ISSN: 3065-7628

Research Article

Journal of Future Medicine and Healthcare Innovation

Insilico Evaluation of the Antiviral Potentials of Selected Natural Compounds Against Sars-Cov-2 Viral Main Protease

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Submitted: 2026, Jan 22; **Accepted:** 2026, Feb 12; **Published:** 2026, Feb 18

Citation: Igwe, O.F., Alo, M. N., Ikechukwu, M. M. E., Awa, D. U., Okwudili, O. N. M., et al. (2026). Insilico Evaluation of the Antiviral Potentials of Selected Natural Compounds Against Sars-Cov-2 Viral Main Protease. *J Future Med Healthcare Innovation, 4*(1), 01-08.

Abstract

The rise of SARS-CoV-2 and the subsequent coronavirus pandemic has posed enormous challenges to universal health systems and economies. Conventional antiviral vaccines and drugs face limitations such as viral resistance, accessibility issues, potential side effects, and the advent of new SARS-CoV-2 variants, necessitating the development of novel therapeutic or preventive options. This study evaluated the insilico antiviral potentials of selected compounds of Nigella sativa and Allium sativum against SARS-COV-2 Viral Main Protease. Four ligands were docked with the SARS-CoV-2 main protease using AutoDock and Python Molecular Viewer. The ligands from Nigella sativa; Dithymoquinone, Thymoquinone, and allicin and dialydisulfide from Allium sativum were analyzed for their binding energies, inhibition constants, and protein-ligand interactions.

The result revealed that Dithymoquinone exhibited the highest binding energy of- 7.39 kcal/mol and the lowest inhibition constant of 3.84 µM, significantly outperforming chloroquine, which had a binding energy of 5.33 kcal/mol and an inhibition constant of 124.62 µM., the ligands exhibited moderate binding energy of -3.26Kcal/mol and - 2.96Kcal/mol respectively for both Allicin and dialidisulfide comparatively lower to chloroquine, which had a binding energy of 5.33 kcal/mol and an inhibition constant of 124.62 µM. Dithymoquinone demonstrates superior potential as an antiviral agent against SARS-CoV-2, highlighting the efficacy of natural compounds in antiviral strategies. This analysis provides valuable insights into the development of natural antiviral agents.

Keywords: Insilico, Antiviral, Sar-cov-2 Viral Main Protease, Compounds, Nigella Sativa and Allium Sativum

1. Background

The outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)—the pathogen responsible for COVID-19—at the end of 2019 presented an unparalleled global public health crisis. The pandemic resulted in millions of deaths worldwide and caused severe disruptions to economic systems, healthcare delivery, and social structures. Although substantial progress has been made in vaccine research and deployment, the continuous emergence of new viral variants and the limitations in vaccine efficacy and accessibility highlight the pressing need for effective antiviral therapeutics (Zhu *et al*., 2020; World Health Organization [WHO], 2021). Within the viral replication cycle, the main protease (Mpro or 3CLpro) plays a critical role by catalyzing the cleavage of viral polyproteins essential for replication and transcription. Inhibition of this protease has been demonstrated to effectively halt viral replication, establishing it as a key molecular target for antiviral drug development (Ullrich & Nitsche, 2020).

Traditional drug discovery processes are often expensive and time-consuming; consequently, computational or in silico methods have become invaluable in modern pharmacological research. Techniques such as molecular docking and molecular dynamics simulations allow for rapid and efficient screening of large compound libraries by predicting the binding affinities and interaction patterns between potential ligands and target proteins (Lionta *et al*., 2014). These approaches have significantly contributed to the identification of potential SARS-CoV-2 inhibitors derived from natural sources.

Medicinal plants have historically served as vital reservoirs of therapeutic agents, offering structurally diverse phytochemicals with documented antiviral, anti-inflammatory, and immunomodulatory properties. Notably, *Nigella sativa* (black seed), *Zingiber officinale* (ginger), and *Allium sativum* (garlic) have long-standing applications in traditional medicine and have been scientifically validated for their broad pharmacological effects, including antimicrobial and antiviral activities [1,2]. Bioactive compounds such as thymoquinone from *Nigella sativa*, gingerols and shogaols from *Zingiber officinale*, and allicin and ajoene from *Allium sativum* have demonstrated capacities to inhibit viral replication and modulate host immune responses [3,4].

