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Research Article

Exploring the Potential of Furofuran Lignans Isolated from *Beilschmiedia pulverulenta* for Drug Development: A Computational Approach

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Abstract: Natural products have played a significant role in drug discovery and continue to be an important source of lead for new drugs. In recent years, computer-based drug discovery methods have emerged as an effective approach for identifying small molecule leads with desirable pharmacokinetic and toxicity profiles. This study investigated the pharmacological and bioactivity of five furofuran lignans, namely, epiexcelsin, sesamin, sesartemin, syringaresinol, and yangambin, isolated from the plant *Beilschmiedia pulverulenta*. In silico studies were conducted to predict the pharmacological activities, toxicity, and drug likeliness properties of the lead compounds. The results showed that all compounds had promising pharmacokinetic activities, with epiexcelsin exhibiting strong binding affinity (-8.13 kcal mol^{-1}) and inhibitory activity (1.1 µM) against estrogen receptor-α, and predicted to be bioavailable and effective lead. The findings of this study provide important insights into the potential therapeutic uses of natural medicinal plants and emphasize the potential of combining traditional medicinal knowledge with modern scientific approaches in drug discovery. Overall, the furofuran lignans isolated from *Beilschmiedia pulverulenta* represent a promising source of natural compounds for the development of effective drugs.

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1. Introduction

Natural medicinal plants are rapidly being recognized as a rich source of bioactive chemicals with therapeutic potential. Among these, the genus *Beilschmiedia*, which contains about 250 species and is common in Africa and Asia, has attracted interest due to its various chemical compositions and therapeutic capabilities (Salleh et al., 2016a, 2019, 2020, and 2021). *Beilschmiedia pulverulenta*, also known as 'medang merah' in Malaysia and found in Peninsular Malaysia, Borneo, and Indonesia, is one such species that thrives in mixed dipterocarp forests on sandy loam soils (Salleh et al., 2016b). Previous phytochemical studies on *Beilschmiedia* species revealed the presence of a variety of natural products, including endiandric acid derivatives, alkaloids, flavonoids, terpenoids, lignans, neolignans, and

essential oils, some of which have antibacterial, antimalarial, and anti-tuberculosis activity (Salleh et al., 2016c, 2016d, and 2016e).

The process of discovering and developing novel drug leads from natural sources is a multistage activity. Unfortunately, many failures occur during the clinical phase, primarily due to pharmacokinetic and toxicity issues. With the capacity to predict potential inaccurate (off-target), identify negative effects, suggest new targets for medicines already in use, and assess affinity and selectivity among protein targets, in silico technologies have recently gained prominence as efficient methods for polypharmacological research (Shantier et al., 2023). Researchers can acquire significant insights into the mechanisms of action and toxicological profiles of natural compounds by utilizing computational approaches, aiding the selection and optimization of promising drug leads. These computational approaches have significantly contributed to the drug discovery field and can potentially drive the development of new drugs from natural sources in a more efficient and targeted manner (Sadybekov and Katritch, 2023).

Furofuran lignans are a class of natural compounds that have been isolated from various plant species. These compounds are characterized by the unique structural features of a furofuran ring system. They are typically found in plants belonging to the family Lauraceae, such as *Persea pyrifolia*, a plant native to South Brazil (Batista et al., 2010). Studies have shown that furofuran lignans possess various pharmacological properties, including anti-inflammatory, antitumor, and antiviral activities. Some furofuran lignans have been shown to inhibit the growth of cancer cells, making them potential candidates for the development of anticancer drugs. In addition, furofuran lignans have been found to have neuroprotective effects, potentially making them useful for the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's disease (Xu et al., 2018). Due to their interesting pharmacological properties, furofuran lignans have gained attention from the scientific community as potential lead compounds for drug discovery.

