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Research Article

Immunomodulatory and Antiallergic Potentials of the Bioactive Compounds of Ginger

B. Lalruatfela[1], P. B. Lalthanpuii[2], C. Lalrinmawia[2], K. Lalchhandama[1,2]*

ABSTRACT

Background: Allergy is an ever-increasing immune disorder and is often fatal under certain circumstances. Lack of total curative medication prompts the search for various compounds as the lead molecules. Ginger, *Zingiber officinale* Roscoe, is a well-established medicinal plant in different traditional practices. Its use as antiallergic or anti-inflammatory agent has been vindicated but the underlying mechanism of action is yet unknown. **Method:** In this study, we analyzed the phytocompounds characterized from ginger for their binding affinities on cysteinyl leukotriene receptor 1 (CysLTR1) and histamine H1 receptor (H1R) by molecular docking. The molecular interactions were compared against known agonists and antagonists of the two receptors. **Results:** The data indicate that ginger compounds have high binding affinity for both LTR1 and H1R comparable to those of antiallergic medications. The highest binding affinities were recorded for gingerenone-A (-7.3 kcal/mol) and zingiberol (-7.2 kcal/mol) on LTR1; and gingerenone-A (-8.7 kcal/mol) and α-curcumene (-8.0 kcal/mol) on H1R. **Conclusion:** In addition to antiallergic activity, molecular predications on the probable biological activities of the ginger compounds show that they can have a variety of medicinal applications including immunomodulatory and anticancer activities.
Key words: Allergy, Ginger, Histamine Receptor; Leukotriene Receptor, Molecular Modelling.

B. Lalruatfela[1], P. B. Lalthanpuii[2], C. Lalrinmawia[2], K. Lalchhandama[1,2]*

[1]Department of Zoology, Pachhunga University College, Mizoram University, Aizawl 796001, INDIA.

[2]DBT-BUILDER National Laboratory, Pachhunga University College, Mizoram University, Aizawl 796001, INDIA.

Correspondence

K. Lalchhandama

Department of Zoology and DBT-BUILDER National Laboratory, Pachhunga University College, Mizoram University, Aizawl 796001, INDIA.

E-mail: chhandama@pucollege.edu.in

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INTRODUCTION

Allergy and related immune hypersensitivity diseases have become one of the most common health issues, affecting about 20% of the global population,[1] and are coincidentally increasing with more civilized lifestyles.[2] As any external or internal particle can be a potential allergen, allergy can take many different forms and sometimes can be fatal, with an estimate of 19 death per 10,000 people every year.[3] Depending on the type of allergens, allergic reactions follow diverse molecular pathways and involve inflammatory immune cells such as mast cells, neutrophils, basophils, and eosinophils.[4]

A major molecular pathway of allergic reaction is the binding of histamines, released by the inflammatory cells, to histamine H1 receptors (H1R). The ligand-H1R binding is exploited by allergic medications such as cetirizine, chlorpheniramine, diphenhydramine, levocetirizine, and pheniramine that bind to H1R as antagonists or inverse agonists, thereby preventing the binding of histamine to H1R and abrogating the cascade of molecular pathway to initiate allergic reaction.[5,6] Cysteinyl leukotriene receptor 1 (CysLTR1) is another receptor that is activated in many allergic responses. The most important and potent agonist of CysLTR1 is cysteinyl leukotriene D4 (LTD4), an anti-inflammatory lipid mediator that is released during degranulation of mast cell and leads to histamine production.[7] Leukotriene C4 (LTC4) and leukotriene E4 (LTE4) are also CysLTR1 agonists. Common drugs like montelukast, zafirlukast and pranlukast are CysLTR1 antagonists. For enhanced allergic suppression, combination drugs are often used to target both H1R and CysLTR1.[8]

Beyond the general use as food condiment, ginger, *Zingiber officinale* Roscoe (family Zingiberaceae), is known to possess several therapeutic properties such as analgesic, anticancer, antidiabetic, anti-inflammatory, antiemetic, anthelminthic, anti-hyperglycaemic, and antimicrobial activities.[9,10] Experimental studies are reported for some of the major medicinal applications. Its major chemical constituents, 6-gingerol and 6-shogaol are shown to be promising lead compounds as anticancer drugs.[11] Its specific use as antiallergic agent is notable. It is variously recorded as a remedy for arthritis, food poisoning,[12] cough, antiallergic, anti-irritant, and anti-inflammatory activities.[13] Other bioactive compounds have also been determined including polyphenols such as 6-dehydrogingerdione, gingerenone-A, paradols, quercetin, and zingerone; terpenes such as β-bisabolene, α-curcumene, α-farnesene, β-sesquiphellandrene and zingiberene.[14] Although the major pharmacological properties, anti-inflammatory and anti-cancer activities, are quite empirically established,[15,16] there is no information on the biological activity of any of the ginger compounds at the molecular level. This study is therefore an attempt to show the molecular picture of the interaction between ginger compounds with the key cell receptors involved in allergic reactions, and the possible targets in other cellular activities.

