Anticancer Evaluation of Methanol Extract of *Ludwigia peruviana* (L.) Hara Against ALK Tyrosine Kinase Receptor Using Molecular Docking

K. K. Midhuna[1], S. V. Rajesh[2*], V. Tamil Bharathi [3] and T. S. Gnanendra[3]

[1]*Department of Botany, Vivekanandha College of Arts and Sciences for Women, Elayampalayam, Tiruchengode, Tamil Nadu, India.*
[2*]*Department of Botany, Ramakrishna Mission Vivekananda College, Mylapore, Chennai – 600 004, Tamil Nadu, India.*
[3]*Department of Biotechnology, Vivekanandha College of Arts and Sciences for Women, Elayampalayam, Tiruchengode, Tamil Nadu, India.*

***Corresponding Author**: S. V. Rajesh*
**Email:* drrajeshbotany@gmail.com

KEYWORDS
Molecular docking, *Ludwigia peruviana*, ALK tyrosine kinase receptor, cancer therapeutics, Cyclohexanone 4-hydroxy

Anaplastic lymphoma kinase (ALK) tyrosine kinase receptor is a crucial target in cancer therapeutics, particularly for ALK-positive malignancies. In this study, the phytochemicals identified from the methanol extract of *Ludwigia peruviana* (L.) Hara were analyzed for their anticancer potential against the ALK tyrosine kinase receptor using *in silico* techniques. Gas Chromatography-Mass Spectrometry (GC-MS) analysis was performed to identify the bioactive compounds present in the extract, which were subsequently subjected to molecular docking studies. Among the identified compounds, Cyclohexanone, 4-hydroxy exhibited the highest binding affinity (-7.3 kcal/mol) for the receptor's active site, outperforming the standard ALK inhibitor, Ceritinib (-6.6 kcal/mol). Key molecular interactions, including hydrogen bonding and hydrophobic contacts with critical active site residues, were observed, suggesting a strong inhibitory potential. These findings indicate that *Ludwigia peruviana* harbors bioactive compounds with promising anticancer activity against ALK, warranting further experimental validation through *in vitro* and *in vivo* studies.

I. Introduction

Plants have been used as medicine since time immemorial, playing a major role in traditional medicines utilized by many cultures worldwide for treating various illnesses and injuries. The plants synthesize hundreds of chemical compounds for various functions, and many of these phytochemicals have the potential to act as drugs [1]. Natural products are a potentially fruitful source of highly bioactive secondary metabolites with significant therapeutic values, offering alternative avenues in drug discovery and development [2]. Recent advancements in fields such as nanotechnology have facilitated the development of various herbal formulations, enhancing the effective transport of active principles to target sites and providing scientific validation for the traditional uses of plants [3-5].

Ludwigia peruviana (L.) Hara, a member of the Onagraceae family commonly known as water primrose, is a medicinal plant widely reported to possess numerous medicinal properties. Native to Mexico, it is a long-lived shrub typically found in marshy areas, growing 2-4 meters tall with much-branched stems, alternately arranged leaves, and flowers with four to five yellow petals and persistent sepals [6]. Ethnobotanical investigations have revealed that, a total of 22 species of *Ludwigia* are used to treat various ailments, showing positive results for conditions such as malaria, hepatic pain, diuretic and kidney problems [7].

Despite its extensive use in traditional medicine, the potential anticancer properties of *Ludwigia peruviana* remain underexplored. *In silico* methods, which provide a cost-effective [8,9]. Its efficient approach to identifying potential bioactive compounds and their mechanisms of action, have revolutionized the early stages of drug discovery [10]. These computational techniques enable the screening of vast compound libraries against specific drug targets, facilitating the identification of promising candidates for further experimental validation. This study investigates the anticancer potential of phytochemicals from the methanol extract of *Ludwigia peruviana* through *In silico* approaches, focusing on their interaction with the ALK (Anaplastic Lymphoma Kinase) protein. Using molecular docking, the binding affinities and dynamic behavior of the phytochemicals in relation to the ALK receptor were assessed. The aim of the study is to identify potential lead compounds that exhibit strong interactions with ALK, a key protein implicated in various cancers. The molecular mechanisms underlying the anticancer effects of *L. peruviana* could be uncovered by analysing these interactions and it could provide a basis for further experimental validation of these compounds as potential ALK inhibitors.

