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Literature Review: Exploration of Natural Compounds for the Development of SARS-CoV2 Antiviruses through Docking-ADMET

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Abstract

Purpose: This study aimed to investigate the antiviral potential of natural compounds against SARS-CoV-2 using an *in-silico* approach. The objective was to identify bioactive molecules from medicinal plants that effectively interact with viral target proteins and exhibit favorable pharmacokinetic and toxicity profiles.

Methodology/Approach: A systematic literature review was conducted on publications from 2020 to 2025 obtained from PubMed, ScienceDirect, and Google Scholar. Studies applying molecular docking and ADMET prediction targeting key SARS-CoV-2 proteins–namely, Mpro, PLpro, RdRp, and TMPRSS2–were selected. Docking simulations were performed using AutoDock Vina, AutoDockTools, and PyRx, and ADMET parameters were analyzed using SwissADME, pkCSM, admetSAR, and ProTox.

Results/Findings: Several compounds, including ginsenoside Rg2, azadirachtin A, Epigallocatechin Gallate (EGCG), curcumin, betulinic acid, and epicatechin-3-O-gallate, showed high binding affinities (-8. to-10. kcal/mol) and favorable pharmacokinetic and safety profiles, suggesting strong antiviral potential.

Limitations: This study is limited to computational predictions without experimental validation. Consequently, the biological efficacy of the compounds remains theoretical and requires further confirmation.

Contributions: This study integrates molecular docking and ADMET analysis to provide a comprehensive understanding of natural compounds as antiviral agents. It contributes to the development of safe, plant-based therapeutics and supports future *in vitro* and *in vivo* research.

Conclusions: The findings confirm that the selected natural compounds possess promising inhibitory activity and acceptable safety against SARS-CoV-2. Validation through experimental and clinical studies is necessary to establish their pharmacological potential.

Keywords: *ADMET Analysis, In Silico Study, Molecular Docking, Natural Compounds, SARS-CoV-2 Antiviral*

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1. Introduction

The COVID-19 pandemic caused by SARS-CoV-2 has had a major impact on public health and the global economy. The effectiveness of existing antivirals and vaccines, such as remdesivir and molnupiravir, remains limited, especially against newer and more resistant variants (Raman et al., 2023). This highlights the need to investigate safer and more effective alternative therapies. Natural compounds are known to have low toxicity profiles and contain bioactive metabolites that can target

key viral proteins, such as 3CLpro and PLpro (Amin, Lutfi, Salsabila, & Andri, 2024). Therefore, the exploration of natural product-based antiviral candidates continues to develop as a promising strategy (Lokwani et al., 2023).

In silico approaches have become a primary method for identifying potential antivirals from plant metabolites. These methods allow the rapid and efficient prediction of ligand–protein interactions, enabling the screening of many compounds in a short time (Amin, Lutfi, et al., 2024). ADMET (absorption, distribution, metabolism, excretion, and toxicity) analysis is also used to evaluate the pharmacokinetic feasibility and safety of drug candidates (Raman et al., 2023). The combination of these two approaches can reduce research costs at the early stages of drug discovery and accelerate the screening process (Lokwani et al., 2023). Thus, in silico methods play an important role in antiviral therapy innovation during and after the pandemic.

Several studies have reported natural compounds with the potential to inhibit key SARS-CoV-2 proteins. According to the study by Metwaly et al. (2024), several African-derived flavonoids show strong affinity for helicase and can inhibit viral replication. However, many studies have focused only on a single plant or a single type of compound without conducting a comprehensive comparison among other potential compounds (Bafandeh et al., 2023). In addition, in silico results are often not accompanied by comprehensive pharmacokinetic and toxicity assessments (Lokwani et al., 2023). This condition creates a data gap in the selection of antiviral candidates that are truly suitable for development. The novelty of this study lies in a comparative cross-medicinal plant approach with the integration of docking results and ADMET parameters.

This comprehensive analysis not only evaluates the strength of ligand–protein interactions but also considers bioavailability and potential toxicity (Bafandeh et al., 2023). This approach is important for formulating clinically viable antiviral candidates, especially in the face of continuously mutating SARS-CoV-2 variants (Raman et al., 2023). Based on this, this study makes a scientific contribution to the development of more effective and safer natural product-based therapies and supports the concept of drug repurposing (Lokwani et al., 2023). The objective of this study is to present a systematic review of docking and ADMET study results from various medicinal plants to identify the most promising natural compounds as SARS-CoV-2 antivirals. This study is expected to serve as a strong foundation for experimental studies in subsequent stages.