As part of drug discovery efforts from natural sources, five furofuran lignans, namely, epiexcelsin, sesamin, sesartemin, syringaresinol, and yangambin were isolated from *B. pulverulenta*. These furofuran lignans have notable anticholinesterase and anti-inflammatory effects (Salleh et al., 2016a). In this work, *in silico* studies were performed to estimate their pharmacological activity, toxicity, drug likeness, quality, pharmacokinetic (ADME) characteristics, and physicochemical properties in order to further evaluate their potential as drug candidates.

2. Material and Methods

2.1. Compound chemical structure format

To evaluate the pharmacokinetic and bioactivity properties of the isolated compounds from the stem bark of *B. pulverulenta*, various *in silico* tools were utilized through web-based platforms. The compounds were analyzed using both 3D SDF and isomeric simplified molecular input line entry system (SMILE) formats, which were obtained from the PubChem database.

2.2. Bioactivity properties

The Molinspiration online server (http://www.molinspiration.com/) (Molinspiration cheminformatics, 2006) was employed to assess the drug likeliness properties of the potential lead molecules. The tested molecules were analyzed for their ability to function as G-protein coupled receptor (GPCR) ligands, ion channel modulators (ICM), kinase inhibitors (KI), nuclear receptor ligands (NRL), protease inhibitors (PI), and enzyme inhibitors (EI) (Pushpa et al., 2022).

2.3. Pharmacological activities

To assess the potential pharmacological activities and toxicities of the lead compounds, they were submitted in SMILE format to the PASS Online tool (http://www.pharmaexpert.ru/passonline/). This tool utilizes a computational approach to predict the activity spectrum and possible toxic effects of chemical compounds based on their structural formula. By analyzing the compounds' molecular structure, the tool provides information on their possible pharmacological activities and potential toxicity (Lee et al., 2022).

2.4. ADME prediction and toxicity risk assessment

To predict the pharmacokinetic (ADME) and physicochemical properties of the lead compounds, we utilized the SwissADME web tool (http://www.swissadme.ch/) (Daina et al., 2017). To assess the potential toxicity risks of the compounds, both Molinspiration online server and OSIRIS Property Explorer open-source program (http://www.organicchemistry.org/prog/peo/) were employed in this study. While the Molinspiration server predicts the toxicity and drug-likeness properties of compounds, the OSIRIS Property Explorer program uses an extensive database of toxicity information to predict various toxicological endpoints, including mutagenicity, carcinogenicity, reproductive effects, and more (Mittal et al., 2021).

2.5. DFT computation and structural analysis

To calculate the structural and electronic properties of the five isolated compounds, we used the DFT/B3LYP method with a 6-31G* basis set in Spartan 14 (Spartan 14, 2013). Various parameters were evaluated, including the energies of the frontier molecular orbitals (HOMO, LUMO, and energy gap). These calculations provide valuable insights into the ligand-protein interactions in the active site of the target protein. Moreover, the electrostatic potential surfaces (EPs) of the molecules were obtained using population analysis computations and visualized with Spartan 14 (Umar and Uzairu, 2023).

2.6. Molecular docking

2.6.1. Preparation of ligands

The 3D structures of the compounds were obtained from the PubChem database in SDF format. To identify the bioactive conformer from the local minima, the energy minimization was performed using the MM2 force field in Spartan 14. Furthermore, optimization of the compounds was carried out using the DFT/B3LYP approach and 6-31G* basis set (Umar and Uzairu, 2023).

2.6.2. Identification of target

To determine the potential target for the selected lead compound, the ChemMapper and PharmMapper server (http://www.lilab-ecust.cn/chemmapper/ and https://www.lilab-ecust.cn/pharmmapper/), respectively utilized (Trosset, 2019; Srivastava et al., 2022). The lead compound was submitted in sdf format, and the target set was limited to human targets while all other parameters were kept as default.

2.6.3. Preparation of protein structure

The 3D structure of the target identified by the ChemMapper and PharmMapper servers was obtained from the Protein Data Bank (PDB ID: 3ERT; http://www.rcsb.org/). The protein files were prepared by removing all water molecules and hetero groups and adding polar hydrogen atoms using Discovery Studio Client software 2021 (BIOVIA Discovery Studio, 2019). It was then imported into PyRx Virtual screening tools which employ Mgltools to energy, minimize and as well apply appropriate and relevant charges (Salihu et al., 2023a).

