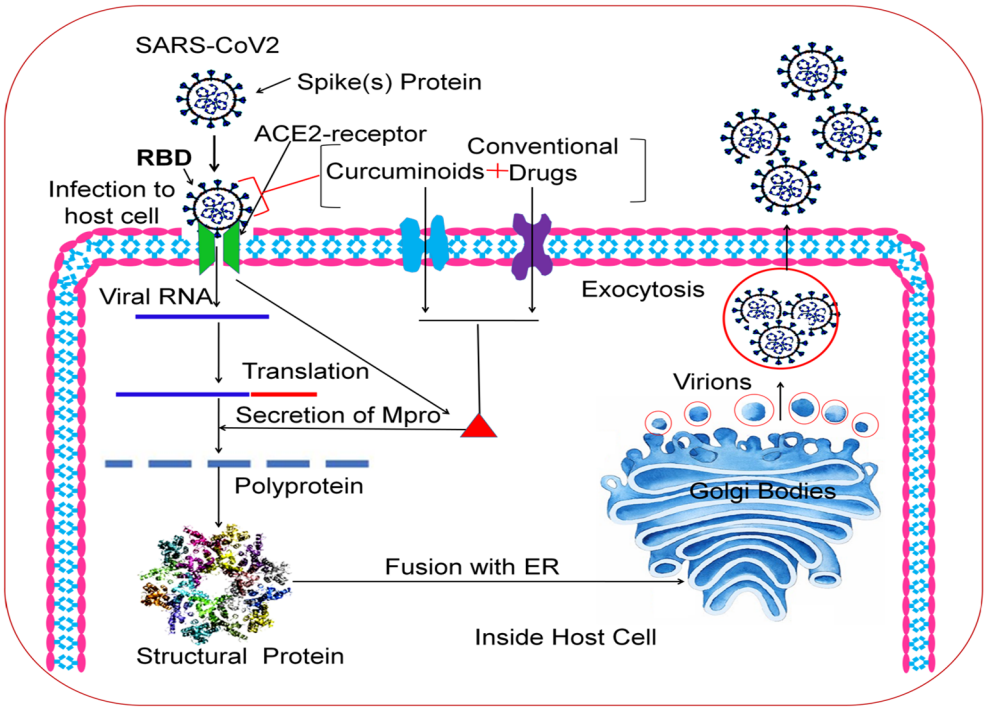

Figure 5. Diagrammatic presentation for a combination therapy of conventional drugs and curcuminoids inhibiting Mpro and RBD proteins, which are involved in the SARS-CoV-2 life cycle.

3. Materials and Methods

3.1. Selection of Ligands and Proteins

The 3D structure of the conventional drugs (HCQ PubChem ID: 3652; FAV PubChem ID: 492405; REM PubChem ID: 121304016) and curcuminoids (CUR PubChem ID: 969516; BDMC PubChem ID: 5315472; DMC PubChem ID: 5469424) were taken from the PubChem database [50] for the in silico study. The 3D structure of Mpro (PDB ID: 6Y84) with a resolution 1.39 Å and of the S1-RBD of SARS-CoV-2 (PDB ID: 2GHV) [12] with a resolution of 2.2 Å were obtained from the Protein Data Bank (PDB) database [53].

3.2. Analysis of Pharmacokinetic Properties of the Selected Molecules

The pharmacokinetic properties such as absorption, distribution, metabolism, excretion, and toxicity of all compounds were detected by using the admetSAR database (http://lmmd.ecust.edu.cn/admetsar1/predict accessed on 12 August 2020) [54]. Also, the new SwissADME web tool, the BOILED-Egg, was used to construct robust predictive models for the target site and pharmacokinetics [53].

3.3. Prediction of Protein Stability

The stability of protein receptors was examined through a web server (http://iupred.enzim.hu and http://iupred.elte.hu; accessed on 25 June 2023) by employing the algorithms IUPred2 and ANCHOR. The FASTA files of the Mpro receptor, containing 306 residues, and S1-RBD, with 203 residues, were uploaded onto the web server (https://iupred2a.elte.hu/ accessed on 25 June 2023) for the determination of protein disorders [35,36].

