Int. J. Adv. Eng. Pure Sci. 2026, 38(1): <10-22>
DOI: 10.7240/jeps.1683116

RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

Assessing Antiviral Mechanisms of N-acetyl-D-glucosamine, N-acetylcysteine and Acetylsalicylic acid on SARS-CoV-2

N-asetil-D-glukozamin, N-asetilsistein ve Asetilsalisilik asidin SARS-CoV-2'ye Antiviral Mekanizmalarının Değerlendirilmesi

Ragıp Soner SİLME [1]

[1]*Istanbul University, Center for Research and Practice in Biotechnology and Genetic Engineering, Fatih-Istanbul, Türkiye*

Abstract

The potential antiviral activity of FDA-approved 3 compounds (N-acetyl-D-glucosamine; GlcNAc, N-acetylcysteine; NAC, and Acetylsalicylic acid; ASA) against SARS-CoV-2 was investigated. Molecular docking analysis of these compounds as ligands with the main 22 viral proteins was made to predict their possible interaction. All molecules showed interactions with the viral proteins; the mean binding scores for GlcNAc and ASA were very close (-6.81 kcal/mol and -6.31 kcal/mol, respectively), while NAC designated the lowest value (-4.69 kcal/mol). GlcNAc showed the highest binding energy of -8.80 kcal/mol against both the target proteins RdRp-RTP site (7BV2) and Helicase-ANP binding site (7NN0). Since these 22 proteins, including main protease (M^{pro}) and Papain-like protease (PL^{pro}), are responsible for replication and various pathogenesis processes, it could be concluded that these FDA-approved commercially available compounds have antiviral properties against SARS-CoV-2, which should be confirmed with further *in vivo* and clinical trials.

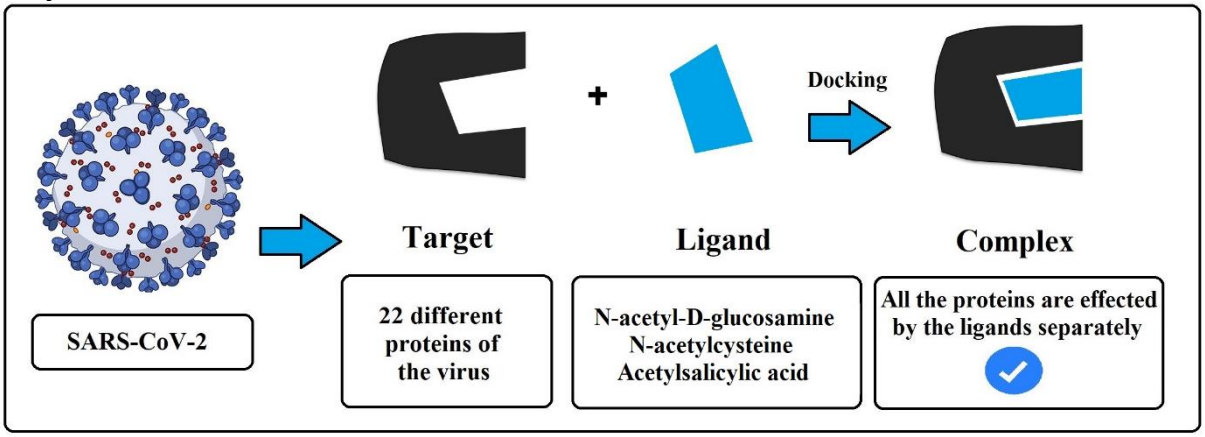
Keywords: bioinformatics, ligand, molecular docking, nCoV, repurposing, SARS-CoV-2

Öz

FDA onaylı 3 bileşiğin (N-asetil-D-glukozamin; GlcNAc, N-asetilsistein; NAC ve Asetilsalisilik asit; ASA) SARS-CoV-2'ye karşı potansiyel antiviral aktivitesi araştırılmıştır. Bu bileşiklerin ligand olarak 22 belli başlı viral proteinle moleküler kenetlenme analizleri yapılarak olası etkileşimleri tahmin edilmiştir. Tüm moleküller viral proteinlerle etkileşim göstermiştir; GlcNAc ve ASA için ortalama bağlanma skorları birbirine çok yakın çıkmıştır (-6.81 kcal/mol ve -6.31 kcal/mol, sırasıyla), NAC ise en düşük değeri göstermiştir (-4.69 kcal/mol). GlcNAc, hedef proteinler olan hem RdRp-RTP bölgesine (7BV2) hem de Helikaz-ANP bağlanma bölgesine (7NN0) -8.80 kcal/mol ile en yüksek bağlanma enerjisini göstermiştir. Bu 22 protein arasında ana proteaz (M^{pro}) ve Papain-benzeri proteaz (PL^{pro}) gibi replikasyon ve çeşitli patogenez süreçlerinden sorumlu proteinler yer aldığından, bu FDA onaylı ve ticari olarak mevcut bileşiklerin SARS-CoV-2'ye karşı antiviral özelliklere sahip olduğu, ancak bunun daha ileri *in vivo* ve klinik çalışmalarla doğrulanması gerektiği sonucuna varılmıştır.

Anahtar kelimeler: Biyoenformatik, ligand, moleküler kenetlenme, nCoV, yeniden amaçlandırma, SARS-CoV-2

Graphical Abstract



Corresponding Author: RAGIP SONER SİLME, **Tel:** (212) 440 00 00 - 15475, **E-mail:** rsoner@istanbul.edu.tr

Submitted: 24.04.2025, **Revised:** 23.09.2025, **Accepted:** 22.12.2025

I. INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) represents a novel strain of coronavirus that has precipitated a global pandemic characterized by acute respiratory illness in humans [1, 2]. This emergence follows previous outbreaks of coronaviruses, namely Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), both of which have contributed to the broader understanding of coronavirus-related diseases [3]. Since the emergence of COVID-19, more than 700 million individuals have been reported to have tested positive for the virus, and over 7 million people have passed away due to the disease [4]. SARS-CoV-2 possesses all the characteristic structural components of other coronaviruses [5]. Nonetheless, when SARS-CoV was compared with SARS-CoV-2, SARS-CoV-2 exhibited specific structural alterations that increased its transmissibility [6].

Similar to SARS-CoV, SARS-CoV-2 gains entry into host cells by binding to its primary functional receptor, angiotensin-converting enzyme 2 (ACE2), a receptor that is ubiquitously expressed on epithelial and endothelial cells across multiple tissues and organs [7, 8]. The widespread distribution of ACE2 in various tissues, coupled with the effects of SARS-CoV-2 infection on the receptor's physiological functions, plays a significant role in shaping the clinical manifestations of the disease [9, 10].

COVID-19 causes a wide spectrum of clinical manifestations, ranging from mild symptoms, including dry cough, fever, and sore throat, to more severe pathological conditions such as acute respiratory distress syndrome, multi-organ failure, and, in some cases, fatality. The severity of the disease is closely associated with the host's immune response to the SARS-CoV-2 virus [1, 11]. A robust immune response is essential for eliminating the virus, while a dysfunctional response results in viral persistence and an overproduction of inflammatory mediators, leading to a cytokine storm and progression of the disease. Different stages of COVID-19 should be treated with customized approaches that consider the pathogenic traits of SARS-CoV-2. In the initial phase of the illness, it is essential to block viral entry and replication, while in the later phase characterized by significant inflammation, strategies to manage or reduce the inflammatory response should be implemented [12, 13].

Vaccination represents a primary and highly effective strategy for preventing SARS-CoV-2 infection and mitigating the severity of the disease. Some international pharmaceutical companies have developed various mRNA-based vaccines derived from the spike protein of the virus during the pandemic [14]. Although these vaccines have been approved for governmental vaccination programmes in many countries [15], there are some concerns about their side effects, and their long-term effects are unknown [16-18]. Therefore, new alternative SARS-CoV-2 treatment methods are also necessary.

Various therapeutic approaches have been proposed for the treatment of COVID-19, including immunomodulatory agents, monoclonal antibodies, and a range of antiviral drugs. However, the widespread application of these treatments has been limited due to one or more of the following challenges: limited efficacy, high cost, and adverse toxicological profiles [19-21]. It is necessary to investigate novel drug candidates considering these limitations.

