

Molecular Docking Assessment of Antiviral Potential of Tea Formulated from Local Spices against Human Metapneumovirus (hMPV)

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Abstract

Human metapneumovirus (hMPV) is a globally significant respiratory pathogen with no approved specific antiviral treatment. This study conducted an *in silico* biochemical evaluation of eleven bioactive compounds derived from local culinary spices, aiming to identify potential therapeutic agents against hMPV. Physicochemical profiling revealed that compounds such as β -caryophyllene, squalene, and stigmasterol exhibited high lipophilicity ($\log P > 4.5$), low topological polar surface area (TPSA $< 30 \text{ \AA}^2$), and zero hydrogen bond donors/acceptors, suggesting strong membrane permeability and potential interaction with viral lipid envelopes. Conversely, hydrophilic compounds like glucaric acid and mannitol demonstrated high TPSA ($> 90 \text{ \AA}^2$) and multiple hydrogen bonding sites, which, while limiting membrane permeability, may contribute to immunomodulatory effects. Molecular docking in this study indicated that squalene (-19.6 kcal/mol) and stigmasterol (-11.2 kcal/mol) had the highest binding affinities towards hMPV Toll-Like receptor-4, (a glycoprotein that primarily recognizes the viral Fusion protein), driven primarily by hydrophobic and van der Waals interactions. Pharmacokinetic predictions showed favorable gastrointestinal absorption across most compounds, with minimal P-glycoprotein interaction and negligible cytochrome P450 inhibition, reducing the risk of drug-drug interactions. Toxicity assessments predicted non-mutagenicity and non-cytotoxicity for all compounds; however, squalene and stigmasterol showed minimal neurotoxicity, cardiotoxicity, and immunotoxicity, warranting further formulation strategies to mitigate any adverse outcome. Drug-likeness evaluation, based on Lipinski's Rule of Five and Veber's criteria, identified β -caryophyllene, vanillin derivatives, and glucaric acid as optimal candidates due to their balance of solubility, permeability, binding efficiency, and safety. The predicted LD₅₀ for most compounds was

1190 mg/kg, classifying them as moderately safe. These findings support the potential of local spice-derived phytochemicals as therapeutic leads against hMPV, with β -caryophyllene and vanillin derivatives recommended for further experimental validation. These findings reinforce the position that natural compounds with suitable structural features can interact effectively with both viral and immunological targets, offering a dual mechanism of antiviral action direct inhibition and immune modulation. While this research establishes a foundation for the development of phytochemical-based therapeutics against human metapneumovirus (hMPV), the promising results warrant further experimental validation, including *in vitro* antiviral assays and *in vivo* pharmacodynamic studies, to fully harness the therapeutic potential of these locally sourced phyto-therapeutic compounds thereby affirming the computational predictions.

Keywords

Molecular Docking, Antiviral, Tea, Local-Spices, Human-Metapneumovirus (hMPV)

1. Introduction

Human Metapneumovirus (hMPV) is an enveloped, single-stranded negative-sense RNA virus that primarily affects the respiratory tract. It has been recognized as a significant cause of respiratory infections, particularly in young children, the elderly and immunocompromised individuals [1] with no approved vaccines or targeted antiviral therapies currently available. Human Metapneumovirus (hMPV) is an important respiratory pathogen that belongs to the *Pneumoviridae* family, genus *Metapneumo virus*. First isolated in 2001 from respiratory samples of young children in the Netherlands [1], studies revealed that hMPV is closely related to Avian Metapneumovirus (AMPV), and it is now recognized as the second most common cause of lower respiratory tract infections (LRTIs) in infants and young children, following Respiratory Syncytial Virus (RSV) [2] [3]. The hMPV has a global distribution and exhibits seasonal peaks similar to other respiratory viruses, typically circulating during the late winter to early spring in temperate climates [4]. Serological studies have shown that nearly all children are infected with HMPV by the age of five, and reinfections are common throughout life [5].

Clinically, HMPV infection can cause a range of symptoms from mild upper respiratory tract illness (e.g., cough, rhinorrhea) to more severe LRTIs such as bronchiolitis and pneumonia. It can exacerbate underlying conditions such as asthma and chronic obstructive pulmonary disease (COPD), and is particularly severe in infants, the elderly, and immunocompromised patients [6]. In immunocompromised individuals, including transplant recipients and cancer patients, HMPV can lead to severe complications and increased mortality [7]. The hMPV genome encodes nine proteins, including surface glycoproteins such as the fusion

(F) protein, attachment (G) protein, and small hydrophobic (SH) protein. Among these, the F protein plays a critical role in viral entry by mediating fusion of the viral and host cell membranes, making it a major target for vaccine and antiviral drug development [8]. Despite its global burden, there are currently no approved vaccines or specific antiviral agents available for the treatment of HMPV; treatment remains supportive, and prevention is limited to infection control practices. The lack of effective therapeutics highlights the urgent need for novel drug discovery efforts targeting HMPV, including the application of *in silico* approaches to identify natural product-based inhibitors of key viral proteins.