2.6.4. In silico molecular docking and visualization

The AutoDock 4.0 software embedded in PyRx was utilized to perform molecular docking. The active residue of the protein was chosen for finding the most favorable binding site. All ligands were docked by selecting the specific residue in contact with the native ligand's, thereby generating a grid box (15.63Å each for X, Y, and Z dimensions at center 29.4152, -0.4138, 24.466 for X, Y, and Z respectively) which covered all binding pocket. The ligand with the highest binding energy (most negative) was considered to have the maximum binding affinity. Finally, the 2D interactions of the resulting docking file with poses exhibiting the lowest binding energies were visualized using DS Visualizer Client 2021 (Salihu et al., 2023b).

3. Results and Discussion

3.1. Bioactivity properties

Drug similarity analysis requires a delicate balance of considering different chemical attributes and structural factors to determine whether a molecule is similar to existing medications. To achieve this, Molinspiration employs a sophisticated Bayesian statistical method that compares the structures of active ligands for a specific target with those of inactive molecules. This approach helps to identify substructure features that are typical of active molecules and determine the physicochemical properties that contribute to drug activity (Alexey et al., 2014). This study evaluated epiexcelsin, sesartemin, sesamin, yangambin, and syringaresinol for their drug ability as GPCR ligands, ion channel modulators (ICM), kinase inhibitors (KI), nuclear receptor ligands (NRL), protease inhibitors (PI), and enzyme inhibitors (EI) and calculated their bioactivity scores. The higher the score value, the greater the likelihood of bioactivity (Paramashivam et al., 2015). Table 1 shows the drug-likeliness of the isolated lead compounds by Molinspiration. Based on the results, it appears that some of the compounds have higher bioactivity scores for certain drug properties compared to others. Syringaresinol has a high bioactivity score as a nuclear receptor ligand, indicating a higher probability that it could be effective as a drug that targets this receptor. Some compounds such as sesartemin and yangambin have negative scores for certain drug properties, indicating a lower probability of bioactivity for those properties. All compounds in the table, except sesartemin and epiexcelsin, have positive scores for enzyme inhibition, indicating that they have potential as inhibitors of enzyme activity.

Table 1. The drug likeliness of the isolated lead compounds by Molinspiration

Compound	Pubchem ID	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Epiexcelsin	489948	-0.03	-0.32	-0.32	-0.16	-0.21	-0.03
Sesartemin	342737	-0.04	-0.32	-0.31	-0.20	-0.22	-0.03
Yangambin	443028	-0.03	-0.25	-0.19	-0.10	-0.16	0.01
Syringaresinol	443023	-0.01	-0.23	-0.17	-0.01	-0.14	0.08
Sesamin	72307	0.02	-0.31	-0.27	-0.09	-0.15	0.03

3.2. Pharmacological activities

The PASS method is a computational tool that predicts the potential pharmacological activities and toxicity of molecules based on their chemical structure. It assumes that the activity of a compound is a function of its structure and uses original descriptors called multilevel neighborhoods of atoms (MNA) to define the chemical structure. This enables the prediction of whether a novel molecule will have a certain impact by comparing its structure to that of a well-known physiologically active drug. The server calculates two probability scores, Pa and Pi, for each studied compound, ranging from 0.000 to 1.000, indicating the compound's pharmacological activity. By predicting the different pharmacological activities of these lead compounds, PASS has proven to be a valuable tool in the estimation of the biological activity profiles of virtual molecules prior to their chemical synthesis and biological testing (Shantier et al., 2023). In this study, the PASS online tool was used to estimate the biological activity profiles of several lead compounds, namely, sesartemin, epiexcelsin, sesamin, syringaresinol, and yangambin. All compounds, including epiexcelsin, exhibited active antineoplastic activity, with epiexcelsin having the highest probability of pharmacological activity (Pa = 0.890) and a low probability of toxicity (Pi = 0.020). Furthermore, epiexcelsin, sesartemin, and sesamin have been shown to exhibit significant probabilities of caspase 3 stimulation (Pa = 0.887, Pi = 0.004 and Pa = 0.800, Pi = 0.005, respectively) and membrane integrity agonism (Pa = 0.802, Pi = 0.036 and Pa = 0.931, Pi = 0.005, respectively). Caspase 3 is an important enzyme involved in the initiation of programmed cell death (apoptosis), which plays a critical role in preventing the development and progression of cancer. Membrane integrity is essential for cellular homeostasis, and its impairment is associated with various pathological conditions.