Repurposing compounds approved by U.S. Food and Drug Administration (FDA) is one of the ways to shorten the developing process for a new treatment. Also, another factor is to determine the target proteins that have key roles in replication machinery of virus. Recent techniques such as molecular docking simulations have improved by increase in computational processing power. These techniques let us examine the molecular aspects of proteins and protein−ligand interactions for new drug candidates or repurposing recent drugs [22-24].

In this study, essential SARS-CoV-2 proteins responsible for replication cycle and pathogenesis were investigated for their interactions with 3 FDA approved compounds; N-acetyl-D-glucosamine (GlcNAc), N-acetylcysteine (NAC), and Acetylsalicylic acid (ASA). This study aims to determine the difference in binding score within selected proteins and compounds, to enhance our understanding of potential therapeutic approaches for the treatment and management of diseases. In particular, it aims to inform the development of novel treatment strategies for future public health challenges arising from coronavirus outbreaks.

II. MATERIALS AND METHODS

To explore the interaction of GlcNAc, NAC, and ASA with the selected proteins of the SARS-CoV-2, molecular docking simulations were performed utilizing the COVID-19 Docking Server 2.0 (https://ncovdock2.schanglab.org.cn) [25]. This novel docking server called "nCoVDock2" was developed by Liu et al. [25] to predict the binding modes between the targeted SARS-CoV-2 proteins and their possible ligands. For the docking of small molecules, AutoDock Vina (ver. 1.2.0) was integrated as the docking engine [26, 27]. Also, Open Babel was utilized for converting formats or generating 3D coordinates for the files that were uploaded [28]. The docking box is specified by the center of the native ligand coordinates and has dimensions of 30 Å × 30 Å × 30 Å to encompass all the residues within the cavity. Homology-modelled structures are characterized based on the details of

active sites or binding sites found in their homologs from SARS-CoV. All parameters were configured to their default settings, and for this study the exhaustiveness value option was set to 16. All the proteins shown in Table 1 were utilized for the docking analysis in this server. The 3D sdf ligand files for the selected molecules were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) [29] and subsequently uploaded to the nCoVDock2 server. The final receptor and ligand interactions were downloaded as. pdbqt files and were converted to .pdb format by using PyMOL (v.3.1.3) and visualized by Biovia Discovery Studio Visualizer (v.25.1.0.24284) and LigPlot+ (v.2.3.1) [30-33]. Autodock Vina binding affinity score was described as score value (SV) and also a machine learning scoring function, which calculates the docking pose generation error on binding affinity prediction, described as RF-Score was used to evaluate the binding affinities for small molecules [25, 34].

III. RESULTS

Molecular docking simulations conducted to assess the binding affinities of GlcNAc, NAC, and ASA with the specific protein sites of SARS-CoV-2, showed all the compounds have strong interactions with the proteins, which show their potential interferences with the life cycle of SARS-CoV-2 (Table 1; Sup. Data 1). The docking results of all compounds with selected proteins according to expressed binding score values (kcal/mol) and RF score values are presented in Table 1. These results correspond to the highest-ranked docking poses, representing the most optimal models of the studied protein–ligand complexes. The strongest bindings were predicted by the lower score values that demonstrated a significant strength of interactions between ligands and proteins.

Table 1. SARS-CoV-2 protein docking results of selected molecules. SV; score value, RF SV; RF score value.

	Protein	GlcNAc		NAC		ASA	
		SV (kcal/mol)	RF SV (pKd)	SV (kcal/mol)	RF SV (pKd)	SV (kcal/mol)	RF SV (pKd)
1	Nsp3-macrodomain (5RSF)	-6.40	4.33	-4.30	4.42	-6.40	4.56
2	Nsp3-ADP ribose phosphatase (6W6Y)	-6.10	4.15	-4.20	4.48	-6.00	4.53
3	Nsp3-MES site (6W6Y)	-7.00	4.54	-5.00	4.38	-6.40	4.61
4	PL^{pro}-WT (7RZC)	-7.40	4.95	-4.70	4.65	-6.90	4.65
5	PL^{pro}-C111S (7SQE)	-7.40	4.97	-4.80	4.68	-6.70	4.44
6	M^{pro}-WT (7SI9)	-6.30	4.55	-4.70	4.44	-5.80	4.40
7	Nsp9-FR6 bound (7KRI)	-5.70	4.60	-3.90	4.23	-5.50	4.60
8	Nsp9-oridonin bound (7N3K)	-6.20	4.40	-4.00	4.38	-5.70	4.45
9	Nsp10-nsp10-14 (7ORR)	-6.20	4.66	-4.00	4.21	-5.10	4.38
10	Nsp10-nsp10-16 (7ORU)	-5.90	4.42	-5.00	4.41	-5.60	4.64
11	RdRp-RTP site (7BV2)	-8.80	5.21	-5.60	5.74	-7.20	4.76
12	RdRp-RNA site (7D4F)	-6.40	4.80	-4.40	4.14	-5.90	4.71
13	Helicase-ANP binding site (7NN0)	-8.80	5.03	-5.70	5.82	-6.40	4.70
14	Helicase-fragment binding site (5RML)	-7.20	5.45	-5.70	5.96	-6.60	4.86
15	Nsp10-14-chapso site (7N0D)	-6.80	4.77	-4.50	4.72	-6.40	4.39
16	Nsp10-14-ExoN (7N0D)	-6.60	4.73	-4.10	4.39	-6.30	4.82
17	Nsp10-14-N7-MTase (7N0D)	-6.80	4.85	-4.60	4.80	-6.40	4.52
18	Nsp15-WT (7K1L)	-6.40	4.29	-4.80	4.38	-6.00	4.41
19	Nsp10-16-MGP site (6WVN)	-7.10	4.50	-4.90	4.32	-7.10	4.90
20	Nsp10-16-SAM site (6W4H)	-7.10	4.55	-4.80	4.59	-7.10	4.90
21	Nsp10-16-GTA site (6WVN)	-7.10	4.50	-5.00	4.37	-7.10	4.89
22	N protein-NCB site (MODEL)	-6.30	4.22	-4.60	4.24	-6.40	4.41
	Mean value	**-6.81**	**4.65**	**-4.69**	**4.62**	**-6.31**	**4.61**

The results in Table 1 show that all the molecules have predicted interactions with Sars-CoV-2 proteins at various levels (thus with different scores). Since there are too many binding results, a holistic perspective seems better to understand the results. Score mean values from highest to lowest are -6.81 kcal/mol (GlcNAc**)**, -6.31 kcal/mol (ASA), and -4.69 kcal/mol (NAC). All the viral proteins in Table 1 have key roles in replication and pathogenesis cycle, but main protease (M^{pro}) was selected in Figure 1 to show its interaction with selected compounds due to its indispensable role in viral replication and have been recognized as key targets for preventing and treating coronavirus causing infectious diseases [35]. As shown in Table 1, the highest interaction score was recorded for GlcNAc (-6.30 kcal/mol) which indicates its inhibitory potential on M^{pro} (Sup. Data 1).

Furthermore, Papain-like protease (PL^{pro}) represents a compelling antiviral target due to its essential role in the replication of coronaviruses [36]. PL^{pro} has acquired an enhanced ability to cleave the ubiquitin-like interferon-stimulated gene 15 (ISG15) protein, due to genomic alterations in SARS-CoV-2, thereby facilitating the virus's evasion of the host innate immune response. Notably, Table 1 shows that PL^{pro} enzymes from wild type (7RZC) and C111S mutant (7SQE) viruses have the same score (-7.40 kcal/mol) for their interaction with GlcNAc, which is higher than the other two compounds, indicating its antiviral potential.

The mean value of RF-Scores resulted as 4.65 (GlcNAc), 4.62 (NAC), and 4.61 (ASA) (Table 1). These results indicate no significant difference for the predicted error levels as described by Li et al. [34].

To provide a clearer understanding of binding affinity, Table 2 summarizes the binding profiles of SARS-CoV-2 proteins with the ligands examined in this study, including the molecular interaction types and their characteristics.

