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Exploring Anti-Inflammatory Drug Leads from *Caesalpinia pulcherrima* (L.) Sw. (Fabaceae) Through Bibliometric and Computational Approaches

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This study integrated a bibliometric technique to chart the landscape of international research on *Caesalpinia pulcherrima* (L.) Sw. (Fabaceae). To further substantiate the utilisation of *C. pulcherrima*, *in silico* analyses was employed to explore prospective phytochemicals found in *C. pulcherrima* as novel inhibitors of NF-κB p50 subunit, a key mediator of inflammation involved in several debilitating conditions including cardiovascular and respiratory diseases, diabetes, cancer and autoimmune disorders. Bibliometric mapping revealed a concentrated global research landscape, led by India and Brazil, with high-impact collaborations centered in Europe. Molecular docking identified bonducellin (**9**) as a top candidate, exhibiting a superior binding affinity (-3.9 kcal/mol) compared to standard drug dexamethasone (**1**) (-3.7 kcal/mol). Two other phytochemicals, galactomannan (**2**) and 5,7-dimethoxyflavone (**8**), inherent in *C. pulcherrima* also gave promising binding energies. Pharmacokinetic profiling indicated promising drug-likeness and blood-brain barrier penetration for several flavonoids. These results support the traditional anti-inflammatory use of *C. pulcherrima* and highlight bonducellin as a potential lead molecule for targeted therapeutic development, requiring further experimental and clinical validation.

Keywords: *Caesalpinia pulcherrima*, Bibliometric analysis, *In silico* molecular simulations, Binding energy, NF-κB p50 subunit.

INTRODUCTION

The COVID-19 pandemic starkly highlighted global disparities in access to medicine, prompting a resurgence of interest in traditional and plant-based therapies to alleviate overburdened healthcare systems [1,2]. Among the many plants recognised for their medicinal properties is the *Caesalpinia pulcherrima* (L.) Sw., a fast-growing shrub of the Fabaceae family, renowned for its vibrant ornamental flowers and long history of ethnobotanical use [3-5]. Indigenous groups in the Amazon Rainforest have traditionally used *C. pulcherrima*, known locally as ayoowiri, to treat fevers, sores and coughs, while its roots have been employed as an abortifacient [6]. Modern scientific inquiry has validated many of these traditional uses, revealing that extracts from various parts of CP possess potent antioxidants, antimicrobial, anti-inflammatory, antiviral and antidiabetic activities [6-8].

The pharmacological potential of *C. pulcherrima* is largely attributed to its rich and diverse profile of bioactive secondary metabolites. For instance, *C. pulcherrima* seeds are a rich source of galactomannan, a β-(1,4)-D-mannan backbone linear hetero-polysaccharide conjugated with single galactose unit side chains, which has industrial and potential clinical applications as a biomaterial [9]. Essential oils from the plant's flowers show strong bioactivity, causing complete mosquito mortality at ppm concentrations, attributed to monoterpenoids such as α-phellandrene, *p*-cymene and γ-terpinene [10].

The antioxidant characteristics of *C. pulcherrima* have been extensively documented through a range of assays, including DPPH, hydrogen peroxide, ABTS free radical scavenging and ferric reducing power protocols [6]. This activity is strongly correlated with the increased flavonoid and phenolic phytochemical composition of plant [11]. Flavonoids, a class of phenolic compounds with a benzo-γ-pyrone structure, are known to regulate cellular activity and combat free radicals that cause oxidative stress. Specific examples of flavonoids isolated from aerial parts of *C. pulcherrima* include derivatives of flavanone, isobonducellin and chalcone such as 2′-hydroxy-

2,3,4′,6′-tetramethoxychalcone, 5,7-dimethoxy-3′,4′-methylenedioxyflavanone, 5,7-dimethoxyflavone and bonducellin [11]. Moreover, cassane-type furanoditerpenoids isolated from *C. pulcherrima* roots and stems have shown impressive antitubercular anti-inflammatory and activities, underscoring the potential of plant as a source of novel therapeutic agents [12-14].

The transcription factor nuclear factor-kappa B (NF-κB) is a key mediator of inflammation, regulating the expression of several pro-inflammatory genes. The p50 subunit, often acting as a homodimer, plays a crucial role in NF-κB signaling. Therefore, inhibiting the DNA-binding activity of the p50 homodimer represents a promising approach for developing novel anti-inflammatory therapeutics [15]. Based on the documented anti-inflammatory properties of *C. pulcherrima* and its diverse bioactive constituents including flavonoids and terpenoids, it is hypothesized that these compounds may exert their effects through direct interaction with and inhibition of the NF-κB p50 subunit [16].

Therefore, this study aims to computationally evaluate the potential of key phytochemicals isolated from *C. pulcherrima* as novel inhibitors of NF-κB p50 subunit, thereby providing a molecular rationale for its traditional anti-inflammatory use. This study was designed with three primary objectives: (i) to conduct a bibliometric analysis mapping the global research landscape and collaborative networks related to *C. pulcherrima*; (ii) to perform *in silico* molecular docking to evaluate the binding affinity and interaction patterns of selected *C. pulcherrima* derived compounds including flavonoids, terpenoids and galactomannan, with the NF-κB p50 homodimer (PDB ID: 1SVC); and (iii) to assess the drug-likeness and pharmacokinetic properties of these compounds to predict their potential as orally bioavailable therapeutics.

EXPERIMENTAL

Bibliometric analysis: A comprehensive bibliometric investigation was conducted to map the global research landscape of *C. pulcherrima*, with the specific objectives of quantifying research output, identifying geographic disparities and analyzing international collaboration networks. The literature data were retrieved from the Scopus database on October 2025. The search query employed the keyword "*Caesalpinia pulcherrima*" in double quotation marks to ensure specificity. The search results were filtered by document type to include only articles, reviews and book chapters and by language to English-language publications. Furthermore, the search was refined to include only open-access documents to facilitate comprehensive access to the full-text records for analysis. The year range of the dataset was dictated by the chronological scope of the publications indexed in Scopus that matched the search criteria. The final dataset, comprising complete bibliographic records, was exported and analysed using VOSviewer software (version 1.6.20), a specialised tool for constructing and visualizing bibliometric networks [17]. To elucidate the structure and dynamics of the *C. pulcherrima* research field, two primary types of maps were generated.

Network visualisation: To examine co-authorship patterns at the country level, revealing clusters of international collaboration. **Density visualisation:** To identify keyword clusters and highlight regions of high research activity and focus based on the frequency and co-occurrence of terms. These visual analyses were complemented by extracting quantitative metrics directly from the Scopus database. Key indicators such as publication counts, citation rates and collaboration linkages were systematically analysed. This integrated approach combining quantitative metrics with visual network analysis enabled a robust assessment of research productivity, impact and the evolving role of different countries and institutions within the global *C. pulcherrima* research landscape.