MATERIALS AND METHODS

Ligand retrieval and processing

The 3D structure of cetirizine ($C_{21}H_{25}ClN_2O_3$, PubChem compound CID: 2678), histamine ($C_5H_9N_3$, PubChem compound CID: 774), leukotriene D4 ($C_{25}H_{40}N_2O_6S$, PubChem compound CID: 5280878), montelukast ($C_{35}H_{36}ClNO_3S$, PubChem compound CID: 5281040), 6-dehydrogingerdione ($C_{17}H_{22}O_4$, PubChem compound CID: 22321203), gingerenone-A ($C_{21}H_{24}O_5$, PubChem compound

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CID: 5281775), gingerol ($C_{17}H_{26}O_4$, PubChem compound CID: 442793), paradol ($C_{17}H_{26}O_3$, PubChem compound CID: 94378), quercetin ($C_{15}H_{10}O_7$, PubChem compound CID: 5280343), zingerone ($C_{11}H_{14}O_3$, PubChem compound CID: 31211), zingiberene ($C_{15}H_{24}$, PubChem compound CID: 92776), zingiberol ($C_{16}H_{28}O$, PubChem compound CID: 6455496), α-curcumene ($C_{15}H_{22}$, PubChem compound CID: 92139), α-farnesene ($C_{15}H_{24}$, PubChem compound CID: 5281516), β-bisabolene ($C_{15}H_{24}$, PubChem compound CID: 403919), β-sesquiphellandrene ($C_{15}H_{24}$, PubChem compound CID: 519764) were retrieved from PubChem, US National Center for Biotechnology Information (NCBI), in structured data file (SDF) formats. Chem Bio 3D Ultra using the force field MMFF94 was used to generate the structure optimization and cumulative potential energy minimization. The ligands were retrieved in protein data bank (PDB) formats for further analysis.

Protein retrieval and processing

X-ray crystal structure of cysteinyl leukotriene receptor 1 (CysLTR1, PDB code: 6RZ5) and histamine H1 receptor (H1R, PDB code: 3RZE) were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB)-PDB database (www.rcsb.org). To obtain clear molecular interactions, molecules attached to the proteins such as co-factors, water and unique ligands were removed with Molegro Molecular Viewer software.[17]

Molecular docking

Molecular docking of the ginger compounds to each of the recovered proteins was carried out on the AutoDock Vina platform, which is appreciated as the most powerful molecular modelling tool for ligand-receptor interactions.[18] Polar hydrogens and Kollman charges were added to all the proteins in the AutoDockTool-1.5.6 before saving the data in protein data bank, partial charge (Q) and atom type (T) (PDBQT) format. On the docking platform, the compounds of ginger were docked to CysLTR1 and H1R. In addition, leukotriene D4 and montelukast were docked to CysLTR1; histamine and cetirizine to H1R (Trott and Olson 2010).[19] Flexible docking was performed on all the proteins. Grid boxes were prepared for CysLTR1 (size_x=40, _y=46, _z=66, center_x=11.082, _y=15.676, _z=-8.069) and H1R (size_x=40, _y=40, _z=50, center_x=16.801, _y=35.487, _z=24.168) to cover all the possible protein binding sites. With an exhaustiveness of 8, the ligands were docked to the proteins and the outcomes were saved for visual analysis.

Visualization and analysis of interaction

Visualization of molecular interactions and docking analyses were performed on BIOVIA Discovery Studio Visualizer 2016 v16.1.0.15350. The software is a comprehensive tool suitable for micro- to macro-molecules for all types of molecular interactions in pharmacological studies.[20] The ligand output and protein PDBQT formats were accessed and defined. Non-bond interactions and ligand interactions were selected and labels were added to each of the residues. The files were then saved and converted to image files. The molecular docking showing lowest binding energy and the root-mean-square deviation (RMSD) were selected for each ligand-protein interaction.

Prediction of activity spectra for substances

To predict to biological activities of the ginger compounds based on their structural resemblance to already known molecules, an online tool, prediction of activity spectra for substances (PASS) (http://www.way2drug.com/passonline/predict.php) was employed.[21] The simplified molecular-input line-entry system (SMILES) data of the compounds retrieved from PubChem as previously mentioned were uploaded for the prediction. Predicted probable biological activities were given with their probability to be active (Pa) and their probability to be inactive (Pi). Pa of more or equal to 0.7 were considered in this study.

RESULTS AND DISCUSSION

Molecular docking results showing the docking score expressed in kcal/mol, amino acid residues of receptors and types of interactions involved in the interaction of the compounds of ginger with CysLTR1 and H1R are shown in Table 1 and Table 2 respectively. Leukotriene D4 and montelukast bind to similar region on CysLTR1 although the amino acid residues they interacted differ (Figure 1, Table 1). Ginger compounds, 6-dehydrogingerdione, gingerenone A, gingerol, paradol, quercetin, zingerone, zingiberol and α-farnesene shared the binding sites with leukotriene D4 and montelukast (Figure 2). Zingiberene, α-curcumene, β-bisabolene, and β-sesquiphellandrene bind to CysLTR1 on different sites and do not interfere with the binding of leukotriene D4 or montelukast, both of which bind to the same site (Figure 3). For H1R, cetirizine and histamine bind to different regions (Figure 3A). 6-Dehydrogingerdione, gingerol, paradol, zingiberene, α-farnesene, β-bisabolene and β-sesquiphellandrene bind in the same binding pocket as cetirizine on the H1R while gingerenone-A, quercetin, zingerone and α-curcumene share similar binding pocket with histamine. However, zingiberol neither binds to similar region on H1R as histamine nor with cetirizine (Figure 3H).