The significant structural difference in crystal structures of SARS-CoV-2 proteins had resulted in different interaction profiles with the ligands. When the interaction profiles in Table 2 are checked by the mean values, the results show number of hydrogen bonds are all the highest in quantity and show similar results as Table 1 (GlcNAc> ASA> NAC). The mean values of Table 2 also showed that GlcNAc has more electrostatic interactions than the other 2 ligands, whereas NAC and ASA have more hydrophobic interactions than GlcNAc with the viral proteins.

IV. DISCUSSION

The SARS-CoV-2 virus exhibits a spherical morphology, with a diameter ranging from approximately 65 to 125 nm. The spike (S) protein, located on the viral surface, imparts the characteristic crown-like ("corona") appearance, from which the virus derives its name [2, 5]. Coronaviruses are characterized by having the largest single-stranded, positive-sense RNA genome, with a length ranging between 26 and 32 kilobases [6, 37, 38]. Approximately two-thirds of the coronaviral genome consists of genes that encode non-structural proteins, including RNA-dependent RNA polymerase (RdRp), proteases, and helicase, all of which are critical for viral replication. The 3′ end of the genome encodes the four major structural proteins of the coronavirus virion: the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins (Figure 2) [6, 38]. Although viruses encode numerous functions essential for their replication, they remain entirely dependent on the host cell's protein synthesis machinery [39]. Therefore, several viral proteins of Coronaviruses manipulate the immune response of the host [40, 41].

Table 2. Interaction profiles between SARS-CoV-2 associated proteins and selected molecules.

Protein	GlcNAc				NAC				ASA			
	N_{HB}[a]	N_{ES}[b]	N_{HP}[c]	N_O[d]	N_{HB}	N_{ES}	N_{HP}	N_O	N_{HB}	N_{ES}	N_{HP}	N_O
Nsp3-macrodomain (5RSF)	5	1	4	1	4	-	3	1	4	-	1	-
Nsp3-ADP ribose phosphatase (6W6Y)	4	-	-	1	2	-	4	-	5	-	1	-
Nsp3-MES site (6W6Y)	5	2	-	-	5	-	5	-	6	1	1	1
PL^{pro}-WT (7RZC)	4	1	2	1	2	1	3	-	3	1	3	1
PL^{pro}-C111S (7SQE)	3	1	2	1	4	1	4	1	4	1	3	-
M^{pro}-WT (7SI9)	2	-	-	-	5	-	2	-	5	2	1	-
Nsp9-FR6 bound (7KRI)	3	3	-	-	4	-	1	-	2	1	-	-
Nsp9-oridonin bound (7N3K)	5	2	1	-	2	2	5	-	2	-	2	-
Nsp10-nsp10-14 (7ORR)	7	-	-	-	3	-	2	-	4	-	1	-
Nsp10-nsp10-16 (7ORU)	6	-	-	-	5	-	3	1	7	-	-	-
RdRp-RTP site (7BV2)	8	3	-	-	2	-	4	-	4	1	3	-
RdRp-RNA site (7D4F)	4	1	2	1	3	1	4	-	2	1	2	1
Helicase-ANP binding site (7NN0)	9	3	-	1	4	3	1	1	8	3	-	1
Helicase-fragment binding site (5RML)	8	1	2	-	4	1	6	1	4	-	2	-
Nsp10-14-chapso site (7N0D)	3	3	-	-	3	-	2	1	5	-	-	-
Nsp10-14-ExoN (7N0D)	8	2	1	-	1	1	5	1	4	2	1	2
Nsp10-14-N7-MTase (7N0D)	11	-	-	1	4	-	2	2	1	-	3	1
Nsp15-WT (7K1L)	8	1	2	-	2	3	4	1	4	3	2	-
Nsp10-16-MGP site (6WVN)	5	1	1	-	4	1	3	-	1	-	1	-
Nsp10-16-SAM site (6W4H)	4	1	-	-	2	1	3	1	2	1	1	-
Nsp10-16-GTA site (6WVN)	5	1	1	-	3	2	3	-	2	-	1	-
N protein-NCB site (MODEL)	4	1	1	-	3	1	6	1	2	1	4	-
Mean values	**5.50**	**1.27**	**0.86**	**0.31**	**3.22**	**0.81**	**3.40**	**0.54**	**3.68**	**0.81**	**1.50**	**0.31**

[a]Number of hydrogen bonds; [b]number of electrostatic interactions; [c]number of hydrophobic interactions; [d]number of other interactions, "-" no results

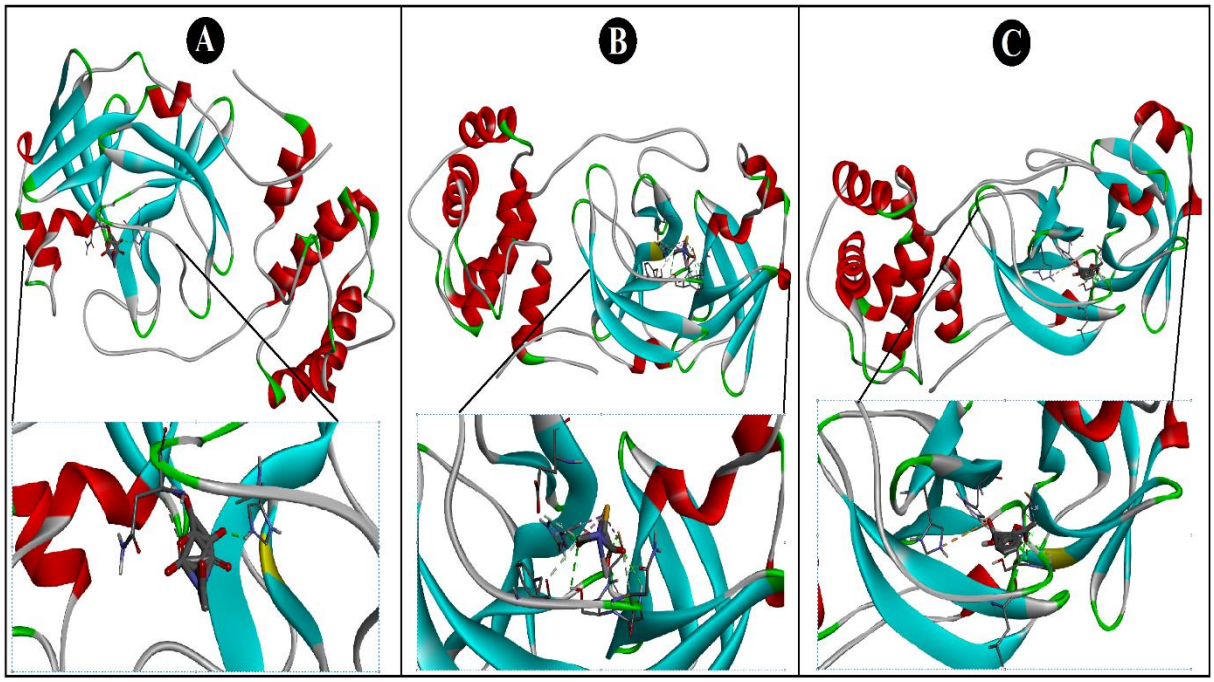


Figure 1. Structural docking simulations of M^{pro} and selected compounds; a) GlcNAc, b) NAC, and c) ASA with their zoomed views shown below.

As described in results section, the papain-like protease (PL^{pro}) and the 3C-like protease ($3CL^{pro}$, also known as main protease M^{pro}) are considered promising molecular targets for the development of therapeutic agents against SARS-CoV-2. Both enzymes, classified as cysteine proteases, play critical roles in the viral life cycle and are essential for viral replication and survival. Antiviral protease inhibitors targeting these enzymes may offer a favourable safety profile in humans, as mammalian proteases typically exhibit distinct substrate specificities. In particular, $3CL^{pro}$ (EC 3.4.22.69) is crucial for the proteolytic cleavage and maturation of viral polyproteins, thereby enabling the formation of functional non-structural proteins required for viral replication [42, 43]. Consequently, medicinal chemistry efforts have been directed toward inhibiting this enzyme [44]. From this perspective, GlcNAc, NAC, and ASA have both interacted with PL^{pro} and M^{pro} as shown in Table 1, and these compounds could have therapeutic potential as antiviral agents. Since the PL^{pro} and M^{pro} plays a central role in many other coronaviruses, this predicted antiviral property of these compounds could also affect them.

