Magna Scientia Advanced Biology and Pharmacy

eISSN: 2582-8363

Cross Ref DOI: 10.30574/msabp

Journal homepage: https://magnascientiapub.com/journals/msabp/

(RESEARCH ARTICLE)

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Determination of inhibitory activities of the constituents of *Curcuma longa* (l) against *Streptococcus pneumoniae* by molecular docking simulation

Chigozie Celestina Ezeagha [1], Amarachi Nnaoma-Gabriel [1], joseph Orjiakor [1], Juliet Orakwe [1], Blessing Ejiro Otarigho [2] and Emmanuel Chuks Oranu [1,*]

[1] *Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Chukwuemeka Odumegwu Ojukwu University, Igbariam Anambra State.*

[2] *Department of Pharmacology and Therapeutics, Faculty of Basic Medical sciences, Delta State University, Abraka, Delta State.*

Magna Scientia Advanced Biology and Pharmacy, 2025, 16(01), 016-027

Publication history: Received on 05 August 2025; revised on 11 September 2025; accepted on 13 September 2025

Article DOI: https://doi.org/10.30574/msabp.2025.16.1.0061

Abstract

Streptococcus pneumoniae is a major cause of community-acquired pneumonia (CAP), particularly affecting children, the elderly, and immunocompromised individuals. Its polysaccharide capsule helps it evade immune defenses, leading to lung infections characterized by fever, cough, and respiratory distress. The bacteria spread through respiratory droplets, posing a significant public health risk. Although pneumococcal vaccines have reduced the incidence of pneumonia, non-vaccine serotypes and antibiotic resistance continue to challenge prevention and treatment efforts. This study aimed to utilize computational methods and tools to predict, analyze, and understand the potential anti-pneumonial effects of phytochemical compounds derived from *Curcuma longa* on the bacterium responsible for causing pneumonia. To accomplish this, a target protein of *Streptococcus pneumoniae* was selected from the Protein Data Bank for further analysis. The receptor (4IVV) was prepared using Chimera-1.10.1, PyMOL-2.3.0, and Autodock Tools-1.5.6, with the same preparation process applied to the reference ligand (EDO). Phytochemicals were selected from Drug Bank and PubChem database, then screened using Data Warrior based on Lipinski's Rule of Five and toxicity criteria. The screened phytochemicals were subsequently extracted and prepared with Autodock Tools-1.5.6. The docking protocol was validated, followed by molecular docking using autodock-vina. The docking results were then analyzed and visualized using PyMOL-2.3.0. After completing the procedures, the reference ligand exhibited a mean binding energy of -2.5 Kcal/mol. In comparison, the 105 phytoconstituents, including the top 10 candidates, showed lower binding energies, ranging from -8.1 Kcal/mol to -6.5 Kcal/mol, indicating a stronger binding affinity than the reference ligand.

Keywords: Pneumonia; Curcuma Longa; Streptococcus Pneumoniae; Community-Acquired Pneumonia (CAP); Phytochemicals; Molecular Docking; Binding Energies; Reference Ligand

1. Introduction

Pneumonia is a severe lung infection characterized by inflammation and the accumulation of fluid or pus in the lung air spaces, leading to symptoms such as coughing, elevated body temperature, shivering, and shortness of breath. This condition can be triggered by a range of microorganisms, including bacteria, viruses, and fungi, with the bacterium *Streptococcus pneumoniae* being the most common bacterial cause [1]. Pneumonia remains a leading cause of morbidity and mortality worldwide, particularly among children under five years of age. In 2019, pneumonia claimed the lives of approximately740,180 children under five, accounting for 14% of all the deaths in this age group [2]. Historical records indicate that awareness of pneumonia, including its symptoms and initial treatments, dates back to ancient civilizations

* Corresponding author: Emmanuel Chuks

such as those in Greece and China [3]. A significant advancement in the understanding of pneumonia occured in the late 19th century when its bacterial cause was discovered, greatly both diagnosis and treatment methods [4].

Prior to the introduction of antibiotics in the 20th century, pneumonia was one of the leading causes of death worldwide, particularlyaffecting vulnerable groups like infants, the elderly, and people with weakened immune systems [5]. The discovery of penicillin and the development of other antibiotics led to a significant reduction in deaths caused by bacterial pneumonia, turning it from a serious health threat into a more treatable illness. Nevertheless, pneumonia remains a major public health concern, especially in developing nations where limited access to medical care and vaccines contributions to the high illness and death rates among children under five [6].