The predicted probable biological activities of 6-dehydrogingerdione, gingerenone-A, gingerol, paradol, quercetin, zingerone, zingiberene, zingiberol, α-curcumene, α-farnesene, β-bisabolene and β-sesquiphellandrene are shown in Table 3 and 4 respectively. Gingerenone-A is predicted to have anti-inflammatory activity with a Pa of 0.759 (Table 3). Interestingly, quercetin is predicted to be a histamine release stimulant (Pa 0.751) as well as histamine release inhibitor (Pa 0.720). Zingiberol is predicted to be anti-inflammatory (Pa 0.763) as well as immunosuppressant (Pa 0.749) (Table 10). α-Farnesene also showed a Pa of 0.816 as G-protein coupled receptor kinase inhibitor (Table 4). β-Bisabolene and β-sesquiphellandrene are predicted to be immunosuppressants while only β-bisabolene is showed to have anti-inflammatory property.

Our result shows that montelukast and leukotriene D4 can bind to similar region of CysLTR1, however, montelukast exhibited lower binding affinity (-9.7 kcal/mol) than leukotriene D4 (-6.5 kcal/mol) (Table 1). Even though leukotriene D4 is released during mast cell degranulation, this may be the reason montelukast acts effectively as an antiallergic medication. In a comparable manner, our result showed that the molecular docking score of histamine to H1R is -4.5 kcal/mol while the docking score of cetirizine, an H1R antagonist, is -7.2 kcal/mol (Table 2).

A clinical trial had shown that ginger extract treatment alleviates the symptoms of allergic rhinitis and the result was found to be comparable to loratadine which is known to directly target H1R.[22] A study in mice indicated that gingerol is the main molecule that suppresses the production of cytokines and subsequent reactions in allergic rhinitis symptoms.[23] The compound is also reported to suppress eosinophilia and interleukin-1 beta-induced MUC5AC gene expression in human airway epithelial cells and also reduced intestinal allergic reactions in irritable bowel syndrome.[24,25] 6-Gingerol, 10-gingerol and 6-shagaol have been reported to relax the smooth muscles of the airway by acting as β-agonists and inhibit phosphodiesterase 4D and phosphatidylinositol-specific phospholipase C.[26] Our result indicates that gingerol has lower affinity for CysLTR1 than leukotriene D4, but a higher affinity for H1R than histamine which may imply that the antiallergic property of gingerol may be through competitive inhibition of H1R.

Another compound of ginger, quercetin, exerts antiallergic property by inhibiting the production of histamine and other pro-inflammatory mediators,[27] which is at par with our results wherein quercetin has high binding affinity for both CysLTR1 and H1R (-8.3 and -9.0 kcal/

Table 1: Molecular interactions of leukotriene D4, montelukast and compounds of ginger with cysteinyl leukotriene receptor 1 (CysLTR1).

Compound	aa-R	aa-P	Types of interaction	MDS (kcal/mol)
Leukotriene D4	Threonine	154	Conventional Hydrogen bond	-6.5
	Proline	176	Alkyl	
	Proline	177		
	Tyrosine	108		
Montelukast	Phenylalanine	112	Conventional Hydrogen bond	-9.7
	Phenylalanine	150	Carbon Hydrogen bond	
	Phenylalanine	158	Pi-Pi Stacked	
	Alanine	161	Alkyl	
	Serine	193	Pi-Alkyl	
	Valine	196		
	Arginine	253		
6-Dehydrogingerdione	Phenylalanine	158	Conventional Hydrogen bond	-6.1
	Proline	177	Carbon Hydrogen bond	
	Serine	193	Pi-Cation	
	Arginine	253	Pi-Pi T-shaped	
Gingerenone-A	Phenylalanine	158	Carbon Hydrogen bond	-7.3
	Valine	186	Pi-Sigma	
	Tyrosine	249	Pi-Pi T-shaped	
	Arginine	253	Pi-Alkyl	
	Valine	277		
	Leucine	281		
Gingerol	Phenylalanine	158	Conventional Hydrogen bond	-6.1
	Serine	193	Carbon Hydrogen bond	
	Tyrosine	249	Pi-Cation	
	Arginine	253	Pi-Pi T-shaped	
Paradol	Phenylalanine	158	Carbon Hydrogen bond	-6.1
	Proline	177	Unfavorable Acceptor-Acceptor	
	Valine	186	Pi-Pi T-shaped	
	Glutamic acid	175		
Quercetin	Tyrosine	249	Unfavorable Acceptor-Acceptor	-8.3
	Arginine	253	Pi-Sigma	
	Histidine	256	Pi-Pi T-shaped	
	Valine	277	Pi-Alkyl	
	Leucine	281		
Zingerone	Tyrosine	104		-6.1
	Tyrosine	249	Conventional Hydrogen bond	
	Arginine	253	Pi-Alkyl	
	Valine	277		
Zingiberene	Phenylalanine	112		-6.0
	Phenylalanine	119		
	Valine	143	Alkyl	
	Isoleucine	147	Pi-Alkyl	
	Isoleucine	200		
	Proline	201		
	Isoleucine	204		
Zingiberol	Proline	176		-7.2
	Proline	177	Conventional Hydrogen bond	
	Arginine	253	Alkyl	
	Histidine	256	Pi-Alkyl	
	Leucine	257		
	Valine	277		
α-Curcumene	Phenylalanine	112		-6.2
	Alanine	116	Pi-Sigma	
	Valine	143	Pi-Pi T-shaped	
	Isoleucine	147	Alkyl	
	Phenylalanine	150	Pi-Alkyl	
	Phenylalanine	158		
α-Farnesene	Tyrosine	249		-6.3
	Arginine	253	Alkyl	
	Valine	277	Pi-Alkyl	
	Leucine	281		
β-Bisabolene	Phenylalanine	112		-5.3
	Valine	143	Alkyl	
	Isoleucine	147	Pi-Alkyl	
	Phenylalanine	150		
β-Sesquiphellandrene	Phenylalanine	112		-6.0
	Valine	143	Alkyl	
	Isoleucine	147	Pi-Alkyl	
	Phenylalanine	150		

aa-R: Amino acid residues on receptor
aa-P: Position of amino acid residues
MDS: Molecular docking score

Table 2: Molecular interactions of histamine, cetirizine and compounds of ginger with histamine H1 receptor (H1R).