Materials and Methods

Sample Collection and Preparation of Extract

Plant specimens of *Ludwigia peruviana* (L.) Hara were collected from the marshy areas of Calicut, Kerala, India. The collected plant materials were washed thoroughly, air-dried under shade conditions for two weeks, and ground into coarse powder for extraction. Sequential solvent extraction was performed using petroleum ether, chloroform, ethyl acetate, and 80% Methanol, in the order of increasing polarity. The extracts were concentrated to dryness using a rotary vacuum evaporator and stored as a fine powder. Based on literature evidence, the Methanol extract was selected for further studies [11].

Gas Chromatography-Mass Spectrometry (GC-MS) Analysis

The Methanol extract was analyzed using a GC-MS system (Thermo GC-Trace Ultra ver. 5.0, Thermo MS DSQ II, Perkin Elmer) equipped with an AOC-20i auto-sampler and a TR5-MS non-polar capillary column (30 m × 0.25 mm × 0.25 µm). The sample was dissolved in Methanol, sonicated, and purged with nitrogen gas. A 0.5 µL aliquot was injected into the column at 250°C using a split ratio of 10:1. Helium gas (99.99%) served as the carrier at a flow rate of 1 mL/min [12]. The column was programmed from 60°C to 230°C (isothermal for 2 minutes) with a ramp of 10°C/min and held for 10 minutes. Ionization was performed with 70 eV, scanning ions from 40 to 550 Da. The mass spectra were analysed using TurboMass ver. 5.2.0 and compared against NIST08S.LIB and WILEY8.LIB databases for compound identification. Relative percentages of components were calculated based on peak areas in the chromatogram.

In Silico Docking Studies

Preparation of Target Protein

The 3D structure of the ALK tyrosine kinase receptor (PDB ID: 3LCS) was retrieved from the Protein Data Bank (https://www.rcsb.org/) and prepared for docking by removing water molecules, adding polar hydrogens, and assigning appropriate charges [13].

Ligand Preparation

Phytochemical compounds identified via GC-MS were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in SDF format [14]. For compounds lacking 3D structures, their isomeric SMILES were converted to 3D structures using ChemSketch. All ligands were energy-minimized before docking.

Molecular Docking

Docking was performed using PyRx software, employing the "AutoDock Vina" tool to evaluate ligand-receptor interactions [15]. Binding affinities were calculated in kcal/mol, and the top-ranking phytochemicals were selected for detailed interaction analysis.

Binding Site Analysis

Protein-ligand interactions were visualized using Discovery Studio Visualizer [16]. Key interactions, including hydrogen bonding, hydrophobic contacts, and electrostatic forces, were identified to elucidate the binding mechanisms and specificity of the ligands to the receptor.

Results and Discussion

GC-MS analysis:

The GC-MS analysis of the Methanol extract of *Ludwigia peruviana* (L.) Hara led to the identification of a diverse range of phytochemical compounds, which include alkaloids, fatty acids, esters, and other bioactive compounds. A total of 44 compounds were identified based on their molecular weights and molecular formulas. These compounds are known to exhibit various biological activities, which is given in Table 1, indicating the potential pharmacological value of this plant. The pharmacological activity of different compounds and their group are discussed below.

Alkaloids and Nitrogen-Containing Compounds

Compounds such as 4-Methylpiperidine-1-carboxylic acid, phenyl ester and Histamine, N-trifluoroacetyl-2-amino- are nitrogen-containing compounds. Alkaloids are known for their wide range of pharmacological properties, including analgesic, anti-inflammatory, and antimicrobial effects [17]. The presence of these alkaloid-like compounds may support some of the traditional uses of *L. peruviana* in folk medicine.

Table 1. GC-MS analysis of Methanol extract of *Ludwigia peruviana* (L.) Hara.

