© 2024 Journal of Pharmacy & Pharmacognosy Research, 12 (5), 881-891, 2024
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres23.1740_12.5.881

Original Article

Epidermal growth factor receptor mutant T790M-L858R-V948R inhibitor from *Calophyllum inophyllum* L. leaf as potential non-small cell lung cancer drugs

[Inhibidor del receptor del factor de crecimiento epidérmico mutante T790M-L858R-V948R de la hoja de *Calophyllum inophyllum* L. como posible fármaco contra el cáncer de pulmón de células no pequeñas]

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Abstract

Context: Non-Small Cell Lung Cancer (NSCLC) is the most common lung cancer type, with 80-85% prevalence. Usually, NSCLC is treated by chemotherapy and radiotherapy in collaboration with gefitinib or other anticancer drugs. Those treatments have many adverse effects, such as shortness of breath, bleeding, fever, hair loss, and radiation pneumonitis. Lack of treatment options and numerous mutations greatly contribute to lung cancer's shocking death toll. Therefore, potential EGFR mutant inhibitors need to be analyzed.

Aims: To identify potential inhibitors of an epidermal growth factor receptor (EGFR) mutant derived from *Calophyllum inophyllum* L. leaf using an *in silico* approach.

Methods: *In silico* analysis and literature study were carried out. Secondary metabolite compounds from *C. inophyllum* were obtained through the PubChem database, and their biological activity and ADMET were analyzed. Molecular docking with EGFR wild-type (5FED) and mutant (5HG7) was carried out using PyRx. Furthermore, amino acid residues were analyzed using Discovery Studio.

Results: Based on overall screening and molecular docking, a non-toxic compound with a low binding affinity with EGFR mutant protein is 4-[2-(4-nitrophenyl)ethylcarbamoyl]benzenesulfonyl. Moreover, interactions and hydrogen bonds at Ala743, Gly796, Leu718, Phe856, Leu844, and Val726 are known to play a crucial role in ATP binding inhibition toward the tyrosine kinase domain, resulting in EGFR mutant inhibition.

Conclusions: 4-[2-(4-nitrophenyl)ethylcarbamoyl]benzenesulfonyl is one of the potential candidates as an EGFR mutant protein by ATP binding inhibition. However, *in vitro* and *in vivo* research needs to be performed to confirm these results.

Keywords: anticancer drug; lung cancer; NSCLC; secondary metabolites; virtual screening.

Resumen

Contexto: El cáncer de pulmón no microcítico (CPNM) es el tipo de cáncer de pulmón más frecuente, con una prevalencia del 80-85%. Por lo general, el CPNM se trata mediante quimioterapia y radioterapia en colaboración con gefitinib u otros medicamentos contra el cáncer. Esos tratamientos tienen muchos efectos adversos, como dificultad para respirar, hemorragias, fiebre, caída del cabello y neumonitis por radiación. La falta de opciones de tratamiento y las numerosas mutaciones contribuyen en gran medida a que el cáncer de pulmón se cobre un número de víctimas alarmante. Por lo tanto, es necesario analizar los posibles inhibidores mutantes del EGFR.

Objetivos: Identificar inhibidores potenciales del receptor del factor de crecimiento epidérmico (EGFR) mutante derivado de la hoja de *Calophyllum inophyllum* L. mediante un enfoque *in silico*.

Métodos: Se llevó a cabo un análisis *in silico* y un estudio bibliográfico. Los compuestos de metabolitos secundarios de *C. inophyllum* se obtuvieron a través de la base de datos PubChem, y se analizó su actividad biológica y ADMET. El acoplamiento molecular con el EGFR de tipo salvaje (5FED) y mutante (5HG7) se llevó a cabo utilizando PyRx. Además, se analizaron los residuos de aminoácidos con Discovery Studio.

Resultados: Basándose en el cribado general y el acoplamiento molecular, un compuesto no tóxico con una baja afinidad de unión con la proteína mutante EGFR es 4-[2-(4-nitrofenil)etilcarbamoil]bencenosulfonil. Además, se sabe que las interacciones y los enlaces de hidrógeno en Ala743, Gly796, Leu718, Phe856, Leu844 y Val726 desempeñan un papel crucial en la inhibición de la unión del ATP hacia el dominio tirosina cinasa, lo que resulta en la inhibición del mutante EGFR.

Conclusiones: El 4-[2-(4-nitrofenil)etilcarbamoil]bencenosulfonil es uno de los candidatos potenciales como proteína mutante del EGFR por inhibición de la unión al ATP. Sin embargo, es necesario realizar investigaciones *in vitro* e *in vivo* para confirmar estos resultados.