For a comprehensive assessment of binding affinity, Table 2 presents the interaction profiles between SARS-CoV-2 proteins and the ligands investigated in this study, detailing the specific molecular interaction types and their physicochemical properties.

Hydrogen bonding (base pairing) has shown to be a key which plays a role in various antiviral molecules tested against viruses such as hepatitis B virus (HBV), human immunodeficiency virus (HIV), and human herpesviruses such as cytomegalovirus [45].

In this study the main interaction with viral proteins corresponding with hydrogen bonding also showed a critical role in antiviral effect (Table 2). The finding indicated that within tested ligands, GlcNAC has shown promising effects on various viral proteins. The highest scores were recorded with GlcNAC (Table 1 and 2) which can be linked to previous studies mentioning that the binding of antiviral ligand would result in dysfunction in viral life cycle, replication and pathogenesis relied on the host cellular machinery [22, 40, 41, 46, 47] Hydrogen bonding also seems to be involved in the inhibitory activity of remdesivir against SARS-CoV-2 as described in previous studies [48, 49].

Electrostatic interactions are recognized as a dominant force among protein–protein interactions involving binding energy [50, 51]. The binding affinity of viruses to host receptors is largely directed by these electrostatic interactions [52, 53]. Alterations in key residues at the binding interface can significantly influence viral–host cell fusion and, consequently, viral infectivity [54–57]. The compounds proposed in the present study may modulate the electrostatic interactions between SARS-CoV-2 proteins and host receptor proteins, potentially leading to disruptions in the viral infection and replication cycle (Table 2). Moreover, the pre-infection immunomodulatory potential of these compounds should be investigated in further studies.

The mean values of interactions in Table 2 indicated that NAC has the highest hydrophobic interaction value (3.40) compared to other 2 ligands. Hydrophobic interactions represent one of the principal driving forces of protein folding and the establishment of three-dimensional protein structures, thereby serving as a

predictive basis for the localization of distinct protein folds. As a fundamental physicochemical property, hydrophobicity is the dominant determinant of protein tertiary structure, which is directly linked to its biological functionality [58, 59]. These interactions are critical for maintaining protein stability and activity, as they minimize solvent-exposed surface area and reduce unfavourable interactions with the aqueous environment [60]. Moreover, the organization of water molecules near hydrophobic surfaces exerts a substantial influence on the folding process [61, 62]. Understanding the rate of protein folding provides valuable insight into the role of hydrophobic interactions at molecular length scales [63]. Since NAC has the highest hydrophobic capacity, it can cause impairment on protein folding and stability of viral virulence proteins (Table 2).

In particular, computational analyses of the hydrophobic profiles of viral proteins from SARS-CoV-2 and SARS-CoV offer valuable molecular-level insights, which may create new opportunities for the development of therapeutic strategies targeting diseases caused by these viruses [64, 65].

Although the global pandemic of SARS-CoV-2 has faded, due to possibility of a new outbreak a continued focus is necessary. The complex pathogenesis of SARS-CoV-2 demands multifaceted strategies to effectively manage the COVID-19 pandemic, wherein modulating the inflammatory response is of equal importance to directly targeting the virus itself. In this perspective, repurposing recent drugs provide us a primary advantage for developing new treatments against SARS-CoV-2. Complementary with this strategy, the previous studies have described anti-inflammatory activities and immune response modulating properties of GlcNAc on SARS-CoV-2, which confirms results of the recent study [46, 47, 66, 67]. Also, the studies on ASA showed its inhibitory effect on SARS-CoV-2 replication cycle [68], which makes it a promising drug candidate for the SARS-CoV-2 treatments [69-72]. Although the mean value of NAC was found to be less than other values of the compounds in this study (Table 1), particularly many studies have shown anti-viral property of NAC on SARS-CoV-2 [73-76]. From these results, it could be concluded that both GlcNAc and ASA could response better in SARS-CoV-2 treatments since their mean value is higher than NAC (Table 1). Though there are limited studies on these compounds, more research on their inhibitory potential on SARS-CoV-2 *in vivo* and clinical trials is necessary.

It is noteworthy that, although these three compounds do not need any prescription, only one of them has a long pharmaceutical history; acetylsalicylic acid, which is better known for more than 125 years under its trade name of Aspirin. The antiviral effects of this compound have been confirmed with testing on both RNA and DNA viruses with several *in vitro* and experimental *in vivo* studies [77]. Also, low-cost production of Aspirin makes it a promising drug candidate for further anti-SARS-CoV-2 studies [78].

As depicted in Figure 3, the molecular structure of these compounds is different, therefore their mode of action is expected to be various in many metabolic pathways. The immunomodulatory properties of these compounds on SARS-CoV-2 are also needed to be investigated in further studies.

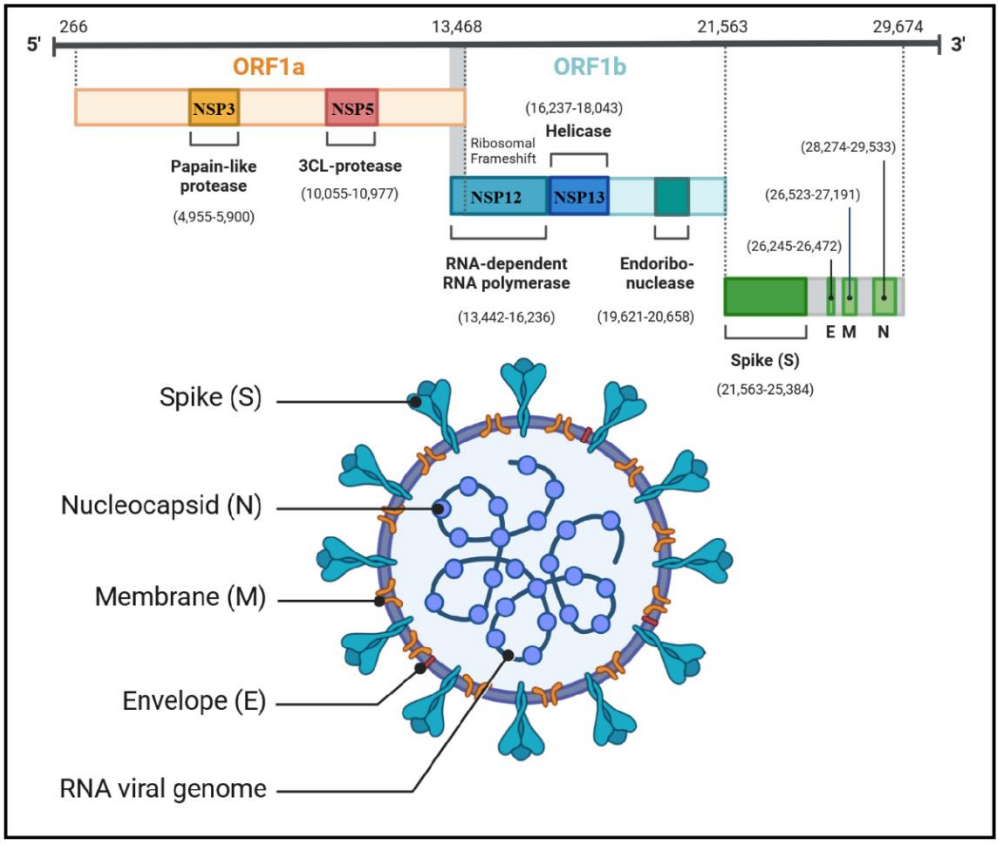


Figure 2. Genomic distribution of SARS-Cov-2 genes (Source: BioRender).