IUPred2 uses an energy prediction method at its core, and this method applies a low-resolution statistical potential to explore the ability of amino acid pairs to make contacts and to be investigated as globular protein structures [55]. The statistical potential determines the energy for all the residues involved in interactions with other contacting residues of the known structure. The sum of such residue-level energy can be used to account for the total stabilizing energy of intrachain interactions in the protein structure. Hence, this promising approach has been designed to predict these energies from the amino acid sequence of the unknown structure [56]. By employing this model, the energy of each single residue in the amino acid sequence is determined by using this formula [35]:

$$e_i^k = \sum_j {}^{=1}{}^{20} P_{ij} C_j^k \quad (1)$$

where e_i^k is the energy of the amino acid in position k of type i, P_{ij} is the ijth factor of the energy predictor parameter, and cj is the jth element of the amino acid composition, indicating the ratio of amino acid type j in the sequence next to position k. P is a 20 × 20 energy prediction factor that relates the amino acid composition vector to the energy of the residue.

Like IUPred2, ANCHOR also employs the energy calculation method for understanding disordered binding sites. Despite the general disorder tendency, two more terms have also been incorporated into the method, which determine the energy based on the interaction of a globular protein and with the adjacent disordered sequence [57]. Such tendencies were united by a linear combination and, finally, were transformed to form a normalized score between 0 and 1, indicating the probability of a residue being part of a disordered binding site. In the present work, residues of disordered binding regions satisfy two distinct principles: (i) they are efficient at producing promising interactions with the binding surface of an ordered protein, and (ii) they should be able to fix a disordered sequence milieu. The formula provided by these two criteria is [35]:

$$S_k = (E_{gain,k}(w_1) - E_{gain,0})(I_k(w_2) - I_0) \quad (2)$$

where S_k is the amino acid score, w_1 is the consecutive half-window of the adjacent residue k, $I_k(w_2)$ is the averaged IUPred score, and $E_{gain,0}$ and I_0 are parameters that determine the minimum energy gain and minimum average disorder tendency, respectively, of a residue.

3.4. Molecular Docking

The molecular docking study was carried out to determine the interactive capacity of antiviral drugs and curcuminoids with the Mpro and S1-RBD proteins of SARS-CoV-2. The interactive study of each compound was performed using the PatchDock online server. The complex was secured to the default with the clustering RMSD: 4.0Å. PatchDock produced the results and the ranks associated with their geometric shape complementarity score. Then, the produced results from PatchDock were processed for the refinement and rescoring of the 10 best solutions among the 1000 top-scoring complexes employing FireDock, which indicated the energy as the global binding energy participating in complex

formation. Each result from FireDock provided a rank and scores based on the energy function. About 3.5 s was spent per candidate solution, which offers large-scale flexible refinement and the scoring of docking compounds to be performed. For the imaging of interactive molecules (antiviral drugs and curcuminoids) with SARS-CoV-2 receptors, a visualizer software, Discovery Studio 4.5 Client, was employed.

4. Conclusions

Various promising antiviral drugs against COVID-19 are being examined, although there have not yet been satisfactory outcomes. This study has focused on exploring the main causes of these drugs' ineffectiveness against the COVID-19 disease. Hence, the two receptor proteins, Mpro and S1-RBD, of SARS-CoV-2 were considered as targets for developing new drugs. The physicochemical properties (ADMET, BOILED-Egg construction, and target class) exhibited by curcuminoids (CUR, BDMC, and DMC) were similar to those of antiviral drugs such as HCQ, FAV, and REM. Rat acute toxicity LD50 of all the compounds was found to be in the low ranges between 2.1259 and 2.7169 mol/kg, indicating that curcuminoids can be investigated further by comparing them with conventional antiviral drugs. The protein disordered outcomes from ANCHOR gained scores of less than 0.5 for residues of Mpro and S1-RBD, indicating that these protein receptors have highly packed residues. Thus, it is relatively difficult to disturb the integrity of such viral proteins by employing a single drug. The binding energy of interactive repurposed conventional antiviral drugs and curcuminoids revealed that they are capable of destabilizing the SARS-CoV-2 receptor proteins. Interestingly, the highest binding energies were observed for BDMC (−27.47 kcal/mol) and CUR (−38.84 kcal/mol) while interacting with Mpro and S1-RBD, respectively, suggesting that these curcuminoid components could be efficient at inhibiting SARS-CoV-2 infection. Thus, the therapeutic potential of repurposed antiviral drugs can be enhanced against SARS-CoV-2 by employing curcuminoids as a combination therapy; however, this needs to be further examined.

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