Compound	aa-R	aa-P	Types of interaction	MDS (kcal/mol)
Histamine	Tyrosine	108	Van der Waals	-4.5
	Serine	111	Conventional hydrogen bond	
	Threonine	112	Pi-Pi T-shaped	
	Isoleucine	115	Amide-Pi Stacked	
	Asparagine	198	Pi-Alkyl	
	Tryptophan	428		
	Phenylalanine	432		
Cetirizine	Proline	161	Conventional hydrogen bond	-7.2
	Tryptophan	158	Unfavorable Acceptor-Acceptor	
	Phenylalanine	190	Pi-Pi Stacked	
	Asparagine	198	Alkyl	
6-Dehydrogingerdione	Tryptophan	158	Conventional Hydrogen Bond	-5.2
	Phenylalanine	190	Pi-Sigma	
			Pi-Pi T-shaped	
Gingerenone-A	Asparagine	84	Conventional Hydrogen Bond	-8.7
	Tyrosine	108	Pi-Sigma	
	Aspartic acid	178	Pi-Pi T-shaped	
	Lysine	179		
	Tyrosine	431		
	Phenylalanine	432		
	Isoleucine	454		
Gingerol	Glycine	164	Conventional Hydrogen Bond	-5.6
	Histidine	167	Carbon Hydrogen Bond	
	Aspartic acid	183	Pi-Cation	
	Valine	187	Pi-Sigma	
			Pi-Pi T-shaped	
Paradol	Tryptophan	158	Conventional Hydrogen Bond	-5.4
	Proline	161	Pi-Pi T-shaped	
	Asparagine	198	Pi-Alkyl	
Quercetin	Aspartic acid	107	Conventional Hydrogen Bond	-9.0
	Tyrosine	108	Carbon Hydrogen Bond	
	Serine	111	Pi-Anion	
	Threonine	112	Pi-Pi T-shaped	
	Lysine	191	Pi-Alkyl	
	Phenylalanine	432		
	Phenylalanine	435		
	Isoleucine	454		
Zingerone	Tyrosine	458	Carbon Hydrogen Bond	-6.9
	Aspartic acid	107	Pi-Pi T-shaped	
	Tyrosine	108		
	Tryptophan	158		
	Phenylalanine	432		
Zingiberene	Isoleucine	160	Alkyl	-5.3
	Leucine	154	Pi-Alkyl	
	Leucine	157		
	Tryptophan	158		
	Proline	161		
	Phenylalanine	190		
	Methionine	193		
Zingiberol	Phenylalanine	116	Pi-Sigma	-6.7
	Phenylalanine	119	Alkyl	
	Isoleucine	120	Pi-Alkyl	
	Alanine	151		
	Leucine	154		
α-Curcumene	Tyrosine	108	Pi-Alkyl	-8.0
	Tryptophan	428		
	Tyrosine	431		
	Phenylalanine	432		
	Phenylalanine	435		
α-Farnesene	Leucine	157	Pi-Sigma	-5.5
	Tryptophan	158	Alkyl	
	Proline	161	Pi-Alkyl	
	Phenylalanine	184		
	Phenylalanine	190		
β-Bisabolene	Leucine	154	Alkyl	-5.3
	Tryptophan	158	Pi-Alkyl	
	Proline	161		
	Phenylalanine	190		
β-Sesquiphellandrene	Histidine	167	Pi-Sigma	-6.2
	Valine	187	Alkyl	
	Tryptophan	189	Pi-Alkyl	
	Phenylalanine	190		

aa-R: Amino acid residues on receptor
aa-P: Position of amino acid residues
MDS: Molecular docking score

Table 3: Probable biological activities of polyphenols from ginger.

