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Molecular docking studies of seven selected medicinal plants against non-small-cell lung cancer (NSCLC) against complex of ERK2 and catechol receptor

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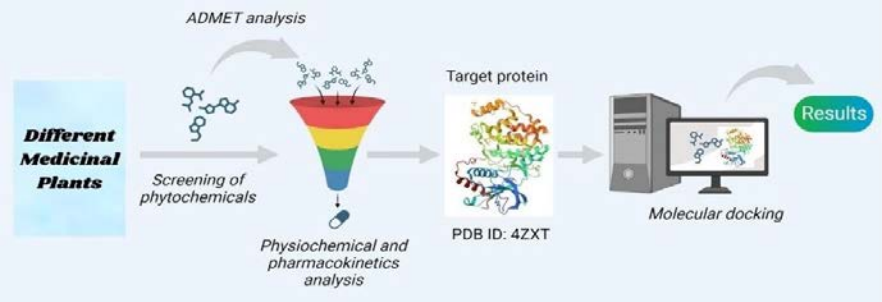
Article

ABSTRACT



There a growing interest in medicinal plants as alternative treatments against lung cancer, as their application provokes minor side effects compared to typical chemotherapy. This study entails the evaluation of the therapeutic potential of bioactive compounds from medicinal plants through their interaction with ERK2, an extracellular signal-regulated kinase 2, which becomes important in pathways of cancer signaling. Molecular docking studies were conducted with seven selected medicinal plants and consequently led to the identification of 41 bioactive compounds with potential inhibitory effects on the ERK2 receptor. Of these, seven compounds showed the most promising binding energies, namely Isovitexin from *Fagopyrum esculentum,* Chrysin-7-O-glucuronide from *Oroxylum indicum,* 2-methyl-3-methoxy anthraquinone from *Oldenlandia diffusa*, Creticoside A from *Pteris multifida,* Ginsenoside Rk2 from *Panax ginseng,* Diosmin from *Scrophularia nodosa,* and 5-Ocaffeoylquinic acid from *Vernonia amygdalina* with their corresponding binding energies -6.85, -7.66, -7.12, -8.78, -8.15, -5.63 and -5.83 kcal/mol, respectively. These findings suggest that these compounds from plant sources have great promise as chemotherapeutic drugs for lung cancer treatment.

Keywords: Molecular Docking, Medicinal Plants, ERK2, non-small-cell lung cancer (NSCLC), health care, global health

INTRODUCTION

Recognizing cancer as a genetic disease and understanding its unique characteristics in the Indian context is essential to develop precision diagnostics, therapeutics, and protocols. Cancer is an increasing public health concern in India, with one in nine people facing the risk of a cancer diagnosis, resulting in 1.5 million new cases and 800,000 deaths annually.[1] Cancer can occur in any part of the body, and cancer cells can invade other organs in different ways. Cancer is frequently associated with the number of mutations that interrupt the key signaling pathways. Cellular signaling pathways are organized as modular networks that communicate in real-time. By 2025, this burden is expected to increase by 12.8%. The complexity of the situation is compounded by challenges such as limited cancer awareness, delayed diagnosis, and reduced effectiveness of standard Western treatment protocols. India has a population of about 1.3 billion people, belonging to diverse ethnicities, cultures, and regions, resulting in significant genomic variations among these groups.[2] Despite this, clinical research has hardly explored these variations, as Indian genomes account for only 0.2% of global genetic databases.[3]

Lung cancer is responsible for 5.9% and 11.7% of all cancer cases in India and globally, respectively, and it accounts for 18% and 8.1% of cancer deaths in worldwide and India, respectively.[4] There are two categories of lung cancer i.e. small-cell lung cancer

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(SCLC) and non-small cell lung cancer (NSCLC). NSCLC is the more prevalent type, accounting for approximately 85% of all cases. Adenocarcinoma and squamous cell carcinoma are the top two subtypes of NSCLC in terms of frequency.[5]

Lung cancer, particularly NSCLC, poses a significant risk due to its different subtypes such as squamous cell, adeno, and large-cell carcinoma. Tumor growth and metastasis are fueled by genetic changes affecting oncogenes like K-RAS, EGFR, and EML4-ALK, as well as tumor-suppressor genes like p53 and p16INK4a. K-RAS mutations disable the GTPase activity, EGFR mutations give cancer cells a proliferative edge, and EML4-ALK fusion triggers uncontrolled cell proliferation.[6] Inactivation of p53 leads to accelerated proliferation and reduced apoptosis, while loss of p16INK4a expression allows cancer cells to proliferate. The RAR-beta gene, crucial for regulating vitamin-A-dependent transcription, is frequently mutated or silenced in NSCLC, contributing to disease progression. The loss of the RASSF1A gene tilts the balance of RAS activity towards a growth-promoting effect, giving NSCLC an even greater foothold in the body. With continued research, this disease can be overcome and give hope to those affected by it.[7]