Molecular docking simulations

Protein preparation: The pdb file of the 3D crystal structure of NF-κB p50 homodimer (PDB ID: 1SVC) was obtained from the protein data bank, https://www.rcsb.org/, accessed on 28 October 2025 (RCSB PDB) [18]. The structure was prepared for docking using BIOVIA Discovery Studio Visualizer v.21.2 (Dassault Systèmes, Waltham, CA, USA) [19]. All water molecules, the native DNA ligand and other heteroatoms were removed from the protein file. Polar hydrogen atoms and Kollman charges were added using AutoDock Tools (ADT) v.1.5.6 (Scripps Research, USA) [20]. The binding site was defined with a grid box centered at XYZ coordinates (27.702003, 30.851276, 27.702665) with dimensions 15 Å × 15 Å × 15 Å. The final prepared protein was saved in the .pdbqt format.

Ligand preparation: The selection of ligands for this study included the control anti-inflammatory drug, dexamethasone (PubChem CID: 5743) and eight phytochemicals previously identified and reported from *C. pulcherrima* (Table-1 and Fig. 1 for structures). The three-dimensional (3D) structural data files (.sdf format) for all compounds were retrieved from the PubChem database, accessed on 28 October 2025 [21]. Subsequently, all ligand structures were prepared for molecular docking using AutoDock Tools (ADT) v.1.5.6) [21]. This preparation involved the addition of polar hydrogen atoms and the assignment of Gasteiger charges. Rotatable bonds within each ligand were defined to allow for conformational flexibility during the docking simulation. Finally, all prepared ligands were converted and saved in the .pdbqt file format, which is required for docking with AutoDock Vina. Concurrently, the canonical SMILES notations for all compounds were obtained from PubChem. These notations served as the primary input for the subsequent *in silico* pharmacokinetic and drug-likeness analysis.

Docking protocol: Molecular docking simulations were performed to predict the binding affinity and interaction modes of the selected ligands with the NF-κB p50 homodimer (PDB ID: 1SVC). All docking calculations were executed using AutoDock Vina [22], which employs a sophisticated scoring function to estimate binding energies.

The grid box for docking was centered on the DNA-binding site of the p50 homodimer, with XYZ coordinates (27.702, 30.851, 27.703) and dimensions of 15 Å × 15 Å × 15 Å, ensuring comprehensive sampling of the key interaction region. The exhaustiveness parameter was set to 8 to ensure sufficient conformational sampling and result reproducibility. For each ligand, the docking run generated multiple binding poses, ranked by their calculated binding affinity.

TABLE-1
NAMES AND IDENTIFIERS OF *Caesalpinia pulcherrima* COMPOUNDS UNDER INSPECTION (https://pubchem.ncbi.nlm.nih.gov/)

Identifier	Name	Isomeric SMILES
1 (control)	Dexamethasone	C[C@@H]1C[C@H]2[C@@H]3CCC4=CC(=O)C=C[C@@]4([C@]3([C@H](C[C@@]2([C@]1(C(=O)CO)O)C)O)F)C
2	Galactomannan	C([C@@H]1[C@@H]([C@@H]([C@H]([C@H](O1)OC[C@@H]2[C@H]([C@@H]([C@@H]([C@@H](O2)O)O)O)O[C@H]3[C@H]([C@H]([C@@H]([C@H](O3)CO)O)O)O)O)O)O)O
3	α-Phellandrene	CC1=CCC(C=C1)C(C)C
4	*p*-Cymene	CC1=CC=C(C=C1)C(C)C
5	γ-Terpinene	CC1=CCC(=CC1)C(C)C
6	(2S)-5,7-Dimethoxy-3',4'-methylenedioxyflavanone	COC1=CC2=C(C(=O)C[C@H](O2)C3=CC4=C(C=C3)OCO4)C(=C1)OC
7	2'-Hydroxy-2,3,4',6'-tetramethoxychalcone	COC1=C(C=C(C=C1)/C=C/C(=O)C2=C(C=C(C=C2OC)OC)O)OC
8	5,7-Dimethoxyflavone	COC1=CC2=C(C(=C1)OC)C(=O)C=C(O2)C3=CC=CC=C3
9	Bonducellin	COC1=CC=C(C=C1)/C=C/2\COC3=C(C2=O)C=CC(=C3)O

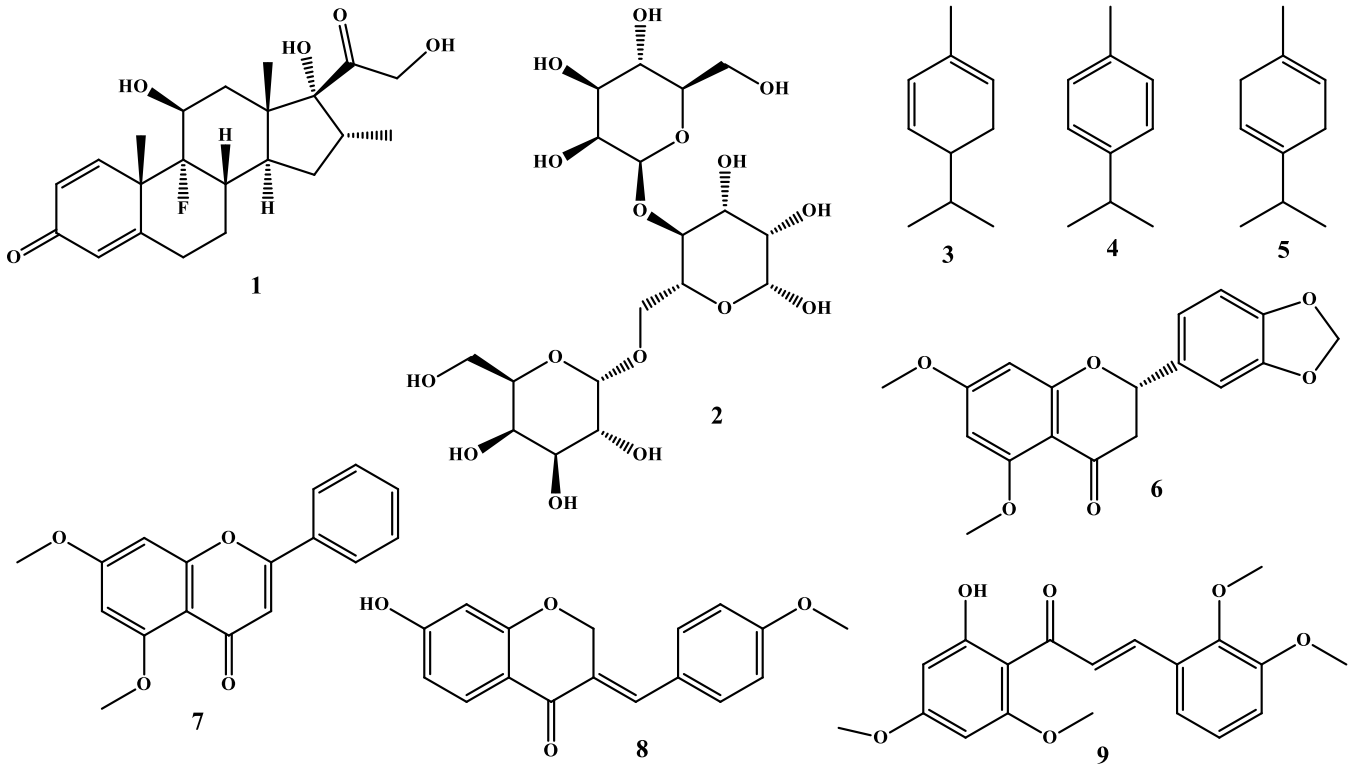

Fig. 1. Structures of isolated constituents from *Caesalpinia pulcherrima*

The resulting ligand-protein complexes were visualised and analysed using BIOVIA Discovery Studio Visualizer [19]. This analysis focused on identifying specific molecular interactions stabilizing the complexes, including conventional hydrogen bonds, carbon-hydrogen bonds, halogen bonds and hydrophobic interactions (*e.g.*, pi-pi stacked, pi-pi T-shaped, pi-alkyl and alkyl-alkyl interactions).

