In Silico Investigation Of Phytochemicals From *Ludwigia Peruviana* As Potential ALK Inhibitors: Molecular Docking And DFT Analysis

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Keywords
Ludwigia peruviana, ALK inhibition, molecular docking, DFT calculations, phytochemicals.

Abstract
Cancer remains a major global health challenge, driving the search for novel therapeutics. This study investigates the anticancer potential of phytochemicals from the ethyl acetate extract of *Ludwigia peruviana* (L.) Hara using an in silico approach. GC-MS analysis identified 12 bioactive compounds, including 1-deoxy-D-mannitol and 2-methoxy-4-vinylphenol, known for their antioxidant and anticancer properties. Molecular docking studies assessed their interaction with anaplastic lymphoma kinase (ALK) receptor tyrosine kinase, a key cancer target. 1-Deoxy-D-mannitol exhibited the highest binding affinity (-6.9 kcal/mol), surpassing the standard drug Ceritinib (-6.6 kcal/mol). Density Functional Theory (DFT) calculations further analyzed their electronic properties, including HOMO-LUMO energy levels, energy gap, ionization energy, and electrophilicity index. Results showed that 1-deoxy-D-mannitol had higher electronegativity and stability, while 2-methoxy-4-vinylphenol displayed balanced electronic properties, reinforcing their potential as ALK inhibitors. Their strong binding affinities and favorable quantum properties highlight their promise as natural ALK inhibitors, warranting further experimental validation for anticancer therapy.

Introduction

The global burden of cancer remains a significant challenge, claiming millions of lives annually despite advances in diagnosis and treatment. Conventional therapies, including chemotherapy and radiation, often lead to severe side effects and drug resistance, emphasizing the need for novel, targeted, and less toxic anticancer agents [1]. Natural products, particularly phytochemicals derived from plants, have emerged as promising alternatives due to their structural diversity and bioactivity. These compounds have historically been a cornerstone in drug discovery, contributing to approximately 50% of FDA-approved anticancer drugs [2].

Medicinal plants are rich sources of bioactive secondary metabolites such as alkaloids, flavonoids, saponins, and tannins, which exhibit various therapeutic properties, including anticancer activity [3]. India, known as the "Botanical Garden of the World," harbors a vast array of medicinal plants used in traditional systems like Ayurveda, where they play a pivotal role in managing chronic diseases [4]. Among these, *Ludwigia peruviana* (L.) Hara, a perennial aquatic shrub, has garnered attention for its diverse bioactivities, including antioxidant, anti-inflammatory, and antimicrobial properties [5].

Phytochemicals from *Ludwigia peruviana* have shown potential in modulating pathways critical to cancer progression, such as oxidative stress and inflammation [6]. Recent studies have emphasized the importance of in silico methods, particularly molecular docking, in screening plant-derived compounds for their interactions with specific protein targets involved in cancer, providing a cost-effective and efficient approach to drug discovery [7]. The anaplastic lymphoma kinase (ALK) receptor tyrosine kinase, implicated in several cancers, is a prominent target for therapeutic intervention due to its role in cell proliferation and survival [8].

This study explores the anticancer potential of phytochemicals identified in the ethyl acetate extract of *Ludwigia peruviana* using an in silico docking approach. The research focuses on evaluating the binding affinities of these compounds with ALK receptor tyrosine kinase and comparing their efficacy to the standard drug Ceritinib, an FDA-approved ALK inhibitor. By combining traditional knowledge of medicinal plants with modern computational tools, this study aims to identify promising lead compounds that can be further validated for cancer therapeutics.

Materials and Methods

Collection of plant material and extract preparation:

Plant specimens were gathered from the marshy regions of Calicut, Kerala. The collected materials were thoroughly washed with water and shade-dried for two weeks. After drying, the plant material was pulverized and sequentially extracted with solvents of increasing polarity, including petroleum ether, chloroform, ethyl acetate, and 80% methanol. The solvents were then evaporated using a rotary vacuum evaporator, and the ethyl acetate extract was chosen for further analysis [9].