Vaccination has played a key role in greatly lowering the number of pneumonia cases. In particular, the pneumococcal conjugate vaccine (PCV) and the Haemophilus influenzae type b (Hib) vaccine has been highly effective in reducing infections caused by these specific bacteria [7]. The PCV protects against Streptococcus pneumoniae, while the Hib vaccine helps prevent illnesses caused by Haemophilus influenzae type b—both of which are major causes of severe pneumonia. Beyond the vaccines specifically targeting pneumonia-causing bacteria, influenza vaccines also play an important indirect role in preventing the disease. By lowering the number of flu infections, they reduce the risk of secondary bacterial pneumonia [8], which often follows when the flu weakens the immune system and makes the body more vulnerable to bacterial infections.

However, despite the progress made through vaccination programs, significant challenges persist due to unequal access to vaccines. Limited availability and coverage continue to fuel outbreaks and contribute to high death rates, especially in low-resource and underserved areas with weak healthcare systems. This imbalance in vaccine distribution remains a major obstacle in the fight against pneumonia, emphasizing the urgent need to strengthen vaccination strategies and reach at-risk populations [9].

Alongside efforts to address antibiotic resistance, public health strategies are focusing on several important areas to lessen the burden of pneumonia. These include expanding vaccination coverage, which has proven effective in reducing cases caused by certain bacteria. Good nutrition is also a priority, as it strengthens the immune system and helps the body fight off infections more effectively [10]. Additionally, ensuring access to clean water and proper sanitation is vital in preventing the spread of disease and lowering pneumonia rates, especially in areas where these basic resources are limited [11].

As international health organisations work to tackle the many challenges surrounding pneumonia, the disease continues to be a central concern. Their goal is to improve public health by advancing diagnostic tools, creating more effective treatments, and strengthening prevention strategies. Continued dedication to these efforts is crucial for lessening the impact of pneumonia and lowering its global burden [12].

Curcuma longa, widely known as turmeric, is a long-living herbaceous plant from the zingiberaceae family. Originating from South Asia, especially India, it has played a significant role in traditional healing practices like Ayurveda and Traditional Chinese Medicine. Its rhizomes, known for their bright yellow hue, have longbeen valued for their therapeutic, culinary, and dyeing uses [13,14].

Turmeric has traditionally been integral to detoxification practices, particularly within Ayurvedic medicine, where it was believed to purify the blood and support hepatic function by facilitating the elimination of toxins [15]. It was commonly administered with warm milk or honey to alleviate respiratory ailments such as coughs, colds, and sore throats due to its soothing properties [16]. Additionally, it played a role in the management of gynecological conditions, including menstrual irregularities and infertility, and was regarded as a general tonic for female reproductive health [17]. The principal pharmacologically active constituents of Curcuma longa are the curcuminoids, comprising curcumin, demethoxycurcumin, and bisdemethoxycurcumin, with curcumin being the most extensively researched due to its potent biological activity and its role in imparting turmeric's distinct yellow color [18]. In addition to these compounds, C. longa also contains a range of essential oils such as turmerone, atlantone, and zingiberene, along with other phytochemicals including proteins, polysaccharides, and resins.

In silico studies involve the use of computer-based tools to simulate and analyze biological processes, particularly for drug discovery [19]. These methods, including molecular docking and virtual screening, help predict how potential drugs interact with biological targets, saving time and resources in early research stages [20, 21]. As computational power and structural data improve, in silico techniques have become essential in modern pharmacology [22].

2. Materials and methods

An *in-silico* approach was used to investigate the potential activity of the phytochemical of *Curcuma longa* against *Streptococcus pnuemonia*. The tools used for such studies include PyMol (version 2.3.0), Chimera (version 1.10.1), AutoDock Tools (version 1.5.6), DataWarrior, Open Babel (version 2.3.2), and MGL Tools (version 1.5.6). For bioinformatic and chemoinformatics mining, we have protein data bank (PDB), PUBCHEM and Drug bank.

Molecular docking and dynamics simulation documents include;

- **Conf. Text:** A text document created on Ubuntu was used to record binding site coordinates and grid box dimensions to ensure accurate representation of the active site during molecular docking simulations.
- **Bash Binbash.sh:** An ODT file contains codes for molecular docking procedures. All computational analyses were carried out on a laoptop running windows 10pro.