Given their diverse bioactive constituents and documented antiviral efficacy, these plants represent promising candidates for the discovery of novel inhibitors targeting the SARS-CoV-2 main protease. Therefore, in silico evaluation of their phytochemical components could yield valuable insights for the development of natural antiviral agents and serve as a foundation for subsequent experimental validation.

Accordingly, this study seeks to investigate the antiviral potentials of selected phytochemicals from *Nigella sativa* and *Allium sativum* against the SARS-CoV-2 main protease through computational molecular docking techniques, thereby contributing to ongoing global efforts aimed at identifying safe, accessible, and cost-effective antiviral compounds.

2. Materials and Methods

2.1. Proteins and Ligands Retrieval

The 3D conformations of the ligands were retrieved from the NCBI-PubChem and downloaded in an SDF file format. The ligands were optimized using Avogadro version 1.2 and docked using AutoDock and Python Molecular Viewer version 1.5.7. The Covid-19 protein was retrieved from the Protein Data Bank (PDB). The retrieved protein is the Covid-19 main protease (M^{pro}) of SARS-COV-2 which is a key enzyme of coronaviruses and has a pivotal role in mediating viral replication and transcription, making it an attractive drug target for SARS-CoV-2. The enzyme has 306 amino acid residues with the crystal structure shown in figure 1.

Binding energies, inhibition constants (Ki), and ligand-receptor interactions were analyzed through Lamarckian Genetic Algorithm at 50 conformations (runs), selecting the conformations with lowest inhibition constant and the highest binding energy for further analysis.

2.2. Molecular Docking Analysis

Molecular docking refers to the computational technique used to envisage the preferred orientation of a ligand (small molecule) when it binds to a protein (macromolecule). The orientation helps to regulate the strength and specificity of the interaction of the molecules with SARS-COV-2 viral main protease.

Flexible Molecular docking was performed on selected bioactive compounds from *Nigella sativa* and *Allium sativum* against the main protease of the SARS-CoV-2 virus, following the methodology described by (Bouchentouf *et al*., 2020; Khan *et al*., 2022), and others [5]. Four active compounds (ligands), including Dithymoquinone, thymoquinone from *Nigella sativa*, and Allicin, Diallyl-disiulfide from *Allium sativum*, were docked against the COVID-19 main protease. Chloroquine was used as a control ligand.

Ligands were retrieved in 3D conformations from the NCBI-PubChem database, optimized using Avogadro version 1.2, and docked using AutoDock and Python Molecular Viewer version 1.5.7. Binding energies, inhibition constants (Ki), and ligand-receptor interactions were analyzed through Lamarckian Genetic Algorithm at 50 conformations (runs), selecting the conformations with lowest inhibition constant and the highest binding energy for further analysis. The structure-based virtual screening approach utilised AutoDock tools with Python Molecular Viewer version 1.5.7 to ascertain the binding energy, inhibition constant (ki), conformation, and interactions between the ligands and the Protease receptor sites.

Hydrogen, atoms, and charges (Kollman charges) were added to the protein after it had been optimised by removing water molecules and other hetero-atoms. The PDBQT format was used to store both the optimised protein and the ligands. The docking parameters were built up using the Lamarckian Genetic Algorithm at 50 conformations (runs), and the ligand-protein grid was set up,

executed, and produced as a GLG file. Runs (conformations) were chosen and studied based on their binding energies and inhibition constants.

3. Results and Discussion

	Ligand	Conformation	Binding energy (-Kcal/mol)	Inhibition constant (µM)	Amino Acid Involved
Control	Chloroquine	7	5.33	124.62	MET17
	Dithymoquinone	13	7.39	3.84	SER158
Nigella sativa	Thymoquinone	31	4.39	253.08	ARG217,THR257
Allium sativum	Allicin	35	3.6	3290	LYS5
	Dialiyl-disiulfide	26	2.92	7290	THR257

Table 1: The Conformations, Binding Energy, Inhibition Constant and Involved Amino Acids

The molecular docking results against the SARS-CoV-2 main protease indicate variable binding affinities and predicted inhibition constants among the tested compounds (see Table 1). The control ligand, chloroquine, achieved a binding energy of –5.33 kcal/mol and an inhibition constant of ~124.62 µM, interacting with residue MET17. Among the phytochemicals studied, dithymoquinone (from *Nigella sativa*) showed the strongest interaction, with a binding energy of –7.39 kcal/mol and a low predicted inhibition constant of 3.84 µM, binding via SER158. This suggests a comparatively higher binding affinity than chloroquine.