Biological activities	6-Dehydroginger-dione		Gingerenone-A		Gingerol		Paradol		Zingerone	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
Preneoplastic conditions treatment	0.936	0.001	0.851	0.003	0.772	0.004	0.892	0.002	0.841	0.003
JAK2 expression inhibitor	0.914	0.003	0.898	0.003	-	-	0.811	0.007	0.870	0.004
HIF1A expression inhibitor	0.912	0.005	0.877	0.007	-	-	-	-	-	-
Mucositis treatment	0.902	0.006	0.750	0.018	-	-	0.787	0.015	0.738	0.020
Feruloyl esterase inhibitor	0.873	0.005	0.822	0.009	0.817	0.010	0.786	0.013	0.863	0.006
Beta-carotene 15,15'-monooxygenase inhibitor	0.862	0.002	-	-	0.707	0.005	-	-	0.784	0.004
MMP9 expression inhibitor	0.855	0.002	0.829	0.003	-	-	0.855	0.002	0.822	0.003
TNF expression inhibitor	0.853	0.003	-	-	-	-	-	-	0.715	0.006
Choleretic	0.817	0.003	-	-	-	-	-	-	-	-
Prostate cancer treatment	0.808	0.004	-	-	-	-	-	-	-	-
Vanillyl-alcohol oxidase inhibitor	0.806	0.002	-	-	-	-	0.729	0.002	-	-
Mucomembranous protector	0.815	0.015	0.778	0.025	-	-	0.844	0.010	0.883	0.005
Antimutagenic	0.789	0.004	0.746	0.005	-	-	0.789	0.004	0.796	0.004
Ubiquinol-cytochrome-c reductase inhibitor	0.810	0.030	0.779	0.040	0.817	0.027	0.851	0.017	0.828	0.024
Gluconate 2-dehydrogenase (acceptor) inhibitor	0.788	0.019	0.784	0.020	0.765	0.027	0.797	0.017	0.921	0.003
1-Acylglycerol-3-phosphate O-acyltransferase inhibitor	0.770	0.003	-	-	-	-	-	-	-	-
Steroid N-acetylglucosaminyltransferase inhibitor	0.768	0.004	0.801	0.003	0.771	0.004	0.854	0.002	0.843	0.002
HMOX1 expression enhancer	0.761	0.004	-	-	-	-	-	-	-	-
GST A substrate	0.766	0.014	-	-	0.717	0.020	-	-	-	-
Antineoplastic	0.763	0.017	-	-	-	-	-	-	-	-
Aspulvinone dimethylallyltransferase inhibitor	0.770	0.042	0.872	0.014	0.740	0.051	0.875	0.014	0.914	0.005
GST M substrate	0.724	0.003	-	-	-	-	-	-	-	-
Linoleate diol synthase inhibitor	0.727	0.010	-	-	0.911	0.003	0.897	0.004	0.906	0.003
GST P substrate	0.717	0.004	0.716	0.004	-	-	-	-	-	-
Reductant	0.711	0.005	-	-	-	-	-	-	-	-
GST P1-1 substrate	0.704	0.004	0.704	0.004	-	-	-	-	-	-
Monophenol monooxygenase inhibitor	0.701	0.004	-	-	-	-	-	-	-	-
Chlordecone reductase inhibitor	0.728	0.034	0.813	0.018	0.730	0.034	0.841	0.013	0.868	0.009
Apoptosis agonist	0.704	0.014	0.760	0.010	-	-	-	-	-	-
CYP2J substrate	0.714	0.045	-	-	-	-	-	-	-	-
Membrane integrity agonist	0.701	0.055	-	-	-	-	-	-	0.794	0.037
5 Hydroxytryptamine release stimulant	-	-	0.799	0.014	0.960	0.003	-	-	0.910	0.005
Beta-carotene 15,15'-monooxygenase inhibitor	-	-	0.785	0.003	-	-	0.811	0.003	-	-
Free radical scavenger	-	-	0.755	0.003	-	-	-	-	-	-
Antiinflammatory	-	-	0.759	0.009	-	-	-	-	-	-
Antieczematic	-	-	0.747	0.031	-	-	0.710	0.042	-	-
Fibrinolytic	-	-	0.707	0.020	0.758	0.008	0.764	0.007	0.867	0.004
CYP2C12 substrate	-	-	0.702	0.057	0.860	0.021	0.874	0.018	0.849	0.024
Macrophage colony stimulating factor agonist	-	-	-	-	0.762	0.007	0.701	0.014	-	-
Beta glucuronidase inhibitor	-	-	-	-	-	-	-	-	0.739	0.003
Polyporopepsin inhibitor	-	-	-	-	0.757	0.027	0.757	0.027	-	-
Vasodilator, peripheral	-	-	-	-	0.730	0.007	-	-	-	-
Chymosin inhibitor	-	-	-	-	0.735	0.035	0.717	0.040	-	-
Mycothiol-S-conjugate amidase inhibitor	-	-	-	-	-	-	0.783	0.003	-	-
Catechol 2,3-dioxygenase inhibitor	-	-	-	-	-	-	0.767	0.002	-	-
Lipid peroxidase inhibitor	-	-	-	-	-	-	0.726	0.005	-	-
Platelet derived growth factor receptor kinase inhibitor	-	-	-	-	-	-	-	-	0.854	0.003
Endothelial growth factor antagonist	-	-	-	-	-	-	-	-	0.747	0.003
Antipyretic	-	-	-	-	-	-	-	-	0.713	0.004
Testosterone 17beta-dehydrogenase (NADP+) inhibitor	-	-	-	-	-	-	-	-	0.722	0.048

Pa = Probability to be active
Pi = Probability to be inactive

Table 4: Probable biological activities of terpenes from ginger.