***In silico* pharmacokinetics and drug-likeness prediction:** The drug-likeness and key pharmacokinetic properties of the selected *C. pulcherrima* derived compounds and the control drug were predicted *in silico* using the SwissADME web tool [23], accessed on 28 October 2025. The canonical SMILES notations obtained from PubChem were used as input for the analysis [21].

The assessment was guided by the widely recognised Lipinski's rule of five [24,25], a fundamental filter to evaluate the potential for oral bioavailability. The criteria for Ro5 com-pliance are molecular weight (MW) < 500 Da, octanol-water partition coefficient (Log P) ≤ 5, number of hydrogen bond donors (HBD) ≤ 5 and number of hydrogen bond acceptors (HBA) ≤ 10. Also, the Topological Polar Surface Area (TPSA), a strong predictor of drug transport properties, was evaluated. A TPSA value < 140 $Å^2$ is indicative of good intestinal absor-ption, while a value < 60 $Å^2$ suggests a high potential for blood-brain barrier (BBB) penetration.

RESULTS AND DISCUSSION

Bibliometric analysis of *C. pulcherrima* research: The initial bibliometric dataset comprised publications from 40 countries, 459 authors and 100 references [7,26-123]. Quantitative analysis revealed significant geographic disparities in

research output and impact (Figs. 2 and 3). The top publishing countries were India (27 publications), Nigeria (13 publications) and Brazil (19), However, a different landscape emerges when analyzing research influence through total citations. Portugal, despite having only 4 publications, accumulated the highest citation count (541), followed closely by Brazil (513) and India (511), indicating a high impact per publication from these regions (Table-2).

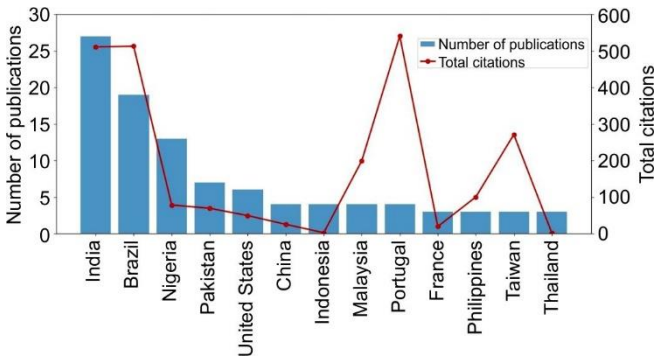

Fig. 2. List of top countries contributing to *C. pulcherrima* research

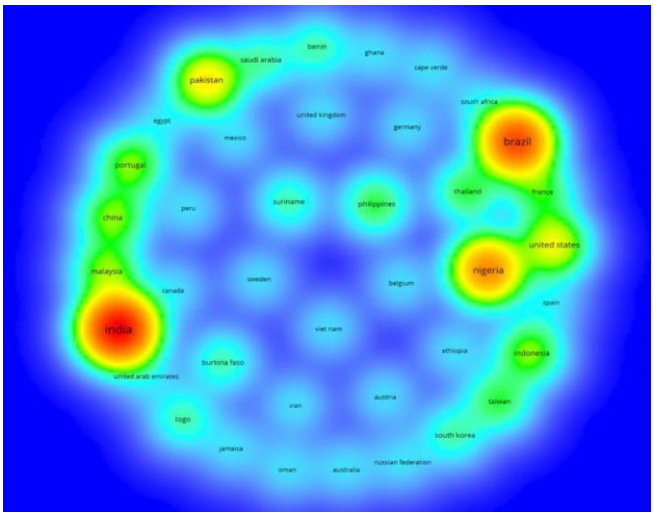

Fig. 3. VOSviewer-generated density visualisation of country clusters in terms of citation. Warmer colours (*e.g.*, yellow) indicate regions of high research activity and collaboration density, while cooler colours (*e.g.*, blue) indicate lower activity. This map visually emphasizes the concentration of research status in specific global regions

TABLE-2
LISTS OF TOP PUBLISHING COUNTRIES IN *Caesalpinia pulcherrima* RESEARCH

Rank	Country	Number of publications	Total citations
1	India	27	511
2	Brazil	19	513
3	Nigeria	13	78
4	Pakistan	7	69
5	United States	6	49
6	China	4	25
7	Indonesia	4	2
8	Malaysia	4	199
9	Portugal	4	541
10	France	3	19
11	Philippines	3	100
12	Taiwan	3	271
13	Thailand	3	1

Network analysis of country co-authorship, which visualizes international collaborations, reduced the 40 countries to 13 connected nodes forming 4 distinct clusters (Fig. 4). These clusters, inferred from the dataset, suggest thematic or strategic research partnerships (Table-3). For instance, cluster 1 (*e.g.* Brazil, Portugal, France) shows strong collaboration often focused on phytochemistry and pharmacological applications. Cluster 2 (*e.g.* India, Thailand, Indonesia, Malaysia) represents collaboration among major Asian research hubs. Cluster 3 (*e.g.* Nigeria, USA, Pakistan) connects African researchers with international institutions and Cluster 4 (*e.g.* China, Taiwan, Philippines) focuses on the isolation of novel bioactive compounds. The most cited organisations were predominantly affiliated with universities in Pakistan and Nigeria (Table-4), reinforcing the influence of specific well-funded hubs in driving the global *C. pulcherrima* research agenda.

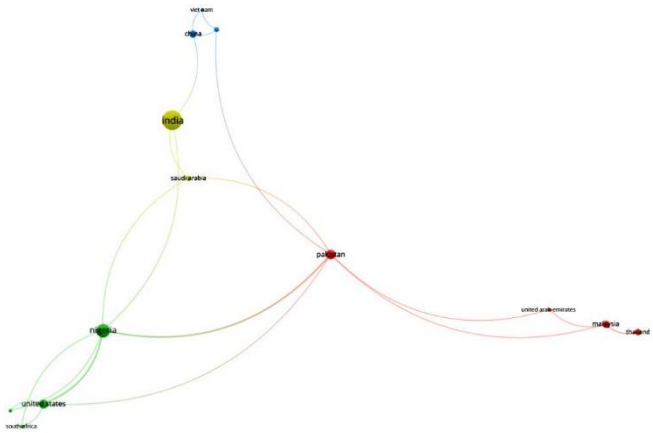

Fig. 4. VOSviewer-generated network visualisation of country collaboration clusters. The size of a node represents the volume of publications and connecting lines represent collaborative ties

Pharmacokinetic profiling and drug-likeness of *C. pulcherrima* compounds: The drug-likeness and ADMET (absorption, distribution, metabolism, excretion and toxicity) properties of the nine investigated compounds were systematically evaluated to assess their potential as orally bioavailable therapeutics. The results (Tables 5 and 6) are based on the Lipinski's rule of five (Ro5) and advanced pharmacokinetic predictions.