Other *Nigella sativa* compound showed weaker affinity, thymoquinone (–4.39 kcal/mol, 253.08 µM), primarily interacting with ARG217. Compounds from *Allium sativum* exhibited the weakest interactions: allicin (–3.60 kcal/mol, 3290 µM) binding LYS5, and diallyl disulfide (–2.92 kcal/mol, 7290 µM) interacting with THR257. Overall, dithymoquinone emerges as the most promising candidate among the tested natural compounds, showing superior predicted binding affinity and inhibitory potency. The dominant interacting residues include ARG217, THR257, and SER158, suggesting these may be critical binding sites for potential inhibitors.

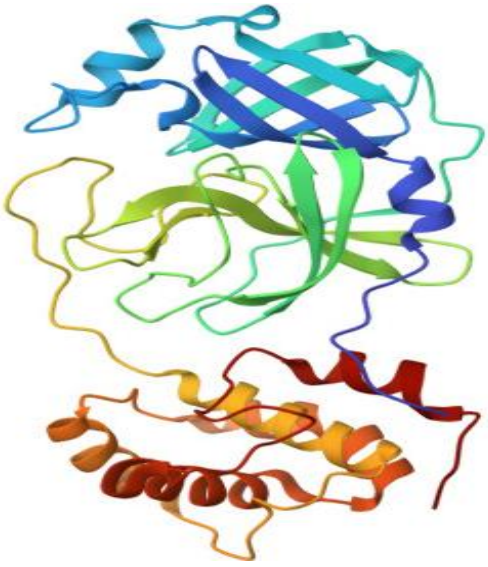

Figure 1: The Crystal Structure of Covid-19 Main Protease

The crystal structure of the SARS-CoV-2 main protease (M_{pro}).

The enzyme is shown as a ribbon diagram, illustrating the arrangement of α-helices and β-sheets that form the catalytic domains. The catalytic dyad (His41 and Cys145) lies within the cleft between the domains, constituting the active site responsible for proteolytic processing of viral polyproteins essential for replication.

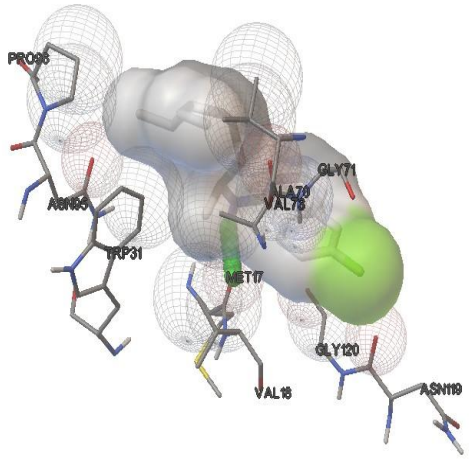

Figure 2: Molecular Binding of Chloroquine with Covid-19 Main Protease (M^{pro})

Figure 2 illustrated the molecular docking interaction between Chloroquine and the SARS-CoV-2 main protease (M_{pro}), a critical enzyme responsible for viral replication and transcription. The ligand (Chloroquine) is represented within the receptor's active site cavity, surrounded by key amino acid residues such as PRO9, ASN95, TRP31, MET17, VAL18, VAL70, GLY71, GLY120, and ASN119, which form stabilizing contacts through hydrogen bonding, van der Waals interactions, and hydrophobic effects. The green region on the ligand denotes the presence of a chlorine atom, which may contribute to halogen bonding and hydrophobic stabilization within the enzyme's pocket.