Biological activities	β-Bisabolene		β-Sesquiphellandrene		α-Farnesene		α-Curcumene		Zingiberene	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
Retinol dehydrogenase inhibitor	0.908	0.001	0.766	0.002	0.881	0.001	0.728	0.002	0.825	0.001
Myc inhibitor	0.904	0.001	-	-	-	-	-	-	-	-
Apoptosis agonist	0.899	0.004	-	-	0.870	0.005	-	-	-	-
Carminative	0.895	0.002	0.708	0.006	0.710	0.006	0.783	0.004	0.836	0.003
Antieczematic	0.868	0.008	0.904	0.005	0.928	0.004	0.872	0.007	0.794	0.020
Antineoplastic	0.856	0.006	0.827	0.009	0.848	0.007	-	-	-	-
Alpha-pinene-oxide decyclase inhibitor	0.798	0.001	-	-	-	-	-	-	-	-
CYP2C substrate	0.789	0.010	-	-	-	-	0.743	0.023	-	-
Mucomembranous protector	0.787	0.022	0.805	0.017	0.952	0.003	0.942	0.004	0.842	0.010
CYP2C19 substrate	0.762	0.005	-	-	0.758	0.020	-	-	-	-
CYP2J substrate	0.771	0.028	0.726	0.042	0.868	0.008	0.849	0.011	0.773	0.028
Chemoprotective	0.723	0.003	-	-	-	-	-	-	-	-
Prenyl-diphosphatase inhibitor	0.720	0.005	-	-	-	-	-	-	-	-
Antiinflammatory	0.726	0.013	-	-	-	-	-	-	-	-
Immunosuppressant	0.722	0.014	0.702	0.016	-	-	-	-	-	-
Antineoplastic (breast cancer)	0.708	0.005	-	-	-	-	-	-	-	-
Transcription factor NF kappa B stimulant	0.707	0.004	-	-	0.725	0.004	-	-	-	-
Transcription factor stimulant	0.707	0.004	-	-	0.725	0.004	-	-	-	-
Alkenylglycerophosphocholine hydrolase inhibitor	-	-	0.789	0.019	-	-	0.825	0.014	0.798	0.018
Prostaglandin-E2 9-reductase inhibitor	-	-	0.760	0.012	-	-	-	-	-	-
Antipsoriatic	-	-	0.750	0.004	-	-	-	-	-	-
Protein-disulfide reductase (glutathione) inhibitor	-	-	0.742	0.015	-	-	0.791	0.010	0.749	0.014
Vitamin-K-epoxide reductase inhibitor	-	-	0.720	0.004	-	-	0.757	0.003	0.728	0.003
Prenyl-diphosphatase inhibitor	-	-	0.720	0.005	0.937	0.001	0.816	0.003	0.736	0.005
Acylcarnitine hydrolase inhibitor	-	-	0.718	0.024	-	-	-	-	0.731	0.022
Ubiquinol-cytochrome-c reductase inhibitor	-	-	0.704	0.067	0.788	0.037	0.876	0.010	0.819	0.027
CYP2E1 inhibitor	-	-	-	-	0.946	0.002	-	-	-	-
Fatty-acyl-CoA synthase inhibitor	-	-	-	-	0.921	0.002	0.781	0.005	-	-
Undecaprenyl-phosphate mannosyltransferase inhibitor	-	-	-	-	0.913	0.001	0.776	0.004	0.703	0.006
Lipid metabolism regulator	-	-	-	-	0.884	0.004	-	-	-	-
Aspulvinone dimethylallyltransferase inhibitor	-	-	-	-	0.885	0.011	0.792	0.036	-	-
BRAF expression inhibitor					0.859	0.001	0.723	0.003		
2.3-Oxidosqualene-lanosterol cyclase inhibitor					0.823	0.001				
Phosphatidylcholine-retinol O-acyltransferase inhibitor					0.822	0.005	0.827	0.005		
All-trans-retinyl-palmitate hydrolase inhibitor					0.818	0.004	0.815	0.004		
G-protein-coupled receptor kinase inhibitor					0.816	0.011				
Beta-adrenergic receptor kinase inhibitor					0.816	0.011				
Dolichyl-phosphatase inhibitor					0.801	0.002				
TRPA1 agonist					0.783	0.002				
Antineoplastic (breast cancer)					0.780	0.005				
Antiviral (Rhinovirus)					0.764	0.002			0.711	0.002
Ecdysone 20-monooxygenase inhibitor					0.757	0.005				
Antiulcerative					0.756	0.004				
Plastoquinol-plastocyanin reductase inhibitor					0.746	0.003	0.756	0.002		
Beta-carotene 15,15'-monooxygenase inhibitor					0.741	0.004	0.739	0.004		
Radioprotector					0.738	0.008				
Alcohol O-acetyltransferase inhibitor					0.732	0.004				
Testosterone 17beta-dehydrogenase (NADP+) inhibitor					0.735	0.044	0.791	0.028		
Sugar-phosphatase inhibitor					0.714	0.031				
CDP-glycerol glycerophosphotransferase inhibitor					0.701	0.054	0.722	0.048		
Linoleate diol synthase inhibitor							0.754	0.008		
Fibrinolytic							0.728	0.014	0.758	0.008

Pa = Probability to be active
Pi = Probability to be inactive

mol respectively). Quercetin is also known to decrease reactive oxygen species (ROS) and TNF-α-induced oxidative stress, apoptosis and inflammation and also suppresses the expression of matrix metalloprotease-9 (MMP9) and intercellular adhesion molecule-1.[28,29] Our result indicates that quercetin may act similarly as HIF1A expression inhibitor, JAK2 expression inhibitor, MMP9 expression inhibitor and histamine release inhibitor (Table 4).

Although the role of gingerenone-A in allergy and inflammation is not well established, our result shows that it has high affinity for both CysLTR1 and H1R and may act as JAK2, HIF1A and MMP9 expressions inhibitor (Table 3). Similarly, zingiberol exhibited relatively high affinity for both LTR1 and H1R (Table 1 & 2). The biological activities predicted for zingiberol include anti-inflammatory and immunosuppressant properties. Zingerone has been demonstrated to have protective effects against oxidative stress, inflammation, asthma, thrombosis and histopathological alterations.[30] It exhibits lower binding energy than histamine for H1R, but has higher binding energy for CysLTR1 than leukotriene D4 suggesting the anti-inflammatory property of zingerone may be through H1R and not CysLTR1. Zingerone has also been predicted to have probable biological activities as JAK2 expression inhibitor, MMP9 expression inhibitor and TNF expression inhibitor (Table 3).