S. No.	Name of the compound	Molecular formula	Molecular weight
1	4-Methylpiperidine-1-carboxylic acid, phenyl ester	$C_{13}H_{19}N_5S$	277
2	N-(1-Methoxycarbonyl-1-methylethyl)-4-methyl-2-aza-1,3-dioxane	$C_7H_{13}NO_4$	175
3	D-Glucopyranoside	$C_{24}H_{40}O_{10}$	488
4	Cyclohexanone	$C_6H_{10}O$	98
5	8-Methyl-6-nonenamide	$C_{10}H_{19}NO$	169
6	4-Methyl itaconate	$C_6H_8O_4$	144
7	Cyclohexanone,4-hydroxy-	$C_6H_{10}O_2$	114
8	Cyclohexanone,4-ethoxy-	$C_8H_{14}O_2$	142
9	2-Furancarboxaldehyde,5-(hydroxymethyl)-	$C_6H_6O_3$	126
10	2-Hexene,3,4,4-trimethyl-	C_9H_{18}	126
11	4-Mercaptophenol	C_6H_6OS	126
12	2-Pentyne,5-methoxy-	$C_6H_{10}O$	98
13	Histamine,N-trifluoroacetyl-2-amino-	$C_7H_9F_3N_4O$	222
14	3-Methylenecyclopropane-trans-1,2-dicarboxylic acid	$C_6H_6O_4$	142
15	7-Octenoic acid	$C_8H_{14}O_2$	142
16	Cyclopentane,1-methyl-3-(2-methylpropyl)-	$C_{10}H_20$	140
17	Fluoroacetic acid, dodecyl ester	$C_{14}H_{27}FO_2$	246
18	Cis-2-Ethylcycloentanecarboxaldehyde	$C_8H_{14}O$	126
19	Cyclononanone	$C_9H_{16}O$	140
20	Nonanoic acid	$C_9H_{18}O_2$	158
21	Oxirane,[(dodecyloxy)methyl]-	$C_{15}H_{30}O_2$	242
22	Cyclododecanol	$C_{12}H_{24}O$	184
23	Z-2-Dodecenol	$C_{12}H_{24}O$	184
24	Z-2-Octadecen-1-ol	$C_{18}H_{36}O$	268
25	10-Methyl-E-11-tridecen-1-ol propionate	$C_{17}H_{32}O_2$	268
26	Pentadecanal-	$C_{15}H_{30}O$	226
27	Heptacosanoic acid, methyl ester	$C_{28}H_{56}O_2$	424
28	Cyclopentanetridecanoic acid, methyl ester	$C_{19}H_{36}O_2$	296
29	Pentadecanoic acid, 14-methyl-, methyl ester	$C_{17}H_{34}O_2$	270
30	Heneicosanoic acid, methyl ester	$C_{22}H_{44}O_2$	340
31	Didodecyl phthalate	$C_{32}H_{54}O_4$	502
32	1,2-Benzenedicarboxylic acid, diundecyl ester	$C_{30}H_{50}O_4$	474
33	Pentadecanoic acid	$C_{15}H_{30}O_2$	242
34	Tetradecanoic acid	$C_{14}H_{28}O_2$	228
35	Tridecanoic acid	$C_{13}H_{26}O_2$	214
36	Heptadecanoic acid	$C_{17}H_{34}O_2$	270
37	2-Imino-6-nitro-2H-1-benzopyran-3-carbothioamide	$C_{10}H_7N_3O_3S$	249
38	Aniline,4-iodo-N-(3-phenylpropenylideno)-	$C_{15}H_{12}IN$	333
39	3-Chloro-2-methyl-6-phenylimidazo[1,2-b][1,2,4]triazine	$C_{12}H_9CIN_4$	244
40	15-Hydroxypentadecanoic acid	$C_{15}H_{30}O_3$	258
41	Triarachine	$C_{63}H_{122}O_6$	974
42	Oxacyclotridecan-2-one	$C_{12}H_{22}O_2$	198
43	Oleic acid	$C_{18}H_{34}O_2$	282
44	Cyclopropaneoctanoic acid,2-hexyl-,methyl ester	$C_{18}H_{34}O_2$	282

Esters and Fatty Acids

A large number of fatty acid esters were identified in the extract, such as Heptacosanoic acid, methyl ester, Cyclopentanetridecanoic acid, methyl ester, and Heneicosanoic acid, methyl ester. Fatty acids and their esters are known for their roles in energy storage and as precursors to signalling molecules. The methyl esters of long-chain fatty acids, such as Pentadecanoic acid, are often associated with antimicrobial and anti-inflammatory activities, making them valuable for therapeutic applications [18].

Carboxylic Acids and Related Compounds
Numerous carboxylic acids were identified, including Nonanoic acid, Tetradecanoic acid, and Oleic acid. Oleic acid, in particular, is a well-known monounsaturated fatty acid with numerous health benefits, such as its anti-inflammatory and antioxidant properties [19]. Its presence in *L. peruviana* adds to the plant's potential as a source of health-promoting compounds.