2.1. Bioinformatics Mining – Target Site Identification.

A search on protein data bank (PDB) for possible target proteins of Streptococcus pneumoniae with the following factors; a resolution of below 2 Å because the lower the Armstrong the better the resolution, an organic compound as a ligand and its relation to Streptococcus pneumoniae pathogenesis was conducted.

2.2. Chemoinformatic Mining

A total of approximately 100 phytochemicals derived from Curcuma longa were obtained from DrugBank and PubChem databases in SDF and PDB file formats. These files were subsequently converted to MOL2 format using the Open Babel software.

2.3. Selection and Preparation of Target Protein

After a thorough search on Protein databank, 1,2-ethanediol with the code 4IVV was found and selected for the study. Its Resolution is 1.05Å and the ligands present in the protein are 1,2-ETHANEDIOL with the chemical formula; C2 H6 O2 and a known metal Zinc (Zn)

The protein of choice (4IVV) was downloaded from protein databank in pdb format. The protein preparation was conducted in both Chimera and autodock tools. In Chimera, the similar chains were deleted leaving only one chain (A). This was saved as “Deleted 4IVV” as an SDF file. All ligands except the ligands of choice (EDO) were deleted. Again, this was saved as “deleted 4IVV+Ligand”. The ligand of choice was then deleted, leaving only the protein behind and the file was saved as “filtered 4IVV”. The target protein saved as the file “filtered 4IVV” was then prepared on Autodock Tools. This was done by opening the protein on autodock tools to edit it by adding polar only hydrogen and Kollman charges. It was then saved as a pdbqt file.

2.4. Selection and Preparation of Target Ligands

The reference ligand was selected based on specific criteria: it had to be an organic compound and capable of binding to the target protein’s active site. Binding interactions were verified using visualization tools such as PyMOL and Chimera, after which EDO was confirmed as the reference ligand. The ligand was obtained from the Protein Data Bank and downloaded in its ideal SDF format. Preparation of both the reference ligand and the phytochemicals was carried out using Open Babel and AutoDock Tools on a Windows 10 Pro system, following these steps: Ligands originally in SDF or PDB formats were converted to MOL2 format using Open Babel, ensuring all structures retained their 3D coordinates prior to conversion. The converted MOL2 files were then transferred to the Windows environment for further processing in AutoDock Tools. In AutoDock Tools, Gasteiger charges were assigned, and all torsional bonds were set to non-rotatable. Finally, the ligands were saved in PDBQT format, making them ready for molecular docking.

2.5. Validation of Docking Protocol

The binding site has now been identified and the proteins are prepared for docking. The application utilized is called autodock tools in Windows 10pro, and the reference ligand was added to autodock tools along with the processed protein after being separated from the protein in Chimera. To cover the ligand in the binding site, a grid box was introduced, and its center and dimensions were noted.

Table 1 Centre and Dimension of Grid Box

Grid box	Center	Dimension
X	38.458	16
Y	30.733	16
Z	10.268	16

2.6. Molecular Docking

Molecular docking simulations were performed using AutoDock Vina on the Ubuntu operating system. The PDBQT files, which included the reference ligand (EDO), the selected phytochemical ligands, and the target protein (PDB ID: 4IVV), were organized within a dedicated folder. This folder was accessed through the terminal, and docking was executed by running the binbash.sh Bash script.

2.7. Post-Docking Analysis

After successfully completing the docking simulations at four different binding sites, all results were compiled into an Excel spreadsheet. The mean binding affinity and standard deviation for each phytochemical were calculated. Leading candidates were identified by comparing the average binding energies of the phytochemicals with that of the reference ligand. The docked ligands within the binding pocket were visualized using PyMOL, with each ligand assigned a distinct color for easy identification. The interactions between the ligands and the amino acid residues were also examined. To enhance clarity, visual representations of ligand binding within the pocket were captured as snapshots and saved in PNG format.

3. Results

There were 104 phytochemicals of Curcuma longa downloaded from Pubchem and drugbank, prepared and docked against the target protein 4IVV and their binding affinities were deterimined. The docked phytochmicals of Curcuma longa were screened on datawarrior using the Lipinski rule of five, their toxicity profile was also considered.