Medicinal plants contain several phytocompounds which have the potential to treat a variety of diseases such as cancer, diabetes, etc. In this study, seven different medicinal plants across the world were selected i.e., *Fagopyrum esculentum, Oroxylum indicum, Oldenlandia diffusa, Pteris multifida, Panax ginseng, Scrophularia nodosa, and Vernonia amygdalina.*

Fagopyrum esculentum or buckwheat is an herbaceous annual coming from the family Polygonaceae, grown for its seed that resembles grain and is used as a cover crop. It grows to about 1-2 meters tall, with large, heart-shaped leaves and small white or pinkish flowers that yield triangular seeds. Buckwheat is known for easy growth in temperate areas, coupled with a reputation for fast growth and improving soil. Besides its agricultural use, buckwheat has medicinal uses, mainly to prevent and fight cancer and a couple of diseases[8]. A range of bioactive compounds are comprised of antioxidants such as rutin and quercetin that can neutralize free radicals, hence reducing oxidative stress; this is where it builds one of the most significant factors that contribute to the cause of cancer. Its bioactive compounds have been linked to showing anti-inflammatory effects in fighting chronic inflammation, which forms one of the factors associated with most cases of cancer as well as various other diseases. Buckwheat provides important nutrients that enhance immune performance and hence prevent several cases of diseases. Studies have shown that buckwheat extracts can inhibit cancerous cell growth and induce programmed cell death. It has also helped in having better cardiovascular health and thus decreased the risk of heart disease and stroke.[9]

Oroxylum indicum, commonly known as the Indian Trumpet Flower or Tree of Damocles, is a deciduous tree from the Bignoniaceae family and originates from tropical Asia, such as India and Southeast Asia. It reaches up to 20 meters and has big, heart-shaped leaves with impressive white or pale yellow, trumpet-shaped flowers which develop into long pod-like fruits. The tree has been used for centuries in Ayurvedic medicine for its medicinal properties.[10] It possesses bioactive compounds such as flavonoids and phenolic acids that are known to be very strong antioxidants, thereby decreasing oxidative stress, a major cause of cancer and chronic diseases. Also, the anti-inflammatory compound in this tree helps to reduce the inflammation that causes cancer. Other studies have also shown that the *Oroxylum indicum* extract prevents the proliferation of cancer cells and promotes apoptosis, making it a potential medicinal herb for this disease. The plant is very nutritious and hence supports the immune function and health generally. Its consumption has also been associated with improved cardiovascular health, hence lowering the chances of suffering from heart and stroke diseases.[11]

Oldenlandia diffusa, commonly known as Snake Needle Grass or Spreading Hedyotis, is an annual herb of the family Rubiaceae, with usage in traditional Chinese medicine widely practiced. Its information can be found in "Guangxi Zhong Yao Zhi," 1959 edition. As a warm, love-to-be-humidous plant, it is found quite readily in wet fields, at the side of roads, and in grasslands. It grows 30-60 cm tall with narrow green stems, lance-shaped leaves, and small white flowers that flower through summer and autumn. The bioactive compounds of the plant, including flavonoids and phenolic acids, make it a potent source of antioxidant activities to achieve a balance of free radicals, hence reducing oxidative stress that leads to cancer and other chronic diseases[12]. Its anti-inflammatory action also prevents or reduces inflammation, which is proven to be a contributing factor to cancer. Other research has shown that extracts from *Oldenlandia diffusa* can inhibit the growth of cancerous cells and cause apoptosis but have not been widely studied for their anticancer functions. Furthermore, nutrient-rich formula provides support to the immune system works to lower the incidences of heart diseases and stroke, and also contributes toward general well-being.[13]

Pteris multifida, or Lemon Button Fern or Lace Fern, is a low-growing fern of the family Pteridaceae, 30-45 cm tall. Rhizome short, erect, with black-brown scales and fronds in a dense cluster; stipes of sterile fronds straw-colored or dark brown. Some herbal medicine makes use of this fern of warm, humid tropical and subtropical regions. It contains bioactive compounds, namely flavonoids and phenolic acids, which enhance strong antioxidant properties that reduce oxidative stress known to accompany cancer and chronic diseases. Its anti-inflammatory effects help in reducing inflammation, which is a known contributor to cancer.[14] Findings of inhibitory effects of *Pteris multifida* extracts on cancer cell growth and programmed death showed its potential as a natural medicine in cancer treatment. It's also highly nutritional, which helps boost immunity while protecting the heart. It reduces dangers in diseases associated with heart conditions and stroke and has improved wellness.[15]