Alcohols and Related Derivatives
Several alcohol derivatives were detected, such as Z-2-Octadecen-1-ol and Cyclododecanol. These long-chain alcohols are known to have antimicrobial and emollient properties, making them useful in cosmetic and pharmaceutical formulations [20].

Miscellaneous Compounds
Other notable compounds include 2-Furancarboxaldehyde, 5-(hydroxymethyl)-, which is a derivative of furan, a compound known for its antioxidant activity [21], and 3-Chloro-2-methyl-6-phenylimidazo[1,2-b][1,2,4]triazine, a heterocyclic compound which may have pharmaceutical relevance due to its complex structure.

Potential Bioactivities
The variety of compounds identified suggests that the Methanol extract of *Ludwigia peruviana* possesses a wide spectrum of biological activities. Fatty acids and esters, in particular, have been associated with antimicrobial, anti-inflammatory, and antioxidant properties. Alkaloids, on the other hand, may contribute to potential analgesic or anti-cancer activities [22].
The identification of compounds such as 15-Hydroxypentadecanoic acid and Triarachine further supports the extract's complex chemical nature, which may explain its traditional use for treating various ailments. The array of bioactive compounds underscores the importance of *Ludwigia peruviana* in both traditional medicine and potential future therapeutic applications.

Molecular docking
Interaction Analysis of Tyrosine Kinase Receptor with Standard Drug (Ceritinib)
The docking score of compounds obtained from methanol extract are given in Table 2. The standard drug Ceritinib demonstrated a binding affinity of -6.6 kcal/mol with the ALK tyrosine kinase receptor, highlighting its potential interaction strength. Key residues involved in the interaction included Leu 1291 and Asp 1270, which predominantly facilitated conventional and carbon hydrogen bonding, essential for the stability of the receptor-ligand complex. Hydrophobic interactions were also observed, mediated by residues such as Lys 1205, Stu 1, and Ala 1126, which engaged in alkyl and Pi-alkyl interactions, further enhancing the complex's binding affinity. Additionally, Arg 1253 played a dual role, forming both hydrogen and hydrophobic interactions, emphasizing its importance in maintaining the structural integrity of the receptor-ligand binding site (Fig. 1). These observations align with earlier reports indicating the critical role of such residues in stabilizing tyrosine kinase inhibitors [23].

Table.2 Docking Scores(kcal/mol) of ALK protein with phytochemical compounds

S. No.	Compound	PubChem ID	Docking Scores (kcal/mol)
1.	4-Methylpiperidine-1-carboxylic acid, phenyl ester	755382	-7
2.	N-(1-Methoxycarbonyl-1-methylethyl)-4-methyl-2-aza-1,3-dioxane	588924	-6
3.	D-Glucopyranoside	5793	-6
4.	Cyclohexanone	7967	-4.9
5.	8-Methyl-6-nonenamide	5365367	-5.3
6.	4-Methyl itaconate	81791	-5
7.	Cyclohexanone,4-hydroxy-	16196969	-7.3
8.	Cyclohexanone,4-ethoxy-	546470	-4.6
9.	2-Furancarboxaldehyde,5-(hydroxymethyl)-	237332	-5.3
10.	2-Hexene,3,4,4-trimethyl-	5369064	-4.9
11.	4-Mercaptophenol	240147	-4.6
12.	2-Pentyne,5-methoxy-	548989	-3.9
13.	Histamine,N-trifluoroacetyl-2-amino-	313087	-6.5