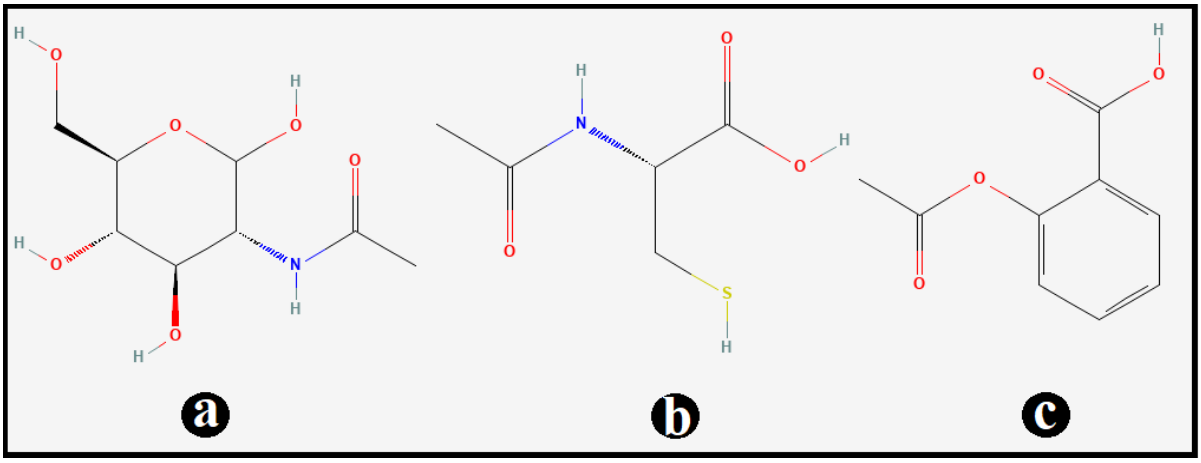


Figure 3. Structural comparison of selected molecules; a) GlcNAc, b) NAC, and c) ASA.

A considerable proportion of individuals recovering from SARS-CoV-2 infection continue to experience a range of physical, psychological, and cognitive symptoms, despite biochemical evidence indicating the cessation of viral replication approximately four weeks following the initial infection [79]. These persistent symptoms were initially referred to by various terms, including post-acute COVID-19, long-haul COVID-19, chronic COVID-19 syndrome, and post-acute sequelae of COVID-19. However, as consistent reports of these symptoms have emerged globally among convalescent patients, the term long COVID has gained international recognition and is now widely adopted to characterize this condition [80]. One proposed explanation for long COVID is the presence of residual SARS-CoV-2 viral reservoirs following the acute phase of infection, which may contribute to sustained inflammation and prolonged immune activation [81-83]. From this perspective, GlcNAc, NAC, and ASA—compounds previously showed antiviral and immunomodulatory properties—may hold potential as therapeutic agents for the management of long COVID.

Viruses exhibit exceptionally rapid replication rates, and their mutation dynamics are strongly influenced by environmental factors, enabling them to swiftly

develop resistance to therapeutic or prophylactic agents. This high mutational capacity represents one of the major challenges in the development of effective vaccines and antiviral therapies, a phenomenon particularly evident in the case of SARS-CoV-2 [84]. The findings indicated that the combination of these three ligands has a potential to fight with SARS-CoV-2 and to diminish possible viral mutations.

The emergence of new mutated variants such as Omicron variant confirms the unpredictable nature of the COVID-19 pandemic, emphasizing the need for repurposing new drugs with ongoing research, adaptability, and global collaboration. The COVID-19 Docking Server 2.0 has a great potential as an integrated bioinformatics tool in research for SARS-CoV-2 protein ligand interactions [25, 85]. The bioinformatics analysis infrastructure available here can guide us in developing treatment methods rapidly, as it contains common or similar proteins across all coronavirus variants.

As presented in this study, repurposing established drugs with well-characterized safety profiles offers the potential to expedite therapeutic development, thereby reducing the time and financial resources typically required for novel drug discovery. Such a strategy could promote faster and more equitable access to effective treatments, thereby strengthening global preparedness and response to ongoing and emerging pandemics.

V. CONCLUSION

This study identified the interaction of 3 FDA approved commercially available and widely used compounds; GlcNAc, NAC, and ASA with 22 main proteins of SARS-CoV-2, which have major roles related to replication and various pathogenesis processes. All the compounds found to have interaction with these viral proteins. Mean values of interactions indicated that GlcNAc (-6.81 kcal/mol) and ASA (-6.31 kcal/mol) have similar results but NAC (-4.69 kcal/mol) was found to have the lowest value. New variants could emerge in near future, due to high evolutionary rate of the SARS-CoV-2. These compounds could be tested in SARS-CoV-2 *in vivo* and clinical trials.

ACKNOWLEDGEMENTS

The article is dedicated to patients who lost their lives during COVID-19 pandemic. The author thanks Emine Şeküre Nazlı Arda, Ph.D. and Ömür Baysal, Ph.D. for their comments and suggestions on the manuscript.

DATA AVAILABILITY STATEMENT

All relevant data are provided in the paper and supplementary data files. Supplementary materials are available online: https://doi.org/10.6084/m9.figshare.30178483.v1

REFERENCES

[1] Tay, M. Z., Poh, C. M., Rénia, L., MacAry, P. A., & Ng, L. F. P. (2020). The trinity of COVID-19: immunity, inflammation and intervention. Nature reviews. *Immunology*, *20*(6), 363–374. https://doi.org/10.1038/s41577-020-0311-8

[2] van Eijk, L. E., Binkhorst, M., Bourgonje, A. R., Offringa, A. K., Mulder, D. J., Bos, E. M., Kolundzic, N., Abdulle, A. E., van der Voort, P. H., Olde Rikkert, M. G., van der Hoeven, J. G., den Dunnen, W. F., Hillebrands, J. L., & van Goor, H. (2021). COVID-19: immunopathology, pathophysiological mechanisms, and treatment options. *The Journal of pathology*, *254*(4), 307–331. https://doi.org/10.1002/path.5642

[3] Zhou, P., Yang, X. L., Wang, X. G., Hu, B., Zhang, L., Zhang, W., Si, H. R., Zhu, Y., Li, B., Huang, C. L., Chen, H. D., Chen, J., Luo, Y., Guo, H., Jiang, R. D., Liu, M. Q., Chen, Y., Shen, X. R., Wang, X., Zheng, X. S., Zhao, K., Chen, Q.-J., Deng, F., Liu, L.-L., Yan, B., Zhan, F.-X., Wang, Y.-Y., Xiao, G.-F., & Shi, Z.-L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, *579*(7798), 270–273. https://doi.org/10.1038/s41586-020-2012-7

[4] Coronavirus disease (COVID-19) Fact sheets, https://www.who.int/news-room/fact-sheets/detail/coronavirus-disease-(covid-19), (August 2023).

[5] Liang, Y., Wang, M. L., Chien, C. S., Yarmishyn, A. A., Yang, Y. P., Lai, W. Y., Luo, Y. H., Lin, Y. T., Chen, Y. J., Chang, P. C., & Chiou, S. H. (2020). Highlight of Immune Pathogenic Response and Hematopathologic Effect in SARS-CoV, MERS-CoV, and SARS-Cov-2 Infection. *Frontiers in immunology*, *11*, 1022. https://doi.org/10.3389/fimmu.2020.01022

[6] Malone, B., Urakova, N., Snijder, E. J., & Campbell, E. A. (2022). Structures and functions of coronavirus replication-transcription complexes and their relevance for SARS-CoV-2 drug design. *Nature reviews. Molecular cell biology*, *23*(1), 21–39. https://doi.org/10.1038/s41580-021-00432-z

[7] Hashimoto, T., Perlot, T., Rehman, A., Trichereau, J., Ishiguro, H., Paolino, M., Sigl, V., Hanada, T., Hanada, R., Lipinski, S., Wild, B., Camargo, S. M., Singer, D., Richter, A., Kuba, K., Fukamizu, A., Schreiber, S., Clevers, H., Verrey, F., Rosenstiel, P., & Penninger, J. M. (2012). ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature*, *487*(7408), 477–481. https://doi.org/10.1038/nature11228

[8] Varga, Z., Flammer, A. J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A. S., Mehra, M. R., Schuepbach, R. A., Ruschitzka, F., & Moch, H. (2020). Endothelial cell infection and endotheliitis in COVID-19. *Lancet (London, England)*, *395*(10234), 1417–1418. https://doi.org/10.1016/S0140-6736(20)30937-5