6-Dehydrogingerdione has been reported to have anti-inflammatory, antiallergic, antitumor and anti-atherosclerotic properties.[31] Paradol is a potent anticancer, chemopreventive, and anti-inflammatory compound.[32,33] Zingiberene is an established anticancer and anti-inflammatory compound.[34] α-Farnesene is a molecule of wide applications from medicine to mechanical appliances.[35] An essential oil, β-bisabolene is used in food flavouring and has anticancer activity.[36] β-sesquiphellandrene has strong anti-neoplastic property.[37] Our data indicates that 6-dehydrogingerdione, paradol, zingiberene, α-curcumene, α-farnesene, β-bisabolene and β-sesquiphellandrene also bind to the same receptor pocket of CysLTR1 as leukotriene D4, they all exhibited higher binding energy and thus may not be able to compete with leukotriene D4 (Table 1). However, all these phytocompounds has lower binding energy for H1R than histamine (Table 2). 6-Dehydrogingerdione and paradol are predicted to act as JAK2 expression inhibitors. Additionally, 6-dehydrogingerdione may also act as HIF1A, TNF and MMP9 expressions inhibitor (Table 3). β-Sesquiphellandrene may have the potential to be prostaglandin-E2 9-reductase inhibitor; while α-farnesene may act as both G-protein coupled receptor kinase and β-adrenergic receptor kinase inhibitor (Table 4).

CONCLUSION

Our molecular models show that the bioactive compounds of ginger interact well with CysLTR1 and H1R indicating that they can play direct role in the antiallergic and anti-inflammatory pathways. Some ginger phytocompounds such as 6-dehydrogingerdione, gingerenone-A, paradol, quercetin, and zingerone are predicted to be potential inhibitors of JAK2, a protein involved in allergic reactions via JAK-STAT pathway. HIF1A is also known to be activated during allergic reactions by IL-4 and IL-13, however, 6-dehydrogingerdione, gingerenone-A and quercetin are predicted to inhibit HIF1A expression. TNF and MMP9 are also involved in allergic reactions and both these may be inhibited by 6-dehydrogingerdione, gingerenone-A, paradol, quercetin and zingerone.

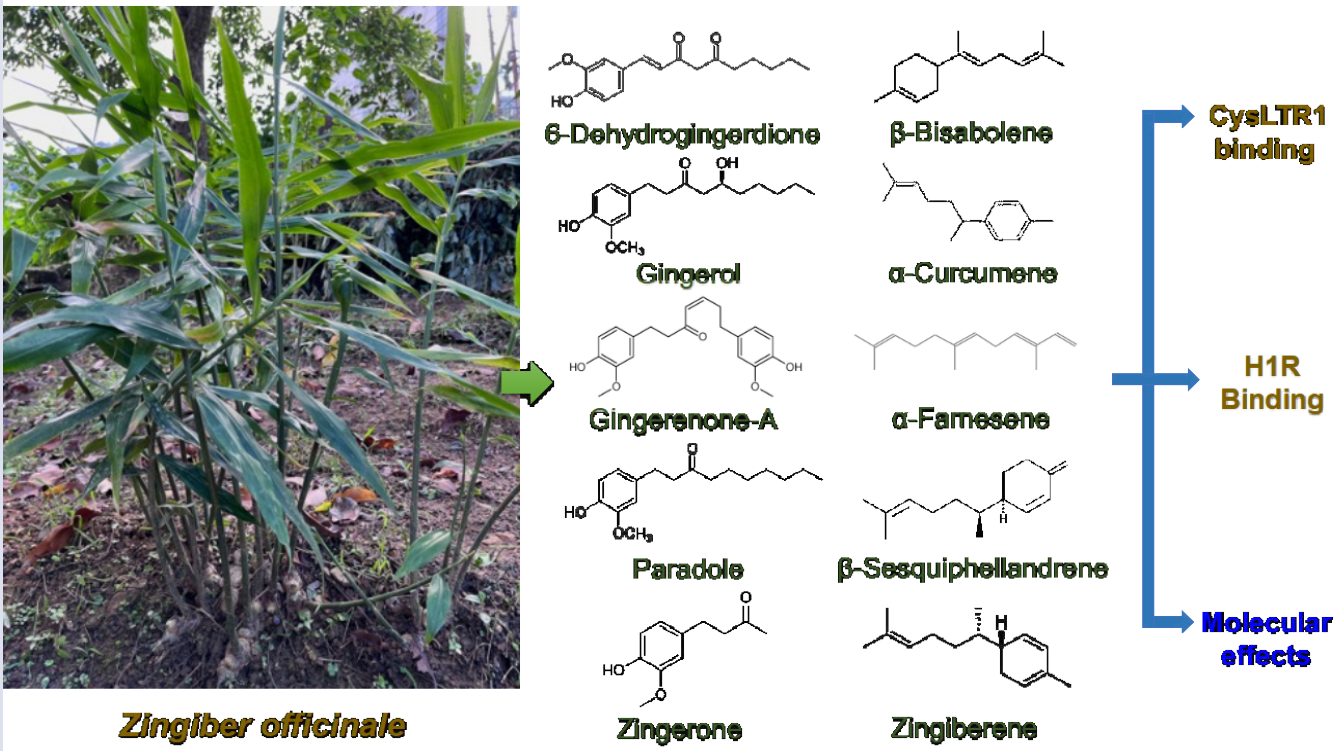

Figure 1: *Zingiber officinale* growing in Aizawl, Mizoram, India, and the chemical structures of the bioactive compounds used for molecular modelling of the pharmacological properties.