Drug-likeness and Ro5 compliance: All small-molecule compounds including dexamethasone (**1**), terpenoids (**3-5**) and flavonoids (**6-9**), adhered to the Lipinski's rule of five (Table-6). This indicates a high probability of oral bioavailability for these molecules as their molecular weight was < 500 Da, Log P ≤ 5, hydrogen bond donors (HBD) ≤ 5 and hydrogen bond acceptors (HBA) ≤ 10. In contrast, galactomannan (**2**), a polysaccharide, significantly exceeded the Ro5 criteria for molecular weight (504.44 Da), HBA (16), HBD (11) and topological polar surface area (TPSA, 268.68 $Å^2$). Despite this, it was included in further analyses due to its documented bioactivity as an anti-inflammatory and antioxidant agent [9].

Pharmacokinetic parameters: Analysis of absorption revealed that control drug (**1**) and flavonoids (**6**, **7**, **8** and **9**) were predicted to have high gastrointestinal (GI) absorption, suggesting favourable oral bioavailability. Terpenoids (**3**, **4**, **5**) and galactomannan (**2**) were predicted to have low GI absorp-

TABLE-3
INFERRED INTERNATIONAL COLLABORATION CLUSTERS IN *Caesalpinia pulcherrima* RESEARCH

Cluster	Core Countries (Inferred)	Potential Research Focus
1	Brazil, Portugal, France	Phytochemistry, polysaccharide extraction, pharmacological applications
2	India, Thailand, Indonesia, Malaysia	Antioxidant, antimicrobial and anticancer activities
3	Nigeria, USA, Pakistan	Isolation and testing of diterpenoids and other compounds
4	China, Taiwan, Philippines	Isolation of novel bioactive compounds (*e.g.*, cassane diterpenoids) and mechanistic studies

TABLE-4
MOST CITED ORGANISATIONS IN *Caesalpinia pulcherrima* RESEARCH

Rank	Organisation	Country	Total citations
1	The H.E.J. Research Institute of Chemistry, University of Karachi	Pakistan	54
2	Department of Pharmaceutical Chemistry, University of Benin	Nigeria	23
3	Department of Chemistry, Federal University of Technology, Akure	Nigeria	21
4	Department of Chemistry, University of Benin	Nigeria	21

TABLE-5
PHARMACOKINETICS PARAMETERS FOR *Caesalpinia pulcherrima* LEAD PHYTOCHEMICALS

	1	2	3	4	5	6	7	8	9
GI absorption	High	Low	Low	Low	Low	High	High	High	High
BBB permeant	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
P-gp substrate	Yes	Yes	No	No	No	Yes	No	No	No
CYP1A2 inhibitor	No	No	No	No	No	Yes	No	Yes	Yes
CYP2C19 inhibitor	No	No	No	No	No	Yes	Yes	Yes	Yes
CYP2C9 inhibitor	No	No	No	No	No	Yes	Yes	Yes	No
CYP2D6 inhibitor	No	No	No	Yes	No	Yes	No	Yes	No
CYP3A4 inhibitor	No	No	No	No	No	Yes	Yes	Yes	Yes
Log Kp (skin permeation) (cm/s)	-7.32	-13.87	-4.85	-4.21	-3.94	-6.41	-5.72	-5.42	-5.93

TABLE-6
THE BINDING ENERGIES OF THE COMPOUNDS AND THEIR DRUG-LIKENESS

Compound name	Code	Binding energy (kcal/mol)	m.f.	Lipinski's rule of five*				
				MW (Da)	LogP ≤ 5	HBA ≤ 10	HBD ≤ 5	TPSA (Å) ≤ 140
Dexamethasone** (CID:5743)	1	-3.7	$C_{22}H_{29}FO_5$	392.46	2.15	6	3	94.83
Galactomannan	2	-3.8	$C_{18}H_{32}O_{16}$	504.44	-5.28	16	11	268.68
α-Phellandrene	3	-2.9	$C_{10}H_{16}$	136.23	2.07	0	0	0.00
p-Cymene	4	-3.1	$C_{10}H_{14}$	134.22	3.50	0	0	0.00
γ-Terpinene	5	-3.1	$C_{10}H_{16}$	136.23	3.35	0	0	0.00
(2S)-5,7-Dimethoxy-3',4'-methylenedioxyflavanone	6	-3.6	$C_{18}H_{16}O_6$	328.32	2.67	6	0	63.22
2'-Hydroxy-2,3,4',6'-tetramethoxychalcone	7	-3.5	$C_{19}H_{20}O_6$	344.36	3.04	6	1	74.22
5,7-Dimethoxyflavone	8	-3.7	$C_{17}H_{14}O_4$	282.29	3.13	4	0	48.67
Bonducellin	9	-3.9	$C_{17}H_{14}O_4$	282.29	2.74	4	1	55.76

*MW: Molecular weight; Log P: lipophilicity; HBD: hydrogen-bond donor; HBA: hydrogen-bond acceptor; TPSA: topographical surface area; **marketed-drug control; ***terpenoid control

tion. Regarding distribution, all flavonoids (**6**-**9**) and terpenoids (**3**-**5**) were predicted to be blood-brain barrier (BBB) permeants, indicating their potential to target neuroinflammatory conditions. Dexamethasone (**1**) and galactomannan (**2**) were predicted not to cross the BBB (Fig. 5).

For metabolism and efflux, several key observations were investigated. Dexamethasone (**1**) and galactomannan (**2**) were predicted to be substrates of P-glycoprotein (P-gp), a major efflux transporter that can limit drug bioavailability. Among cytochrome P450 enzymes, flavonoids, particularly compounds **6**, **8** and **9**, showed strong potential to inhibit multiple CYP isoforms, including CYP1A2, CYP2C19, CYP2C9 and CYP3A4. This suggests a potential risk for drug-drug interactions if developed as therapeutics. The skin permeation (Log Kp) values for all compounds were below the threshold of -3.0 cm/s, indicating a low potential for transdermal delivery [124].

Molecular docking and binding interactions: Molecular docking simulations were performed to evaluate the binding affinity and interaction modes of the selected compounds with the NF-κB p50 homodimer (PDB ID: 1SVC). The calculated binding energies are summarised in Table-6.