[9] Bourgonje, A. R., Abdulle, A. E., Timens, W., Hillebrands, J. L., Navis, G. J., Gordijn, S. J., Bolling, M. C., Dijkstra, G., Voors, A. A., Osterhaus, A. D., van der Voort, P. H., Mulder, D. J., & van Goor, H. (2020). Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). *The Journal of pathology*, *251*(3), 228–248. https://doi.org/10.1002/path.5471

[10] Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y., & Zhou, Q. (2020). Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science (New York, N.Y.)*, *367*(6485), 1444–1448. https://doi.org/10.1126/science.abb2762

[11] Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., & Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)*, *395*(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

[12] Kim, J. S., Lee, J. Y., Yang, J. W., Lee, K. H., Effenberger, M., Szpirt, W., Kronbichler, A., & Shin, J. I. (2021). Immunopathogenesis and treatment of cytokine storm in COVID-19. *Theranostics*, *11*(1), 316–329. https://doi.org/10.7150/thno.49713

[13] Schurink, B., Roos, E., Radonic, T., Barbe, E., Bouman, C. S. C., de Boer, H. H., de Bree, G. J., Bulle, E. B., Aronica, E. M., Florquin, S., Fronczek, J., Heunks, L. M. A., de Jong, M. D., Guo, L., du Long, R., Lutter, R., Molenaar, P. C. G., Neefjes-Borst, E. A., Niessen, H. W. M., van Noesel, C. J. M., Roelofs, J. J. T. H., Snijder, E. J., Soer, E. C., Verheij, J., Vlaar, A. P. J., Vos, W., van der Wel, N. N., van der Wal, A. C., van der Valk, P., & Bugiani, M. (2020). Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *The Lancet Microbe*, *1*(7), e290–e299. https://doi.org/10.1016/S2666-5247(20)30144-0

[14] Bettini, E., & Locci, M. (2021). SARS-CoV-2 mRNA Vaccines: Immunological Mechanism and Beyond. *Vaccines*, *9*(2), 147. https://doi.org/10.3390/vaccines9020147

[15] Yadav, T., Kumar, S., Mishra, G., & Saxena, S. K. (2023). Tracking the COVID-19 vaccines: The global landscape. *Human vaccines & immunotherapeutics*, *19*(1), 2191577. https://doi.org/10.1080/21645515.2023.2191577

[16] Yasmin, F., Najeeb, H., Naeem, U., Moeed, A., Atif, A. R., Asghar, M. S., Nimri, N., Saleem, M., Bandyopadhyay, D., Krittanawong, C., Fadelallah Eljack, M. M., Tahir, M. J., & Waqar, F. (2023). Adverse events following COVID-19 mRNA vaccines: A systematic review of cardiovascular complication, thrombosis, and thrombocytopenia. *Immunity, inflammation and disease*, *11*(3), e807. https://doi.org/10.1002/iid3.807

[17] Haider, S. M. S., Alvi, S. A., Khan, H., Majeed, R., Syed, T., Anwar, A., & Hashmi, A. A. (2023). Common side effects of Pfizer COVID-19 vaccine: An experience from Pakistan. *Cureus*, *15*(6), e40878. https://doi.org/10.7759/cureus.40878

[18] Abukhalil, A. D., Shatat, S. S., Abushehadeh, R. R., Al-Shami, N., Naseef, H. A., & Rabba, A. (2023). Side effects of Pfizer/BioNTech (BNT162b2) COVID-19 vaccine reported by the Birzeit University community. *BMC infectious diseases*, *23*(1), 5. https://doi.org/10.1186/s12879-022-07974-3

[19] Sha, A., Liu, Y., & Hao, H. (2023). Current state-of-the-art and potential future therapeutic drugs against COVID-19. *Frontiers in cell and developmental biology*, *11*, 1238027. https://doi.org/10.3389/fcell.2023.1238027

[20] Focosi, D., Sullivan, D. J., & Franchini, M. (2025). Development of antiviral drugs for COVID-19 in 2025: unmet needs and future challenges. *Expert review of anti-infective therapy*, *23*(6), 351–358. https://doi.org/10.1080/14787210.2025.2473044

[21] Hurt, A. C., & Wheatley, A. K. (2021). Neutralizing antibody therapeutics for COVID-19. *Viruses*, *13*(4), 628. https://doi.org/10.3390/v13040628

[22] Baysal, Ö., & Silme, R. S. (2021). Utilization from computational methods and omics data for antiviral drug discovery to control of SARS-CoV-2. IntechOpen. https://doi.org/10.5772/intechopen.98319

[23] Rodrigues, L., Bento Cunha, R., Vassilevskaia, T., Viveiros, M., & Cunha, C. (2022). Drug repurposing for COVID-19: a review and a novel strategy to identify new targets and potential drug candidates. *Molecules (Basel, Switzerland)*, *27*(9), 2723. https://doi.org/10.3390/molecules27092723

[24] Herrera-Rodulfo, A., Andrade-Medina, M., & Carrillo-Tripp, M. (2023). Repurposing drugs as potential therapeutics for the SARS-Cov-2 viral infection: automatizing a blind molecular docking high-throughput pipeline. IntechOpen. https://doi.org/10.5772/intechopen.105792

[25] Liu, K., Lu, X., Shi, H., Xu, X., Kong, R., & Chang, S. (2023). nCoVDock2: a docking server to predict the binding modes between COVID-19 targets and its potential ligands. *Nucleic acids research*, *51*(W1), W365–W371. https://doi.org/10.1093/nar/gkad414

[26] Eberhardt, J., Santos-Martins, D., Tillack, A. F., & Forli, S. (2021). AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings. *Journal of chemical information and modeling*, *61*(8), 3891–3898. https://doi.org/10.1021/acs.jcim.1c00203

[27] Trott, O., & Olson, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of computational chemistry*, *31*(2), 455–461. https://doi.org/10.1002/jcc.21334

[28] O'Boyle, N. M., Banck, M., James, C. A., Morley, C., Vandermeersch, T., & Hutchison, G. R. (2011). Open Babel: An open chemical toolbox. *Journal of cheminformatics*, *3*, 33. https://doi.org/10.1186/1758-2946-3-33

[29] NCBI-National Center for Biotechnology Information (2025). PubChem Compound Summary for a) CID 439174, N-Acetyl-D-Glucosamine, b) CID 12035, Acetylcysteine and c) CID 2244, Aspirin Retrieved March 23, 2025 from a) https://pubchem.ncbi.nlm.nih.gov/compound/N-Acetyl-D-Glucosamine, b) https://pubchem.ncbi.nlm.nih.gov/compound/Acetylcysteine, and c) https://pubchem.ncbi.nlm.nih.gov/compound/Aspirin

[30] The PyMOL Molecular Graphics System, Version 3.1.3 Schrödinger, LLC. https://www.pymol.org

[31] BIOVIA, Dassault Systèmes, BIOVIA Discovery Studio Visualizer, version 25.1.0.24284, San Diego, 2025

[32] Wallace, A. C., Laskowski, R. A., & Thornton, J. M. (1996). LIGPLOT: a program to generate schematic diagrams of protein-ligand interactions. *Protein engineering*, *8*(2), 127–134. https://doi.org/10.1093/protein/8.2.127

[33] Laskowski, R. A., & Swindells, M. B. (2011). LigPlot+: multiple ligand-protein interaction diagrams for drug discovery. *Journal of chemical information and modeling*, *51*(10), 2778–2786. https://doi.org/10.1021/ci200227u

[34] Li, H., Leung, K. S., Wong, M. H., & Ballester, P. J. (2016). Correcting the impact of docking pose generation error on binding affinity prediction. *BMC bioinformatics*, *17*(Suppl 11), 308. https://doi.org/10.1186/s12859-016-1169-4

[35] Hu, Q., Xiong, Y., Zhu, G. H., Zhang, Y. N., Zhang, Y. W., Huang, P., & Ge, G. B. (2022). The SARS-CoV-2 main protease (M^{pro}): Structure, function, and emerging therapies for COVID-19. *MedComm*, *3*(3), e151. https://doi.org/10.1002/mco2.151