2. Literature Review and Hypothesis Development

2.1 In Silico Approach in Antiviral Drug Discovery

In silico approaches are computational methods that utilize molecular models to efficiently predict interactions between ligands and target proteins without requiring complex experimental stages. Molecular docking techniques are used to study ligand-protein binding affinity through binding free energy values, whereas ADMET analysis (Absorption, Distribution, Metabolism, Excretion, and Toxicity) is used to evaluate the pharmacokinetic aspects and safety of compounds (Oso, Olaoye, & Omeike, 2021). The integration of these two methods in Computer-Aided Drug Design (CADD) provides high efficiency in the early-stage screening of bioactive compounds from natural products.

By combining docking results and ADMET predictions, researchers can obtain a comprehensive overview of potential biological activity, bioavailability, and compound toxicity (Rahmadi, Andika, & Nashihah, 2021). The emphasis on computational methods is in line with various modern studies, including the Goodwood article, which emphasizes the importance of in silico approaches in the exploration of bioactive compounds (Amin, Azijah, & Gunawan, 2025)**.** This approach has become an important strategy for accelerating the discovery of effective and safe natural product-based drugs (Vardhan & Sahoo, 2020).

2.2 SARS-CoV-2 Protein Targets and Inhibition Mechanisms

SARS-CoV-2 has several important functional proteins that serve as primary targets in antiviral development, including the Main Protease (Mpro/3CLpro), Papain-Like Protease (PLpro), RNA-

dependent RNA Polymerase (RdRp), and host protease Transmembrane Serine Protease 2 (TMPRSS2). Mpro and PLpro play roles in processing viral polyproteins into functional enzymes required for replication, with residues HIS41, CYS145, and GLU166 on Mpro functioning as the main catalytic sites. Compounds that strongly interact with these residues have the potential to inhibit protease activity and suppress viral replication (Khatabi et al., 2021).

RdRp is an essential enzyme in genomic RNA synthesis, where inhibitors that bind strongly to its active site can inhibit the replication process. Meanwhile, TMPRSS2, which is present in host cells, plays a role in activating the spike protein and mediating viral entry into cells; its inhibition can prevent the membrane fusion process. Recent computational studies have shown that Mpro and PLpro are the most predictive targets for screening natural compounds, as discussed in the Goodwood article on the docking of herbal compounds against SARS-CoV-2 proteases (Amin, Andini, Alfarizi, & Pratomo, 2025). Overall, the inhibition of these proteins can disrupt the SARS-CoV-2 life cycle, forming a rational basis for the selection of molecular targets in in silico studies to assess the potential of natural bioactive compounds as viral inhibitors (Aqeel, Bilal, Majid, & Majid, 2022).

2.3 Potential of Natural Compounds as SARS-CoV-2 Antiviral Candidates

Bioactive compounds from medicinal plants have been widely studied for their antiviral activity against SARS-CoV-2 through mechanisms involving the inhibition of key proteins. Cozac, Medzhidov, and Yuki (2020) reported that ginsenoside Rg2 and azadirachtin A have binding energies of −10.7 kcal/mol against Mpro and exhibit good pharmacokinetic profiles. Najiah, Kusumaningsih, Amin, and Kamila (2025) found that Epigallocatechin Gallate (EGCG) from *Camellia sinensis* has an affinity of −9.0 kcal/mol toward Mpro and fulfills Lipinski's Rule of Five and is non-hepatotoxic. The compound epicatechin-3-O-gallate from *Psidium guajava* showed an energy value of −9.08 kcal/mol against 3CLpro with good oral absorption and low toxicity. Zubair et al. (2021) reported ar-curcumene from *Zingiber officinale* var. *rubrum*, which binds strongly to PLpro (−8.5 kcal/mol) and is stable in a 10 ns molecular dynamics simulation.