Binding affinity: Among the tested compounds, bonducellin (**9**) demonstrated the most favourable binding energy of -3.9 kcal/mol, which was slightly stronger than the control

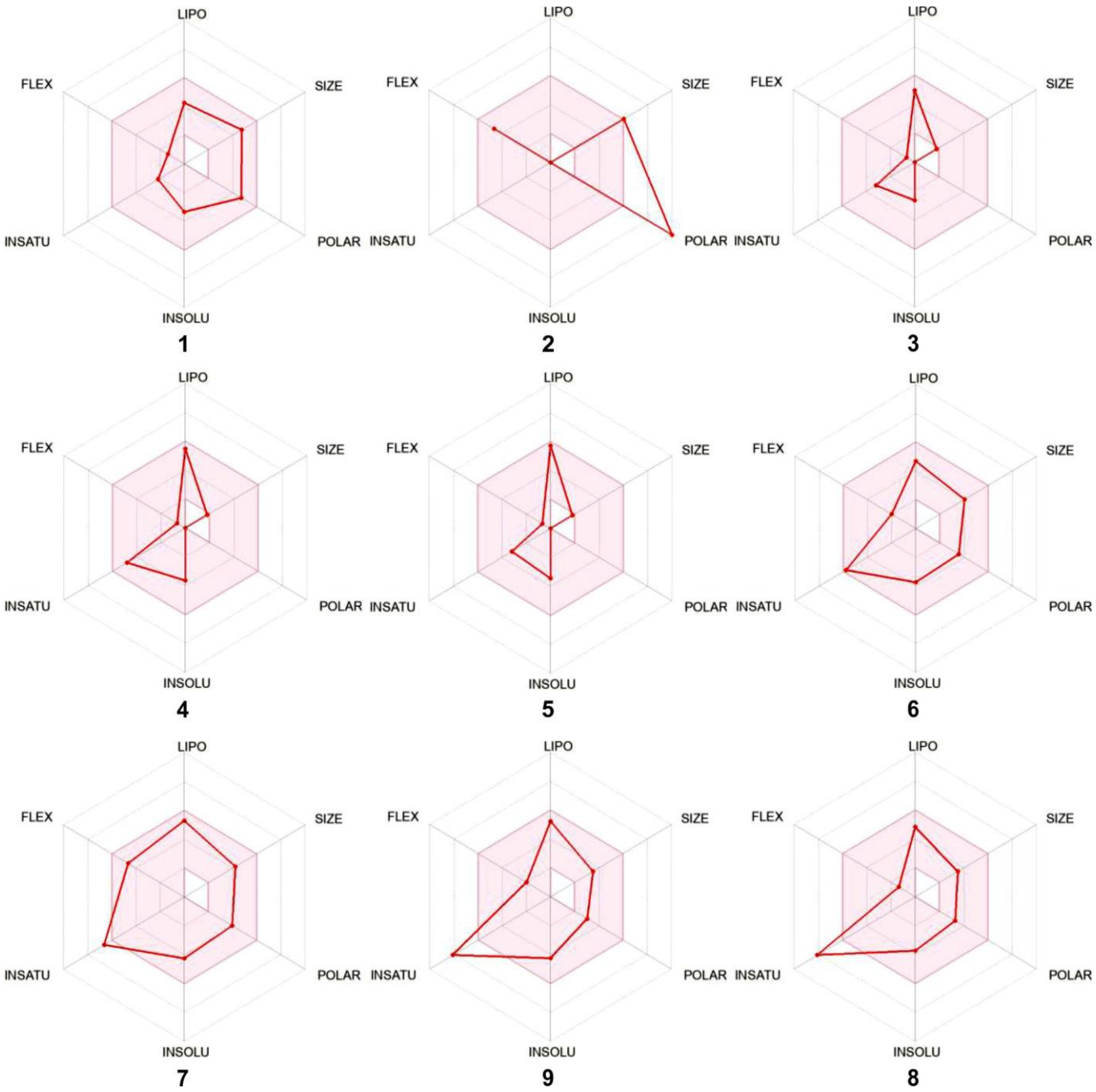

Fig. 5. Radar maps for ADME for the isolated compounds of *C. pulcherrima*

drug, dexamethasone (**1**; -3.7 kcal/mol). Another flavonoid, 5,7-dimethoxyflavone (**8**), exhibited a binding affinity equivalent to dexamethasone (-3.7 kcal/mol). Galactomannan (**2**) also showed a promising binding energy of -3.8 kcal/mol, despite its unfavourable pharmacokinetic profile for oral administration. The other flavonoids, compounds **6** (-3.6 kcal/mol) and **7** (-3.5 kcal/mol), along with the terpenoids (**3**, **4**, **5**; -2.9 to -3.1 kcal/mol), showed moderate to lower binding affinities.

Analysis of molecular interactions: A detailed analysis of the binding poses for the top-performing compounds (**1**, **2**, **8** and **9**) revealed critical pharmacophore interactions with key amino acid residues within the DNA-binding site of the p50 subunit (Table-7).

Molecular docking results demonstrated ligand-specific interaction patterns within the NF-κB p50 binding pocket, where dexamethasone (**1**) formed hydrogen-bond interactions with LYS P:244 and GLN P:309 (Fig. 6), galactomannan (**2**) established an extensive hydrogen-bonding network with LYS P:244, LYS P:275 and GLN P:309 accompanied by a π-cation interaction (Fig. 7), 5,7-dimethoxyflavone (**8**) displayed combined electrostatic and hydrophobic interactions involving LYS P:275, LYS P:244 and PRO P:246 (Fig. 8), while bonducellin (**9**), the highest-affinity ligand, was predominantly stabilised through hydrophobic π-alkyl and alkyl interactions with LYS P:244 and PRO P:246, suggesting favourable accommodation within the hydrophobic region of