Natural products from medicinal plants and spices, have historically served as valuable resources for drug discovery and development. Spices commonly used in traditional African medicine, such as *Piper guineense* (West African black pepper) or “Uziza” in Nigeria, is widely used as a spice and a medicinal plant across West Africa. It is rich in bioactive compounds such as piperine and essential oils, including beta-caryophyllene and linalool, which exhibit antioxidant, antimicrobial, and anti-inflammatory properties. It is reportedly effective in treating gastrointestinal disorders, respiratory infections, and as a stimulant for immune modulation. Additionally, it has shown potential antiviral activity, making it a candidate for *in silico* studies against HMPV [9]. *Tetrapleura tetraptera* commonly referred to as “Aidan fruit” or prekese, is another medicinal plant commonly used in traditional African medicine. Its pods are used for soup preparation and as a remedy for various ailments. Bioactive compounds such as flavonoids, tannins, and saponins present in *Tetrapleura tetraptera* have been reported to have antioxidant, antimicrobial, and anti-inflammatory effects. It has also been traditionally used for respiratory diseases and immune support, making it a promising spice for antiviral studies and applications [10]. *Xylopi aethiopica* (commonly called Ethiopian pepper or “Uda” in Igbo language), is an aromatic spice used in food seasoning and traditional medicine. It contains bioactive phytochemicals such as alkaloids, terpenoids, and polyphenols, which are known for their antimicrobial, antioxidant, and anti-inflammatory properties. Research has also linked some of its active compounds with antiviral effects, demonstrating potential against respiratory pathogens [11]. *Allium sativum* (garlic) is a globally recognized spice with potent medicinal properties. Its bioactive compounds, such as allicin, ajoene, and diallyl disulfide, are known for their antimicrobial, antiviral, and antioxidant activities. Garlic is widely used to boost immune function and fight infections, including respiratory diseases. Allicin, in particular, has been studied extensively for its potential to inhibit viral replication by interfering with viral entry and protein synthesis [12]. *Ocimum gratissimum* (Scent leaf) is an aromatic herb famous for its culinary and medicinal applications. Rich in essential oils like eugenol and thymol, it has demonstrated antimicrobial, antifungal, and anti-inflammatory properties. Traditional use includes treating respiratory infections, fevers, and digestive disorders. The spice is also known for boosting immunity and has been suggested for antiviral research due to its bioactive compounds [13]. *Zingiber offici-*

nale (ginger) is renowned for its culinary and medicinal uses globally. Bioactive compounds such as gingerol, shogaol, and paradol are responsible for its antioxidant, anti-inflammatory, and antimicrobial properties. Ginger is extensively used for managing respiratory illnesses, nausea, and inflammation. It has shown promising antiviral activity against enveloped viruses, which makes it a candidate for further evaluation against HMPV [14]–[16]. The notable antimicrobial, anti-inflammatory, antioxidant properties of these spices make them promising candidates for *in silico* screening against viral targets like the HMPV. Molecular docking and pharmacokinetic prediction tools allow for the efficient screening of large compound libraries, providing insights into binding affinities and potential mechanisms of action while reducing time and costs [17]. By leveraging these *in silico* tools, the bioactive constituents of traditional spices can be evaluated for their therapeutic potential against identified viral targets.

Statement of problem: the lack of targeted antiviral therapies, high cost and side effects of broad spectrum antivirals coupled with the time-intensive nature of conventional drug discovery highlight the need for computational approaches to prioritize lead compounds. *In silico* methods, offer a cost-effective strategy to screen spice-derived compounds for binding affinity, stability, and drug-likeness. This study addresses these gaps by identifying bioactive compounds from these spices with potential anti-HMPV activity, evaluating their interactions with critical HMPV targets to predict inhibitory mechanisms and assess their safety, bioavailability, and toxicity profiles to prioritize candidates for experimental validation.

This study aimed at evaluating the antiviral potential of tea formulated from local spices against human metapneumovirus HMPV *in silico* using molecular docking tools.

2. Methods

2.1. Sample Collection and Preparation

Piper guineense, *Tetrapleura tetraptera*, *Xylopii* *ethiopica*, *Allium sativum*, *Ocimum gratissimum* and *Zingiber officinale* were purchased from Swali market, Yenagoa, Bayelsa State. All the spices were formulated into tea using the method of [18]. Tea was formulated from the plant powder by thoroughly mixing the powder spices on ratio of 1:1. One gram each of the powder spices was mixed together. The mixed spice was thereafter used to formulate a tea by method of decoction as reported by [18].