Yangambin and syringaresinol were found to exhibit strong potential as inhibitors of Feruloyl esterase (Pa = 0.839, Pi = 0.008 and Pa = 0.865, Pi = 0.006, respectively) and Aspulvinone

dimethylallyltransferase (Pa = 0.823, Pi = 0.027 and Pa = 0.871, Pi = 0.015, respectively), based on their calculated probability scores from the PASS Online tool. The former enzyme is involved in the hydrolysis of ester linkages in plant cell wall materials, while the latter enzyme is important in the biosynthesis of secondary metabolites in fungi. These findings suggest that yangambin and syringaresinol may have potential applications in drug discovery as inhibitors of these enzymes.

Table 2. Predicted pharmacological activities of the isolated compound PASSonline

Compounds	Activities									
	Antineoplastic		Caspase 3 stimulant		Membrane integrity agonist		Feruloyl esterase inhibitor		Aspulvinone dimethylallyl-transferase inhibitor	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
Epiexcelsin	0.890	0.020	0.849	0.004	0.866	0.020	-	-	-	-
Sesartemin	0.850	0.007	0.887	0.004	0.802	0.036	-	-	-	-
Sesamin	0.787	0.013	0.800	0.005	0.931	0.005	-	-	-	-
Yangambin	0.869	0.005	-	-	-	-	0.839	0.008	0.823	0.027
Syringaresinol	0.824	0.009	-	-	-	-	0.865	0.006	0.871	0.015

3.3. ADME prediction and toxicity risk assessment

In the process of drug discovery, it is crucial to identify promising hits or leads that specifically target the desired receptor, while also considering their physicochemical properties and toxicity risks. These factors are vital in determining the pharmacokinetic parameters and the eventual biological effects of lead compounds. Additionally, identifying promiscuous compounds that give false positives in high-throughput screening, known as pan assay interference compounds (PAINS), is important to avoid wasting time and resources on non-specific compounds. To assess the possibility of the tested compounds being PAINS, substructure filters were used in the SwissADME web tool. Fortunately, none of the compounds showed alerts for PAINS, indicating that they are promising leads. Furthermore, the SwissADME tool was also used to predict the pharmacokinetic (ADME) and physicochemical properties of the isolated compounds in the SMILE format, providing valuable information for drug design and optimization.

Table 3. Physicochemical properties and toxicity profile of the isolated compounds by SwissADME

Ligand	MW	nRB	nHA	nHD	TPSA	Log P	Water sol	RO5 Viol.
Epiexcelsin	414.4	4	8	0	73.84	2.75	Soluble	0
Sesartemin	430.4	6	8	0	73.84	2.89	Soluble	0
Yangambin	446.4	8	8	0	73.84	3.04	Moderately soluble	0
Syringaresinol	418.4	6	8	2	95.84	2.33	Soluble	0
Sesamin	354.3	2	6	0	55.38	2.79	Soluble	0

MW = molecular weight; nRB = number of rotatable bonds; nHD = number hydrogen bond donor; nHA = number hydrogen bond acceptors; TPSA = topological polar surface area; water sol= water solubility; RO5 viol. = lipinski's rule of five violations.