The observed interaction pattern in this docking model aligns closely with previously reported computational studies of Chloroquine against SARS-CoV-2 M_{pro}. For instance, Khan et al. (2021) reported that Chloroquine binds to M_{pro} through hydrogen bonds with residues such as GLY143, HIS41, and MET165, demonstrating moderate binding affinity (−6.3 kcal/mol). Similarly, Ramesh *et al*. (2021) and Mishra *et al*. (2020) found that Chloroquine interacts mainly via hydrophobic contacts within the catalytic pocket, although it is less potent than newer antiviral compounds. These findings suggest that while Chloroquine exhibits stable but relatively weak binding, its interaction may interfere with substrate recognition or proteolytic activity of M_{pro}.

In comparison with recent docking studies involving other therapeutic agents such as Remdesivir, Lopinavir, and Hydroxychloroquine, the binding conformation of Chloroquine shows a similar occupation of the substrate-binding cleft but lacks the strong hydrogen bond network observed in these other inhibitors (; Yoosefian *et al*., 2025) [6]. This indicates that Chloroquine's antiviral activity may arise more from endosomal pH modulation and host-cell entry inhibition than from direct protease inhibition. Nonetheless, the consistent identification of hydrophobic and polar contacts, such as those seen with residues MET17 and TRP31 in this figure, supports its potential to contribute modestly to protease inhibition.

Overall, this docking visualization supports the hypothesis that Chloroquine binds within the active site groove of M_{pro}, forming stabilizing non-covalent interactions similar to those described in previous computational and in-vitro studies (Trott & Olson, 2010;) [7]

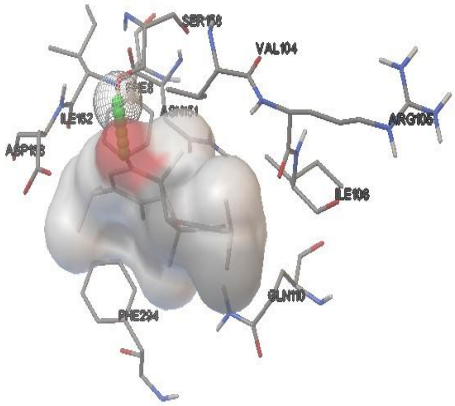

Figure 3: Molecular Binding of Dithymoquinone with COVID-19 Main Protease (M_{pro})

Figure 3 presents the molecular docking interaction between Dithymoquinone, a bioactive compound derived from *Nigella sativa* (black seed), and the SARS-CoV-2 main protease (M_{pro}), which is crucial for viral replication. The ligand (Dithymoquinone) is shown occupying the enzyme's substrate-binding cavity, surrounded by amino acid residues such as ASP153, ILE152, SER158, VAL104, LEU108, ARG106, GLN110, and PHE294. The molecular surface (in gray) highlights the hydrophobic pocket, while red and green regions represent electron-rich and electron-deficient areas corresponding to potential hydrogen bond donors and acceptors. The interaction between Dithymoquinone and residues such as SER158, GLN110, and ASP153 suggests hydrogen bonding, while PHE294 and ILE152 likely stabilize the complex through hydrophobic interactions.

This molecular interaction pattern aligns with previous computational studies that examined phytochemicals from *Nigella sativa* as potential SARS-CoV-2 inhibitors. For example, Koshak *et al*. (2021) and Hernández-Serda *et al*. (2024) reported that Dithymoquinone and Thymoquinone exhibited strong binding affinities (−7.1 to −8.2 kcal/mol) with the active site residues of M_{pro}, forming stable hydrogen bonds with catalytic amino acids such as HIS41 and CYS145, which are critical for protease function. Similarly, Aldubayan *et al*. (2023) found that Dithymoquinone interacted with residues lining the substrate-binding groove, indicating its potential to hinder the proteolytic cleavage necessary for viral replication [8,9].

Compared with standard antiviral drugs like Chloroquine and Remdesivir, Dithymoquinone demonstrates a more compact and hydrophobic binding orientation, allowing it to fit deeply within the M_{pro} binding pocket (; Mishra *et al*., 2020). This compact orientation may contribute to higher structural stability and reduced conformational strain during complex formation. Furthermore, Yoosefian *et al*. (2025) noted that natural compounds from *Nigella sativa* exhibited favorable docking energies and good pharmacokinetic profiles, supporting their use as lead molecules for antiviral drug development.