Palabras Clave: cáncer de pulmón; CPNM; cribado virtual; fármaco anticanceroso; metabolitos secundarios.

ARTICLE INFO
Received: July 14, 2023.
Accepted: March 4, 2024.
Available Online: April 17, 2024.

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INTRODUCTION

Lung cancer is the most common cause of cancer death, with 1.8 million deaths in 2020, according to the World Health Organization (WHO, 2022). Most lung cancer patients have non-small cell lung cancer (NSCLC), with a prevalence of 80–85% (Bareschino, 2011; Widyananda et al., 2021). Standard therapeutic methods to treat NSCLC include chemotherapy and radiotherapy in collaboration with gefitinib or other anticancer drugs. These treatments commonly cause several adverse effects, such as shortness of breath, bleeding, fever, hair loss, and radiation pneumonitis (Al-Sahlawi et al., 2024; Cersosimo, 2006). The lack of treatment options and numerous mutations significantly contribute to the death toll of lung cancer. Most NSCLCs are caused by epidermal growth factor receptor (EGFR) mutations. EGFR is a tyrosine kinase cell surface receptor that plays a key role in signal transduction processes and is found on most cell surfaces (Metro and Crino, 2012). Under normal conditions, it plays a vital role in cell proliferation via the mitogen-activated protein kinase (MAPK) pathway. Cell proliferation is important for cell regeneration. Mutations in EGFR, especially in T790M, L858R, and V948R, result in EGFR overexpression (Pratama, 2015). This leads to uncontrolled cell division and cancer. Cancer cell proliferation, angiogenesis, and metastasis are associated with EGFR mutations. By inhibiting the activity of the EFGR mutant, cancer cell proliferation can be reduced, thus revealing a rational strategy for NSCLC treatments (Metro and Crino, 2012; Haryati and Mayasari, 2020; Sembiring et al., 2023).

Tyrosine-kinase inhibitors (TKIs) are small compounds that inhibit EGFR activity during cell proliferation. These compounds have long been used as lung cancer drugs (Zubair and Bandyopadhyay, 2023). First-generation TKI drugs, such as gefitinib and erlotinib, result in resistance in many patients with lung cancer (Nand et al., 2016). Hence, it is important to discover new drugs that target EGFR-TKIs. According to previous research, *Calophyllum inophyllum* is a native coastal plant from Indonesia that has been commonly used by generations as traditional medicine due to its antioxidant potency. It is used to treat skin or tissue infection and inflammation (Emilda, 2019; Fadhillah et al., 2023). Moreover, recent research has also demonstrated that *C. inophyllum* seed has the potential to be a lung cancer drug since it can induce cytotoxicity in NSCLC cells (Hsieh et al., 2018). However, research on secondary metabolites of C. *inophyllum*, aside from seed, has remained unclear. Therefore, this study aimed to identify novel EGFR-TKIs from *C. inophyllum* leaf secondary metabolites and their mechanism as potential NSCLC drugs.

MATERIAL AND METHODS

An *in silico* study was performed to determine the inhibition potential of *C. inophyllum*'s leaf secondary metabolites with EGFR mutant protein. This study was performed from June until July 2023 in the Faculty of Biotechnology, University of Surabaya, using hardware specification Macbook Pro 2010, processor Intel i5 2.4 GHz, RAM 8GB, graphic Intel HD Graphics 3000, and operating system MacOS X El Capitan.

Protein and ligand preparation

Secondary metabolite compounds from *C. inophyllum* leaf based on previous research (Periyasamy et al., 2017) were collected from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and gefitinib (CID: 123631) was selected as a control by using reference compound (Table 1). Its canonical SMILES and 3D structures were collected. The 3D structures were then converted into pdb.qt format with PyRx software. The structure of wild-type EGFR (5FED) and EGFR Mutant T790M-L858R-V948R (5HG7) bound to a small molecule was collected from RCSB PDB (https://www.rcsb.org/). Furthermore, the preparation process, which involved removing water molecules and native ligands, was performed using ChimeraX software (Aini et al., 2023; Widyananda et al., 2023a).

Biological activity analysis

Biological activity analysis was performed using the PASS Online web server (http://www.way2drug.com/passonline/). Canonical SMILES structures of the compound were added, and the probability of activity (Pa) values were analyzed. The Pa value higher than 0.7 indicated a high potential for biological activities, which was proven by computation and experimental approach (Lagunin et al., 2000; Suhargo et al., 2023; Widyananda et al., 2021).