Panax ginseng, also known as Asian Ginseng or Korean Ginseng, is an evergreen plant of the family Araliaceae grown in Korea, China, and Russia. It has a height of 1-2 meters tall, preferring rich soil with well-drained soil in shaded mountainous districts. The leaves have alternate leaflets with 3-5 leaflets, bearing minute greenish-white flowers that are followed by red berries. The root of the plant is traditionally valued with medicinal properties and used for adaptogenic, immune-boosting, and increasing energy activity.[16] Ginsenosides in the plant are bioactive compounds that

have been found to have powerful antioxidant activities, resulting in neutralization of free radicals and reduction in oxidative stress, which contributes to carcinogenesis and chronic diseases. The inflammatory process involved in carcinogenesis and other disorders is also prevented by the root by reducing the whole inflammatory process. Studies have found that *Panax ginseng* extracts are inhibitors of cancer cell growth and can produce apoptosis, with a potential anticancer benefit. Further, it helps in preserving immune function and the health system, also improving cardiovascular health, and lowering risks for heart disease and stroke, thus helping to improve well-being in general.[17]

Scrophularia nodosa is also called Woodland Figwort or Common Figwort and belongs to the Scrophulariaceae family. It is an herbaceous perennial with the Northern Hemisphere temperate. It attains 150 cm, with thick, square stems, and opposite ovate-lanceolate leaves that are toothed. The small flowers are green or purple. According to records, the plant has been used in traditional medicine for centuries.[18] The various bioactive compounds present in it include flavonoids and phenolic acids, which provide strong antioxidant effects that will neutralize free radicals and produce a decline in oxidative stress, linked to cancer and chronic diseases. *Scrophularia nodosa* also reveals anti-inflammatory properties as the inflammation it reduces is one of the well-known risk factors for cancer. Research depicts its drug's potential as an agent to inhibit the growth of cancer cells and to induce apoptosis. Additionally, the plant is nutritious with a host of nutrients that promote the health of the immune system and heart disease reduction, making it easy to reduce the incidence of various diseases such as heart disease and stroke.[19]

Vernonia amygdalina, also called Bitter Leaf, is an evergreen shrub widely distributed in tropical Africa, and it's majorly used in practice medicine. It is 2-5 meters tall. The dark green lanceolate leaves have their typical bitter taste, while its clusters of small white to purplish flowers will show in its plant structure. The plant is rich in flavonoids, saponins, and tannins, providing antioxidant properties in eliminating free radicals or the reduction of oxidative stress which may lead to cancer and chronic diseases. *Vernonia amygdalina* also has strong anti-inflammatory effects.[20] It reduces the inflammation that is known to contribute to cancer. The research found anticancer activity by preventing the growth of cancer cells and inducing apoptosis. This also tends to support immune health, improve cardiovascular function, and regulate blood sugar, thereby aiding in disease conditions like diabetes. Overall, such a wide range of therapeutic benefits will make Bitter Leaf a vital addition to the diet.[21]

The discipline of computational biology is very important as it uses computer-based methodologies to analyze and make sense of biological data. A primary computational tool in this discipline is the technique of molecular docking, which researchers use to predict interactions between small molecules, such as therapeutic drugs or natural compounds, and target proteins based on their chemical and structural characteristics.[22] This technique has been significantly important in drug discovery and development since it contributes to the identification of potential candidates for drug with therapeutic activity in the treatment of a variety of diseases like lung cancer. Molecular docking also gives insights into the binding affinity of a small molecule to a target protein. Such information will prove crucial in pinpointing promising potential candidates for therapeutic effects, which will allow further steps in the area of treatment of lung cancer and some other conditions related to it.[23]

For this study medicinal plants such as *Fagopyrum esculentum*, *Oroxylum indicum*, *Oldenlandia diffusa*, *Pteris multifida*, *Panax ginseng*, *Scrophularia nodosa*, and *Vernonia amygdalina*, were selected with a focus on antioxidant, anti-inflammatory, and anticancer properties. The study thus makes use of a computational biology approach, including molecular docking and ADMET analysis, to evaluate the interactions between bioactive compounds from these plants and specific molecular targets related to cancer and other chronic diseases. By introducing traditional knowledge with advanced in silico methods, this paper gives a science-based rationale for potential future therapeutic applications, moving to address the interests of the scientific community in drug discovery and natural product research.

EXPERIMENTAL PROTOCOLS

MATERIAL AND METHODS

PubChem Sketcher V2.4 software[24] was used to create the 2D structure of phytochemical constituents which were drawn in mol file format and later converted into the.pdb format. SwissADME computes physicochemical descriptors and predicts the pharmacokinetic characteristics, ADME parameters, drug-likeness, and compatibility with the medicinal chemistry of one or multiple tiny molecules to aid the discovery of a drug.[25] To produce ligands and receptors for molecular docking, AutoDock 4.2 software was utilized. For generating the molecular docking score, AutoDock Vina software was employed.[26]

Ligand preparation:

The process of creating ligands from the phytochemical compounds of seven medicinal plants was conducted using the Biovia Discovery Studio visualization software for molecular docking analysis. Next, the two-dimensional structure of the various phytochemical components found in different plants is transformed into pdbqt format in preparation for molecular docking.[27] The compound database was used to prepare the chemical structure of phytochemicals from *Fagopyrum esculentum*[28], *Oroxylum indicum*[29], *Oldenlandia diffusa*[30], *Pteris multifida*[31], *Panax ginseng*[32], *Scrophularia nodosa*[33], and *Vernonia amygdalina*[34] with the help of the PubChem Sketcher online tool.