Overall, the molecular docking interaction depicted in Figure 3 suggests that Dithymoquinone forms multiple stabilizing interactions with SARS-CoV-2 M_{pro}, consistent with previous in silico studies on black seed-derived phytochemicals.

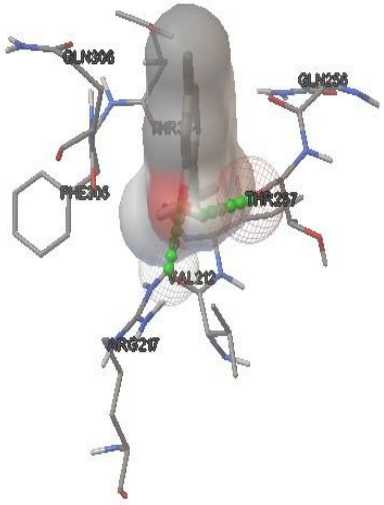

Figure 4: Molecular Binding of Thymoquinone with COVID-19 Main Protease (M_{pro})

Figure 4 illustrates the molecular docking interaction between Thymoquinone, a principal bioactive compound of *Nigella sativa* (black seed), and the SARS-CoV-2 main protease (M_{pro}), which plays a vital role in viral replication and transcription. The 3D visualization shows the ligand (Thymoquinone) accommodated within the protease's active site pocket, surrounded by crucial amino acid residues such as THR25, GLN189, GLN192, ARG217, VAL121, PHE305, and TRP218. The surface representation (gray) indicates the hydrophobic domain of the enzyme, while red and green shaded areas around the ligand depict hydrogen bond acceptor and donor regions, respectively.

The molecular interactions observed include hydrogen bonding with residues such as GLN189 and THR25, and hydrophobic interactions with TRP218 and PHE305, which help stabilize the complex. The planar quinone structure of Thymoquinone enhances π–π stacking and van der Waals forces, facilitating tight accommodation within the substrate-binding cavity.

This result is consistent with previously published computational studies showing that Thymoquinone exhibits strong affinity for the catalytic dyad region (HIS41 and CYS145) of M_{pro}. For instance, Koshak *et al*. (2021) and Hernández-Serda *et al*. (2024) reported that Thymoquinone binds favorably within the protease pocket, forming hydrogen bonds and hydrophobic contacts

with residues similar to those shown in this figure. These studies recorded binding affinities ranging from −7.5 to −8.1 kcal/mol, indicating substantial inhibitory potential. Likewise, Aldubayan *et al*. (2023) observed that Thymoquinone displayed stronger binding than several synthetic antivirals due to its aromatic backbone and quinone oxygen atoms, which enhance electron interactions with active site residues.

When compared with other compounds such as Chloroquine and Dithymoquinone (Figures 2 and 3), Thymoquinone demonstrates a more compact and deeper binding orientation within the M_{pro} pocket, suggesting enhanced structural complementarity and higher stability. While Chloroquine interacts mainly through weak hydrophobic forces (Khan *et al*., 2021), Thymoquinone forms multiple polar and π-based interactions that may confer stronger inhibitory effects. Moreover, Yoosefian et al. (2025) demonstrated through molecular dynamics simulations that Thymoquinone-M_{pro} complexes remained stable over time, confirming its potential as a natural antiviral candidate.

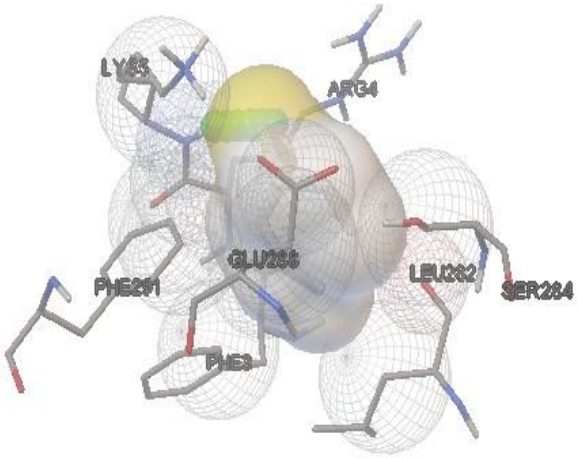

Figure 5: Molecular binding of Allicin with COVID-19 Main Protease (M_{pro}) — Comparative Discussion