Furthermore, 1,3-O-dicaffeoylquinic acid from *Artemisia annua* has a binding energy below −9.0 kcal/mol against Mpro and shows an ADMET profile supporting high bioavailability and low toxicity. These results indicate that natural compounds have great potential to be developed as safe natural antivirals. Research from the Goodwood publisher also supports the potential of flavonoid and phenolic compounds as SARS-CoV-2 antivirals through docking against Mpro and PLpro, particularly in studies evaluating bay leaf flavonoids against 3CLpro (Amin, Heryanto, Athaya, & Fitri, 2025). In addition, Goodwood has also published computational studies of herbal compounds showing activity against SARS-CoV-2 proteases (Amin, Mustafidah, Nabila, & Maharani, 2025).

2.4 Comparison of Previous Studies

Comparison of previous research results is important to examine the relationship between compound binding strength to target proteins and their pharmacokinetic properties. In silico studies have shown that the lower the binding energy value, the more stable the ligand–protein interaction with SARS-CoV-2 proteins. However, the effectiveness of a compound also depends on its ADMET characteristics (Absorption, Distribution, Metabolism, Excretion, and Toxicity), which determine the compound's ability to function optimally in the body. Therefore, the combination of molecular docking analysis and ADMET prediction provides a more comprehensive approach for assessing the potential of natural antivirals.

Several previous studies have reported compounds from plants, such as *Panax ginseng*, *Camellia sinensis*, *Psidium guajava*, *Zingiber officinale* var. *rubrum*, and *Artemisia annua*, as having strong binding affinity and good ADMET profiles. Other Goodwood articles have also provided a comparative basis, particularly studies on the potential of natural bioactive compounds tested through docking and

analyzed using ADMET to evaluate pharmacokinetic feasibility (Amin, Supriatna, Ardian, & Abdurrahman, 2025). A summary of these research results is presented in Table 1.

Table 1. Summary of previous in silico studies on natural bioactive compounds against SARS-CoV-2 target proteins

No	Plant Source	Active Compound	Target Protein	ΔG Value (kcal/mol)	ADMET Profile	Reference
1	*Panax ginseng*, *Azadirachta indica*	Ginsenoside Rg2, Azadirachtin A	Mpro	−10.7	Non-toxic, good bioavailability	(Jin et al., 2020)
2	*Camellia sinensis*	EGCG	Mpro	−9.0	Non-hepatotoxic, complies with Lipinski's Rule	(Najiah et al., 2025)
3	*Psidium guajava*	Epicatechin-3-O-gallate	3CLpro	−9.08	Good oral absorption, low toxicity	(Rahmadi et al., 2021)
4	*Zingiber officinale var. rubrum*	Ar-curcumene	PLpro	−8.5	Safe, stable in 10 ns MD	(Suherman & Maulidya, 2023)
5	*Artemisia annua*	1,3-O-Dicaffeoylquinic acid	Mpro	< −9.0	Good pharmacokinetics, non-toxic	(Amin, Rianty, & Hidayat, 2024)

2.5 Research Gap and Direction

Although various studies have reported the potential of natural compounds as SARS-CoV-2 inhibitors, most studies are limited to the molecular docking stage without further validation through molecular dynamics simulations or biological testing (Arif, 2022). In addition, the relationship between binding energy values and pharmacokinetic parameters, such as absorption and toxicity, has not been widely discussed systematically. This gap indicates the need for a comparative approach that integrates docking and ADMET results to obtain a more complete picture of compound effectiveness and safety (Niazi, Magoola, & Mariam, 2024). Therefore, this study aimed to assess the relationship between binding affinity and pharmacokinetic feasibility to provide a rational basis for the development of effective and safe natural antiviral candidates (Amin, Pujiyani, Rusiyana, & Azzahra, 2025).

2.6 *Research Hypothesis*

Based on the theoretical review and previous research findings, it can thus be assumed that natural compounds with high binding affinity toward SARS-CoV-2 target proteins and ADMET profiles that support bioavailability and safety have great potential to be developed as natural antiviral candidates through the docking–ADMET approach.

3. Research Methodology

This study used a systematic literature review method to identify the potential of natural compounds as SARS-CoV-2 antivirals through computational analysis. Literature searches were conducted in three reputable databases, namely, PubMed, ScienceDirect, and Google Scholar, which provide relevant scientific publications in the fields of biomedicine, pharmacy, and computational chemistry. The publication year range used was 2020–2025 to ensure that the reviewed data correspond to the most recent developments in COVID-19 research. The search keywords included "natural compounds," "SARS-CoV-2 antiviral," "molecular docking," "ADMET analysis," and "in silico study." Article selection was based on the following inclusion criteria: studies evaluating the antiviral activity of natural

compounds against SARS-CoV-2 using molecular docking methods and ADMET analysis, availability in full-text form, and publication between 2020 and 2025.