GCMS analysis:

The ethyl acetate extract was analyzed using a GC-MS system (Thermo GC-Trace Ultra ver. 5.0, Thermo MS DSQ II, Perkin Elmer) 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 ethyl acetate, sonicated, and purged with nitrogen gas. A 0.5 µL aliquot was injected at 250°C with a split ratio of 10:1. Helium (99.99%) was used as the carrier gas at a flow rate of 1 mL/min [10]. The column temperature was programmed from 60°C to 230°C (isothermal for 2 minutes) at a rate of 10°C/min, followed by a 10-minute hold. Ionization was performed at 70 eV, scanning ions within 40–550 Da. The spectra were analyzed using TurboMass ver. 5.2.0 and compared with NIST08S.LIB and WILEY8.LIB databases for compound identification. The relative percentages of components were determined based on peak areas in the chromatogram.

In silico docking studies:

Preparation of Target Protein:

In cancer cells, the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase plays a crucial role in cell growth and development. Therefore, ALK was selected as the drug target. The 3D structure of the protein in PDB format was obtained from the Protein Data Bank (PDB) website (https://www.rcsb.org/) using the PDB ID: 3LCS and utilized for molecular docking studies and protein-ligand interaction analysis [11].

Ligand Preparation:

The 3D SDF files of the standard drug and phytochemical compounds identified through GC-MS analysis were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) for docking studies [12]. Additionally, for compounds without available 3D structures in PubChem, isomeric SMILES representations were generated using the ChemSketch tool to construct their 3D models. This approach ensured a comprehensive dataset for docking analysis.

Molecular Docking:

Molecular docking analysis was performed using AutoDock Vina to investigate ligand-macromolecule interactions at the atomic level [13]. This approach allowed for the evaluation of binding affinities (in kcal/mol), enabling the identification of top-performing phytochemical compounds. The strongest binding candidates were selected, highlighting their potential for further experimental validation.

Binding site analysis:

Protein-ligand interactions were analyzed using Discovery Studio Visualizer [14] to identify and visualize active amino acid residues involved in hydrogen bonding, hydrophobic interactions, and electrostatic forces. This analysis provided valuable insights into the molecular mechanisms governing binding specificity and affinity between the protein and ligand.

Quantum chemical descriptors using DFT analysis

Density Functional Theory (DFT) calculations were performed to evaluate the electronic properties of the selected phytochemicals, including 1-deoxy-d-mannitol, 2-methoxy-4-vinylphenol, and the standard drug Ceritinib. The calculations were carried out using the Gaussian 09 software package with the B3LYP hybrid functional and the 6-311+G(d,p) basis set. Geometry optimization was conducted to obtain the most stable molecular conformations, followed by frequency calculations to confirm the absence of imaginary frequencies, ensuring that the structures correspond to true minima on the potential energy surface. The electronic properties, including the highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), energy gap (ΔE), ionization energy (IE), electron affinity (EA), electronegativity (χ), molecular hardness (η), molecular softness (S), and electrophilicity index (ω), were calculated based on Koopmans'

theorem. These quantum chemical descriptors provide insights into the stability, reactivity, and potential inhibitory activity of the studied compounds against the ALK receptor tyrosine kinase.

Result and Discussion

GC-MS analysis:

The GC-MS analysis of the ethyl acetate extract of *Ludwigia peruviana* (L.) Hara yielded a range of bioactive compounds with diverse functional groups, including alcohols, ethers, phenols, fatty acids, carbohydrates, and hydrocarbons. By referring the NIST database a sum of 12 compounds were identified on the basis of molecular weights and molecular formulas and are given in Table 1. The compounds are summarized as follows:

1-Deoxy-d-mannitol is a sugar alcohol is known for its antioxidant, osmoregulatory, and anti-inflammatory properties. Studies have reported its use in reducing oxidative stress and as a diuretic agent in clinical applications [15]. Hexyl octyl ether is a Ethers like hexyl octyl ether exhibit antibacterial activity and are used as surfactants in drug delivery systems. This compound's presence suggests potential in enhancing bioavailability in pharmaceutical formulations [16]. 2-Methoxy-4-vinylphenol is a phenolic derivative, it possesses antioxidant, anti-inflammatory, and antimicrobial properties, and has been identified as a key bioactive compound in traditional herbal medicines. It also acts as a flavoring agent, which further enhances its therapeutic appeal in functional foods [17,18]. (R)-(-)-4-Methyl-hexanoic acid is a branched fatty acid has been linked to anti-inflammatory and neurological benefits, particularly in modulating nerve signaling. Its derivatives have been studied for applications in treating neuropathic pain [19] L-Glucose R are sugars such as L-glucose have demonstrated anti-cancer and hypoglycemic effects in preclinical studies. Its use as a low-calorie sweetener also contributes to managing metabolic disorders, including diabetes and obesity [20]. Undecanoic acid and N-Decanoic acid is a Medium-chain fatty acids like undecanoic and decanoic acids exhibit antimicrobial, antifungal, and antiviral activities. They have been employed in topical formulations to treat infections and in dietary supplements for gut health [21,22]. 9,9-Dimethoxybicyclo(3,3,1)nona-2,4-dione is a bicyclic compound, though less studied, is structurally related to diketones that show potential anti-tumor and antioxidant activities. Its role as a precursor for synthetic drugs warrants further exploration [23]. Heptadecane, 2,6,10,15-tetramethyl- is primarily an energy-storage molecule, branched hydrocarbons have demonstrated anti-inflammatory and antioxidant activities, particularly in dermal formulations for treating skin inflammation [24]. 4-Fluoro-1-methyl-5-carboxylic acid, ethyl ester is a Fluorinated esters, critical in medicinal chemistry for their anti-cancer, antimicrobial, and enzyme-inhibitory properties. They are widely used as building blocks in the synthesis of pharmaceuticals targeting multiple diseases [25]. Dodecane, 2,6,10-trimethyl- is a hydrocarbon demonstrates antimicrobial and anti-inflammatory effects. It is also a common excipient in formulations enhancing drug delivery [26].

Interaction analysis of tyrosine kinase receptor with standard drug (Ceritinib)

The phytochemical constituents of the medicinal plant showed different binding activities with the tyrosine kinase receptor protein ALK ranging from −4.4 kcal/mol to −6.4 kcal/mol (Table 1). Remarkably, the standard drug exhibited a binding affinity of −6.6 kcal/mol. This analysis shows that amino acids such as Leu 1291 and Asp 1270 mainly promote traditional carbon-hydrogen bond interactions with the standard drug (ceritinib), while hydrophobic interactions with alkyl and pi-alkyl chains 1205, Stu 1, and Ala 1126. Additionally, Arg 1253 was observed to contribute to both hydrogen and hydrophobic interactions. (Fig.1).

Table.1 Docking Scores of ALK protein (Ethyl extract) with phytochemical compounds

S. No.	Compound	PubChem ID	Docking Scores (kcal/mol)
1	1-Deoxy-d-mannitol	121864	-6.9
2	Hexyl octyl ether	519362	-4.4
3	2-Methoxy-4-vinylphenol	332	-6.7
4	(R)-(-)-4-methyl-hexanoic acid	12600623	-4.7
5	L-Glucose	10954115	-5.2
6	Undecanoic acid	8180	-4.9
7	N-Decanoic acid	2969	-4.8
8	9,9-Dimethoxybicyclo(3,3,1)nona-2,4-dione	537288	-5

9	Heptadecane,2,6,10,15-tetramethyl-	41209	-5.4
10	4-Fluoro-1-methyl-5-carboxylic acid, ethyl(ester)	534521	-5.1
11	Dodecane,2,6,10-trimethyl-	19773	-5.3
12	Ceritinib – Control	57379345	-6.6

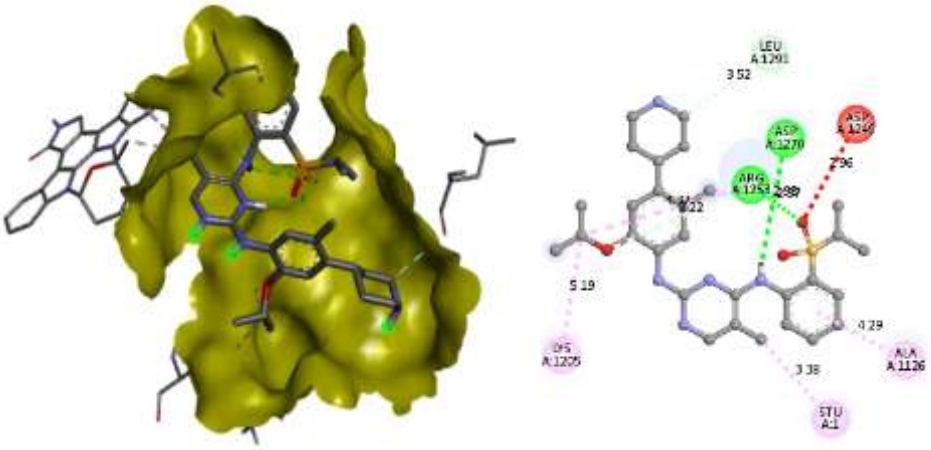

Fig.1 Docking complex and the interaction of the standard drug with ALK protein(Binding affinity: -6.6 kcal/mol)