Druglikeness analysis

Druglikeness analysis was carried out using the SWISS ADME webserver (http://www.swissadme.ch/index.php). It aimed to analyze the druglikeness of compound samples based on Lipinski's rule of five. The rule included molecular weight <500 g/mol, partition coefficient log P with a score of 5, hydrogen bond donor <5, hydrogen bond

Table 1. Characteristics of secondary metabolites compound from *C. inophyllum* and gefitinib.

No.	Compound	CID	Canonical SMILES
1	Caryophyllene	5322111	CC1=CCCC(=C)C2CC(C2CC1)(C)C
2	Z, Z, Z-1,4,6,9-nonadecatetraene	5362676	CCCCCCCCCC=CCC=CC=CCC=C
3	Juniperol	6432447	CC1(CCCC2(C3C1C(C2(CC3)C)O)C)C
4	Z, E-2-methyl-3, 13, octadecadein-1-ol	5364521	CCCCC=CCCCCCCCCC=CC(C)CO
5	E,E,Z-1,3,12-nonadecatriene-5,14-diol	5364768	CCCCCC(C=CCCCCCCC(C=CC=C)O)O
6	Ethyl palmitate	12366	CCCCCCCCCCCCCCCC(=O)OCC
7	Phytol	5280435	CC(C)CCCC(C)CCCC(C)CCCC(=CCO)C
8	Dasycarpidan-1-methanol, acetate (ester)	550072	CCC1C2CCN(C1C3=C(C2COC(=O)C)NC4=CC=CC=C43)C
9	7-Ethenylundec-5-ene	549034	CCCCC=CC(CCCC)C=C
10	Methyl 3-(3-hydroxypropyl)benzoate	15282060	COC(=O)C1=CC=CC(=C1)CCCO
11	4-[2-(4-nitrophenyl)ethylcarbamoyl]benzenesulfonyl fluoride	309203	C1=CC(=CC=C1CCNC(=O)C2=CC=C(C=C2)S(=O)(=O)F)[N+](=O)[O-]
12	Gefitinib (first-generation of TKIs)	123631	COC1=C(C=C2C(=C1)N=CN=C2NC3=CC(=C(C=C3)F)Cl)OCCCN4CCOCC4

Table 2. Center and dimension of specific docking.

Center	5FED	5HG7	Size	5FED	5HG7
Center X	-1.5685	-13.3855	Size X	14.1130	14.1130
Center Y	51.6045	15.1875	Size Y	13.9263	14.6521
Center Z	-19.7647	-25.7106	Size Z	16.1820	13.9710

acceptor <10, and molar refractivity score between 40-130 (Nusantoro and Fadlan, 2020). All the data for each compound was collected for further analysis. A compound with no violation and one violation of Lipinski's rule of five was considered a potential compound (Choy and Prausnitz, 2011; Kharisma et al., 2022).

Toxicity analysis

Toxicity analysis was accomplished by using a ProTox-II webserver (https://tox-new.charite.de/protox_II/index.php?site=compound_input). Analyses based on the Globally Harmonized System were performed to predict the LD_{50} and toxicity class values of each compound. The toxicity class was defined by class number 1 to 6. Meanwhile, compounds from the higher class were considered less toxic. Furthermore, its toxicity endpoints and organ toxicity were also analyzed (Banerjee et al., 2018).

Molecular docking and visualization of ligands in complex with VP35

The interaction between compounds of *C. inophyllum* and the target protein was simulated using Pyrx software (Kharisma et al., 2023; Widyananda et al., 2023b). The specific docking method simulation was performed on the binding site of 5X4 as an EGFR wild-type (5FED) inhibitor and 630 as an EGFR mutant (5HG7) inhibitor. The specific coordinate for the docking site, such as position and dimension (Å), was determined and shown in Table 2. The negative binding affinity score was considered as the strength of bonding interaction between the target protein and compound. A lower binding affinity score means a stronger bond interaction between the target protein and compound. Furthermore, the visualization of protein-compound complexed, and amino acid residues interaction was visualized by using Chimera X and Discovery Studio software, respectively (Dallakyan and Olson, 2015; Pettersen et al., 2004) (Fig. 1).

RESULTS

Biological activity analysis

In biological activity analysis using the PASS Online web server, apoptosis agonist, anticarcinogenic, antimutagenic, and antineoplastic activities were analyzed. The results showed that gefitinib only has antineoplastic activity with a Pa value of 0.177. Meanwhile, caryophyllene showed the highest activity in apoptosis agonist and antineoplastic (lung cancer) with Pa values of 0.847 and 0.763, respectively. In terms of antimutagenic activity, Z,Z,Z-1,4,6,9-nona-

decatetraene showed the highest score with a Pa value of 0.785. Furthermore, E,E,Z-1,3,12-nonadecatriene-5,14-diol showed the highest anticarcinogenic activity with a Pa value of 0.436. Compounds with those four biological activities showed higher Pa values than control gefitinib (Table 3).