The following shows the results obtained after the first screening of the ligands in table 2, then the front runners on table 3 contains the first 10 compounds with better binding affinity as compared with the reference ligand (EDO) which was determined after docking with the selected protein 4IVV. Lipinski rule/toxicity screening done and the results which were collated on table 4 and 5 after comparison of the phytochemicals with the reference ligand during the post docking analysis and further discussion on them was done.

Table 2 Binding affinity of the constituents of Curcuma longa when docked with receptor 4IVV

S/N	Constituents	E1	E2	E3	E4	Mean	SD
1	Desmethoxycurcumin	-8.2	-7.7	-8.2	-8.2	-8.1	0.3
2	Bisdemethoxycurcumin	-8.1	-8.0	-8.0	-8.0	-8.0	0.1
3	Caryophyllene	-8.0	-8.0	-8.0	-8.0	-8.0	0.0
4	Cyclocurcumin	-8.0	-8.0	-8.0	-8.0	-8.0	0.0
5	Calebin	-7.9	-7.6	-7.6	-8.0	-7.8	0.2
6	Dmethylcurcumin	-7.9	-7.5	-7.5	-7.5	-7.6	0.2
7	Tetrahydroxy curcumin	-7.1	-7.0	-7.1	-7.8	-7.2	0.4
8	Bixin	-7.1	-7.0	-7.0	-6.2	-6.8	0.4
9	2_hydroxymethyl_anthraquinone	-6.6	-6.6	-6.6	-6.6	-6.6	0.0
10	Bisacurone C	-6.5	-6.5	-6.6	-6.6	-6.5	0.1
11	Dicumylperoxide	-6.5	-6.5	-6.6	-6.5	-6.5	0.1

12	Bisabolone	-6.5	-6.5	-6.5	-6.5	-6.5	0.0
13	Gitoxigenin	-6.5	-6.5	-6.5	-6.5	-6.5	0.0
14	Norbixin	-6.4	-6.6	-6.5	-6.4	-6.5	0.1
15	Stigmasterol	-6.7	-6.2	-6.1	-6.7	-6.4	0.3
16	Cineole	-6.4	-6.4	-6.4	-6.4	-6.4	0.0
17	Turmeronol A	-6.1	-6.4	-6.3	-6.4	-6.3	0.1
18	Gamma_atlantone	-6.3	-6.3	-6.3	-6.3	-6.3	0.0
19	Bisacurone	-6.2	-6.2	-6.3	-6.3	-6.2	0.1
20	Caffeic_acid	-6.2	-6.2	-6.2	-6.2	-6.2	0.0
21	Alphapinene	-6.1	-6.1	-6.1	-6.1	-6.1	0.0
22	beta_sitosterol	-6.0	-6.1	-6.1	-6.2	-6.1	0.1
23	Betapinene	-6.1	-6.1	-6.1	-6.1	-6.1	0.0
24	Bisacumol	-5.8	-6.2	-6.2	-6.2	-6.1	0.2
25	Bisacurone B	-6.1	-6.1	-6.1	-6.1	-6.1	0.0
26	Turmeronol B	-6.0	-6.2	-6.0	-6.0	-6.1	0.1
27	Arturmerone	-6.0	-6.0	-6.1	-5.8	-6.0	0.1
28	Bisacurone A	-6.0	-6.0	-6.0	-5.9	-6.0	0.1
29	Curcumenol	-5.9	-5.9	-5.9	-5.9	-5.9	0.0
30	Curdione	-5.8	-6.1	-6.0	-5.7	-5.9	0.2
31	curcumanolideA	-5.8	-5.9	-5.9	-5.9	-5.9	0.1
32	Epiprocurcumenol	-5.9	-5.8	-5.9	-5.9	-5.9	0.1
33	Ferulicacid	-5.7	-5.9	-5.9	-5.8	-5.8	0.1
34	Sabinene	-5.8	-5.8	-5.8	-5.9	-5.8	0.1
35	corymbolone	-5.8	-5.8	-5.8	-5.8	-5.8	0.0
36	Germacrone-13-al	-5.8	-5.8	-5.8	-5.7	-5.8	0.1
37	Dehydrozingerone	-5.8	-5.8	-5.7	-5.7	-5.7	0.1
38	Curcumene	-5.7	-5.8	-5.7	-5.7	-5.7	0.1
39	Ar-curcumene	-5.7	-5.7	-5.7	-5.7	-5.7	0.0
40	Germacrone	-5.7	-5.7	-5.7	-5.7	-5.7	0.0
41	L_alpha_curcumene	-5.7	-5.7	-5.7	-5.7	-5.7	0.0
42	Vanillic acid	-5.7	-5.7	-5.7	-5.7	-5.7	0.0
43	Zingerone	-5.7	-5.7	-5.7	-5.7	-5.7	0.0
44	Norpinanone	-5.6	-5.6	-5.5	-6.0	-5.7	0.2
45	Himachalene	-5.6	-5.7	-5.6	-5.7	-5.6	0.1
46	Alpha_atlantone	-5.6	-5.6	-5.6	-5.7	-5.6	0.1
47	Beta_sesquiphellandrene	-5.6	-5.6	-5.6	-5.7	-5.6	0.1
48	Ascorbic	-5.6	-5.6	-5.6	-5.6	-5.6	0.0
49	P_methoxycinnamic_acid	-5.5	-5.6	-5.6	-5.5	-5.5	0.1