Receptors and binding sites: The 3D configuration of the ERK2 and catechol complex (PDB-4ZXT)[35,36] was obtained from the website www.rcsb.org.[37] The 3D configuration of the protein was created by eliminating water molecules, detaching the ligand from the proteins, and transforming the format of the structure through the use of AutoDock 4.2.[38] After that, molecular docking was performed with this protein using AutoDock with identified phytochemicals derived from seven different medicinal plants. The molecular docking analysis showed that these phytochemicals have a binding affinity with multiple amino acids of proteins.

One of the proteins in the RAS/RAF/MEK/ERK pathway is ERK2, and among all cancers, lung cancer shows a constitutive

activation. Thus, ERK2 represents an attractive site for therapeutic intervention. The bioactive small molecule catechol directly binds to the active site of the ERK2 enzyme, thereby inhibiting it, disrupting the ERK2/c-Myc signaling axis, and thus reducing tumor growth both in vitro and in vivo. The crystal structure of the ERK2-catechol complex (PDB: 4ZXT) provides the most critical basis for the development of computational studies on synthetic inhibitors aimed at lung cancer therapy.[39]

Physicochemical properties: The SwissADME predicted the drug-like activities of all 41 phytocompounds by analyzing their physiochemical properties such as the weight of the molecule, hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), topological polar surface area (TPSA), and LogP (Lipinski's rule of 5)[40]. Drug-likeness screening of various cannabinoids, including those below the cut-off value in terms of binding energy relative to a control, would lead to revisiting six essential parameters for bioavailability radar by SwissADME. The said parameters include solubility, size, lipophilicity, polarity, flexibility, and saturation. For each of these radars comes a graphical form of the prediction of the compound's bioavailability based on its physicochemical features. The Bioavailability Radar is, therefore a useful tool for researchers to evaluate the drug-likeness and oral absorption potential of a compound by demonstrating their key attributes including molecular weight, lipophilicity, solubility, gastrointestinal absorption, and permeability.[41] A radar plot thus indicates the potential issues that may affect the bioavailability and researchers can pinpoint optimization efforts towards the issues indicated. A multiple comparison of compounds is also easily made with the aid of this radar plot to help identify those showing a better profile in bioavailability. It evaluates how changes in property result in the improvement or worsening of bioavailability, thus optimizing drug efficacy and delivery. Overall, the Bioavailability Radar provided within the SwissADME tool is one of the important tools in the analysis of drugs for good decision-making by researchers within the process of designing and developing drugs.[42]

RESULTS AND DISCUSSION

ADME Analysis Test

This research utilized SwissADME, an easily accessible web tool, to forecast the physical and chemical traits, pharmacokinetics, and drug-like qualities of the newly created rotenone derivatives. The website's interface processed the 2D structures in standard simplified molecular-input line-entry system (SMILES) format and generated the ADMET properties.[43] Table S1 presents the calculated physicochemical properties of the analyzed compounds and Table 1 includes the physiochemical properties of the selected phytocompounds that have an importance in this study. Moreover, Table 2 includes the 2D structures for the phytocompounds that have been selected as a potential phytocompound. Pharmacokinetics refers to the study of a drug's movement in the body and its outlook; therefore, the result of drug effects over time.[44] It is not the same as PD, since this involves what the drug does in the body and the pharmacological effect at the target site. The four steps above in the ADME process are how the drug is absorbed, distributed, metabolized, and eliminated by the body.[45] Its ADME properties are vital to the development of both safe and effective pharmacotherapies.[46] The 2D structures of the compounds were designed using PubChem Sketcher and are summarized in Table S1, including the computed physicochemical properties of the screened compounds. Among the six compounds from Fagopyrum esculentum, zero compounds had no violations of rules, two compounds had one violation, and the other had two or more violations. For Oroxylum indicum, three of the seven compounds had no violations, one of them had one violation, and the rest had two or more. In Oldenlandia diffusa, one of the five compounds had no violations, and the other had two or more violations. Moreover, in Pteris multifida, all the compounds showed zero violations. Furthermore, in Panax ginseng, one compound showed 1 violation, and other compounds showed two violations. Scrophularia nodosa, all of the four compounds showed more than two violations. Vernonia amygdalina, two compounds showed less than two violations, and other compounds showed more than two violations.[47]

Molecular Docking

In the field of computer-assisted drug design and structural molecular biology, molecular docking is a vital tool. Predicting a ligand primary binding mode with a protein that has a known 3-D structure is its goal.[48] Through molecular docking-based virtual screening, Isovitexin (from *Fagopyrum esculentum*), Chrysin-7-O-glucuronide (from *Oroxylum indicum*), 2-methyl-3-methoxy anthraquinone (from *Oldenlandia diffusa*), Creticoside A (from *Pteris multifida*), Ginsenoside Rk2 (from *Panax ginseng*), Diosmin (from *Scrophularia nodosa*), and 5-O-caffeoylquinic acid (from *Vernonia amygdalina*) showed the best binding energy as -6.85, -7.66, -7.12, -8.78, -8.15, -5.63, -5.83 (kcal/mol), respectively. The docking score of compounds with 4ZXT that are generated from various medicinal plants is displayed in Table 3.