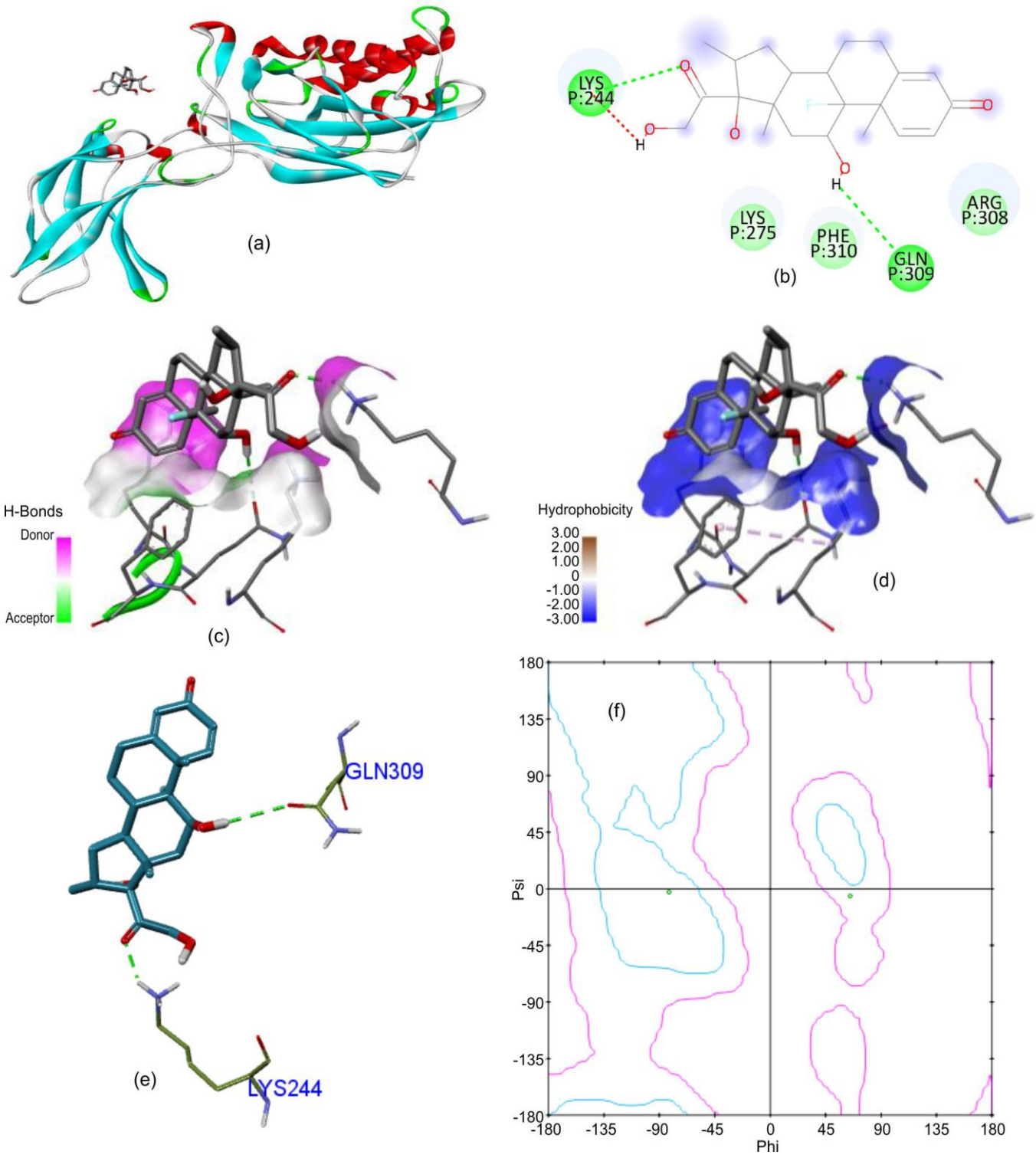

Fig. 6. Binding interactions of **1** with p50 subunit. (a) Receptor = ligand interaction, (b) two-dimensional display of ligand 3CLpro interactions, (c) H-bond property of binding pocket, (d) hydrophobicity profile of binding pocket, (e) detailed interactions of ligand and active site amino acid residues and (f) Ramachandran plot of ligand-interacting amino acid residues

the p50 subunit and potential disruption of the protein-DNA interaction interface (Fig. 9) [125]. The interacting amino acid residues for all four compounds were found within the most favoured regions of the Ramachandran plot, confirming the structural integrity and reliability of the binding site conformation used in the docking simulations.

Global research landscape and collaborative networks: The bibliometric findings illustrate a concentrated yet collaborative global research effort on *C. pulcherrima*. The high publications output from India, Brazil and Nigeria underscores the research interest in regions where the plant is native or widely cultivated [2,126]. However, citation metrics indi-

TABLE-7
FAVOURABLE RECEPTOR-LIGAND INTERACTION PHARMACOPHORE
DESCRIPTORS OF THE CONTROL AND BEST PERFORMING INHIBITORS

Compound	Amino acid	Distance (Å)	Category	Types
1 (Dexamethasone)	GLN309	2.82	Conventional hydrogen bond	Hydrophilic
	LYS244	2.06	Conventional hydrogen bond	Hydrophilic
	LYS244	1.31	Donor-donor	Electrostatic
2 (Galactomannan)	LYS244	2.52	Conventional hydrogen bond	Hydrophilic
	LYS275	2.46	Conventional hydrogen bond	Hydrophilic
	LYS275	2.22	Conventional hydrogen bond	Hydrophilic
	GLN309	2.77	Conventional hydrogen bond	Hydrophilic
8 (5,7-Dimethoxyflavone)	LYS244	2.77	Pi-Cation; Pi-Donor	Electrostatic
	LYS244	4.93	Pi-Alkyl	Hydrophobic
	PRO246	3.77	Alkyl	Hydrophobic
	LYS275	2.43	Conventional hydrogen bond	Hydrophilic
9 (Bonducellin)	PRO246	4.06	Alkyl	Hydrophobic
	LYS244	5.26	Pi-Alkyl	Hydrophobic

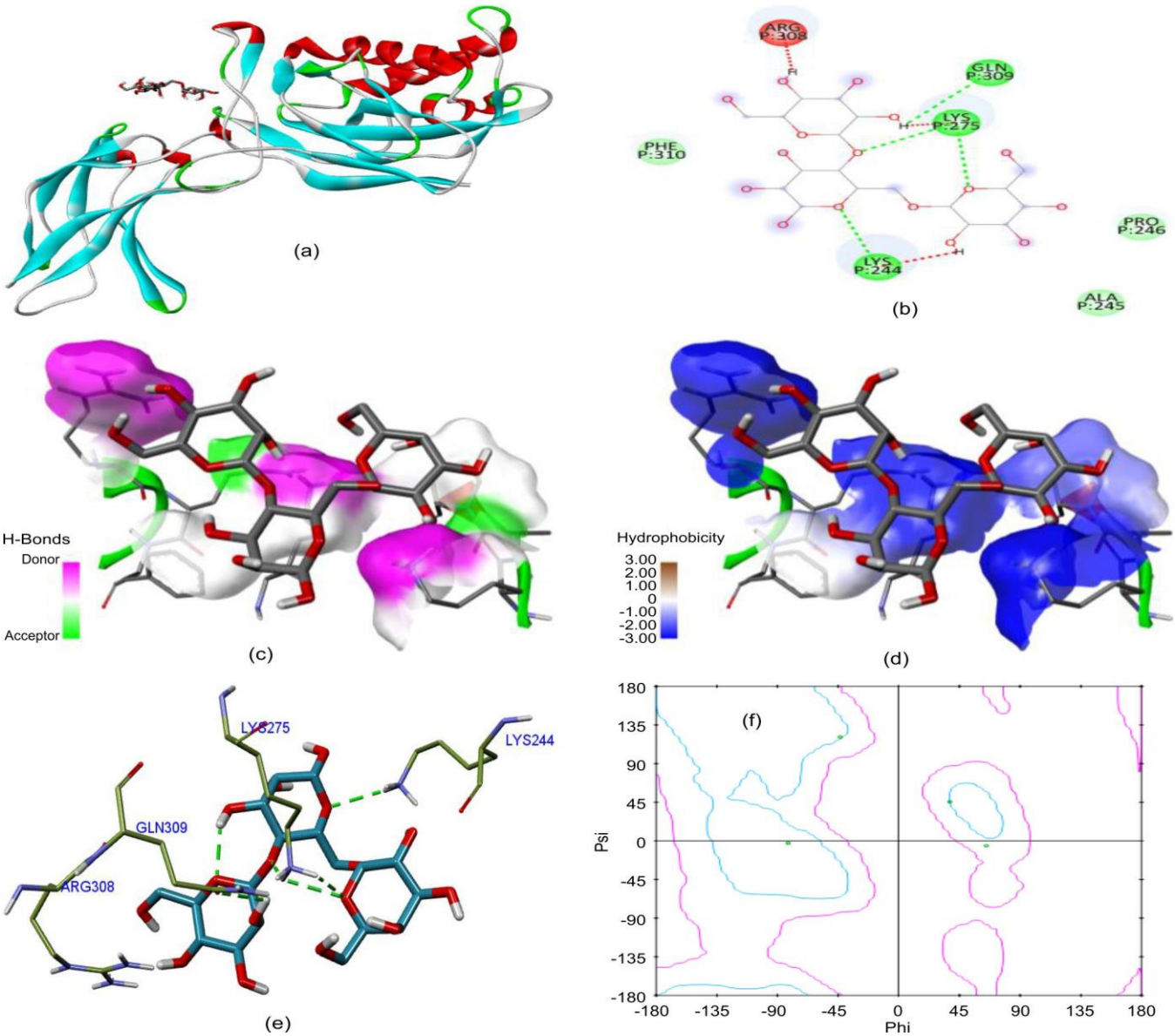

Fig. 7. Binding interactions of **2** with p50 subunit. (a) Receptor = ligand interaction, (b) two-dimensional display of ligand 3CLpro interactions, (c) H-bond property of binding pocket, (d) hydrophobicity profile of binding pocket, (e) detailed interactions of ligand and active site amino acid residues and (f) Ramachandran plot of ligand-interacting amino acid residues