Articles were excluded from the review if they did not present clear analytical data, were not relevant to the topic focus, or were not scientific publications, such as editorials and commentaries. To ensure research reproducibility, the software used in the selected articles was also recorded, including AutoDock Vina/AutoDockTools to analyze the binding strength between ligands and viral proteins, as well as SwissADME and pkCSM to predict the compounds' behavior in the body and their safety. All data were analyzed descriptively to link ligand–protein interaction results with the pharmacokinetic and toxicity profiles of the studied compounds.

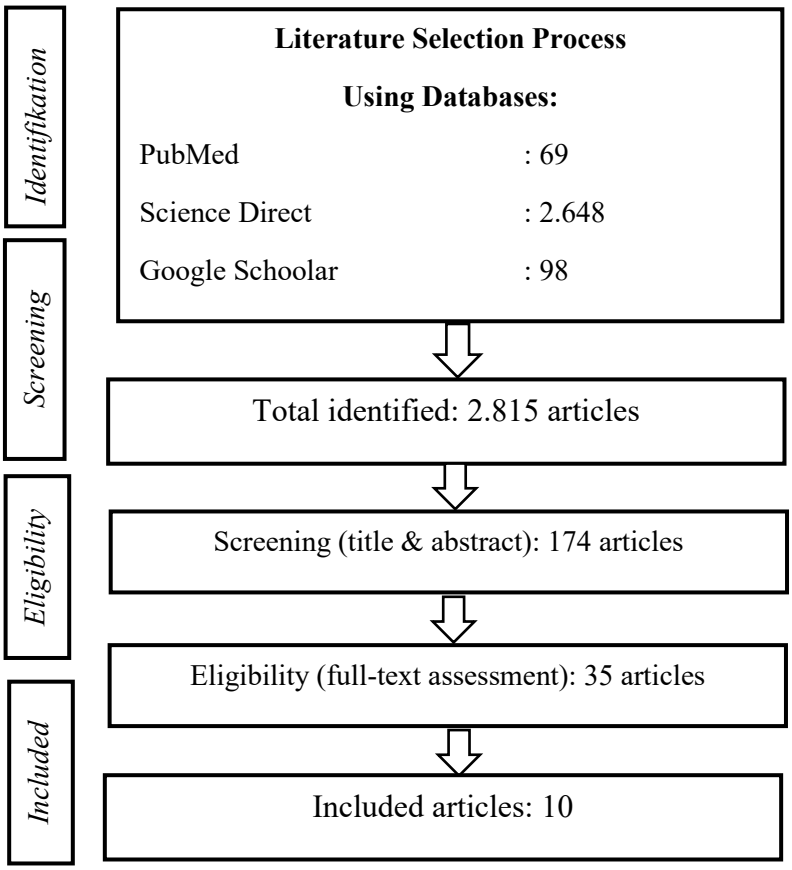

Figure 1. PRISMA flowchart of the literature search

4. Results and Discussion

The discovery and development of natural compound-based antiviral candidates against SARS-CoV-2 is a complex process that requires significant time and financial resources. To optimize this process, in silico approaches are widely employed, as they can efficiently accelerate the identification and evaluation of bioactive compounds. This method integrates molecular docking techniques, which predict the binding strength between natural ligands and viral target proteins, with ADMET analysis (Absorption, Distribution, Metabolism, Excretion, and Toxicity), which evaluates the pharmacokinetic properties and safety of compounds.

Based on the conducted literature review, several studies have reported the potential of natural compounds from various medicinal plants as antiviral candidates against SARS-CoV-2. Each study applied a combination of molecular docking and ADMET methods to assess inhibitory activity against key viral proteins, including Main Protease (Mpro/3CLpro), Papain-Like Protease (PLpro), RNA-dependent RNA Polymerase (RdRp), and host protease, Transmembrane Protease and Serine 2 (TMPRSS2). A summary of the findings from these ten studies is presented in Table 2.