Interaction analysis of tyrosine kinase receptor with compounds exhibiting superior docking

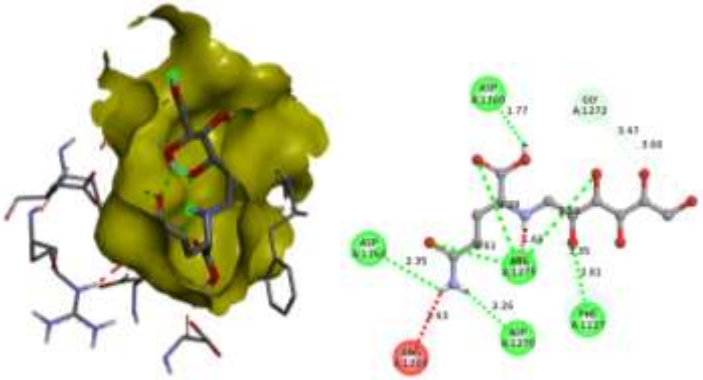

Fig.2 Docking complex and the interaction of protein ALK with the compound 1-Deoxy-d-mannitol (PubChem ID: 121864) (Binding affinity: -6.9 kcal/mol

The compound 1-deoxy-d-mannitol showed the closest binding affinity at −6.9 kcal/mol compared to the standard drug. It formed conventional carbon-hydrogen bonds with Phe 1127, Arg 1275, Asp 1276, Asp 1163, Asp 1160, and Gly 1272 (Fig.2).

The binding affinity of compound 2-Methoxy-4-vinylphenol was found to be -6.7 kcal/mol. Specifically, it forms conventional hydrogen bonds with Lys 1150, a distinct residue. Moreover, it exhibits simultaneous electrostatic interactions with Arg 1275 and non-covalent hydrophobic interactions with Lys 1285 and Phe 1127 (Fig.3).

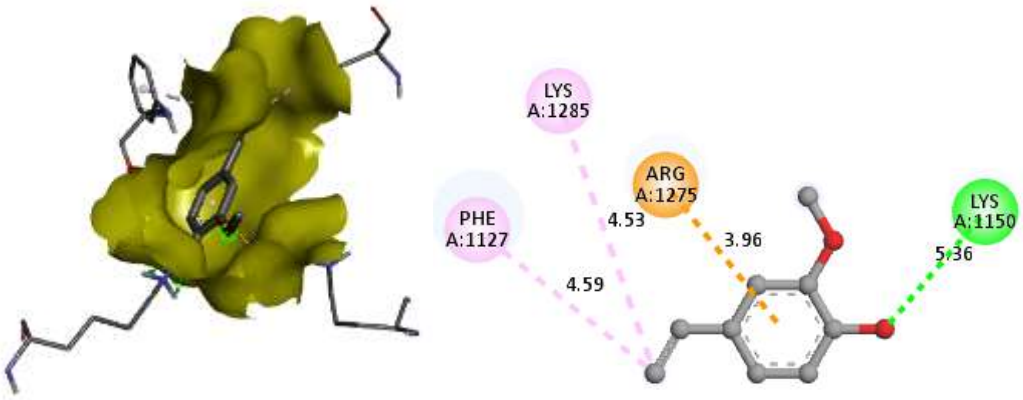

Fig.3 Docking complex and the interaction of protein ALK with the compound 2-Methoxy-4-vinylphenol (PubChem ID: 332) (Binding affinity: -6.7 kcal/mol)

Table.2 Interactions between amino acid (aa) residues of Thyrosine Kinase receptor ALK and potent phytochemicals of Ethyl acetate extract derived from *Ludwigia peruviana* (L.)