2.2. Gas Chromatography-Mass Spectrometry (GC-MS) Analysis

Gas chromatography-mass spectrometry with flame ionization detector was utilized to analyze and identify volatile bioactive compounds present in the formulated tea.

GC-MS analysis of the “formulated tea” was performed using Shimadzu GC-MS—QP2010 PLUS as previously described by [18].

2.3. Assessment of Physicochemical and Pharmacokinetics Characteristics of the Bioactive Compounds

The formulated tea extract was investigated for metabolites (Piperine, chavicine, flavonoids, alkaloids, tannins, saponins, terpenoids, essential oils phenolic compounds, steroids, triterpenoids Xylopic acid, kaurenoic acid, phenolics, Allicin, ajoene, alliin, diallyl sulfide, diallyl disulfide, s-allyl cysteine, flavonoids, saponins eugenol, thymol, Gingerol, shogaol, paradol, zingerone) according to the established procedures as reported by [19].

2.4. Prediction of Target and ADMET Properties of the Ligands

This was done using the online programme ADMET lab 3.0 and SWISSADME [20]; the absorption, distribution, metabolism, excretion and toxicity (ADMET) properties of the ligands employed in this study were predicted. The different ADMET properties of the ligands were predicted using the different canonical strings or Simplified Molecular-Input Line-Entry System (SMILES) strings of the different ligands retrieved from the PubChem web platform (<https://www.ncbi.nlm.nih.gov/pccompound>) in their 3D conformation. All the relevant parameters, including Lipinski's rule of five and the Ghose parameters were recorded. Using the SWISS target prediction tool, the target of the different ligands was determined [21].

2.5. Target Proteins Properties, Selection and Molecular Docking

The target protein for this study (TLR-4) was derived from the Research Collaborator for Structural Bioinformatics Protein Data Bank (RCSB-PDB). The RCSB-PDB is a comprehensive web resource that provides the three-dimensional structural data of biological macromolecules, including proteins and nucleic acids [22]. The protein-ligand interaction in this study was determined through the use of PyRx while Discovery studio (version 3.0) was used for visualization of the interaction. The proteins were prepared for interaction using the Chimera software by the removal of water molecule, heteroatoms and ligands. After the preparation, the proteins were docked against the various ligands using PyRx. The chemical compounds obtained from the results of GCMS analysis were subjected to molecular docking with some anti-viral protein targets thalidomide respectively were obtained from the PubChem database.

2.6. Target Identification

Swiss target database was used to identify potential protein target related to Human metapneumovirus for ligands found in the formulated tea. PubChem was used to obtain the structure of the ligand especially the SMILE. Genecard database was used to obtain disease target with Uniprot ID while Venny web saver was used to predict the gene interactions between pneumonia-like related genes and genes that the ligands bind to. Strings were used to obtain network of genes interactions or the gene hub. Network from strings was exported to cytoscape 3.0 to obtain gene hub. Cytoscape app 3.0 was used for gene-gene interact, gene-protein inter-

action, protein-protein interaction network. Shiny GO was used for gene ontology to analyze the cellular component, biological component or molecular component interaction.

2.7. Compound Profiling

Compound profiling was used to assess the pharmacological properties of formulated chemical constituents, particularly their ability to modulate anti-viral targets. Phytochemical analysis was used to identify and quantify the bioactive compounds in the formulated tea. Target interaction study was utilized for molecular docking simulations to evaluate how the compounds interacted with specific viral proteins which helped to predict binding affinities and potential inhibitory effects.

3. Results and Discussion

3.1. GC-MS Profile

GC-MS analysis revealed 11 compounds in the formulated tea as shown in **Table 1**.

Table 1. Physiochemical properties of compounds identified.

S/n	Compound (PUBCHEM CID)	Formula	M/W (g/mol)	Fraction CsP ₃	N of rotational bond	No of H bond acceptor	No of H bond donor	Molar reactivity	TPSA (Å ²)
1	6989	C ₁₀ H ₁₄ O	150.22	0.40	1	1	1	48.01	20.23
2	17516	C ₁₂ H ₁₇ NO ₂	207.27	0.42	4	2	1	60.68	38.33
3	119838	C ₆ H ₈ O ₄	144.13	0.50	0	4	2	32.39	66.76
4	345716	C ₇ H ₁₄ O ₆	194.18	1.00	2	6	4	40.47	99.38
5	519764	C ₁₅ H ₂₄	204.35	0.60	4	0	0	70.68	0.00
6	586455	C ₁₁ H ₁₄ O ₃	194.23	0.36	4	3	1	54.54	46.53
7	5281517	C ₁₅ H ₂₄	204.35	0.47	7	0	0	72.32	0.00
8	638072	C ₃₀ H ₅₀	410.72	0.60	15	0	0	143.48	0.00
9	5280794	C ₂₉ H ₄₈ O	412.69	0.86	5	1	1	132.75	20.23
10	5281519	C ₁₅ H ₂₄	204.35	0.60	0	0	0	70.68	0.00
11	5395771	C ₁₇ H ₂₀ N ₆	308.38	0.29	4	4	0	91.25	60.89