Table 2. Summary of in silico studies on natural compounds as potential SARS-CoV-2 antivirals

No.	Tested Plant(s)	Main Active Compound(s)	Methods (Molecular Docking & ADMET)	Key Findings Against SARS-CoV-2	Reference
1	*Panax ginseng Bupleurum falcatum*, *Glycyrrhiza-glabra*,*Azadi-rachta indica*	GinsenosideRg,Saikosaponin A, Glycyrrhizin, Azadirachtin A	Molecular Docking (AutoDock Vina) against Mpro, PLpro, RdRp; MD Simulation; ADMET (SwissADME, pkCSM)	Ginsenoside Rg2 and azadirachtin A showed strong binding to the Mpro active site (ΔG −10.7 kcal/mol) with high complex stability. ADMET analysis confirmed favorable pharmacokinetics and safety, indicating potential inhibition of viral replication.	Jin et al. (2020)
2	*Azadirachta indica* (*Nimba) Glycyrrhiza glabra (Akar Manis*)	Limonin, Maslinic acid, Urso-lic acid, Obacu-none	Molecular Docking (AutoDock Vina) on 3CLpro, PLpro, Spike; ADMET (pkCSM, BOILED-Egg)	Obacunone and maslinic acid exhibited the highest binding energies (~ −10 kcal/mol) to 3CLpro and PLpro. Strong affinity combined with good ADMET profiles suggests that they have high potential as SARS-CoV-2 protease inhibitors.	Vardhan and Sahoo (2020)
3	*Moringa oleifera (Daun Kelor) Zingiber office-nale*, *Artemi-sia annua*	Niazirin, Moringyne, Quercetin	Molecular Docking (AutoDock 4.2) on TMPRSS2; ADMET (admetSAR 2.0)	Niazirin and moringyne strongly bind to TMPRSS2 (ΔG −8.23 kcal/mol) and inhibit host protease, which is critical for spike protein activation. ADMET analysis supports high permeability and safety, highlighting their potential as host-targeted antiviral agents.	Oyedara et al. (2021)
4	*Curcuma longa (Kunyit), Camellia sinensis (Teh Hijau*)	Curcumin, Epi-gallocatechin gallate (EGCG), Catechin	Molecular Docking (AutoDock Vina) against Mpro (PDB 6LU7); ADMET validation (SwissADME, pkCSM)	kcal/mol) for Mpro, inhibiting the Main Protease of SARS-CoV-2 with good ADMET profiles and low toxicity, making them promising natural antivirals.	Bharadwaj et al. (2021)
5	*Azadirachta indica (Nim-*	Betulinic acid, Saikosaponin	Molecular Docking (PyRx, AutoDock	BA and Sa exhibited strong binding (−9.5 to	Oso et al. (2021)

	ba), Panax ginseng (Ginseng), Bupleurum falcatum (Saiko)	A, Glycyrrhizin, Soyasapogenol C	Vina) on Mpro, PLpro, RdRp; ADMET (pkCSM)	−10.2 kcal/mol) and stable interactions with the Mpro and RdRp catalytic residues. ADMET analysis indicated good bioavailability and synergistic antiviral replication inhibition.	
6	*Psidium guajava L. (Daun Jambu Biji)*	Epicatechin-3-O-Gallate, Glycitin, Ononin	Molecular Docking (AutoDockTools 4.2.6); ADMET (pkCSM)	Epicatechin-3-O-gallate had the highest affinity for 3CLpro (ΔG −9.08 kcal/mol), forming strong bonds with GLU166 and CYS145, potentially inhibiting viral replication.	Rahmadi et al. (2021)
7	*Ocimum basilicum L. (Kemangi/ Basil)*	Apigenin-7-glucu-ronide, Dihydrokaempferol-3-glucoside, Aesculetin	Molecular Docking & ADMET (pkCSM, ProTox)	Apigenin-7-glucuronide and dihydrokaempferol-3-glucoside showed high affinity toward Mpro (ΔG −8.96 to −8.77 kcal/mol), good intestinal absorption, and low toxicity.	Kurnia et al. (2023)
8	*Azadirachta indica (Daun Nimba/ Neem)*	Myricetin, Quercitrin, Hyperoside, Rutin, Isomargolonone	Molecular Docking (AutoDock 1.5.6); ADMET (pkCSM)	Myricetin and isomargolonone exhibited the lowest ΔG values against RdRp and Mpro (−6.41 to −8.17 kcal/mol), with good solubility and bioavailability.	Masduki, Tilaqza, and Damayanti (2024)
9	*Zingiber officinale var. rubrum (Jahe Merah)*	Ar-curcumene, α-Zingiberene, β-Sesquiphellandrene	Molecular Docking (AutoDock Vina), ADMET (PreADMET), MD Simulation (OpenMM 10 ns)	Ar-curcumene showed the best affinity for PLpro (ΔG −8.5 kcal/mol); the complex remained stable during MD simulation and met safety criteria.	Suherman and Maulidya (2023)
10	*Artemisia annua L. (Artemisin)*	1,3-O-Dicaffeoylquinic acid, Methyl-3,4-di-O-caffeoy-	Molecular Docking & ADMET (pkCSM, CHEMAIRS)	1,3-O-Dicaffeoylquinic acid exhibited a very high affinity for Mpro (< −90), indicating strong	Amin, Rianty, et al. (2024)