Interactions

2D ligand interactions from the compounds in various medicinal plants are shown in Table 4 for the key compounds and for the other plants the compounds have been mentioned in Table S2, while they interact with the ERK2 complex with catechol at the catalytically active site.

The compound Isovitexin from *Fagopyrum esculentum* has a total of 4 van der Waals interactions at ILE324, ALA325, PRO328, and LYS330; 3 conventional hydrogen bond interactions at TYR139, GLU326, and ALA327; 1 carbon-hydrogen bond interaction at ARG79; 1 Pi-lone pair interaction at ARG77; 2 Pi-Pi T-shaped interaction at PHE329 and PHE331.

The compound Chrysin-7-O-glucuronide from *Oroxylum indicum* has a total of 4 van der Waals interactions at LYS330, PRO328, ALA325, and PHE78; 5 conventional hydrogen bond interactions at ALA327, TYR139, GLU326, ARG353, and LEU76; 1 carbon-hydrogen bond interaction at ARG79; 2 Pi-Pi T-shaped interactions at PHE329, and PHE331; 1 Pi-alkyl interaction at ARG77.

The compound 2-methyl-3-methoxy anthraquinone from *Oldenlandia diffusa* has a total of 4 van der Waals interactions at ASP149, CME166, GLY34, and THR68; 1 conventional hydrogen bond interaction at LYS54; 1 carbon-hydrogen bond interaction at GLY169; 3 (Pi-cation and Pi-anion) interactions at ARG67,

ASP167, and GLU71; 1 Pi-Pi Tshaped interaction at TYR36; 3 (alkyl and Pi-alkyl) interactions at LEU170, ALA35, and ILE56.

The compound Creticoside A from *Pteris multifida* has a total of 11 van der Waals interactions at LYS151, ALA35, GLN105, ILE84, ASP106, GLY34, LYS114, ILE31, LEU107, GLY32, and GLU33; 3 conventional hydrogen bond interactions at ASP167, SER153, and MET108; 1 carbon-hydrogen bond interaction at CME166; 1 unfavorable acceptor-acceptor interaction at ASN154; 4 alkyl interactions at LEU156, ALA52, LYS54, andVAL39.

The compound Ginsenoside Rk2 from *Panax ginseng* has a total of 7 van der Waals interactions at PRO176, ASP177, ASP175, VAL173, ARG 172, MET333, and ASP332; 3 conventional hydrogen bond interactions at ALA174, PHE331, and GLU334; 1 unfavorable donor-donor interaction at ASN144; 1 alkyl interaction at PRO328.

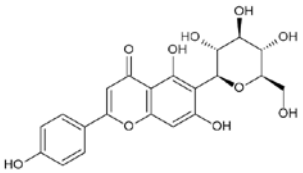
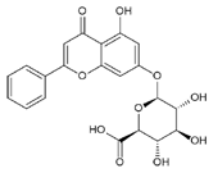
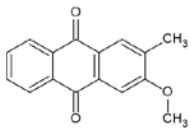
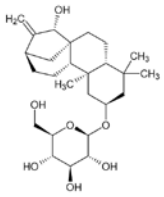
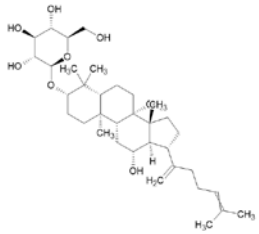
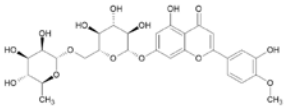
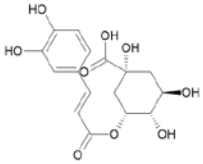
The compound Diosmin from *Scrophularia nodosa* has a total of 12 van der Waals interactions at ALA35, CME166, GLY32, VAL39, ILE31, LYS54, SER153, GLN105, ALA52, ILE84, LEU156, and LEU107; 5 conventional hydrogen bond interactions at ARG67, ASN154, ASP106, MET108, and GLU33; 2 carbon-hydrogen bond interactions at GLY34, and LYS151; 1 Pi-anion interaction at ASP167.