14.	3-Methylenecyclopropane-trans-1,2-dicarboxylic acid	736643	-5.2
15.	7-Octenoic acid	543977	-5
16.	Cyclopentane,1-methyl-3-(2-methylpropyl)-	520404	-5.5
17.	Fluoroacetic acid, dodecyl ester	549944	-5.3
18.	Cis-2-Ethylcyclopentanecarboxaldehyde	91692536	-5
19.	Cyclononanone	76877	-5.9
20.	Nonanoic acid	8158	-4.9
21.	Oxirane,[(dodecyloxy)methyl]-	17163	-5
22.	Cyclododecanol	15595	-6.6
23.	Z-2-Dodecenol	5364955	-4.7
24.	Z-2-Octadecen-1-ol	5365011	-5.1
25.	10-Methyl-E-11-tridecen-1-ol propionate	5365029	-4.7
26.	Pentadecanal-	17697	-4.6
27.	Heptacosanoic acid, methyl ester	41517	-3.6
28.	Cyclopentanetridecanoic acid, methyl ester	554135	-5.3
29.	Pentadecanoic acid, 14-methyl-, methyl ester	21205	-4.6
30.	Heneicosanoic acid, methyl ester	22434	-5
31.	Didodecyl phthalate	17082	-6.4
32.	1,2-Benzenedicarboxylic acid, diundecyl ester	19283	-5.8
33.	Pentadecanoic acid	13849	-4.5
34.	Tetradecanoic acid	11005	-4.9
35.	Tridecanoic acid	12530	-4.8
36.	Heptadecanoic acid	10465	-5.3
37.	2-Imino-6-nitro-2H-1-benzopyran-3-carbothioamide	5365432	-6.8
38.	Aniline,4-iodo-N-(3-phenylpropenylideno)-	5366955	-6.6
39.	3-Chloro-2-methyl-6-phenylimidazo[1,2-b][1,2,4]triazine	618433	-7.2
40.	15-Hydroxypentadecanoic acid	78360	-5
41.	Triarachine	522017	-5
42.	Oxacyclotridecan-2-one	70354	-6.8
43.	Oleic acid	445639	-5
44.	Cyclopropaneoctanoic acid,2-hexyl-, methyl ester	543331	-4.5
45.	**Ceritinib- Standard drug**	**57379345**	**-6.6**

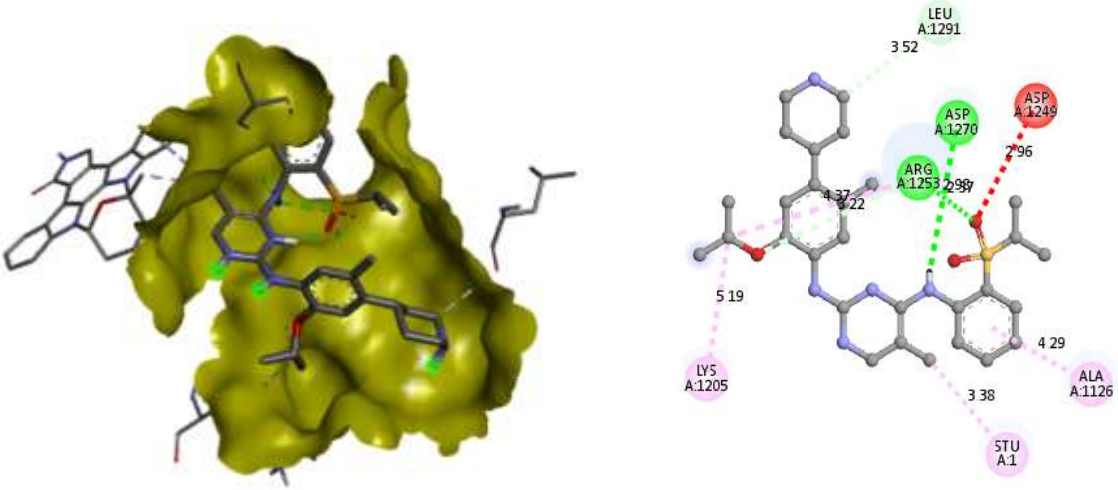

Fig.1 Docking complex and the interaction of the standard drug with ALK protein(Binding affinity: -6.6 kcal/mol)

Interaction Analysis of Tyrosine Kinase Receptor with Phytochemical Compounds

Cyclohexanone, 4-hydroxy exhibited the highest binding affinity of -7.3 kcal/mol, surpassing that of Ceritinib, indicating its potential as a potent inhibitor. Interaction analysis revealed that Arg 1275 and Glu 1167 were

involved in conventional hydrogen bonding, which is crucial for anchoring the ligand within the receptor's binding pocket. Additionally, non-covalent hydrophobic interactions with Phe 1127 and Ala 1126 further stabilized the complex (Fig. 2). These interactions are consistent with findings that hydrophobic contacts play a vital role in ligand-receptor stabilization and specificity [24].