[36] Varghese, A., Liu, J., Liu, B., Guo, W., Dong, F., Patterson, T. A., & Hong, H. (2025). Analysis of structures of SARS-CoV-2 papain-like protease bound with ligands unveils structural features for inhibiting the enzyme. *Molecules (Basel, Switzerland)*, *30*(3), 491. https://doi.org/10.3390/molecules30030491

[37] V'kovski, P., Kratzel, A., Steiner, S., Stalder, H., & Thiel, V. (2021). Coronavirus biology and replication: implications for SARS-CoV-2. *Nature reviews. Microbiology*, *19*, 155–170. https://doi.org/10.1038/s41579-020-00468-6

[38] Wang, Y., Grunewald, M., & Perlman, S. (2020). Coronaviruses: an updated overview of their replication and pathogenesis. In: Coronaviruses. Methods in Molecular Biology, Maier, H., Bickerton, E. (eds.), vol 2203, Humana, New York, NY, USA, pp. 1–29. https://doi.org/10.1007/978-1-0716-0900-2_1

[39] Walsh, D., & Mohr, I. (2011). Viral subversion of the host protein synthesis machinery. *Nature Reviews Microbiology*, *9*, 860–875. https://doi.org/10.1038/nrmicro2655

[40] Minkoff, J. M., & tenOever, B. (2023). Innate immune evasion strategies of SARS-CoV-2. *Nature reviews. Microbiology*, *21*(3), 178–194. https://doi.org/10.1038/s41579-022-00839-1

[41] Wong, L. R., & Perlman, S. (2022). Immune dysregulation and immunopathology induced by SARS-CoV-2 and related coronaviruses - are we our own worst enemy? *Nature reviews. Immunology*, *22*, 47–56. https://doi.org/10.1038/s41577-021-00656-2

[42] Thiel, V., Ivanov, K. A., Putics, Á., Hertzig, T., Schelle, B., Bayer, S., Weißbrich, B., Snijder, E. J., Rabenau, H., Doerr, H. W., Gorbalenya, A. E., & Ziebuhr, J. (2003). Mechanisms and enzymes involved in SARS coronavirus genome expression. *The Journal of general virology*, *84*(Pt 9), 2305–2315. https://doi.org/10.1099/vir.0.19424-0

[43] Zhu, W., Xu, M., Chen, C. Z., Guo, H., Shen, M., Hu, X., Shinn, P., Klumpp-Thomas, C., Michael, S. G., & Zheng, W. (2020). Identification of SARS-CoV-2 3CL protease inhibitors by a quantitative high-throughput screening. *ACS pharmacology & translational science*, *3*(5), 1008–1016. https://doi.org/10.1021/acsptsci.0c00108

[44] Dai, W., Zhang, B., Jiang, X. M., Su, H., Li, J., Zhao, Y., Xie, X., Jin, Z., Peng, J., Liu, F., Li, C., Li, Y., Bai, F., Wang, H., Cheng, X., Cen, X., Hu, S., Yang, X., Wang, J., Liu, X., Xiao, G., Jiang, H., Rao, Z., Zhang, L.-K., Xu, Y., Yang, H., & Liu, H. (2020). Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. *Science (New York, N.Y.)*, *368*(6497), 1331–1335. https://doi.org/10.1126/science.abb4489

[45] De Clercq, E. (2023). Hydrogen bonding (Base Pairing) in antiviral activity. *Viruses*, *15*(5), 1145. https://doi.org/10.3390/v15051145

[46] Baysal, Ö., Silme, R. S., Karaaslan, İ. Ç., & Ignatov, A. N. (2021a). Genetic uniformity of a specific region in SARS-CoV-2 genome and repurposing of N-acetyl-d-glucosamine. *Fresenius Environmental Bulletin*, *30*(3), 2848-2857. https://doi.org/10.5281/zenodo.4621319

[47] Baysal, Ö., Abdul Ghafoor, N., Silme, R. S., Ignatov, A. N., & Kniazeva, V. (2021b). Molecular dynamics analysis of N-acetyl-D-glucosamine against specific SARS-CoV-2's pathogenicity factors. *PloS One*, *16*(5), e0252571. https://doi.org/10.1371/journal.pone.0252571

[48] De Clercq, E. (2021). Perspectives for antivirals to limit SARS-CoV-2 infection (COVID-19). *Microbiology Australia*, *42*, 47–53.

[49] Vishwakarma, K., Ravi, S., & Mittal S. (2024). Ab initio modeling of hydrogen bonding of Remdesivir and Adenosine with Uridine. *ChemPhysChem*, *25*(3), e202300552. https://doi.org/10.1002/cphc.202300552

[50] Nicholls, A., & Honig, B. (1995). Classical electrostatics in biology and chemistry. *Science*, *268*(5214), 1144–1149. https://doi.org/10.1126/science.7761829

[51] Shang, J., Ye, G., Shi, K., Wan, Y., Luo, C., Aihara, H., Geng, Q., Auerbach, A., & Li, F. (2020). Structural basis of receptor recognition by SARS-CoV-2. *Nature*, *581*, 221–224. https://doi.org/10.1038/s41586-020-2179-y

[52] Norel, R., Sheinerman, F., Petrey, D., & Honig, B. (2008). Electrostatic contributions to protein-protein interactions: fast energetic filters for docking and their physical basis. *Protein Science*, *10*(11), 2147–2161. https://doi.org/10.1110/ps.12901

[53] Sheinerman F. (2000). Electrostatic aspects of protein–protein interactions. *Current Opinion in Structural Biology*, *10*(2), 153–159. https://doi.org/10.1016/S0959-440X(00)00065-8

[54] Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (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.e8. https://doi.org/10.1016/j.cell.2020.02.052

[55] Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y., & Zhou, Q. (2020). Structural basis for the recognition of SARSCoV-2 by full-length human ACE2. *Science*, *367*(6485), 1444–1448. https://doi.org/10.1126/science.abb2762

[56] Ali, F., Elserafy, M., Akordi, M.H., Amin, M. (2020). ACE2 coding variants in different populations and their potential impact on SARS-CoV-2 binding affinity. *Biochemistry and Biophysics Reports*, *24*, 100798. https://doi.org/10.1016/j.bbrep.2020.100798

[57] Amin, M., Sorour, M. K., & Kasry, A. (2020). Comparing the binding interactions in the receptor binding domains of SARS-CoV-2 and SARS-CoV. *The journal of physical chemistry letters*, *11*(12), 4897–4900. https://doi.org/10.1021/acs.jpclett.0c01064

[58] Sarkar, A., & Kellogg, G. E. (2010). Hydrophobicity--shake flasks, protein folding and drug discovery. *Current topics in medicinal chemistry*, *10*(1), 67–83. https://doi.org/10.2174/156802610790232233

[59] Simm, S., Einloft, J., Mirus, O., & Schleiff, E. (2016). 50 years of amino acid hydrophobicity scales: revisiting the capacity for peptide classification. *Biological research*, *49*, 31. https://doi.org/10.1186/s40659-016-0092-5

[60] Aydin, H., Al-Khooly, D., & Lee, J.E. (2014). Influence of hydrophobic and electrostatic residues on SARScoronavirus S2 protein stability: insights into mechanisms of general viral fusion and inhibitor design. *Protein science*, *23*(5), 603–617. https://doi.org/10.1002/pro.2442

[61] Nelson, D. L., & Cox, M. M. (2008). Lehninger Principles of Biochemistry. 5th Edition, 1-1294.