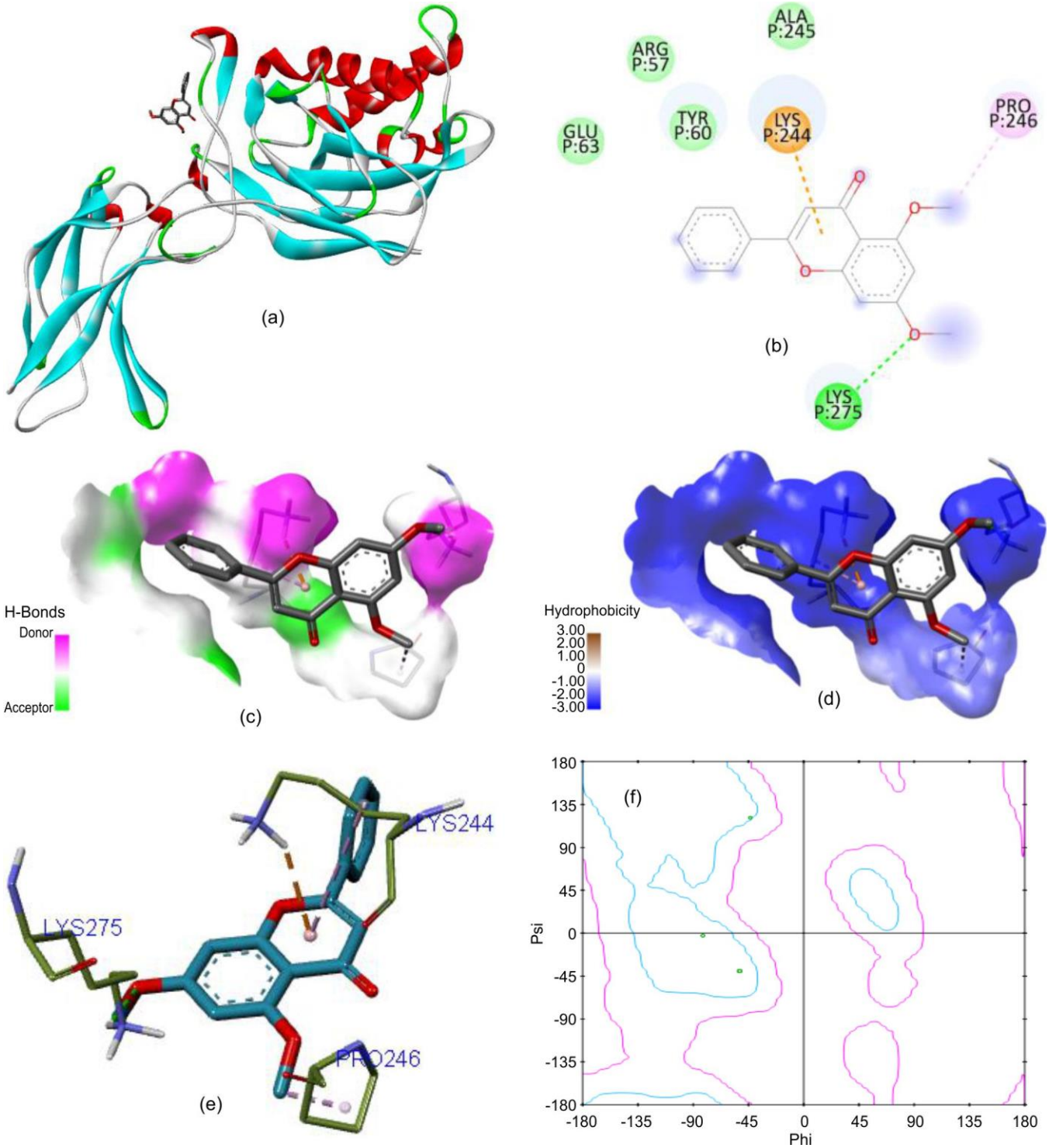

Fig. 8. Binding interactions of **8** with p50 subunit. (a) Receptor = ligand interaction, (b) two-dimensional display of ligand 3CLpro interactions, (c) H-bond property of binding pocket, (d) hydrophobicity profile of binding pocket, (e) detailed interactions of ligand and active site amino acid residues and (f) Ramachandran plot of ligand-interacting amino acid residues

cate a more complex trend; European nations like Portugal, despite a lower publication count, accumulated a high number of citations, suggesting a focus on high-impact research. The network visualisation (Fig. 4) reveals that international collaboration is a key driver of research visibility. Southeast Asian institutions, while active, appear predominantly on the periphery of these core collaborative networks, suggesting a current role as contributors rather than leaders in shaping the global *C. pulcherrima* research agenda. This supports the concept that a few well-funded centers often dominate a research field [18] and highlights an opportunity for more centralised leadership from regions with direct access to the phytochemical resources.

Therapeutic potential of *C. pulcherrima* phytochemicals: The integrated *in silico* pharmacokinetic and molecular