		lquinic acid, Dauceterol		inhibition of viral protease activity.	

4.1 Molecular Docking Results

The results of a review of ten *in silico* studies conducted between 2020 and 2025 indicate that natural compounds have high potential as primary inhibitors of SARS-CoV-2 proteins. The main target proteins in various studies include Main Protease (Mpro), Papain-Like Protease (PLpro), RNA-dependent RNA polymerase (RdRp), and the host protease, Transmembrane Protease and Serine 2 (TMPRSS2). The binding energy values obtained from molecular docking simulations range from −8.17 to −10.7 kcal/mol, indicating that most compounds are capable of strong interactions with the catalytic residues of the target proteins.

Compounds belonging to the triterpenoid and saponin groups have the highest affinities. Ginsenoside Rg2 derived from *Panax ginseng* and azadirachtin A from *Azadirachta indica* showed binding energy values of −10.7 kcal/mol against the Mpro protein (Jin et al., 2020). This high affinity is associated with the ability of the hydroxyl and glycoside groups to form multiple hydrogen bonds with residues HIS41 and CYS145. Similar results were obtained in a study by Oso et al. (2021), in which Betulinic acid and Saikosaponin A showed binding energies of −10.2 kcal/mol against Mpro and RdRp. These values indicate that triterpenoid and saponin compounds have potential as multi-target inhibitors capable of inhibiting more than one key enzyme in viral replication.

Meanwhile, compounds from the polyphenol and flavonoid groups also showed competitive affinities. *Curcumin from Curcuma longa and epigallocatechin gallate (EGCG) from Camellia sinensis exhibited binding energies ranging from −8.9 to −9.7 kcal/mol against Mpro* (Bharadwaj et al., 2021). These interactions were formed through strong hydrogen bonds with residues GLU166 and HIS41, supported by π–π stacking interactions on the aromatic rings of the compounds. This mechanism enhances the stability of the protein–ligand complex and has the potential to inactivate the proteolytic activity of the virus.

In addition to these two groups, studies have also identified the role of flavonoid compounds derived from *Psidium guajava* and *Ocimum basilicum*. Epicatechin-3-O-gallate showed a binding energy of −9.08 kcal/mol against 3CLpro with strong interactions at residues GLU166 and CYS145 (Rahmadi et al., 2021). Meanwhile, apigenin-7-glucuronide produced a value of −8.96 kcal/mol, indicating similar complex stability (Kurnia et al., 2023). These results demonstrate that flavonoid compounds are not only active against the Main Protease but also possess stable binding profiles toward various other viral targets. Several studies have proposed inhibitory approaches that target host proteins. Niazirin and moringine from *Moringa oleifera* targeted TMPRSS2, an enzyme involved in the activation of the SARS-CoV-2 spike protein, with binding energy values of −8.23 kcal/mol (Oyedara et al., 2021).

This approach provides a new perspective in the development of natural antivirals based on host-targeted therapy, which can reduce the risk of resistance due to viral mutations. These results are consistent with the study by Hoffmann et al. (2020), who demonstrated that TMPRSS2 inhibitors effectively inhibit SARS-CoV-2 infection in human lung epithelial cells. Overall, the molecular docking results indicate that ginsenoside Rg2, betulinic acid, azadirachtin A, curcumin, EGCG, and epicatechin-3-O-gallate have the lowest binding energy values with high binding stability; thus, they can be considered potential candidates for the development of natural product-based antiviral drugs (Mangas-Sanjuan et al., 2020).