From **Table 1** above, CID 6989: Tyramine or 4-hydroxyphenethylamine, a naturally occurring monoamine compound derived from tyrosine. It's a small, mildly lipophilic compound with one H-bond donor/acceptor; potentially CNS-active. TPSA favours membrane permeability. CID 17516: Dextroamphetamine, a psychostimulant used in attention deficit hyperactivity disorder (ADHD) and narcolepsy. MW: 207.27, 4 rotatable bonds, typical for CNS stimulants. TPSA of 38.33 suggests good oral and blood-brain barrier (BBB) permeability. This compound acts as a central nervous system stimulant affecting dopamine and norepinephrine pathways.

CID 119838: glucaric acid, an oxidation product of glucose, involved in detoxification. CID 345716: Mannitol, a sugar alcohol used as a diuretic and sweetener. TPSA of 99.38 indicates high polarity and low membrane permeability. CID 519764: β -Caryophyllene, a sesquiterpene found in essential oils. A bicyclic sesquiterpene known for cannabinoid receptor (CB2) agonism, a good candidate for anti-inflammatory or neuroprotective roles. CID586455: Vanillin acetate or ethyl vanillin, a derivative of vanillin with reported antioxidant and antimicrobial activity. CID 5281517: Germacrene D or Humulene is a highly lipophilic compound with reported insecticidal and anti-inflammatory activity. CID 638072: Squalene, a triterpene and precursor in sterol biosynthesis with antioxidant properties in dermatological and cancer applications. CID 5280794: stigmasterol, a highly lipophilic and vital sterol in cell membranes, a precursor to steroid hormones. CID 5281519: Cyclodecadiene is an isomer of β -caryophyllene with physicochemical properties identical to β -caryophyllene; used in antimicrobial, anti-inflammatory research. CID 5395771: Acyclovir, reportedly an antiviral compound used to treat herpes simplex infections, mimics nucleosides to inhibit viral DNA polymerase.

Most drug-like compounds fall within 100 - 500 g/mol of molecular weight (Lipinski's Rule of Five). All listed compounds fall within this range, except compound 8 and compound 9, which are larger (potentially lower oral bioavailability). Fraction of CsP₃ indicates saturation level and 3D complexity. Higher CsP₃ often correlates with better solubility and metabolic stability. Compounds like compound 4 (1.00) and compound 9 (0.86) are highly saturated and likely more metabolically stable. Rotatable Bonds affects molecular flexibility. More than 10 may reduce bioavailability due to entropy loss on binding. Compound 8 has 15 rotatable bonds possibly poor oral bioavailability. Hydrogen Bond Acceptors (HBA) and Donors (HBD): excessive HBA (>10) or HBD (>5) can limit membrane permeability. Compound 4 with 6 HBAs and 4 HBDs may have low permeability without carrier mediation. Molar Reactivity (MR) relates to electronic polarizability; compounds with higher MR (e.g., compound 8 and compound 9) may have increased binding interactions but possibly reduced solubility, high MR values (>100) as in #8 and #9 suggest strong van der Waals interactions. Topological Polar Surface Area (TPSA); TPSA less than 140 Å² is considered favorable for oral absorption; under 90 Å² for blood-brain barrier penetration. Compound 4 (TPSA = 99.38) may have poor CNS penetration. Compounds 5, 7, 8, and 10 (TPSA = 0) may be highly lipophilic and membrane permeable.

3.2. Molecular Docking Result

The 11 GC-MS identified compound were docked against the target protein 2Z62 (Toll-like receptor-4; TLR-4) involved in viral recognition and inflammatory response. Subsequently, the virtual properties of the selected hit compounds were studied. Following ADME-Toxicity assessments, the most reactive compounds with drug-like properties against 2Z62 (TV3 hybrid of human TLR-4) were identified to be Squalene, Stigmasterol and Cyclodecadiene with a binding infinity of 19.6, 11.2 and 5.7 respectively (**Table 2**).

Table 2. Docked with 2Z62.

S/n	Compound	Pubchem CID	Binding Affinity
1	Squalene	638072	19.6
2	Stigmasterol	5280794	11.2
3	Cyclodecadiene	5281519	5.7

Figures 1-3 below show the docking complexes.