Ceritinib (ID:57379345)	1-Deoxy-d-mannitol **(ID:121864)**	2-Methoxy-4-vinylphenol **(ID:332)**
#Ala 1126	-	-
-	Gly 1272	-
Asp 1249	-	-
-	-	#Lys 1285
-	Asp 1276	-
*Leu1291	-	-
*Asp 1270	-	-
-	Asp 1163	-
-	Asp 1160	-
*#Arg 1253	-	-
-	#Phe 1127	#Phe 1127
#Lys 1205	-	-
#Stu1	-	-
-	*Arg 1275	Arg 1275
-	Arg 1284	-
-	-	*Lys 1150

**Hydrogen bond* *#Hydrophobic*

Molecular docking studies were conducted to evaluate the binding affinity of the selected inhibitors, Ceritinib, 1-deoxy-d-mannitol, and 2-Methoxy-4-vinylphenol, against the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase, a critical target in cancer progression. The docking scores obtained for these inhibitors were -6.6 kcal/mol for Ceritinib, -6.9 kcal/mol for 1-deoxy-d-mannitol, and -6.7 kcal/mol for 2-Methoxy-4-vinylphenol. These values suggest that the natural inhibitors, 1-deoxy-d-mannitol and 2-Methoxy-4-vinylphenol, exhibit stronger binding affinities toward ALK compared to the synthetic inhibitor Ceritinib. The superior docking scores of these natural inhibitors indicate their potential as effective ALK inhibitors.

Quantum chemical descriptors using DFT analysis

To further assess the stability and chemical reactivity of these compounds, density functional theory (DFT) calculations were performed, and the HOMO-LUMO energy levels were analyzed. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energy levels were found to be -0.28824 eV and 0.08090 eV for Ceritinib, -0.39288 eV and 0.15864 eV for 1-deoxy-d-mannitol, and -0.28516 eV and 0.11845 eV for 2-Methoxy-4-vinylphenol, respectively. The energy gap (ΔE) values, which indicate the chemical reactivity of the molecules, were calculated as 0.36914 eV for Ceritinib, 0.55152 eV for 1-deoxy-d-mannitol, and 0.40361 eV for 2-Methoxy-4-vinylphenol. A lower energy gap is associated with higher

reactivity, suggesting that Ceritinib is the most reactive among the three. However, reactivity alone does not determine the efficacy of an inhibitor; other quantum chemical parameters also play a significant role in understanding the inhibitory potential of these molecules.

The ionization energy (IE) and electron affinity (EA) values were also computed, where the IE values were -HOMO and the EA values were -LUMO. These properties contribute to the determination of electronegativity (χ), electronic chemical potential (μ), molecular hardness (η), molecular softness (S), and the electrophilicity index (ω). The calculated electronegativity values were 0.10367 eV for Ceritinib, 0.11712 eV for 1-deoxy-d-mannitol, and 0.08336 eV for 2-Methoxy-4-vinylphenol, indicating that 1-deoxy-d-mannitol has a greater tendency to attract electrons. The electronic chemical potential (μ) values were -0.10367 eV, -0.11712 eV, and -0.08336 eV for Ceritinib, 1-deoxy-d-mannitol, and 2-Methoxy-4-vinylphenol, respectively, reinforcing the trend of electron-attracting potential.