4.2 ADMET Parameter Analysis

The pharmacokinetic properties and toxicity of the compounds were evaluated using SwissADME, pkCSM, and ProTox platforms. The analysis showed that most compounds met Lipinski's Rule of Five criteria, with molecular weights below 500 Da, logP values <5, and an appropriate number of hydrogen bond donors and acceptors (Purdey, Miller, & Bowden, 2020). These parameters indicate good pharmacokinetic feasibility and the possibility of optimal oral absorption. Compounds such as

curcumin, EGCG, and Epicatechin-3-O-gallate exhibited the best ADMET profiles because they are non-hepatotoxic, non-mutagenic, and have high membrane permeability.

This indicates high safety potential and good biological penetration ability, supporting their use as natural antiviral agents (Bharadwaj et al., 2021; Rahmadi et al., 2021). In contrast, triterpenoid compounds such as Ginsenoside Rg2 and Azadirachtin A have relatively large molecular sizes, which may affect oral absorption, although they still show sufficient bioavailability based on pkCSM predictions (Jin et al., 2020). In addition, volatile compounds such as Ar-curcumene from *Zingiber officinale* var. *rubrum* have advantages in terms of metabolism and toxicity. Based on 10 ns molecular dynamics simulations, the protein–ligand complexes showed high stability without significant fluctuations (Suherman & Maulidya, 2023). Overall, the analysis results indicate that none of the compounds exhibited carcinogenic potential or significant systemic toxic effects, making them suitable for subsequent *in vitro* and *in vivo* testing stages.

4.3 Comparative Discussion

Based on the comparative results, ginsenoside Rg2, betulinic acid, and azadirachtin A showed the best binding affinity toward Mpro with energies below −10 kcal/mol. This group of compounds possesses long glycoside chains and hydroxyl groups, enabling the formation of multiple hydrogen bonds with the catalytic residues, HIS41 and CYS145. This mechanism has proven effective in inactivating viral proteolytic enzymes that play an essential role in RNA replication (Jin et al., 2020; Oso et al., 2021). Meanwhile, polyphenol and flavonoid compounds, such as curcumin, EGCG, and epicatechin-3-O-gallate, exhibit moderate affinity but excel in terms of bioavailability and toxicological safety. Their favorable ADMET profiles make these compounds ideal for the development of natural oral formulations that function dually as antivirals and immunomodulators.

The inhibitory mechanisms exhibited by flavonoids tend to involve non-covalent interactions within the catalytic pocket of Mpro, contributing to complex stability without causing toxic side effects. Interestingly, compounds targeting TMPRSS2, such as niazirin and moringine, demonstrate an alternative approach to inhibiting viral infection. This host-targeted therapy approach opens opportunities for the development of natural antivirals with dual mechanisms of action, targeting both viral and host proteins. In addition, 1,3-O-Dicaffeoylquinic acid from *Artemisia annua* showed an affinity value < −9.0 kcal/mol with a good ADMET profile (Amin, Lutfi, et al., 2024). The presence of dual caffeoyl groups is believed to enhance the compound's ability to form multiple hydrogen bonds that strengthen the stability of the protein ligand complex.

4.4 Analysis of Binding Energy Data

A comparison of the binding energy values among the main compounds is presented in Table 2. These values serve as the basis for determining the relative affinity levels of each compound toward SARS-CoV-2 target proteins.