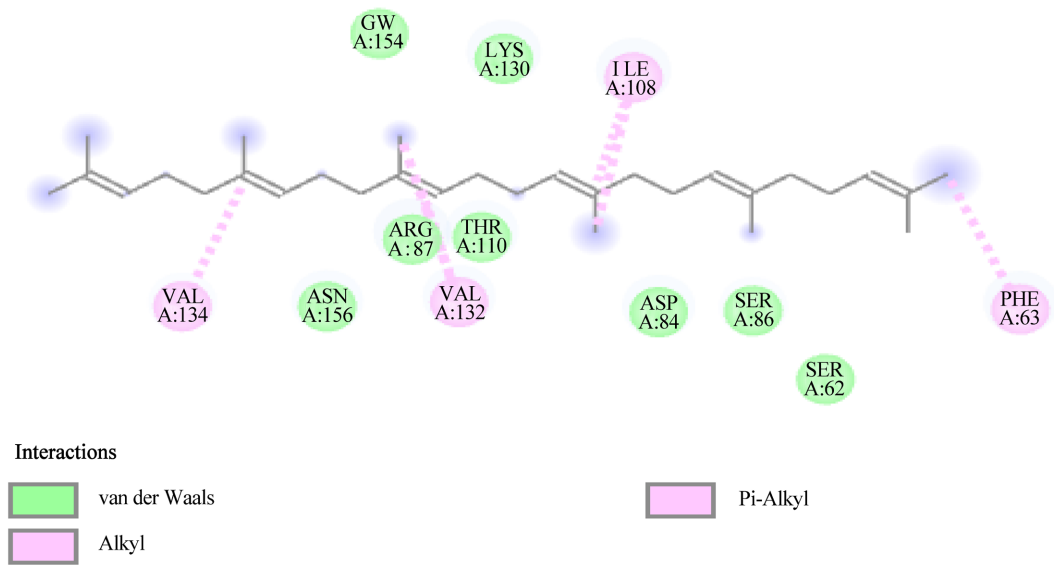


Figure 1. 2Z62 docked against Squalene_M1.

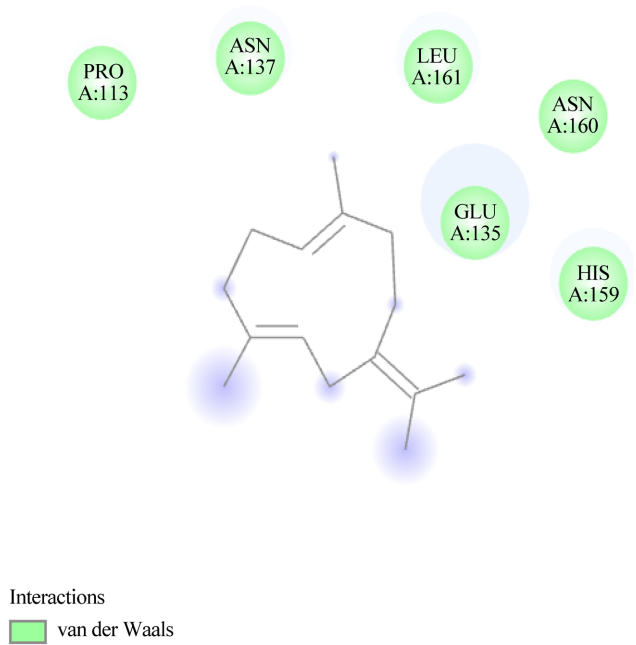


Figure 2. 2Z62 docked against 1,5-Cyclodecadiene, 1,5-dimethyl-8-(1-methylethylidene)_M1.

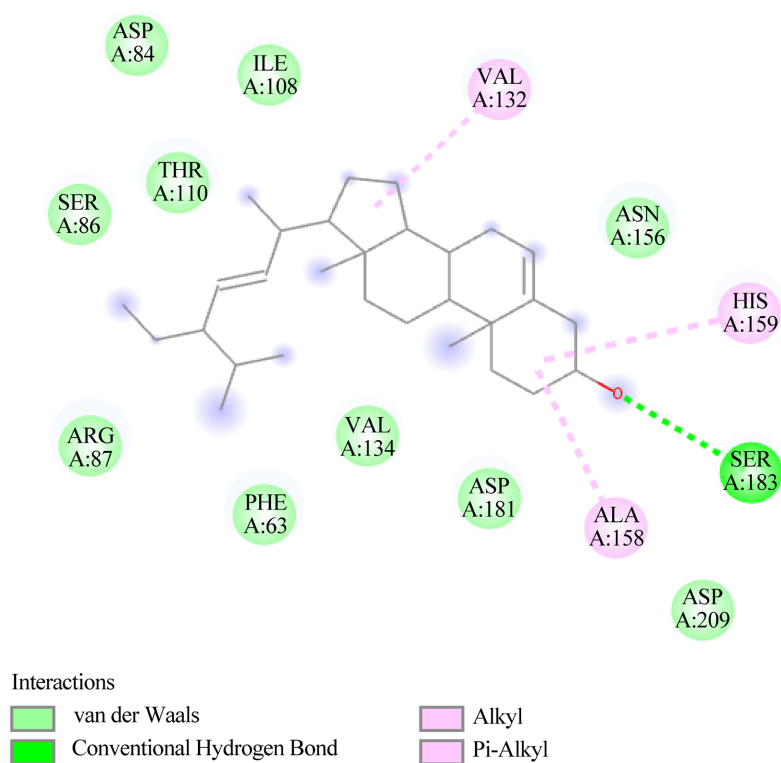


Figure 3. 2Z62 docked against Stigmasterol_M1.