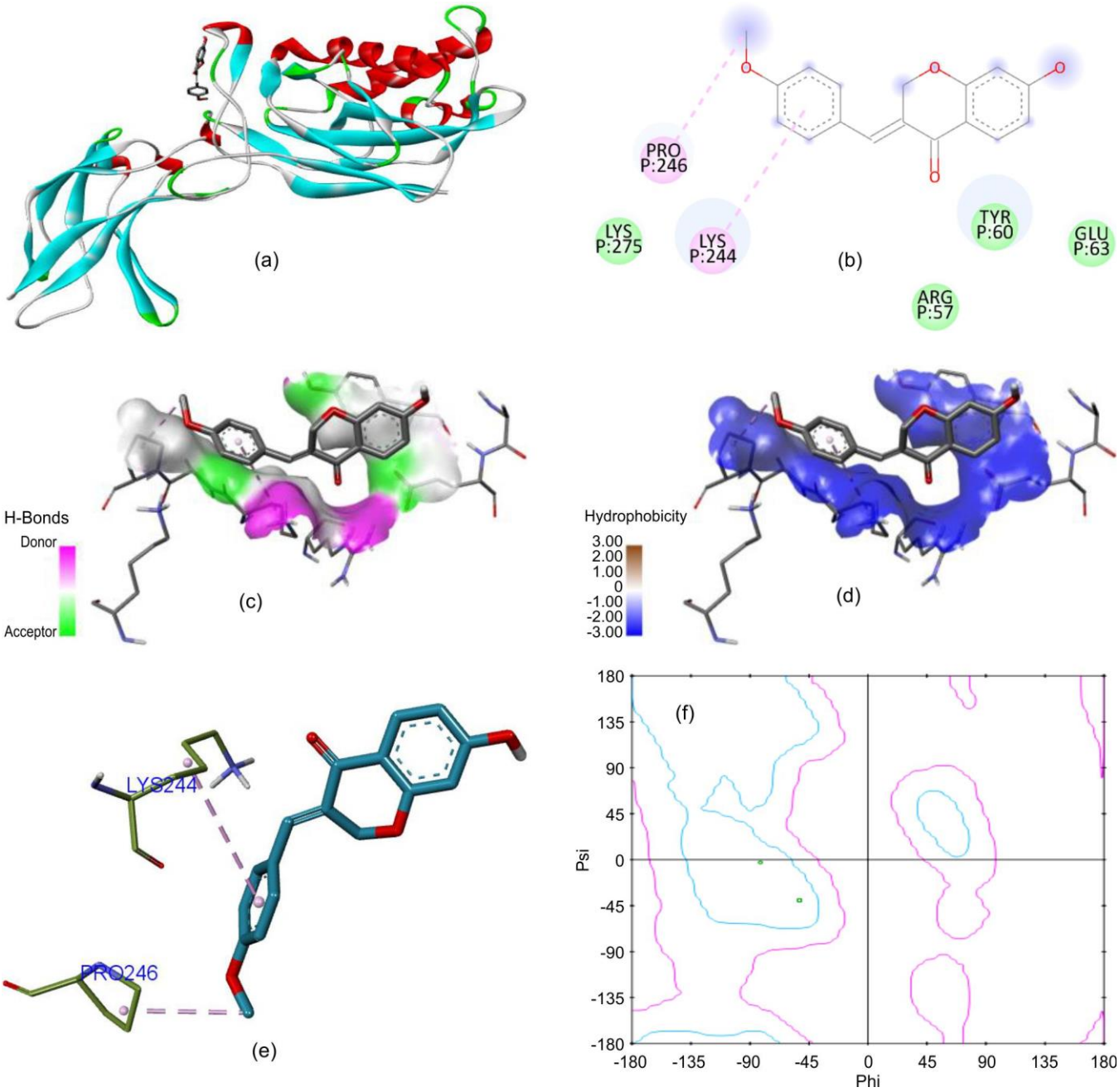

Fig. 9. Binding interactions of **9** with p50 subunit. (a) receptor = ligand interaction, (b) two-dimensional display of ligand 3CLpro interactions, (c) H-bond property of binding pocket, (d) hydrophobicity profile of binding pocket, (e) detailed interactions of ligand and active site amino acid residues and (f) Ramachandran plot of ligand-interacting amino acid residues

docking results provide a robust molecular rationale for the traditional use of *C. pulcherrima* in treating inflammatory conditions [111,127] and position its phytoconstituents as promising candidates for modern drug development. The findings of this study are particularly significant given the pivotal role of NF-κB p50 subunit in orchestrating inflammatory responses and in the pathogenesis of chronic inflammatory diseases including cancer [125]. Inhibitors targeting this subunit hold immense promise for modulating dysregulated immune responses.

Present study identified three phytoconstituents, galactomannan (**2**), 5,7-dimethoxyflavone (**8**) and bonducellin (**9**) as particularly promising p50 inhibitors, as their binding affinities were equivalent to or surpassed that of the control drug, dexamethasone (-3.7 kcal/mol). The most significant result was the superior binding energy of bonducellin (**9**) at -3.9 kcal/mol. Guided by pharmacophore analysis [128], the binding modes of these top compounds revealed diverse yet strategic interactions with key residues in the DNA-binding pocket. Bonducellin (**9**) primarily stabilised its complex through hydrophobic interactions (pi-alkyl and alkyl) with residues LYS P:244 and PRO P:246. This binding mode is highly favourable for disrupting the protein-DNA interface, as it effectively occupies the hydrophobic core of the binding site [15]. In contrast,

dexamethasone (**1**), a WHO essential medicine for decades, relied heavily on conventional hydrogen bonds with LYS P:244 and GLN P:309 [129]. The ability of bonducellin (**9**) to achieve a stronger binding affinity through predominantly hydrophobic forces suggests a potentially novel mechanism of p50 inhibition compared to the standard corticosteroid.

The interaction profile of galactomannan (**2**) is especially significant. Despite a favourable binding energy (-3.8 kcal/mol) driven by an extensive network of hydrogen bonds and a pi-cation interaction with key lysine residues, its pharmacokinetic profile predicts low oral bioavailability due to its high molecular weight and polarity. Despite this limitation, galactomannan (**2**) retains therapeutic relevance due to its reported anti-inflammatory and antioxidant properties [9], along with evidence that galactomannan-rich extracts exhibit antihyperglycemic activity [130], suggests its development may be more suitable for topical formulations, biomaterials or as a nutraceutical supplement where oral absorption is not a primary requirement. Previous research has successfully utilised natural polymers like galactomannan (**2**) to enhance nasal drug absorption [115] indicating a viable alternative delivery route.

The favourable drug-likeness and ADME profiles of the flavonoids (**6**-**9**) significantly enhance their therapeutic appeal. Their predicted high GI absorption and BBB permeation expand their potential applicability beyond peripheral inflammation to include neuroinflammatory disorders, a domain where many anti-inflammatory drugs are ineffective. Furthermore, the finding that 5,7-dimethoxyflavone (**8**) has been shown to inhibit intestinal efflux transporters like P-gp and breast cancer resistance protein (BCRP) [131] adds a compelling layer to its profile. This activity could not only enhance its own bioavailability but also potentially augment the absorption of coadministered drugs, a valuable property for combination therapies that could address issues of poor solubility and absorption common to many natural products [132].

It is found that flavonoids isolated from *C. pulcherrima*, particularly compounds **6**, **8** and **9**, were predicted to be inhibitors of several major cytochrome P450 enzymes. This indicates a potential liability for drug-drug interactions, which must be thoroughly investigated in subsequent preclinical studies. However, this property could also be explored for therapeutic synergies in specific controlled contexts. Despite their lower binding affinity and predicted poor gastrointestinal absorption, terpenoids (**3**-**5**) remain pharmacologically relevant. Their historical efficacy in traditional remedies such as use of *C. pulcherrima* essential oils for their insecticidal properties [10], suggests they may contribute to the overall bioactivity of whole *C. pulcherrima* extracts through synergistic effects or *via* mechanisms not captured by p50 docking alone.

The broader pharmacological context of these compounds reinforces their promise. Bonducellin (**9**), a homoisoflavonoid also found in *Caesalpinia bonduc*, has been investigated for its potential to treat endocrine disorders like polycystic ovary syndrome (PCOS) through integrated network pharmacology [133]. This aligns with the growing understanding of inflammation as a key driver in such metabolic and genetic diseases. Similarly, the presence of 5,7-dimethoxyflavone (**8**) in other medicinal plants like black ginger underscores its broad bioactivity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language. The authors reviewed and edited the content and take full responsibility for the published work.

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