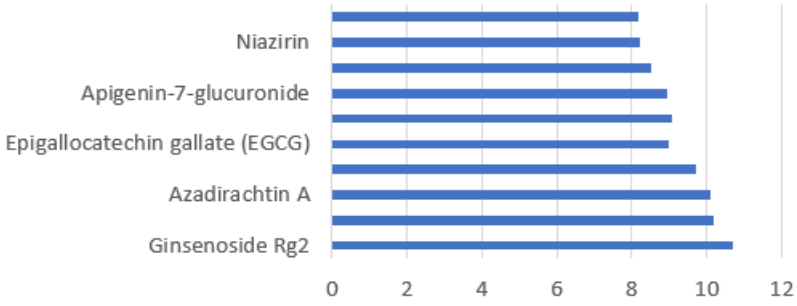

Figure 2. Comparison of Binding Energy Values of Compounds against SARS-CoV-2 Target Proteins

These data indicate that the lower the binding energy value, the greater is the ability of a compound to interact with the target protein. Compounds with energies below −10 kcal/mol (ginsenoside Rg2, betulinic acid, and azadirachtin A) are categorized as having very strong affinity. To support visual analysis, these values can be presented in the form of a bar chart, with the X-axis representing compound names and the Y-axis showing the binding energy (kcal/mol).

4.5 Implications and Future Research Directions

The integration of molecular docking results and ADMET analysis provides a comprehensive understanding of the potential of natural compounds as SARS-CoV-2 antiviral candidates. This approach enables the efficient initial screening of thousands of natural compounds without requiring direct biological testing. However, because the obtained results are still predictive in nature, subsequent stages should include experimental validation through *in vitro* and *in vivo* tests to confirm the actual biological activity and toxicological safety of the compounds. Long-term molecular dynamics simulations should also be conducted to assess the stability of protein–ligand interactions under more complex physiological conditions (Rudrapal et al., 2022).

Furthermore, to enhance the bioavailability of high-molecular-weight compounds, such as triterpenoids and saponins, formulation strategies based on nanoparticles, liposomes, or targeted delivery systems may be considered. This approach not only improves absorption but can also enhance overall pharmacological effectiveness. In general, the results of this study reinforce the great potential of natural compounds as natural antiviral agents that act through multi-target inhibitory mechanisms. The combination of binding strength, molecular stability, and favorable pharmacokinetic profiles forms a rational basis for the development of safe, effective, and sustainable natural product-based therapies.

5. Conclusions

5.1. Conclusion

Based on the results of the literature review and in silico analyses utilizing molecular docking and ADMET approaches, several natural compounds were identified as promising antiviral candidates against SARS-CoV-2. Among the most promising compounds Epigallocatechin Gallate (EGCG) from Camellia sinensis, curcumin from Curcuma longa, and betulinic acid from Azadirachta indica these exhibited strong binding affinities (≤ −9.0 kcal/mol) towards key viral proteins, including Mpro, PLpro, RdRp, and TMPRSS2, alongside favorable ADMET profiles that suggest good bioavailability. These findings demonstrate that the combination of strong binding energies, stability of protein–ligand complexes, and pharmacokinetic feasibility positions these compounds as viable candidates for further development as natural antiviral drugs. Furthermore, the study underscores the significant role of computational methods in accelerating the identification of natural active compounds, contributing to the potential development of safe and effective herbal antiviral therapies.

5.2. Research Limitations

This review has certain limitations that should be considered. Firstly, the analysis is based solely on in silico methods, meaning the findings are theoretical and require biological validation through experimental studies. The molecular docking and ADMET analyses involved variations in algorithms, parameters, and software (such as AutoDock, PyRx, SwissADME, and pkCSM), which may lead to discrepancies in affinity values and pharmacokinetic interpretations, thus limiting the consistency of the comparative results across different studies. Additionally, some reviewed studies lacked advanced simulations, such as molecular dynamics or in-depth toxicity evaluations, which leaves the stability of protein–ligand interactions and the safety aspects of the compounds unverified.

5.3. Suggestions and Directions for Future Research

To overcome the limitations mentioned, future research should focus on integrating experimental validation (both in vitro and in vivo) with computational studies to confirm the effectiveness and safety of natural antiviral compounds. It is also crucial to develop more advanced computational models by incorporating molecular dynamics simulations, artificial intelligence, and omics-based data analysis.

These improvements are expected to enhance the predictive accuracy of in silico methods and provide a more solid scientific foundation for the development of clinically applicable and safe natural antiviral therapies. Furthermore, exploring nanoparticle-based delivery formulations for these compounds could enhance their bioavailability and efficacy in clinical settings, thereby facilitating their transition into standardized antiviral treatments.

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Author Contributions

HTA Conceptualization, study design, data collection, manuscript drafting, and revision. AAW Data collection, analysis, manuscript drafting, and revision. SA Supervision, analysis, manuscript revision, and final approval.

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