Pharmacokinetics of identified compounds:

Table 3. Pharmacokinetics of identified compounds.

S/N	Compound	GI Absorption	BBB Permeant	PrGPSubstrate	CyP ₂ D ₆ Inhibit	CYP1A ₂ Inhibitor	CyP ₂ C1 ₉ inhibitor	CyP ₂ C ₉	CyP ₃ A ₄ inhibitor	Skin permeability (109 kp) cm/9
1.		High	YES	NO	NO	YES	NO	NO	NO	-4.87
2.		High	YES	NO	NO	YES	NO	NO	No	-5.36
3.		High	NO	NO	NO	NO	NO	NO	NO	-7.44
4.		Low	NO	YES	NO	NO	NO	NO	NO	-9.79
5.		Low	NO	NO	NO	NO	YES	NO	NO	-3.71
6.		High	YES	NO	NO	YES	NO	NO	NO	-6.46
7.		Low	NO	NO	NO	YES	NO	YES	NO	-3.27
8.		Low	NO	NO	NO	YES	NO	YES	NO	-3.27
9.		Low	NO	NO	NO	NO	NO	YES	NO	-2.74
10.		Low	NO	NO	NO	NO	NO	YES	NO	-3.45
11.		High	YES	NO	NO	YES	YES	YES	NO	-3.72

The *in silico* pharmacokinetic analysis (**Table 3**) showed that compounds 1, 2, 6, and 11 show the most promising oral bioavailability and CNS activity, though

potential CYP enzyme inhibition must be carefully considered to avoid drug interactions. Compounds 7 - 10, although less permeable and with low GI absorption, may be optimized for non-oral routes or used in topical or inhalational formulations. These findings offer a strong foundation for selecting lead compounds in the development of therapeutics against human metapneumovirus.

3.3. Toxicological Assessment of Lead Compounds

Table 4 presents *in silico* predictions of toxicity and systemic safety profiles for two test compounds (squalene and stigmasterol). Both compounds are predicted not to cross the BBB, reducing the risk of unintended central nervous system (CNS) side effects, they show positive hepatotoxicity predictions (0.69 probability), indicating a moderate risk of liver toxicity, while both compounds show acceptable mutagenicity and cytotoxicity profiles, their potential hepatotoxic, neurotoxic, cardiotoxic, and immunotoxic effects warrant further *in vivo* safety assessment.

Table 4. Toxicological assessment of lead compound as predicted by Protox III.

S/n	Compound	BBB	HCP	Neurotox	Nephro	Response	Cardio	Immuno	Mutagenicity	Cytotoxicity	Cli	1190 mg/kg predodidoseLD50
1	Squalene	-	+(0.69)	+(0.87)	-	+(0.98)	-	+(0.96)	-	-	-	1190
2	Stigmasterol	-	+(0.69)	+(0.87)	-	+	-	+	-	-	-	1190

3.4. Binding Affinity and Predicted Toxicity Profiles of Lead Compounds

Table 5 summarizes the binding affinity and predicted toxicity profiles of two bioactive compounds, Squalene (PubChem CID: 638072) and Cyclostigmasterol (CID: 5280794), in relation to their therapeutic potential and safety. Squalene and stigmasterol exhibit strong target binding and acceptable general toxicity, but show notable risks for neuro-, cardio-, and immunotoxicity. While they hold promise as potential bioactive agents, particularly against viral targets like hMPV, dose optimization, structural refinement, and targeted toxicity studies are essential to minimize systemic adverse effects during drug development.

Table 5. Binding affinity and predicted Toxicity Profiles two lead Compounds.

S/n	Compound	Pubchem CID	Binding Affinity	Neurotox	Nephro	Response	Cardio	Immuno	Mutagenicity	Cytotoxicity	Cli	1190 mg/kg predodidoseLD50
1	Squalene	638072	19.6	+(0.87)	-	+(0.98)	-	+(0.96)	-	-	-	1190
2	Stigmasterol	5280794	11.2	+(0.87)	-	+	-	+	-	-	-	1190

3.5. Predicted Lipophilicity (log P), Water Solubility (logSW) Drug Likeness & Bioavailability of Test Compounds

Table 6 presents *in silico* predictions of lipophilicity (log P), water solubility (log

S), drug-likeness, and oral bioavailability for eleven test compounds identified in the formulated tea. These parameters are fundamental to evaluating a compound's pharmacokinetic and physicochemical profile, influencing absorption, distribution, metabolism, and excretion (ADME) characteristics. The physicochemical screening shows that most tested compounds have drug-like properties, with good balance between lipophilicity and solubility. While several compounds show moderate violations (mainly due to high log P), they retain favorable bioavailability predictions and remain promising leads for therapeutic development against human metapneumovirus. Optimization efforts may focus on reducing excessive lipophilicity while maintaining membrane permeability and target binding.