[62] Wang, H.-J., Xi, X.-K., Kleinhammes, A., & Wu, Y. (2008). Temperature-induced hydrophobic-hydrophilic transition observed by water adsorption. *Science*, *322*(5898), 80–83 https://doi.org/10.1126/science.1162412

[63] Meyer, E. E., Rosenberg, K. J., & Israelachvili, J. (2006). Recent progress in understanding hydrophobic interactions. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(43), 15739–15746. https://doi.org/10.1073/pnas.0606422103

[64] Kumar, S., Thambiraja, T. S., Karuppanan, K., & Subramaniam, G. (2022). Omicron and Delta variant of SARS-CoV-2: A comparative computational study of spike protein. *Journal of medical virology*, *94*(4), 1641–1649. https://doi.org/10.1002/jmv.27526

[65] Brogi, S., Ramalho, T. C., Kuca, K., Medina-Franco, J. L., & Valko, M. (2020). Editorial: *In silico* methods for drug design and discovery. *Frontiers in chemistry*, *8*, 612. https://doi.org/10.3389/fchem.2020.00612

[66] Hassan, A. E. (2021). An observational cohort study to assess N-acetylglucosamine for COVID-19 treatment in the inpatient setting. *Annals of medicine and surgery*, *68*, 102574. https://doi.org/10.1016/j.amsu.2021.102574

[67] Qi, Q., Chen, Q., Dong, Y., Wang, K., Wang, J., Jin, G., Zheng, A., Zhang, R., Deng, Y., Li, Y., Qin, C., & Duan, X. (2023). Oral administration of D-glucosamine confers broad-spectrum protection against human coronaviruses including SARS-CoV-2. *Signal transduction and targeted therapy*, *8*, 250. https://doi.org/10.1038/s41392-023-01483-8

[68] Geiger, N., König, E. M., Oberwinkler, H., Roll, V., Diesendorf, V., Fähr, S., Obernolte, H., Sewald, K., Wronski, S., Steinke, M., & Bodem, J. (2022). Acetylsalicylic acid and salicylic acid inhibit SARS-CoV-2 replication in precision-cut lung slices. *Vaccines*, *10*(10), 1619. https://doi.org/10.3390/vaccines10101619

[69] Bianconi, V., Violi, F., Fallarino, F., Pignatelli, P., Sahebkar, A., & Pirro, M. (2020). Is acetylsalicylic acid a safe and potentially useful choice for adult patients with COVID-19? *Drugs*, *80*, 1383–1396. https://doi.org/10.1007/s40265-020-01365-1

[70] Cacciapuoti, F., & Cacciapuoti, F. (2021). Could low doses acetylsalicylic acid prevent thrombotic complications in COVID-19 patients? *Clinical and applied thrombosis/hemostasis: official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis*, *27*, 10760296211014592. https://doi.org/10.1177/10760296211014592

[71] Mazik M. (2022). Promising therapeutic approach for SARS-CoV-2 infections by using a rutin-based combination therapy. *ChemMedChem*, *17*(11), e202200157. https://doi.org/10.1002/cmdc.202200157

[72] Rizk, J. G., Lavie, C. J., & Gupta, A. (2021). Low-dose aspirin for early COVID-19: does the early bird catch the worm? *Expert opinion on investigational drugs*, *30*(8), 785–788. https://doi.org/10.1080/13543784.2021.1950687

[73] Avdeev, S. N., Gaynitdinova, V. V., Merzhoeva, Z. M., & Berikkhanov, Z. G. (2022). N-acetylcysteine for the treatment of COVID-19 among hospitalized patients. *The Journal of infection*, *84*(1), 94–118. https://doi.org/10.1016/j.jinf.2021.07.003

[74] Faverio, P., Rebora, P., Rossi, E., Del Giudice, S., Montanelli, F., Garzillo, L., Busnelli, S., Luppi, F., Valsecchi, M. G., & Pesci, A. (2021). Impact of *N*-acetyl-l-cysteine on SARS-CoV-2 pneumonia and its sequelae: results from a large cohort study. *ERJ open research*, *8*(1), 00542-2021. https://doi.org/10.1183/23120541.00542-2021

[75] Izquierdo-Alonso, J. L., Pérez-Rial, S., Rivera, C. G., & Peces-Barba, G. (2022). N-acetylcysteine for prevention and treatment of COVID-19: Current state of evidence and future directions. *Journal of infection and public health*, *15*(12), 1477–1483. https://doi.org/10.1016/j.jiph.2022.11.009

[76] Wong, K. K., Lee, S. W. H., & Kua, K. P. (2021). N-Acetylcysteine as Adjuvant Therapy for COVID-19 - A perspective on the current state of the evidence. *Journal of inflammation research*, *14*, 2993–3013. https://doi.org/10.2147/JIR.S306849

[77] Werz, O., Stettler, H., Theurer, C., & Seibel, J. (2024). The 125th anniversary of Aspirin-the story continues. *Pharmaceuticals (Basel, Switzerland)*, *17*(4), 437. https://doi.org/10.3390/ph17040437

[78] Tantry, U. S., Bliden, K. P., & Gurbel, P. A. (2022). Further evidence for the use of aspirin in COVID-19. *International journal of cardiology*, *346*, 107–108. https://doi.org/10.1016/j.ijcard.2021.11.021

[79] Ballering, A. V., van Zon, S. K. R., Olde Hartman, T. C., Rosmalen, J. G. M., & Lifelines Corona Research Initiative (2022). Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *The Lancet (London, England)*, *400*(10350), 452–461. https://doi.org/10.1016/S0140-6736(22)01214-4

[80] O'Mahoney, L. L., Routen, A., Gillies, C., Ekezie, W., Welford, A., Zhang, A., Karamchandani, U., Simms-Williams, N., Cassambai, S., Ardavani, A., Wilkinson, T. J., Hawthorne, G., Curtis, F., Kingsnorth, A. P., Almaqhawi, A., Ward, T., Ayoubkhani, D., Banerjee, A., Calvert, M., Shafran, R., Stephenson, T., Sterne, J., Ward, H., Evans, R. A., Zaccardi, F., Wright, S., & Khunti, K. (2023). The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *eClinicalMedicine*. *55*, 101762. https://doi.org/10.1016/j.eclinm.2022.101762

[81] Oronsky, B., Larson, C., Hammond, T. C., Oronsky, A., Kesari, S., Lybeck, M., & Reid, T. R. (2023). A review of persistent post-COVID syndrome (PPCS). *Clinical reviews in allergy & immunology*, *64*(1), 66–74. https://doi.org/10.1007/s12016-021-08848-3

[82] Bonilla, H., Peluso, M. J., Rodgers, K., Aberg, J. A., Patterson, T. F., Tamburro, R., Baizer, L., Goldman, J. D., Rouphael, N., Deitchman, A., Fine, J., Fontelo, P., Kim, A. Y., Shaw, G., Stratford, J., Ceger, P., Costantine, M. M., Fisher, L., O'Brien, L., Maughan, C., Quigley, J. G., Gabbay, V., Mohandas, S., Williams, D., & McComsey, G. A. (2023). Therapeutic trials for long COVID-19: A call to action from the interventions taskforce of the RECOVER initiative. *Frontiers in immunology*, *14*, 1129459. https://doi.org/10.3389/fimmu.2023.1129459

[83] Váncsa, S., Dembrovszky, F., Farkas, N., Szakó, L., Teutsch, B., Bunduc, S., Nagy, R., Párniczky, A., Erőss, B., Péterfi, Z., & Hegyi, P. (2021). Repeated SARS-CoV-2 positivity: analysis of 123 cases. *Viruses*, *13*(3), 512. https://doi.org/10.3390/v13030512

[84] Korber, B., Fischer, W. M., Gnanakaran, S., Yoon, H., Theiler, J., Abfalterer, W., Hengartner, N., Giorgi, E. E., Bhattacharya, T., Foley, B., Hastie, K. M., Parker, M. D., Partridge, D. G., Evans, C. M., Freeman, T. M., de Silva, T. I., Sheffield COVID-19 Genomics Group, McDanal, C., Perez, L. G., Tang, H., Moon-Walker, A., Whelan, S. P., LaBranche, C. C., Saphire, E. O., & Montefiori, D. C. (2020). Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. *Cell*, *182*(4), 812–827.e19. https://doi.org/10.1016/j.cell.2020.06.043

[85] Kong, R., Yang, G. B., Xue, R., Liu, M., Wang, F., Hu, J. P., Guo, X. Q., & Chang, S. (2020). COVID-19 Docking server: a meta server for docking small molecules, peptides and antibodies against potential targets of COVID-19. *Bioinformatics*, *36*(20), 5109–5111. https://doi.org/10.1093/bioinformatics/btaa645