The physicochemical characteristics of drug-like molecules can be computed using Lipinski's rule of five, which takes into account factors such as molecular weight, hydrogen bond donors and acceptors, and logP. Compounds that break more than one of these criteria may have issues with bioavailability (Lipinski, 2000; Shams et al., 2022). In addition, Verber et al. (2002) noted that compounds with fewer than 10 rotatable bonds and a total polar surface area (TPSA) of 140 or less are more likely to have high bioavailability (Ramadan et al., 2022). Our study, summarized in Tables 3 and 4, revealed that all five isolated compounds adhered to these rules, including the number of hydrogen bonds and TPSA. They were also predicted to have molecular weights of less than 500 Da, making them easily transportable, diffusible, and absorbable compared to heavier molecules (Srimai et al., 2013). However, yangambin was predicted to have moderate solubility (Log P=3.04), while the remaining four compounds were found to be soluble and therefore have good bioavailability. It is worth noting that solubility can also influence the ADME profile, and the acceptable solubility profile of our compounds is a positive sign for their eventual success as drug candidates (Utomo et al., 2022).

Table 4. Predicted ADME properties of isolated compounds SwissADME webserver

Compound	A	B	C	D	E	F	G	H	I
Epiexcelsin	High	Yes	Yes	No	No	Yes	Yes	Yes	-6.97
Sesartemin	High	Yes	No	No	No	No	Yes	No	-6.97
Yangambin	High	Yes	No	No	No	No	Yes	No	-6.98
Syringaresinol	High	No	Yes	No	No	No	Yes	No	-7.27
Sesamin	High	Yes	No	No	Yes	No	Yes	Yes	-6.56

A= human gastrointestinal absorption; B = permeant; blood–brain barrier permeability; C = permeability glycoprotein substrate; D = CYP1A2 inhibitor; E = CYP2C19 inhibitor; F = CYP2C9 inhibitor; G = CYP2D6 inhibitor; H = CYP3A4 inhibitor; I = log Kp (cms-1): skin permeability coefficient.

3.4. DFT computation and structural analysis

Figure 1 shows that the geometry-optimized structures of epiexcelsin conform to a global minimum as obtained from DFT computations. The frontier molecular orbitals (HOMO and LUMO) play a crucial role in charge transfer interactions between the ligands and the active site of the target protein. The positive and negative regions of the orbitals are represented by blue and red colors, respectively, as shown in Figure 1. The frontier molecular orbitals, namely, HOMO and LUMO, are highly informative in predicting the most reactive position in π-electron systems and in explaining various types of reactions within the conjugated system. Additionally, the HOMO and LUMO energy levels can provide insights into the relative chemical stability and biological activity of the molecules. The difference in energy between these two orbitals, known as the HOMO-LUMO energy gap, can be utilized to determine the strength and stability of the molecule. Generally, a molecule with a smaller HOMO-LUMO energy gap is more polarizable and exhibits greater chemical reactivity (Shams et al., 2022; Umar & Uzairu, 2023).

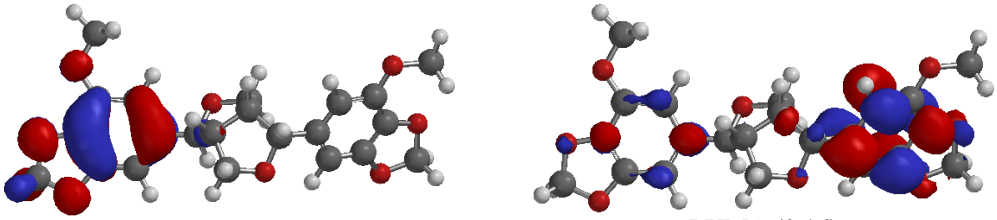
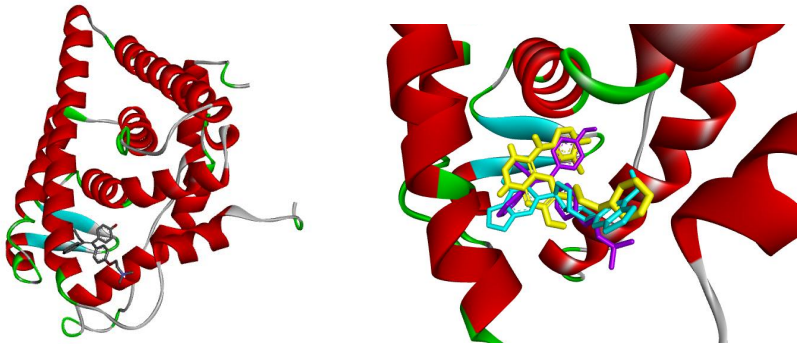