The compound 5-O-caffeoylquinic acid from *Vernonia amygdalina* has a total of 8 van der Waals interaction at LYS330, PHE331, ALA143, ILE324, PHE329, ALA325, PHE78, and ARG79; 4 conventional hydrogen bond interaction at PRO328, TYR139, GLU326, and ARG77; 1 Pi-sigma interaction at ALA327.

Table 1: Physicochemical properties of screened compounds from different medicinal plants

Plant Name	Compounds	H Bond Donor	H Bond Acceptor	TPSA (Å²)	Log P (iLOGP)	Violations	Bioavailability Score
Fagopyrum esculentum	Isovitexin	7	10	181.05	1.94	1	0.55
Oroxylum indicum	Chrysin-7-O-glucuronide	5	10	166.89	2.05	0	0.11
Oldenlandia diffusa	2-methyl-3-methoxy anthraquinone	0	3	43.37	2.48	0	0.55
Pteris multifida	Creticoside A	5	7	119.61	3.45	0	0.55
Panax ginseng	Ginsenoside Rk2	5	7	119.61	5.41	1	0.55
Scrophularia nodosa	Diosmin	8	15	238.20	3.05	3	0.17
Vernonia amygdalina	5-O-caffeoylquinic acid	6	9	164.75	0.96	1	0.11

Table 2: 2D Structures of screened compounds from different medicinal plants

Plant Name	Compound	2D Structures
Fagopyrum esculentum	Isovitexin	
Oroxylum indicum	Chrysin-7-O-glucuronide	
Oldenlandia diffusa	2-methyl-3-methoxy anthraquinone	
Pteris multifida	Creticoside A	
Panax ginseng	Ginsenoside Rk2	
Scrophularia nodosa	Diosmin	
Vernonia amygdalina	5-O-caffeoylquinic acid = Neochlorogenic acid	

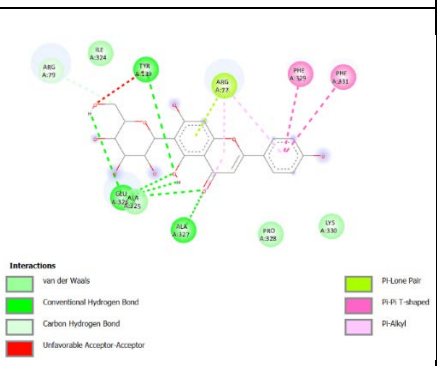
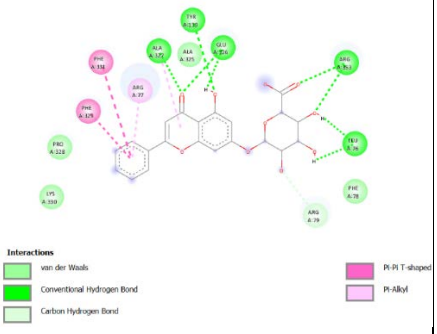
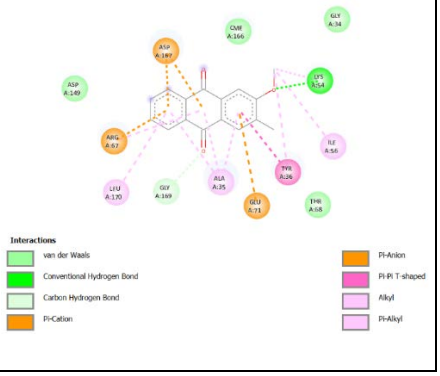
Bioavailability Radar

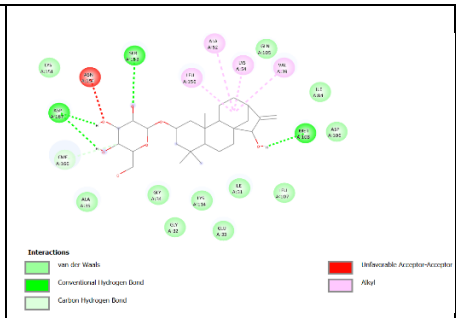
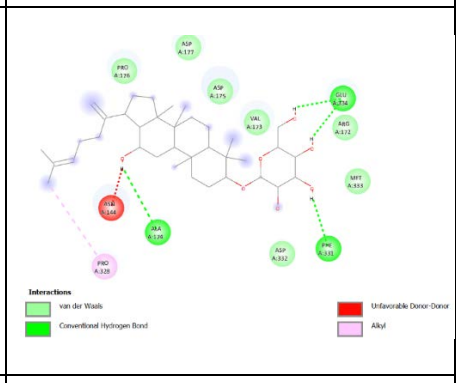
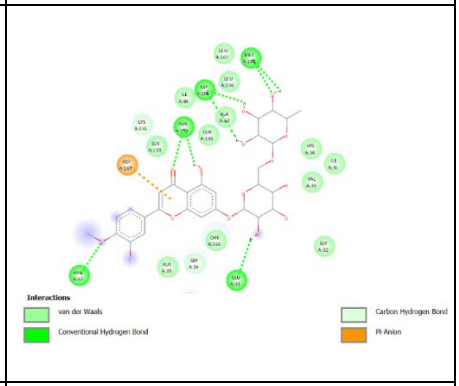
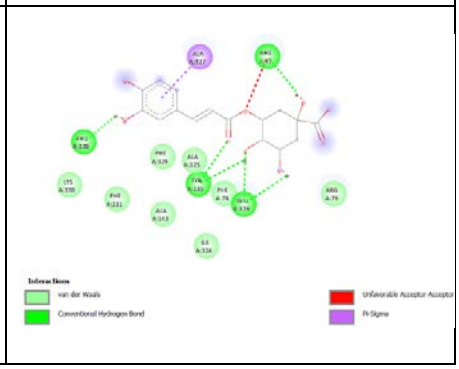
A plot of physicochemical characteristics was passed down to obtain the bioavailability radar. This graph was created using metrics from the SwissADME database, including size, polarity, flexibility, insaturation, insolubility, and lipophilicity of a chemical