50	Chrysanthenylacetate	-5.5	-5.5	-5.5	-5.5	-5.5	0.0
51	Cubebene	-5.5	-5.5	-5.5	-5.5	-5.5	0.0
52	P-coumaric acid	-5.5	-5.5	-5.5	-5.5	-5.5	0.0
53	citronellylpentanoate	-5.6	-5.3	-5.3	-5.6	-5.4	0.2
54	Ascaridole	-5.4	-5.4	-5.4	-5.4	-5.4	0.0
55	Bisabolene	-5.4	-5.4	-5.4	-5.4	-5.4	0.0
56	Geranic acid	-5.5	-5.3	-5.5	-5.3	-5.4	0.1
57	Nerolidylpropionate	-5.2	-5.3	-5.4	-5.5	-5.3	0.1
58	Eugenol	-5.3	-5.3	-5.3	-5.3	-5.3	0.0
59	Thymol	-5.3	-5.2	-5.3	-5.3	-5.3	0.1
60	Cinnamicacid	-5.2	-5.2	-5.2	-5.2	-5.2	0.0
61	Humulene	-5.2	-5.2	-5.2	-5.2	-5.2	0.0
62	p-methylacetophenone	-5.2	-5.2	-5.2	-5.1	-5.2	0.1
63	Palmitic acid	-5.1	-5.3	-5.3	-4.9	-5.1	0.2
64	7-epi-sesquithujene_	-5.1	-5.1	-5.1	-5.1	-5.1	0.0
65	Geraniol	-5.1	-5.1	-5.1	-5.1	-5.1	0.0
66	Methyleugenol	-5.1	-5.1	-5.1	-5.1	-5.1	0.0
67	Oleicacid	-4.9	-5.1	-5.0	-5.3	-5.1	0.2
68	Linoleicacid	-5.0	-5.2	-4.9	-5.1	-5.1	0.1
69	Aristolene	-5.0	-5.0	-5.0	-5.0	-5.0	0.0
70	Dihydrocarvone	-4.9	-4.9	-4.9	-4.9	-4.9	0.0
71	Vanillin	-4.9	-4.9	-4.9	-4.9	-4.9	0.0
72	Adoxal	-4.8	-5.2	-4.9	-4.6	-4.9	0.3
73	1,3,8-paramenthatriene	-4.8	-4.8	-4.8	-4.8	-4.8	0.0
74	Carvone	-4.8	-4.8	-4.8	-4.8	-4.8	0.0
75	Terpinolene	-4.8	-4.8	-4.8	-4.8	-4.8	0.0
76	Menthofuran	-4.8	-4.7	-4.8	-4.8	-4.8	0.1
77	P-cymene	-4.7	-4.8	-4.8	-4.8	-4.8	0.1
78	Cuminyl_alcohol	-4.8	-4.8	-4.8	-4.7	-4.8	0.1
79	gamma_terpinene	-4.7	-4.8	-4.8	-4.7	-4.7	0.1
80	Sabinol	-4.8	-4.8	-4.7	-4.6	-4.7	0.1
81	3-bornanone	-4.7	-4.7	-4.7	-4.7	-4.7	0.0
82	m-cymene	-4.7	-4.7	-4.7	-4.7	-4.7	0.0
83	Niacin	-4.7	-4.7	-4.7	-4.7	-4.7	0.0
84	Geranial	-5.0	-4.6	-4.6	-4.6	-4.7	0.2
85	2-carene	-4.6	-4.7	-4.6	-4.7	-4.6	0.1
86	Linalool	-4.6	-4.7	-4.6	-4.7	-4.6	0.1
87	(Z)-cinerone	-4.5	-4.7	-4.7	-4.7	-4.6	0.1