Figure 1. The 3D HOMO and LUMO frontier orbitals of the selected compound (Epiexcelsin).

3.5. Molecular docking

Upon completion of the analysis of the physicochemical and pharmacological properties of the isolated compounds, the potential target for these compounds was predicted using the ChemMapper and PharmMapper servers. The results revealed that the estrogen receptor-α could be a promising target for these compounds, with a fit score of 2.801 and a normalized fit score of 0.933. Moreover, the Estrogen Receptor-α (PDB ID: 3ERT) (Figure 2(A)) was downloaded from the protein data bank. The 3ERT target is particularly relevant to this study, as it has been shown to play a key role in the development and progression of breast cancer. Estrogen receptor-positive breast cancer is the most common type of breast cancer. It is often treated with drugs that target the estrogen receptor, such as tamoxifen and aromatase inhibitors (Yu et al., 2022). However, resistance to these drugs is a major clinical challenge, and there is a need for new therapies that can overcome this resistance (Tsoi et al., 2022). The potential of natural compounds to modulate the activity of the estrogen receptor and other proteins involved in hormone signaling pathways makes them promising candidates for developing new therapies for estrogen receptor-positive breast cancer and other hormone-dependent diseases (Khan et al., 2020; Talib et al., 2022).



(**A**) (**B**)

Figure 2. The 3D structure of (**A**) estrogen receptor-α together with native ligand, (**B**) redocked native ligand (magenta), Epiexcelsin (cyan), and gefitinib (yellow).

Table 5 presents the docking scoring results, inhibition constants (Ki), and the types of interactions formed by furofuran lignans and a known drug (Gefitinib) with the Estrogen Receptor-α (ER-α). The docking results show the binding affinity of each ligand, represented as the docking score, which is a measure of the predicted strength of ligand-receptor interaction. The lower the docking score, the higher the predicted binding affinity. The inhibition constants (Ki) are also reported, which provide an estimate of the potency of the ligands in inhibiting the activity of ER-α. Lower Ki values indicate higher potency. From the results, it can be observed that epiexcelsin has the lowest docking score (-8.13 kcal mol^{-1}) and the lowest Ki value (1.1 µM), suggesting it has the highest predicted binding affinity and potency among the tested furofuran lignans.

To validate the docking, we performed redocking of the native ligand and superimposed our test ligands in the identical binding conformation (Figure 2(B)). It can be seen that the compounds including gefitinib binds in the same pocket as the native ligand and in a similar conformation. The docking scores and interactions of furofuran lignan ligands with estrogen receptor-α were compared to gefitinib, an approved drug. Epiexcelsin showed the highest binding affinity with a docking score of -8.13 kcal mol^{-1}, surpassing gefitinib with a docking score of -7.04 kcal mol^{-1}, indicating a potentially stronger interaction with estrogen receptor-α. Epiexcelsin also had a lower inhibition constant (Ki) of 1.1 µM compared to gefitinib's Ki of 6.93 µM, suggesting higher potency in inhibiting estrogen receptor-α activity.

Both epiexcelsin and gefitinib formed hydrogen bonds with the receptor, but epiexcelsin formed three hydrogen bonds with His524, Leu346, and Ala350, while gefitinib formed two hydrogen bonds with Asp351 and Arg394. Additionally, epiexcelsin exhibited similarities with gefitinib in forming hydrophobic interactions with various residues, including Leu354, Leu387, Leu428, Leu525, Met421, Met388, and Ile424, as well as π-alkyl interactions with Leu525, His524, Ala350, and Trp383. However, epiexcelsin also showed unique interactions, such as a π-π stacking interaction with Trp383, which was not observed in gefitinib. This suggests that epiexcelsin may have additional binding modes or interactions that could contribute to its higher binding affinity and potency compared to gefitinib.