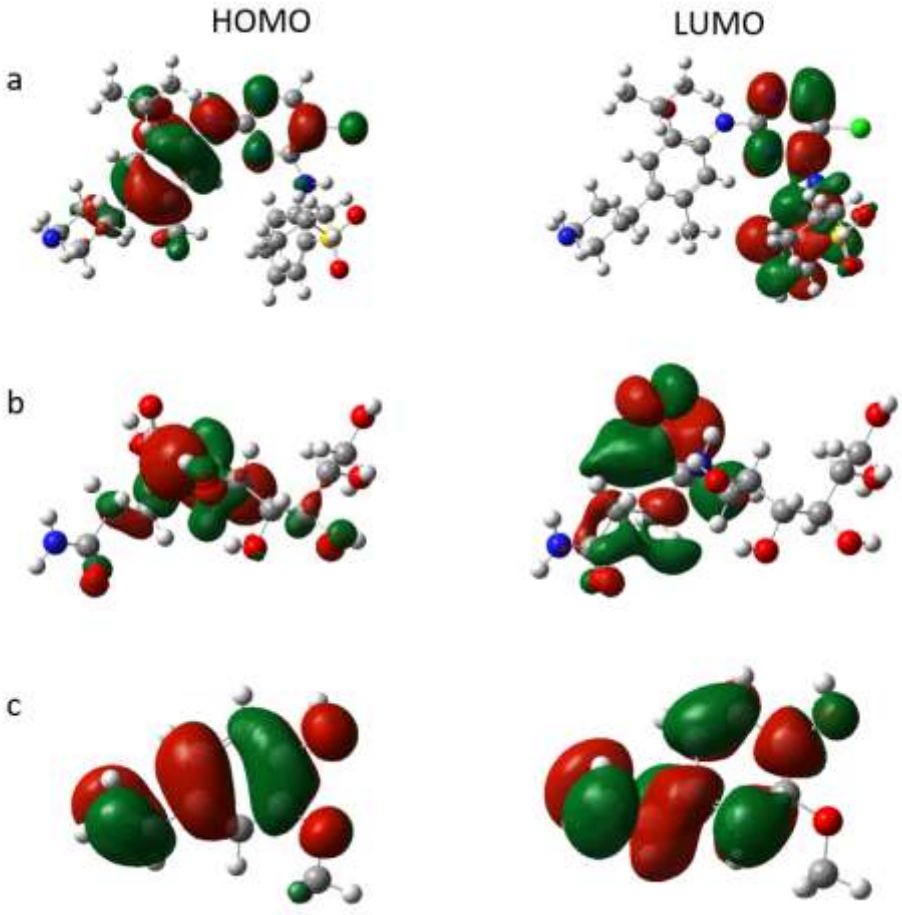

Fig. 4: **HOMO (left) and LUMO (right) molecular orbitals of selected anaplastic lymphoma kinase (ALK) receptor tyrosine kinase inhibitors, determined through Density Functional Theory (DFT) calculations. (a) Ceritinib, (b) 1-Deoxy-D-mannitol, and (c) 2-Methoxy-4-vinylphenol. The electron density distribution highlights the charge transfer potential, which plays a crucial role in molecular reactivity and interaction with the target protein.**

Table 4. DFT-Based Quantum Chemical Properties (in eV) of best docked compounds 1-Deoxy-D-mannitol, 2-Methoxy-4-vinylphenol and Ceritinib (Standard drug) with anaplastic lymphoma kinase (ALK) receptor tyrosine kinase.

Properties	1-Deoxy-D-mannitol	2-Methoxy-4-vinylphenol	Ceritinib
HOMO-LUMO Gap (ΔE)	0.55152 eV	0.40361 eV	0.36914 eV
Ionization Potential (IE)	0.39288 eV	0.28516 eV	0.28824 eV
Electron Affinity (EA)	-0.15864 eV	-0.11845 eV	-0.08090 eV
Electronegativity (χ)	0.11712 eV	0.08336 eV	0.10367 eV
Electrochemical Potential (μ)	-0.11712 eV	-0.08336 eV	-0.10367 eV
Hardness (η)	0.27576 eV	0.20180 eV	0.18457 eV
Softness (σ)	1.8129 eV	2.4776 eV	2.7109 eV

The molecular hardness (η), which is an indicator of molecular stability, was observed to be the highest for 1-deoxy-d-mannitol (0.27576 eV), followed by 2-Methoxy-4-vinylphenol (0.20180 eV) and Ceritinib (0.18457 eV). A higher hardness value correlates with greater molecular stability and lower reactivity, suggesting that 1-deoxy-d-mannitol is the most stable among the three inhibitors. Conversely, molecular softness (S), which is inversely related to hardness, was found to be the highest for Ceritinib (2.7109 eV), followed by 2-Methoxy-4-vinylphenol (2.4776 eV) and 1-deoxy-d-mannitol (1.8129 eV). The electrophilicity index (ω), which measures the capacity of a molecule to accept electrons, was the highest for Ceritinib (0.0291 eV), followed by 1-deoxy-d-mannitol (0.0249 eV) and 2-Methoxy-4-vinylphenol (0.0172 eV). While higher electrophilicity suggests greater ability to interact with the active site, a balance between stability and reactivity is crucial for effective inhibition.

Conclusion

The results of this study suggest that while Ceritinib exhibits high reactivity, the natural inhibitors, 1-deoxy-d-mannitol and 2-Methoxy-4-vinylphenol, demonstrate superior binding affinity and favorable electronic properties, making them promising alternatives for ALK inhibition. Natural inhibitors are often associated with fewer side effects and better biocompatibility compared to synthetic drugs, further strengthening their potential as therapeutic candidates. The strong binding affinity, along with their stability and effective electronic properties, indicates that 1-deoxy-d-mannitol and 2-Methoxy-4-vinylphenol could serve as viable natural alternatives to Ceritinib in targeting ALK-related cancers. Further experimental validation through in vitro and in vivo studies would be beneficial to confirm their inhibitory potential and therapeutic applicability.

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