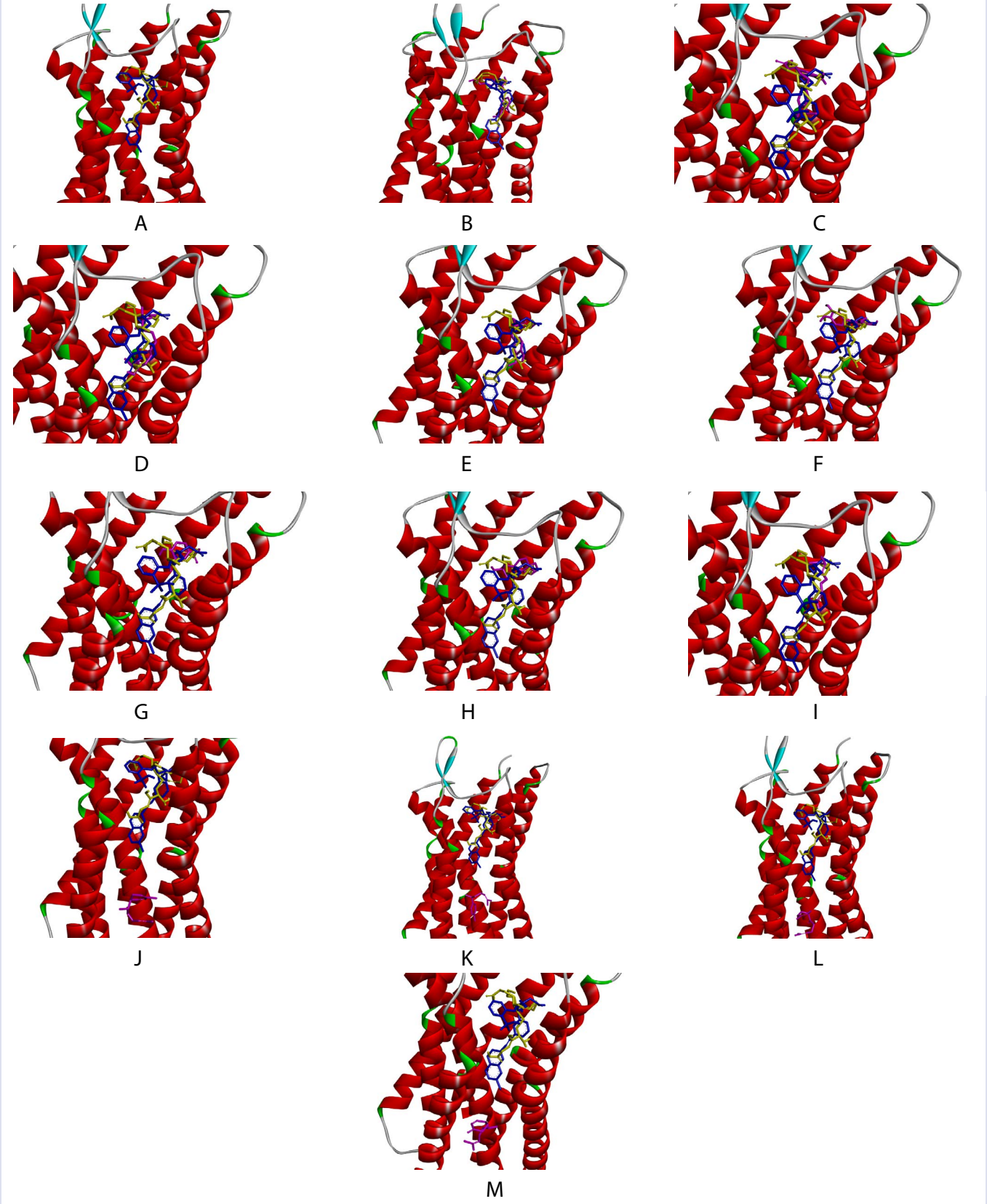

Figure 2: 3D model of the molecular binding site on cysteinyl leukotriene receptor 1 (CysLTR1) for antiallergic agents. A) Leukotriene D4 (LTD4) (brown) and montelukast (blue) share the same site. B) Binding of 6-dehydrogingerdione (purple). C) Binding of gingerenone-A (purple). D) Binding of gingerol (purple). E) Binding of paradol (purple). (purple). F) Binding of quercetin (purple). G) Binding of zingerone (purple). H) Binding of zingiberol (purple). I) Binding of α-farnesene (purple). J) Binding of zingiberene (purple). K) Binding of α-curcumene (purple). L) Binding of β-bisabolene (purple). M) Binding of β-sesquiphellandrene (purple).

Figure 3: 3D model of the molecular binding site on histamine H1 receptor (H1R) for antiallergic agents. A) Binding sites of cetirizine (brown) and histamine (blue). B) Binding of 6-dehydrogingerdione (purple). C) Binding of gingerenone-A (purple). D) Binding of gingerol (purple). E) Binding of paradol (purple). (purple). F) Binding of quercetin (purple). G) Binding of zingerone (purple). H) Binding of zingiberol (purple). I) Binding of α-farnesene (purple). J) Binding of zingiberene (purple). K) Binding of α-curcumene (purple). L) Binding of β-bisabolene (purple). M) Binding of β-sesquiphellandrene (purple).

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CONFLICTS OF INTEREST

None declared.

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