In our previous work, these five compounds were successfully isolated and displayed notable anticholinesterase and anti-inflammatory activities with IC_{50} ranging from 168.8 – 504.2 µM and 21.0 – 59.4 µM respectively (Salleh et al., 2016a). Recent study by Rabaan et al. (2023), epiexcelsin demonstrated a significantly high minimum binding energy of −7.4 kcal/mol in its best pose compared to all other compounds investigated against SARS-CoV-2 RdRp protein, and even its worst pose displayed a notable binding energy of −6.5 kcal/mol. This exceptional binding affinity of epiexcelsin highlights its potential importance as a lead compound for further exploration in drug discovery efforts. We are aware of the limits of our computational work and the critical need for additional experimental validation to support and expand the results reported in this study. Incorporating experimental data will improve the validity and precision of our findings while also shedding important light on the applicability and viability of our suggested approach. To improve the general validity and application of the findings in real-world circumstances, we recommend future studies to prioritize experimental verification.

Table 5. Docking scoring, inhibition constant, and the type of interactions formed by furofuran lignans with eastrogen receptor-α

Ligands	Binding affinity (kcal mol^{-1})	Inhibition constant (Ki)	Total number and residues involved in Hbonds	Hydrophobic bond and miscellaneous
Sesamin	-7.64	2.5μM	1 His524 (8vdw)	5 alkyl (Leu536, Leu539, Leu525, Met421, Ala350); 1 π- anion (Asp351); 1 π-sulphur (Met421) 1 π- δ (Met343); 4 π-alkyl (His524, Leu346, Leu525, Ala350)
Sesartemin	-6.88	9.02 μM	3 Thr347, Asp351, Glu419 (7vdw)	10 alkyl (Ala350, Leu525, Leu384, Leu354, Leu428, Met388, 2 x Met421, 2 x Ile424); 1 π- anion (Asp351) 2 π- π staking (Trp383); 4 π-alkyl (Leu346, Ala350 and 2 x Trp383)
Syringeresinol	-6.24	26.68 μM	3 Thr347, Leu346, Asp351 (6vdw)	6 alkyl (Ala350, Leu354, Leu391, Leu525, Met421, Ile424); 1 π- anion (Asp351); 1 π-sulphur (Met421); 1 π- δ (Trp383); 2 π-alkyl (Ala35 and Phe404)
Yangambin	-6.56	15.53 μM	2 Thr347, Asp351 (2vdw)	12 alkyl (Leu354, Leu536, Leu387, Leu428, Leu525, 2 x Leu391, Ala350, 2 x Met421, Met343); 1 π- anion (Asp351); 2 π-sulphur (Met421, Met343); 1 π- δ (leu346); 3 π-alkyl (Trp383, Phe404 and Ala350)
Epiexcelsin	-8.13	1.1 μM	3 His524, Leu346, Ala350 (7 Vdw)	7 alkyl (Leu354, Leu387, Leu428, Leu536, Met421, Met388, Ile424); 1 π- π staking (Trp383); 5 π-alkyl (Leu525,His524 , Ala350 and 2 x Trp383)
Gefitinib (approved drug)	-7.04	6.93 μM	2 Asp351, Arg394 (6vdw)	6 alkyl (Leu354, Leu346, Leu349, Leu525 and 2 x Ala350); 1 Sulphur-x (Met343); 4 π-alkyl (Leu387, Leu391, 2 x Trp383); 3 halogen (Arg394, Phe404 and Glu353)

vdw = vanderwaal interaction.