Druglikeness analysis

All of the ligands have fulfilled Lipinski's criteria. Therefore, those ligands are eligible as drug candidates (Table 4).

Toxicity analysis

The analysis showed that all compounds showed toxicity classes 4-5. Moreover, gefitinib showed activity in hepatotoxicity analysis. Meanwhile, all the compounds exhibited an inactive/below-threshold probability for their toxicity endpoint (Table 5).

Molecular docking and visualization of protein-ligand interactions

Among the 12 compounds of potential ligands, all showed a binding potential with targeted protein based on their negative score, but none showed lower binding affinity than the native ligands. Results from molecular docking with two proteins showed that overall compounds have a lower binding affinity with EGFR mutant rather than wild-type EGFR. The top three compounds which have the lowest binding affinity in both proteins were 4-[2-(4-nitrophenyl) ethylcarbamoyl]benzenesulfonyl fluoride, dasycarpidan-1-methanol, acetate (ester), and caryophyllene (Table 6).

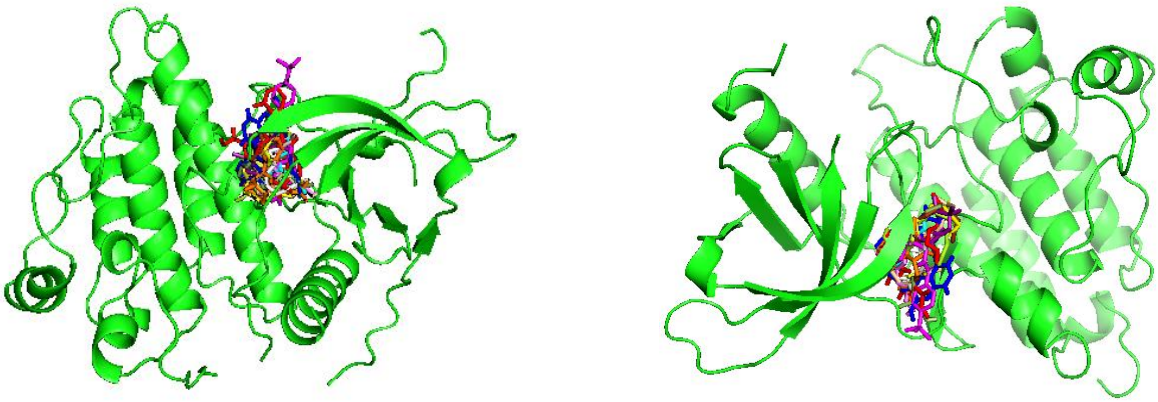

Figure 1. Molecular docking result visualization of 4-[2-(4-nitrophenyl)ethylcarbamoyl]benzenesulfonyl fluoride (magenta); Dasycarpidan-1-methanol, acetate (ester) (orange); Caryophyllene (white); Methyl 3-(3-hydroxypropyl)benzoate (violet); Z, E-2-methyl-3, 13, octadecadein-1-ol (smudge); E,E,Z-1,3,12-nonadecatriene-5,14-diol (limon); Ethyl palmitate (yellow); Phytol (wheat); Juniperol (deep purple); Gefitinib (blue); 7-Ethenylundec-5-ene (cyan); Z, Z, Z-1,4,6,9-nonadecatetraene (brown); and native ligands 5X4 (left) and 630 (right) (red) towards EGFR wild type (left) and mutant (right) (PDB: 5FED & 5HG7).

Table 3. Probability of biological activity (Pa) as apoptosis agonist, anticarcinogenic, antimutagenic, and antineoplastic results.

No	Compound	Apoptosis agonist	Anticarcinogenic	Antimutagenic	Antineoplastic (lung cancer)
1	Caryophyllene	0.847	0.216	0.156	0.763
2	Z, Z, Z-1,4,6,9-nonadecatetraene	0.813	0.392	0.785	0.159
3	Juniperol	0.837	0.303	0.188	0.431
4	Z, E-2-methyl-3, 13, octadecadein-1-ol	0.513	0.334	0.489	0.163
5	E,E,Z-1,3,12-nonadecatriene-5,14-diol	0.346	0.436	0.529	0.384
6	Ethyl palmitate	0.336	0.301	0.432	-
7	Phytol	0.531	0.409	0.169	0.205
8	Dasycarpidan-1-methanol, acetate (ester)	0.258	-	-	0.199
9	7-Ethenylundec-5-ene	0.675	0.285	0.616	0.197
10	Methyl 3-(3-hydroxypropyl)benzoate	0.243	0.262	0.317	-
11	4-[2-(4 nitrophenyl) ethylcarbamoyl] benzenesulfonyl fluoride	-	-	-	-
12	Gefitinib (first-generation of TKIs)	-	-	-	0.177

Pa value higher than 0.7 indicated a high potential for biological activities.