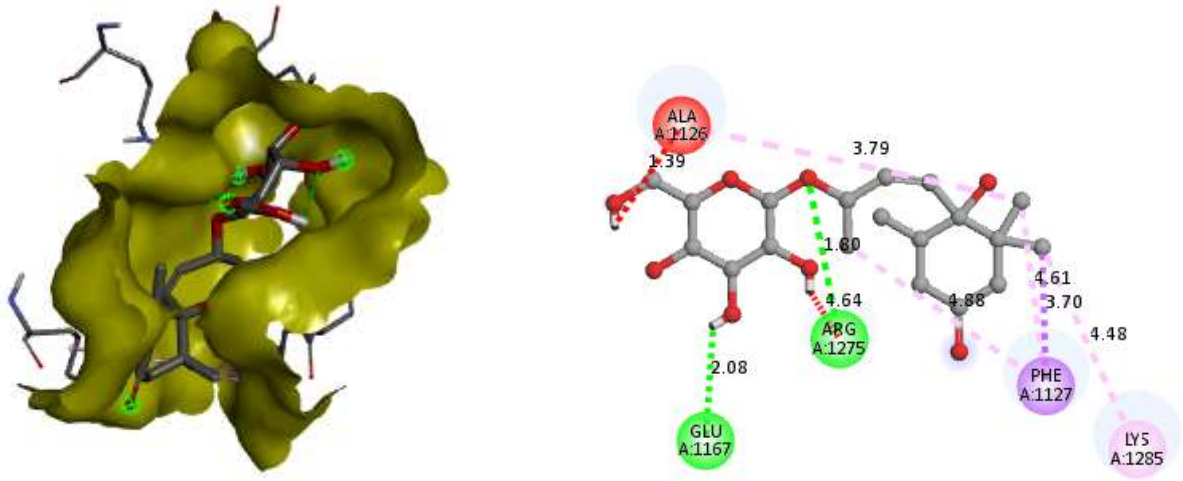

Fig.2 Docking complex and the interaction of protein ALK with the compound Cyclohexanone, 4-hydroxy-(16196969)(Binding affinity: -7.3 kcal/mol)

3-Chloro-2-methyl-6-phenylimidazo[1,2-b][1,2,4]triazine demonstrated a binding affinity of -7.2 kcal/mol, comparable to Cyclohexanone, 4-hydroxy-. The compound formed hydrophobic interactions (Table 3) with Stu 1 and Ala 1126, which are known to enhance binding specificity. Electrostatic interactions with Arg 1275 and Asp 1270 provided additional stability, corroborating the significance of charged residues in ligand binding. Furthermore, Phe 1127 facilitated both hydrogen bonding and hydrophobic interactions, indicating its dual role in ligand anchoring and complex stabilization (Fig. 3). These results highlight the potential of this compound as a strong ALK tyrosine kinase inhibitor, aligning with prior studies on receptor-ligand binding mechanisms [25].

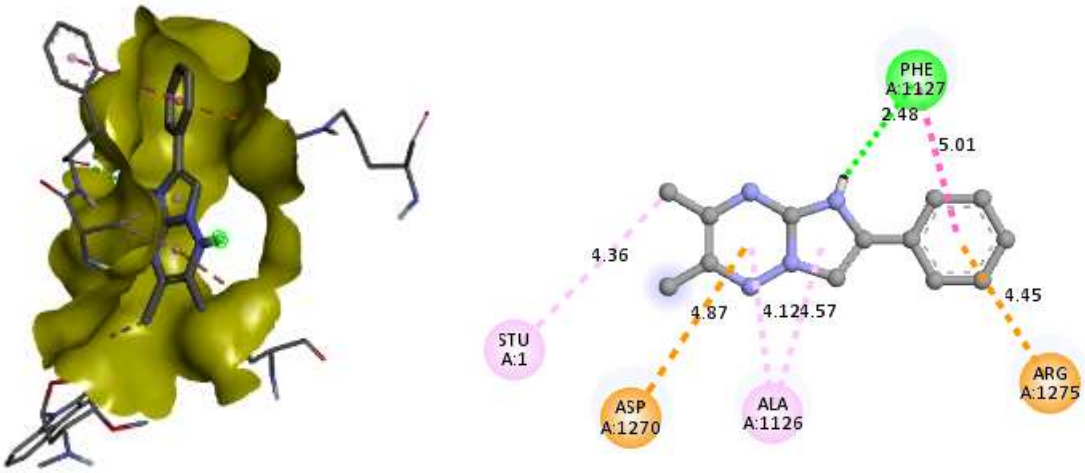

Fig.3 Docking complex and the interaction of protein ALK with the compound 3-Chloro-2-methyl-6-phenylimidazo[1,2-b][1,2,4]triazine (618433) (Binding affinity: -7.2 kcal/

Table.3 Interactions between amino acid (aa) residues of Thyrosine Kinase receptor ALK and potent phytochemicals derived from *Ludwigia peruviana* (L.)