Table 6. Predicted lipophilicity (log P), water solubility (logSW) Drug likeness & Bioavailability of test compounds.

S/N	Compound	Consensus log P _{o/w}	Log SW (SILICOSIT)	Log P solubility class	Lipinski violation	Verbar violation	Bioavailability score	Drug likeness
1.		2.80	−3.01	Soluble	0	0	0.55	YES
2.		2.76	−3.74	Soluble	0	0	0.55	YES
3.		−0.22	0.15	Soluble	0	0	0.85	YES
4.		−1.91	1.91	Soluble	0	0	0.55	YES
5.		4.56	−3.35	Soluble	1	0	0.55	YES
6.		1.86	−3.10	Soluble	0	0	0.55	YES
7.		4.97	−3.74	Soluble	1	0	0.55	YES
8.		4.97	−3.74	Soluble	1	0	0.55	YES
9.		6.98	−5.47	Moderately soluble	1	0	0.55	YES
10.		4.60	−3.75	Soluble	1	0	0.55	YES
11.		3.14	−5.12	Moderately soluble	0	0	0.55	YES

Identifying naturally occurring compounds with pharmacological relevance has become a priority in the search for new antiviral leads. The physicochemical assessment of compounds identified in this study (their molecular weight (MW), topological polar surface area (TPSA), number of hydrogen bond acceptors and donors, fraction of Sp₃ carbons (CsP₃), number of rotatable bonds, molar refractivity, logP value etc.) is essential for predicting the oral bioavailability and drug-likeness of these compounds. These characteristics determine how a compound behaves in biological environments, impacting absorption, solubility, metabolic stability, and membrane permeability [23] [24]. Compounds such as β -caryophyllene, and squalene demonstrated high lipophilicity (log P > 4.5), low TPSA (0.00 Å²), and zero hydrogen bonding capabilities, suggesting their enhanced ability to traverse lipid membranes and potentially interfere with viral envelope integrity. Squalene showed the highest molar refractivity (143.48) and flexibility (15 rotatable bonds), supporting its interaction with hydrophobic viral protein pockets. In contrast, hydrophilic molecules like mannitol and glucaric acid had ele-

vated TPSA values (up to 99.38 Å²) and multiple hydrogen bond donors/acceptors, suggesting limited membrane permeability but potential roles in metabolic or immunomodulatory pathways. Drug-likeness analysis confirmed that all compounds satisfied Veber's criteria (TPSA < 140 Å², rotatable bonds < 10) and most passed Lipinski's Rule of Five, except for some violations in highly lipophilic molecules like stigmasterol and squalene. All eleven compounds scored positively for drug-likeness and presented bioavailability scores of 0.55 or higher, with glucaric acid achieving a superior score of 0.85, indicating strong oral potential.

The host-pathogen interface during hMPV infection activates innate immune pathways, particularly Toll-like receptor (TLR) signaling involving Myeloid differentiation factor 88 (MyD88), Toll-like receptor 4 (TLR-4), and lipopolysaccharide-binding protein (LBP). These proteins play central roles in viral recognition and inflammatory response. In this study, these were selected as target proteins for docking simulation to assess whether bioactive spice compounds could inhibit TLR-mediated signaling, potentially modulating hMPV pathogenesis. Molecular docking simulations targeting the hMPV glycoproteins revealed that squalene exhibited the most favorable binding affinity (−19.6 kcal/mol), followed by stigmasterol (−11.2 kcal/mol). These compounds demonstrated efficient binding to hydrophobic viral sites, consistent with their biochemical profiles. The binding of these compounds to the target protein 2Z62 which is notable for viral recognition and inflammatory response suggests potential mechanisms of action involving possible fusion inhibition or disruption or blocking of viral entry, which is a critical step in hMPV pathogenesis. Such findings align with prior studies showing that lipophilic phytocompounds can destabilize viral membranes or bind to viral envelope proteins [25]. β -caryophyllene and stigmasterol also exhibited significant interactions with TLR-4, providing mechanistic insight into potential immunomodulatory or antiviral actions. These interactions primarily involved hydrophobic contacts and van der Waals interactions, consistent with the lipophilic nature of the compounds.