88	Alpha-thujene	-4.6	-4.6	-4.6	-4.6	-4.6	0.0
89	Piperitone	-4.6	-4.6	-4.6	-4.6	-4.6	0.0
90	1,8-cineole	-4.5	-4.5	-4.5	-4.5	-4.5	0.0
91	Terpinen-4-ol	-4.5	-4.5	-4.5	-4.5	-4.5	0.0
92	Teresantalol	-4.4	-4.5	-4.5	-4.5	-4.5	0.1
93	Sylvestrene	-4.4	-4.4	-4.5	-4.4	-4.4	0.1
94	Camphor	-4.6	-4.4	-4.4	-4.3	-4.4	0.1
95	Cis-ocimene	-4.4	-4.4	-4.4	-4.4	-4.4	0.0
96	Citronellal	-4.5	-4.3	-4.3	-4.4	-4.4	0.1
97	R_citronellene	-4.4	-4.2	-4.3	-4.4	-4.3	0.1
98	3_carene	-4.3	-4.3	-4.3	-4.3	-4.3	0.0
99	Arabinose	-4.3	-4.3	-4.3	-4.3	-4.3	0.0
100	Caprylicacid	-4.3	-4.3	-4.3	-4.3	-4.3	0.0
101	Myrcene	-4.3	-4.3	-4.3	-4.3	-4.3	0.0
102	Phellandral	-4.3	-4.3	-4.2	-4.3	-4.3	0.1
103	Camphene	-4.2	-4.2	-4.2	-4.2	-4.2	0.0
104	Isoborneol	-4.2	-4.2	-4.2	-4.2	-4.2	0.0
105	EDO	-2.5	-2.5	-2.5	-2.5	-2.5	0.0

Table 3 Binding energies (E1-E4) of the frontrunners and the ligand when docked with 4IVV receptor

S/N	**Constituents**	**E1**	**E2**	**E3**	**E4**	**MEAN**	**SD**
1	Demethoxycurcumin	-8.2	-7.7	-8.2	-8.2	-8.1	0.3
2	Bis_desmethoxycurcumin	-8.1	-8.0	-8.0	-8.0	-8.0	0.1
3	caryophyllene	-8.0	-8.0	-8.0	-8.0	-8.0	0.0
4	cyclocurcumin	-8.0	-8.0	-8.0	-8.0	-8.0	0.0
5	Calebin-A	-7.9	-7.6	-7.6	-8.0	-7.8	0.2
6	dmethylcurcumin	-7.9	-7.5	-7.5	-7.5	-7.6	0.2
7	tetrahydroxycurcumin	-7.1	-7.0	-7.1	-7.8	-7.2	0.4
8	Bixin	-7.1	-7.0	-7.0	-6.2	-6.8	0.4
9	2-hydroxymethyl-anthraquinone	-6.6	-6.6	-6.6	-6.6	-6.6	0.0
10	Bisacurone-C	-6.5	-6.5	-6.6	-6.6	-6.5	0.1
11	1,2-ETHANEDIOL(EDO)	-2.5	-2.5	-2.5	-2.5	-2.5	0.0