Table 3. Docking score of compounds derived from different medicinal plants with Complex of ERK2 with catechol (PDB: 4ZXT)

Plant Name	Compounds	Binding Energy (ΔG)(kcal/mol)	Ligand Efficiency	Inhibition Constant (μM)	Intermolecular Energy (kcal/mol)	Vdw H-bond desolvation (kcal/mol)
Fagopyrum esculentum	Hyperoside	-4.53	-0.14	481.73	-8.11	-7.7
	Isoorientin	-7.15	-0.22	5.78	-10.43	-9.85
	Isovitexin	-6.85	-0.22	9.56	-9.83	-9.54
	Kaempferol-3-rutinoside	-4.72	-0.11	344.23	-9.2	-8.9
	Orientin	-7.23	-0.23	4.98	-10.52	-9.79
	Vitexin	-5.5	-0.18	93.43	-8.48	-8.19
Oroxylum indicum	Baicalein	-7.58	-0.38	2.77	-8.77	-8.33
	Baicalein-7-O-gentiobioside	-6.24	-0.15	26.56	-11.02	-10.46
	Baicalein-7-O-glucoside	-6.24	-0.2	26.74	-9.22	-8.48
	Baicalein-7-O-glucuronide	-6.51	-0.2	16.97	-9.49	-8.29
	Chrysin	-7.62	-0.4	2.62	-8.51	-8.21
	Chrysin-7-O-beta-gentiobioside	-5.48	-0.13	95.82	-9.96	-9.2
	Chrysin-7-O-glucuronide	-7.66	-0.25	2.42	-10.35	-8.7
Oldenlandia diffusa	2-methyl-3-methoxy anthraquinone	-7.12	-0.37	6.02	-7.42	-6.93
	Quercetin 3-0-glucopyranoside	-5.32	-0.16	125.34	-8.9	-8.16
	Quercetin 3-0-sambubioside	-4.2	-0.1	835.93	-8.97	-8.17
	Quercetin 3-0-sophoroside	-4.52	-0.1	484.5	-9.89	-9.15
	Quercetin 3-0-rutinoside	-4.85	-0.11	276.87	-9.63	-9.2
Pteris multifida	Pterokaurane R	-8.38	-0.36	723.05	-9.57	-9.17
	2-hydroxypterosin C	-6.3	-0.35	23.92	-7.8	-7.49
	(2R,3S)-pterosin C	-6.3	-0.37	24.1	-7.49	-7.09
	(2R)-pterosin B	-6.17	-0.39	29.77	-7.07	-6.56
	Creticoside A	-8.78	-0.27	368.4	-11.16	-10.86
	Pterokaurane P1	-7.67	-0.33	2.4	-8.56	-8.46
Panax ginseng	Ginsenoside Rh4	-6.62	-0.15	14.11	-10.2	-9.72
	Ginsenoside Rh1	-6.1	-0.14	33.6	-10.28	-9.57
	Ginsenoside Rh5	-5.67	-0.12	69.75	-9.85	-9.45
	Ginsenoside Rh7	-6.2	-0.14	28.74	-10.37	-10.19
	Ginsenoside Rk2	-8.15	-0.19	1.06	-11.73	-10.96
	Ginsenoside Rk3	-6	-0.14	40.18	-9.88	-9.25
	Ginsenoside F1	-5.51	-0.12	91.13	-9.69	-9.12
Scrophularia nodosa	Diosmin	-5.63	-0.13	74.09	-10.11	-9.78
	Jionoside D	-3.31	-0.07	3.77	-9.27	-8.53
	Verbascoside A	-4.88	-0.1	266.49	-10.25	-9.83
	Verbascoside	-2.8	-0.06	8.87	-8.77	-8.58
Vernonia amygdalina	1,5-O-dicaffeoylquinic acid	-5.88	-0.16	48.97	-10.65	-9.71
	3,4-O-dicaffeoylquinic acid	-5.25	-0.14	142.46	-10.02	-8.81
	3,5-O-dicaffeoylquinic acid = Isochlorogenic acid A	-6.69	-0.18	12.45	-11.46	-10.82
	4,5-Dicaffeoylquinic acid = Isochlorogenic acid C	-6.26	-0.17	25.71	-11.03	-9.64
	5-O-caffeoylquinic acid = Neochlorogenic acid	-5.83	-0.23	53.08	-9.11	-8.51
	Glucuronolactone	-4.36	-0.36	634.8	-5.85	-5.24