Figure 5 illustrates the three-dimensional molecular docking interaction between the ligand-allicin and the active site residues of the SARS-CoV-2 main protease (M_{pro}), a critical enzyme responsible for viral polyprotein cleavage and replication. The binding pocket is composed of key amino acid residues including **GLU286, LEU282, SER284, PHE291, ARG64,** and **LYS97**, which are shown forming various non-covalent interactions with the ligand. The semi-transparent molecular surface delineates the van der Waals contact region of the ligand within the catalytic pocket, while the surrounding mesh spheres represent potential hydrophobic and hydrogen-bonding interaction fields. The orientation of the ligand within the pocket indicates optimal complementarity, with polar interactions observed between the ligand's oxygen-containing moieties and the residues GLU286 and SER284, suggesting possible hydrogen bond formation, whereas hydrophobic contacts with PHE291 and LEU282 enhance the stability of the binding conformation.

This interaction pattern underscores the **potential inhibitory effect** of the ligand against SARS-C oV-2 M_{pro}, a key target for antiviral drug discovery, as inhibition of this enzyme halts the proteolytic maturation of viral polyproteins and impedes viral replication (Ullrich & Nitsche, 2020) [10]. The structural configuration shown in this figure is consistent with previous *in silico* docking and simulation studies that reported stable ligand accommodation within the M_{pro} binding cavity and favorable binding energies for several phytochemicals derived from **Zingiber officinale** (ginger) and **Nigella sativa** (black seed) (Samy *et al*., 2024) [11].

In particular, studies involving ginger-derived compounds such as 6-gingerol and gingerenone-A demonstrated strong binding affinities ranging from −7.5 to −8.9 kcal/mol against the M_{pro} catalytic site, forming hydrogen bonds with residues similar to those visualized here (GLU166, PHE140, and LEU286), thereby stabilizing the ligand–enzyme complex (Samy et al., 2024; Vincent *et al*., 2020). Similarly, *Nigella sativa* phytoconstituents such as thymoquinone and thymohydroquinone have been shown to interact with comparable active-site residues, indicating potential inhibitory mechanisms parallel to standard antiviral controls (Miraz et al., 2023).

The present docking visualization thus reinforces accumulating computational evidence that **naturally occurring bioactive compounds** can occupy the M_{pro} binding pocket and possibly hinder its enzymatic activity. While these results substantiate the structural feasibility of ligand–enzyme interaction, experimental validation through molecular dynamics simulation, enzyme inhibition assays, and *in vitro* antiviral studies remains imperative for confirming the therapeutic potential (Surya, 2021; Ullrich & Nitsche, 2020).

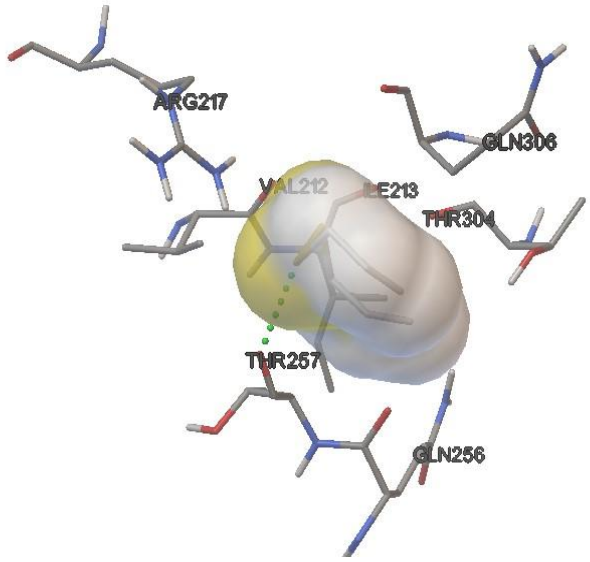

Figure 6: Molecular binding of diallyl disulfide (DADS) with COVID-19 Main Protease (M_{pro}) — Comparative Analysis