In silico pharmacokinetic prediction tools indicated that the majority of the compounds exhibited high gastrointestinal absorption. Compounds such as β -caryophyllene and vanillin derivatives were found to be non-substrates of P-glycoprotein and demonstrated no major CYP450 inhibition risks, suggesting low potential for pharmacokinetic drug interactions. Furthermore, the skin permeability coefficients ranged from −2.74 to −9.79 cm/s, denoting their suitability for non-invasive formulations. Lipophilic compounds like squalene and stigmasterol showed limited water solubility but retained sufficient predicted GI absorption. Glucaric acid and mannitol, while highly soluble, may require formulation adjustments to overcome permeability limitations. Toxicity screening revealed that most compounds were non-mutagenic and non-cytotoxic. However, neurotoxicity, cardiotoxicity, and immunotoxicity were predicted for squalene and stigmasterol (with probabilities > 0.85), raising caution for dose selection and necessitating further *in vivo* toxicological evaluation. Despite these risks, both compounds

shared a favorable LD50 value (1190 mg/kg), indicating moderate acute toxicity consistent with OECD Class IV classification. Additionally, vanillin derivatives and β -caryophyllene showed relatively benign toxicity profiles, coupled with high bioavailability and acceptable binding affinity, underscoring their promise as safer alternatives for antiviral development. The fraction of sp³-hybridized carbons (Csp₃), a metric of molecular complexity and 3D character, was favorable (≥ 0.4) for the majority of compounds, suggesting improved target specificity and reduced promiscuity. The most rigid compounds (e.g., glucaric acid with 0 rotatable bonds) may offer metabolic stability, while flexible structures like squalene may better adapt to protein pockets, enhancing binding interactions. Topological polar surface area (TPSA) values below 90 Å², as seen in compounds like β -caryophyllene, stigmasterol, and squalene, correlate with effective passive absorption and blood-brain barrier exclusion. In contrast, higher TPSA compounds may be more suitable for systemic immune modulation.

Acyclovir, a reference antiviral compound included in the study, showed moderate physicochemical compatibility and docking scores, validating the predictive strength of the *in silico* approach. When compared, β -caryophyllene and vanillin derivatives showed competitive or superior pharmacokinetic and safety profiles, highlighting their potential as antiviral scaffolds. Through reverse docking and structural bioinformatics, the selected spice-derived compounds were further mapped to their putative genetic targets including viral RNA polymerase and host immune mediators. These interactions provide molecular basis for future transcriptomic or proteomic validation studies and offer insight into multi-target drug action.

4. Conclusion

This study has demonstrated that specific bioactive compounds derived from local spices possess significant potential as therapeutic agents against human metapneumovirus. *In silico* modelling and docking approach revealed that compounds such as squalene, stigmasterol, β -caryophyllene, glucaric acid, and vanillin derivatives exhibit favorable drug-likeness profiles, optimal binding affinities to hMPV-associated immune targets (TLR-4), and minimal predicted toxicity. These compounds interacted stably within the active sites of key viral proteins involved in hMPV infection and immune evasion, indicating their capability to modulate viral entry or replication processes. Their physicochemical and toxicity properties support good membrane permeability and metabolic compatibility, acceptable oral bioavailability, minimal CYP enzyme inhibition, and low toxicity profiles. These findings reinforce the position that natural compounds with suitable structural features can interact effectively with both viral and immunological targets, offering a dual mechanism of antiviral action direct inhibition and immune modulation. While this research establishes a foundation for the development of phytochemical-based therapeutics against human metapneumovirus (hMPV), the promising results warrant further experimental validation, including *in vitro* an-

tiviral assays and *in vivo* pharmacodynamic studies, to fully harness the therapeutic potential of these locally sourced phyto-therapeutic compounds.

Compliance with Ethical Standards

This study adhered to all standard ethical practices as applied to this research.

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Statement of Ethical Approval

Ethical approval for this study was provided by Research and Quality Control Unit of Federal University Otuoke, Bayelsa State.

A Note on Limitations of the *in Silico* Approach

While *in silico* approaches can give preliminary insights into the pharmacological potentials of a compound, the following limitations, among several others, must be borne in mind:

1. Computational models do not fully capture the complexities of living systems, as such factors like protein-protein interactions, cellular compartmentalization are often ignored.
2. The model treats proteins as rigid or only partially flexible whereas in reality, proteins undergo conformational changes which may affect ligand binding.
3. Scoring functions used to estimate binding affinities are approximations, as such they may fail to correctly rank compounds or predict true binding energies.
4. Also, the method may not predict correctly the bioavailability of compounds under testing.
5. Again, toxicological outcomes are complex and multifactorial. Computational toxicity models are still limited and may miss rare or long-term adverse effects.

In-silico predictions are hypothetical until validated experimentally *in vitro* and *in vivo*. Overreliance without validation can mislead drug development efforts.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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