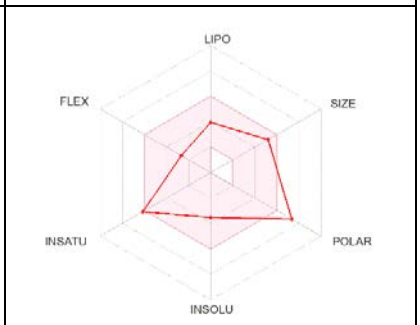
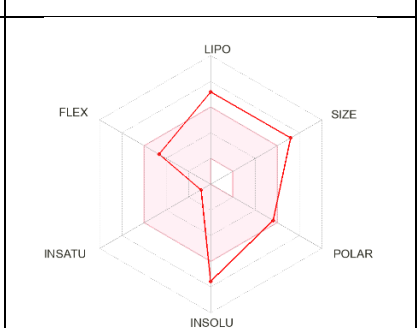
Table 4. 2D Ligand interactions generated by screened compounds from selected medicinal plants with Complex of ERK2 with catechol (PDB: 4ZXT) at the catalytically active site

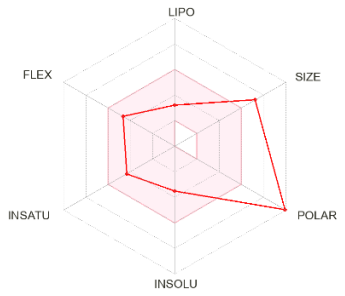
Plant Name	Compound	Interactions
Fagopyrum esculentum	Isovitexin	
Oroxylum indicum	Chrysin-7-O-glucuronide	
Oldenlandia diffusa	2-methyl-3-methoxy anthraquinone	

Pteris multifida	Creticoside A	
Panax ginseng	Ginsenoside Rk2	
Scrophularia nodosa	Diosmin	
Vernonia amygdalina	5-O-caffeoylquinic acid = Neochlorogenic acid	

substabce.[49] The following ranges are included in this space: size (molecular weight b/w 150 and 500 g/mol), polarity (TPSA b/w 20 and 130 Å2), flexibility (not more than 9 rotational bonds), insaturation (carbons in sp^3 hybridization not less than 0.25), insolubility (logS do not exceed 6), and lipophilicity (XLOGP3 b/w -0.7 and +5.0).[50] The bioavailability radar analysis shown in Table 5 provides a rapid evaluation of a molecule's drug-like characteristics of the screened phytocompounds and all the other bioavailability radar have been listed in Table S3.

Table 5. Bioavailability Radar of screened compounds from selected medicinal plants generated using SwissADME

Plant Name	Compound	Bioavailability Radar
Fagopyrum esculentum	Isovitexin	
Oroxylum indicum	Chrysin-7-O-glucuronide	
Oldenlandia diffusa	2-methyl-3-methoxy anthraquinone	
Pteris multifida	Creticoside A	
Panax ginseng	Ginsenoside Rk2	

Scrophularia nodosa	Diosmin	
Vernonia amygdalina	5-O-caffeoylquinic acid = Neochlorogenic acid	

CONCLUSION

The objective of the *in-silico* study is to comprehensively evaluate the potential anti-cancer activity of specific phytochemical compounds through molecular docking analysis. After conducting the analysis, it was observed that Isovitexin (derived from *Fagopyrum esculentum*), Chrysin-7-O-glucuronide (extracted from *Oroxylum indicum*), 2-methyl-3-methoxy anthraquinone (obtained from *Oldenlandia diffusa*), Creticoside A (derived from *Pteris multifida*), Ginsenoside Rk2 (derived from *Panax ginseng*), Diosmin (extracted from *Scrophularia nodosa*), and 5-O-caffeoylquinic acid (obtained from *Vernonia amygdalina*) exhibited notable interactions with the ERK2 complex bound with cathecol. These interactions involved various types of bonds including van der Waals, C-H bonds, Pi-Pi T-shaped, alkyl bonds, pi-bond, and conventional hydrogen bonds. Furthermore, it was observed that the physicochemical properties of the identified compounds from the seven different medicinal plants align with Lipinski's rule of five, which indicates their potential as drug candidates for lung cancer managment.

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CONFLICT OF INTEREST STATEMENT

The author shows no conflict of interest.

SUPPLEMENTARY INFORMATION

The supplementary information file contains the data of ADMET and Bioavailability Radar studies.

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