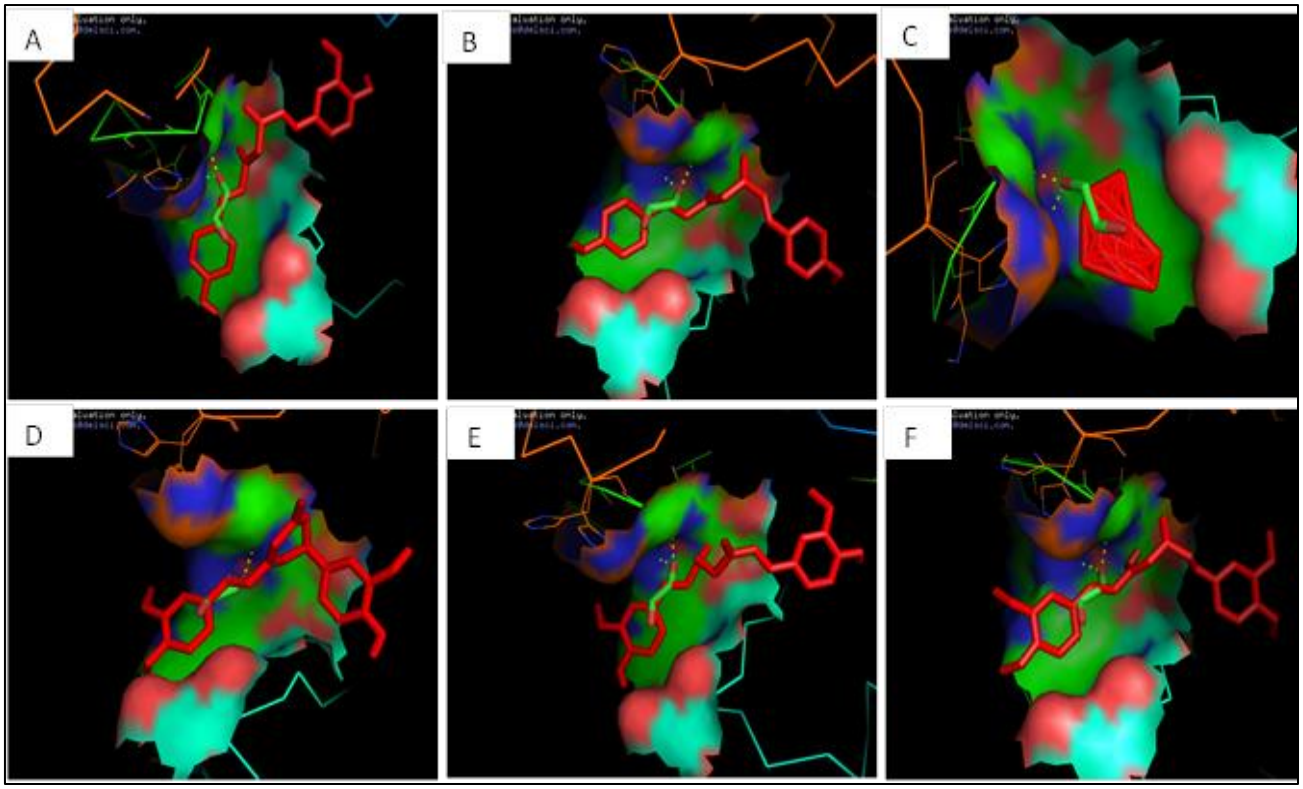

Figure 1 The first six front runner ligands on the table and the reference ligand EDO within the binding pocket of the selected protein 4IVV

Table 4 The molecular descriptors of the front runners

S/N	Constituents	CHEMICAL FORMULA	MW	Clog P	HBA	HBD
1	Demethoxycurcumin	C20H18O5	338.3	3.0	5.0	2.0
2	Bis_desmethoxycurcumin	C19H16O4	308.3	3.1	4.0	2.0
3	Caryophyllene	C15H24	204.3	5.5	0.0	0.0
4	Cyclocurcumin	C21H20O6	368.3	3.0	6.0	2.0
5	calebinA	C21H20O7	384.3	2.6	7.0	2.0
6	Dimethylcurcumin	C23H24O6	396.4	4.1	6.0	1.0
7	tetrahydroxycurcumin	C21H24O6	372.4	3.2	6.0	2.0
8	Bixin	C25H30O4	394.5	7.2	4.0	1.0
9	2_hydroxymethyl_anthraquinone	C15H10O3	238.2	2.4	3.0	1.0
10	bisacuroneC	C15H24O3	252.3	2.4	3.0	2.0

Table 5 The toxicity profile of the frontrunners.

S/n	Name of ligands	Turmorigenicity	Mutagenicity	Reproductive effect	Irritant effect
1	Demethoxycurcumin	NONE	NONE	NONE	NONE
2	Bis_desmethoxycurcumin	NONE	NONE	NONE	NONE
3	Caryophyllene	NONE	NONE	NONE	NONE
4	Cyclocurcumin	NONE	NONE	NONE	NONE
5	calebinA	NONE	NONE	NONE	NONE
6	Dimethylcurcumin	NONE	NONE	NONE	NONE
7	Tetrahydroxycurcumin	NONE	NONE	NONE	NONE
8	Bixin	NONE	NONE	NONE	NONE
9	2_hydroxymethyl_anthraquinone	NONE	HIGH	NONE	HIGH
10	bisacuroneC	NONE	NONE	NONE	HIGH

4. Discussion

Understanding the binding affinities of phytochemicals to specific protein receptors is essential in evaluating their therapeutic potential [23]. Binding affinity is often estimated using scoring methods, which provide a rapid, basic measure linked to Gibbs free energy. A more negative Gibbs binding energy suggests a spontaneous and stronger interaction, meaning that the lower the value, the tighter the ligand binds to its target. Conversely, a positive or less negative value indicates weaker binding.