Ceritinib	**16196969**	**618433**
#Ala 1126	#Ala 1126	#Ala 1126
Asp 1249		
	Lys 1285	
*Leu1291		
*Asp 1270		Asp 1270
	*Glu 1167	
*#Arg 1253		
	#Phe 1127	*#Phe 1127
#Lys 1205		
#Stu1		#Stu1
	*Arg 1275	Arg 1275

**Hydrogen bond #Hydrophobic*

The observed binding affinities and interaction patterns suggest that phytochemical compounds, particularly Cyclohexanone, 4-hydroxy-, and 3-Chloro-2-methyl-6-phenylimidazo[1,2-b][1,2,4]triazine, possess significant potential as inhibitors of the ALK tyrosine kinase receptor. Their superior binding affinities, compared to the standard drug Ceritinib, underscore the promise of these compounds as candidates for further experimental validation and drug development [26]. These findings are consistent with the established role of hydrogen bonding, hydrophobic interactions, and electrostatic forces in stabilizing protein-ligand complexes.

Conclusions

This study explored the interaction of phytochemical compounds from the methanolextract of *Ludwigia peruviana* with the ALK tyrosine kinase receptor through molecular docking. Cyclohexanone, 4-hydroxy- (-7.3 kcal/mol) and **3**-Chloro-2-methyl-6-phenylimidazo[1,2-b][1,2,4]triazine (-7.2 kcal/mol) demonstrated higher binding affinities compared to Ceritinib (-6.6 kcal/mol). These compounds showed strong interactions with critical residues (Arg 1275, Phe 1127, and Ala 1126), essential for ligand-receptor stability. The superior binding affinities and interaction profiles indicate their potential as lead molecules for anticancer therapy, particularly against cancers associated with aberrant ALK signalling. Further validation through *In vitro*, *In vivo*, and molecular dynamics studies is recommended to confirm their therapeutic potential.

References

1. Chaachouay N, Zidane L. Plant-derived natural products: a source for drug discovery and development. Drugs and Drug Candidates. 2024 Feb 19;3(1):184-207.
2. Benkhnigue O, Chaachouay N, Khamar H, El Azzouzi F, Douira A, Zidane L. Ethnobotanical and ethnopharmacological study of medicinal plants used in the treatment of anemia in the region of Haouz-Rehamna (Morocco). J. Pharm. Pharmacogn. Res. 2022;10(2):279-302.
3. Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. Life sciences. 2005 Dec 22;78(5):431-41..
4. Chandrakant Katiyar CK, Arun Gupta AG, Satyajyoti Kanjilal SK, Shefali Katiyar SK. Drug discovery from plant sources: an integrated approach.
5. Veeresham C. Natural products derived from plants as a source of drugs. Journal of advanced pharmaceutical technology & research. 2012 Oct 1;3(4):200-1.
6. Barua IC. The genus Ludwigia (Onagraceae) in India. Rheedea. 2010;20(1):59-70.
7. Dike IP, Obembe OO, Adebiyi FE. Ethnobotanical survey for potential anti-malarial plants in south-western Nigeria. Journal of ethnopharmacology. 2012 Dec 18;144(3):618-26.
8. Chunarkar-Patil P, Kaleem M, Mishra R, Ray S, Ahmad A, Verma D, Bhayye S, Dubey R, Singh HN, Kumar S. Anticancer Drug Discovery based on Natural products: from computational approaches to Clinical studies. Biomedicines. 2024 Jan 16;12(1):201.
9. Shah A, Patel V, Perumal S, Dave R, Zachariah N, Parmar G, Chudasama JM. Bioactive Small Molecules and Drug Discovery. Computational Methods for Rational Drug Design. 2025 Jan 20:25-48.