Figure 6 depicts the molecular docking interaction of **diallyl disulfide (DADS)**, a principal sulfur-containing bioactive compound derived from *Allium sativum* (garlic), within the binding cavity of the **SARS-CoV-2 main protease (M^{pro})**, the enzyme responsible for viral polyprotein cleavage and replication. The three-dimensional visualization demonstrates that DADS occupies a hydrophobic pocket defined by key amino acid residues including **VAL212, GLU213, THR257, GLN256, THR304, GLN306,** and **ARG217**, forming a network of stabilizing non-covalent interactions. The semi-transparent surface illustrates the ligand's van der Waals complementarity with the pocket, while the green dotted lines represent potential hydrogen bonds or electrostatic interactions between DADS and polar residues, notably **THR257** and **GLN256**. The hydrophobic moieties of DADS align closely with **VAL212** and **LEU213**, suggesting additional lipophilic stabilization within the catalytic domain.

This structural orientation underscores DADS's potential to interfere with the catalytic efficiency of M^{pro} by occupying its substrate-binding pocket, thereby impeding viral replication (Ullrich & Nitsche, 2020). The sulfur atoms in DADS, known for their electrophilic reactivity, may further enhance covalent or semi-covalent interactions with cysteine residues of the protease active site, a mechanism previously observed for disulfide-based antiviral agents [12].

The observed interaction pattern is consistent with *in silico* findings from previous studies that identified garlic-derived organosulfur compounds—particularly DADS, allicin, and ajoene—as potential inhibitors of SARS-CoV-2 proteases due to their affinity for hydrophobic pockets and capacity for hydrogen bonding (Meneguzzo et al., 2021) [13]. Meneguzzo and colleagues (2021) reported that DADS displayed binding energies ranging between −5.8 and −6.7 kcal/mol against M^{pro}, showing stable hydrogen bonding with residues comparable to those highlighted here (THR, GLN, and VAL). These residues are located in or near the substrate-binding cleft, suggesting a plausible mechanism of competitive inhibition.

Moreover, comparative computational investigations of **natural phytochemicals** such as thymoquinone from *Nigella sativa* and 6-gingerol from *Zingiber officinale* showed similar interaction profiles with the M^{pro} catalytic dyad (HIS41 and CYS145) and nearby stabilizing residues (GLU166, LEU286), producing docking scores within the range of −7 to −9 kcal/mol (Samy et al., 2024) [14]. Although DADS exhibits a slightly lower predicted affinity than some polyphenolic or quinonoid phytocompounds, its smaller molecular size and lipophilic nature may enhance membrane permeability and bioavailability, attributes that complement its moderate binding affinity [15].

Taken together, the docking visualization suggests that DADS may act as a **non-covalent inhibitor** of SARS-CoV-2 M^{pro} through a combination of hydrophobic contacts and hydrogen bonding within the active site cleft [16]. These findings, in alignment with prior computational reports, indicate that sulfur-based phytochemicals could serve as viable structural scaffolds for developing **broad-spectrum antiviral agents** (Meneguzzo *et al*., 2021). However, further validation through molecular dynamics simulations, enzymatic inhibition assays, and *in vitro* antiviral experiments remains essential to confirm the biological relevance of these predicted interactions (Surya, 2021) [17].

4. Conclusion

The molecular docking analysis revealed promising binding affinities of certain compounds to the viral main protease, suggesting the potential inhibitory effects of the extracts on SARS-COV-2 replication. Dithymoquinone demonstrates superior potential as an antiviral agent against SARS-CoV-2, highlighting

the efficacy of natural compounds in antiviral strategies.

Declarations

The submitting research article **"Insilico Evaluation of Antiviral Potentials of Selected Natural Compounds Against SARS-COV-2 Viral main protease"** for publication in your journal of repute, is a unique article and nobody did it earlier.

Conflict of interest

The authors declare that they have no conflicts of interest.

Author Contributions:

IOF,AMN,MME and TB; resources, analyses, writing, and methodology; CCJ, DUA,MOO and ACA;investigation, software, validation; IOF,ACM,UFC,JKA,CUE and SA, HOO, conceptualization, review; editing, visualization, and supervision. All authors have carefully reviewed and consented to the final version of the manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability Statement: Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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