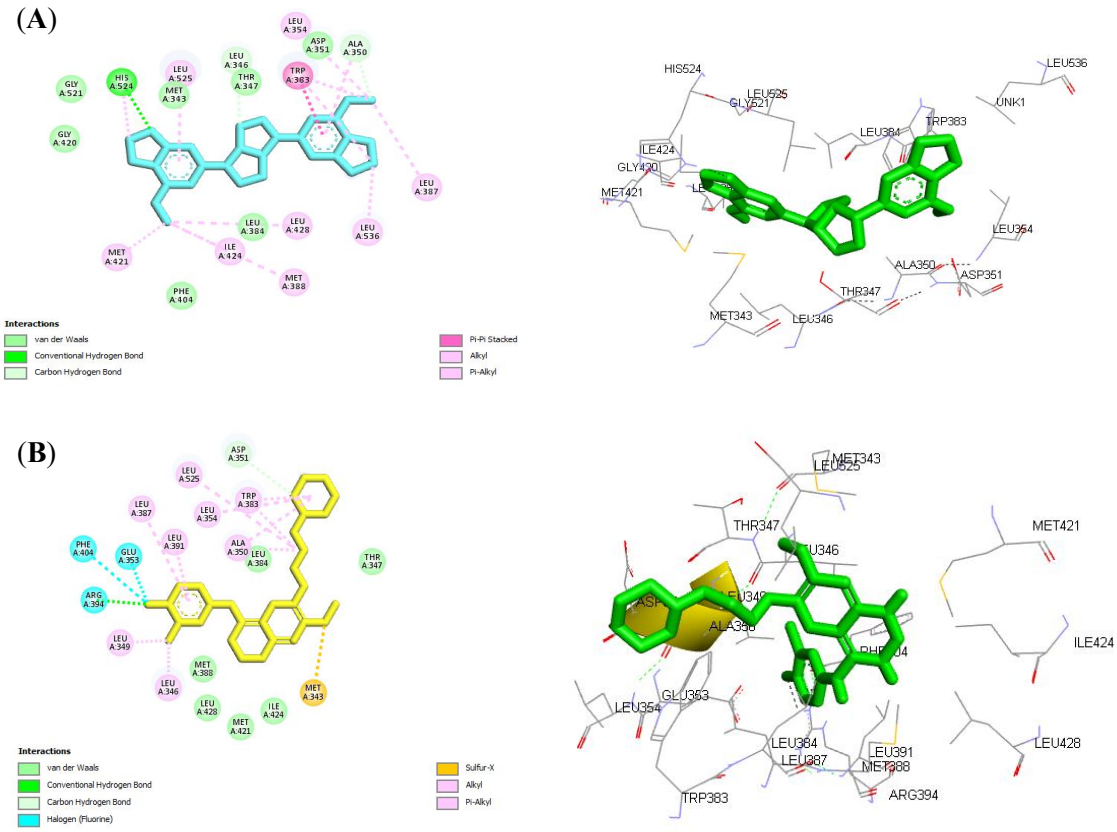


Figure 3. The 2D interactions and residue surrounding of (**A**) epiexcelsin and (**B**) gefitinib in the binding site of the eastrogen receptor-α.

4. Conclusion

This study utilized computer-based drug discovery to investigate the pharmacological and bioactivity of five isolated compounds, namely, epiexcelsin, sesamin, sesartemin, syringaresinol, and yangambin from *Beilschmiedia pulverulenta*. All compounds showed promising pharmacokinetic activities, with epiexcelsin exhibiting strong binding affinity and inhibitory activity against estrogen receptor-α. This furofuran lignan compound was predicted to be a bioavailable and effective lead, potentially outperforming gefitinib, an approved drug. The identification of these compounds highlights the potential of natural medicinal plants for drug development, and the use of computational methods in drug discovery to predict potential drug targets and estimate drug likeliness properties can help reduce the likelihood of failure in clinical phases. Therefore, this study contributes to the growing body of research on natural products as a source of drug lead, while also emphasizing the significance of integrating traditional medicinal knowledge with modern scientific approaches.

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