10. Thomford NE, Senthebane DA, Rowe A, Munro D, Seele P, Maroyi A, Dzobo K. Natural products for drug discovery in the 21st century: innovations for novel drug discovery. International journal of molecular sciences. 2018 May 25;19(6):1578.
11. Moomin A, Russell WR, Knott RM, Scobbie L, Mensah KB, Adu-Gyamfi PK, Duthie SJ. Season, storage and extraction method impact on the phytochemical profile of Terminalia ivorensis. BMC plant biology. 2023 Mar 25;23(1):162.
12. Ma X, Wang F, Hang T, Dramou P. Degradation study of rutin as template from magnetic composite molecularly imprinted polymer supernatant samples by liquid chromatography–mass spectrometry. Journal of Chromatography A. 2022 Jun 21;1673:463199.
13. Berman, H.M.; Battistuz, T.; Bhat, T.N.; Bluhm, W.F.; Bourne, P.E.; Burkhardt, K.; Feng, Z.; Gilliland, G.L.; Iype, L.; Jain, S.; Fagan, P. The protein data bank. *Acta Crystallogr. D Biol. Crystallogr.* **2002**, *58*, 899–907
14. Kim, S.; Thiessen, P.A.; Bolton, E.E.; Chen, J.; Fu, G.; Gindulyte, A.; Han, L.; He, J.; He, S.; Shoemaker, B.A.; Wang, J.; Yu, B.; Zhang, J.; Bryant, S.H. PubChem Substance and Compound databases. *Nucleic Acids Res.* **2016**, *44*, D1202–D1213.
15. Trott, O.; Olson, A.J. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J. Comput. Chem.* **2010**, *31*, 455–461.
16. Dassault Systèmes BIOVIA. *Discovery studio 2017 R2 Client*; Dassault Systèmes: San Diego, CA, USA, 2017.
17. Souto AL, Tavares JF, Da Silva MS, Diniz MD, de Athayde-Filho PF, Filho JM. Anti-inflammatory activity of alkaloids: an update from 2000 to 2010. Molecules. 2011 Oct 11;16(10):8515-34.
18. Ali O, Szabó A. Review of eukaryote cellular membrane lipid Composition, with special attention to the fatty acids. International Journal of Molecular Sciences. 2023 Oct 28;24(21):15693.
19. Santa-María Pérez C, López Enriquez S, Montserrat de la Paz S, Geniz I, Reyes-Quiroz ME, Moreno M, Palomares F, Sobrino Beneyto F, Alba Jiménez G. Update on Anti-Inflammatory Molecular Mechanisms Induced by Oleic Acid. Nutrients, 15 (1), 224.. 2023.
20. Rabasco Álvarez AM, González Rodríguez ML. Lipids in pharmaceutical and cosmetic preparations. Grasas y Aceites, 51 (1-2), 74-96.. 2000.
21. Kumar N, Gusain A, Kumar J, Singh R, Hota PK. Anti-oxidation properties of 2-substituted furan derivatives: A mechanistic study. Journal of Luminescence. 2021 Feb 1;230:117725.
22. Thawabteh A, Juma S, Bader M, Karaman D, Scrano L, Bufo SA, Karaman R. The biological activity of natural alkaloids against herbivores, cancerous cells and pathogens. Toxins. 2019 Nov 11;11(11):656.
23. Vidal-Limon A, Aguilar-Toalá JE, Liceaga AM. Integration of molecular docking analysis and molecular dynamics simulations for studying food proteins and bioactive peptides. Journal of Agricultural and Food Chemistry. 2022 Jan 6;70(4):934-43.
24. López-Blanco JR, Aliaga JI, Quintana-Ortí ES, Chacón P. iMODS: internal coordinates normal mode analysis server. Nucleic acids research. 2014 Jul 1;42(W1):W271-6.
25. Araujo SC, Maltarollo VG, Honorio KM. Computational studies of TGF-βRI (ALK-5) inhibitors: Analysis of the binding interactions between ligand–receptor using 2D and 3D techniques. European Journal of Pharmaceutical Sciences. 2013 Jul 16;49(4):542-9.
26. Gemelli M, Albini A, Catalano G, Incarbone M, Cannone M, Balladore E, Ricotta R, Pelosi G. Navigating resistance to ALK inhibitors in the lorlatinib era: a comprehensive perspective on NSCLC. Expert Review of Anticancer Therapy. 2024 Jun 2;24(6):347-61.