Recent literature classifies binding affinities into four categories: weak, moderate, strong, and extremely strong [24]. For instance, flavonoids' binding to the androgen receptor (AR) demonstrates varying interaction strengths, each with distinct pharmacological implications.

In this study, 104 phytochemicals derived from Curcuma longa were docked with the target protein 4IVV using autodock vina. The reference ligand, 1, 2-ethanediol, exhibited the lowest binding affinity at -2.5 kcal/mol. In contrast, all the screened phytochemicals demonstrated higher binding affinities, suggesting a more favorable interaction with the receptor.

Based on binding energy values, the compounds were categorized into four levels

- **Mild binding affinity**: Aristolene to 1,8-cineole
- **Moderate binding affinity**: Curcuminol to linoleic acid
- **Strong binding affinity**: BisacuroneA to stigmasterol
- **Very strong binding affinity**: Norbixin to demethoxycurcumin

Table 2 summarizes the binding affinities of the top-performing compounds. All ten frontrunners exhibited binding energies significantly lower than the reference ligand, ranging from -8.1 to -6.8 kcal/mol. Visual analysis (Figures A-F) shows that these compounds fit snugly into the 4IVV receptor's binding pocket, indicating potential for biological activity.

Furthermore, compliance with Lipinski's Rule of Five—a benchmark for assessing oral bioavailability—was evaluated using DataWarrior software. This rule specifies that drug-like molecules should meet the following criteria [25]

- *≤5 hydrogen bond donors*
- *≤10 hydrogen bond acceptors*
- *Molecular weight ≤500 g/mol*
- *CLogP ≤5*

All ten frontrunners were screened, and except for bixin and caryophyllene (with cLogP >5), the remaining compounds met all the criteria, indicating their potential drug-likeness. This aligns with recent studies affirming the rule's validity in modern drug discovery [26], although alternative parameters such as polar surface area and molecular flexibility are gaining traction [27].

Toxicological screening was also conducted to ensure safety. All constituents, except 2-(hydroxymethyl) anthraquinone and bisacurone C, were found non-toxic. These two compounds displayed high mutagenicity, indicating potential genotoxic effects, and 2-(hydroxymethyl)anthraquinone also showed significant irritant properties. Identifying toxicity is critical in early-phase drug development, and computational (*in silico*) toxicology provides an ethical and cost-effective alternative to in vivo models [28]. These models are useful for predicting, ranking, and filtering compounds before advancing to experimental validation.

This study demonstrates that several phytochemicals derived from *Curcuma longa* exhibit superior binding affinities to the 4IVV receptor compared to the reference ligand. Among these, demethoxycurcumin recorded the highest binding affinity. Out of the ten top-performing compounds, eight complied with Lipinski's Rule of Five, suggesting good oral bioavailability. Moreover, six of these drug-like compounds—bis-demethoxycurcumin, calebin A, cyclocurcumin, desmethoxycurcumin, dimethyl curcumin, and tetrahydroxy curcumin—exhibited no predicted toxicity, reinforcing their potential as safe therapeutic agents.

5. Conclusion

In conclusion, the favorable pharmacokinetic profiles and low toxicity of these compounds, particularly desmethoxycurcumin, emerge as promising candidates for development as anti-pneumoniae agents. The integration of computer-aided drug design, molecular docking, and in silico screening tools has significantly streamlined the early stages of drug discovery. These approaches not only enhance efficiency but also reduce the time and cost associated with conventional drug development pipelines. Future work should focus on experimental validation and in vivo testing to confirm these findings and support the progression of these phytochemicals into preclinical and clinical phases.

Compliance with ethical standards

Acknowledgement

The authors wish to acknowledge the Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Chukwuemeka Odumegwu Ojukwu University, Igbariam for the provision of the facility for this study.

Disclosure of conflict of interest

The authors stated in this study declare no conflict of interest.

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