Table 4. Druglikeness analysis result.

No	Compound	MW (<=500 Da)	HBD (<=5)	HBA (<=10)	MLogP (<=4.15) [Solu]	MR (40-130)	Lipinski's Violation [BA: 0.55]	GI Abs	CYP3A4 Inhib
1	Caryophyllene	204.35	0	0	4.63 [MS-S]	68.78	1	Low	No
2	Z, Z, Z-1,4,6,9-nonadecatetraene	260.46	0	0	5.80 [PS-MS]	91.55	1	Low	No
3	Juniperol	222.37	1	1	3.81 [MS-S]	68.26	0	High	No
4	Z, E-2-methyl-3, 13, octadecadein-1-ol	280.49	1	1	4.91 [PS-MS]	93.66	1	High	No
5	E,E,Z-1,3,12-nonadecatriene-5,14-diol	294.47	2	2	3.89 [PS-S]	94.35	0	High	No
6	Ethyl palmitate	284.48	0	2	4.67 [PS-MS]	89.92	1	High	No
7	Phytol	296.53	1	1	5.25 [PS-MS]	98.94	1	Low	Yes
8	Dasycarpidan-1-methanol, acetate (ester)	326.43	1	3	2.82 [MS-S]	100.17	0	High	No
9	7-Ethenylundec-5-ene	180.33	0	0	4.50 [MS-S]	63.66	1	Low	No
10	Methyl 3-(3-hydroxypropyl)benzoate	194.23	1	3	1.96 [S]	53.46	0	High	No
11	4-[2-(4-Nitrophenyl)ethylcarbamoyl] benzenesulfonyl fluoride	352.34	1	6	1.62 [MS-S]	85.89	0	High	No
12	Gefitinib (First-generation of TKIs)	446.90	1	7	2.82 [PS-MS]	121.66	0	High	Yes

MW: Molecular Weight; HBD: Hydrogen Bond Donors; HBA: Hydrogen Bond Acceptors; MLogP: High Lipophilicity; MR: Molar Refractivity; Solu=Solubility; MS: Moderately Soluble; S: Soluble; PS: Poorly Soluble; GI Abs: Gastrointestinal absorption; CYP3A4 Inhib: CYP3A4 Inhibitor; BA: Bioavailability Score.

Table 5. Toxicity analysis result.

Compounds	Toxicity class	LD_{50} (mg/kg)	Accuracy (%)	Probability toxicity		
				H	Ca	M
Caryophyllene	5	5300	70.97	0.80 (I)	0.70 (I)	0.95 (I)
Z, Z, Z-1,4,6,9-nonadecatetraene	4	1680	69.26	0.75 (I)	0.59 (I)	1.0 (I)
Juniperol	4	2000	72.90	0.77 (I)	0.73 (I)	0.85 (I)
Z, E-2-methyl-3, 13, octadecadein-1-ol	4	1016	70.97	0.80 (I)	0.54 (I)	0.94 (I)
E,E,Z-1,3,12-nonadecatriene-5,14-diol	5	2100	69.26	0.73 (I)	0.65 (I)	0.95 (I)
Ethyl palmitate	5	5000	100	0.76 (I)	0.56 (BT)	0.99 (I)
Phytol	5	5000	100	0.79 (I)	0.76 (I)	0.97 (I)
Dasycarpidan-1-methanol, acetate (ester)	4	1190	100	0.69 (BT)	0.62 (I)	0.97 (I)
7-Ethenylundec-5-ene	5	3650	70.97	0.78 (I)	0.65 (I)	0.88 (I)
Methyl 3-(3-hydroxypropyl)benzoate	4	1500	68.07	0.78 (I)	0.75 (I)	0.89 (I)
4-[2-(4-nitrophenyl)ethylcarbamoyl] benzenesulfonyl fluoride	4	1500	67.38	0.60 (I)	0.51 (I)	0.59 (BT)
Gefitinib (First-generation of TKIs)	5	2935	67.38	0.73 (A)	0.52 (I)	0.50 (I)

H: Hepatotoxicity; Ca: Carcinogenicity; M: Mutagenicity. Numbers given in probability toxicity are confidence estimates for the prediction, followed by its status: I: Inactive; A: Active; BT: Below Threshold.

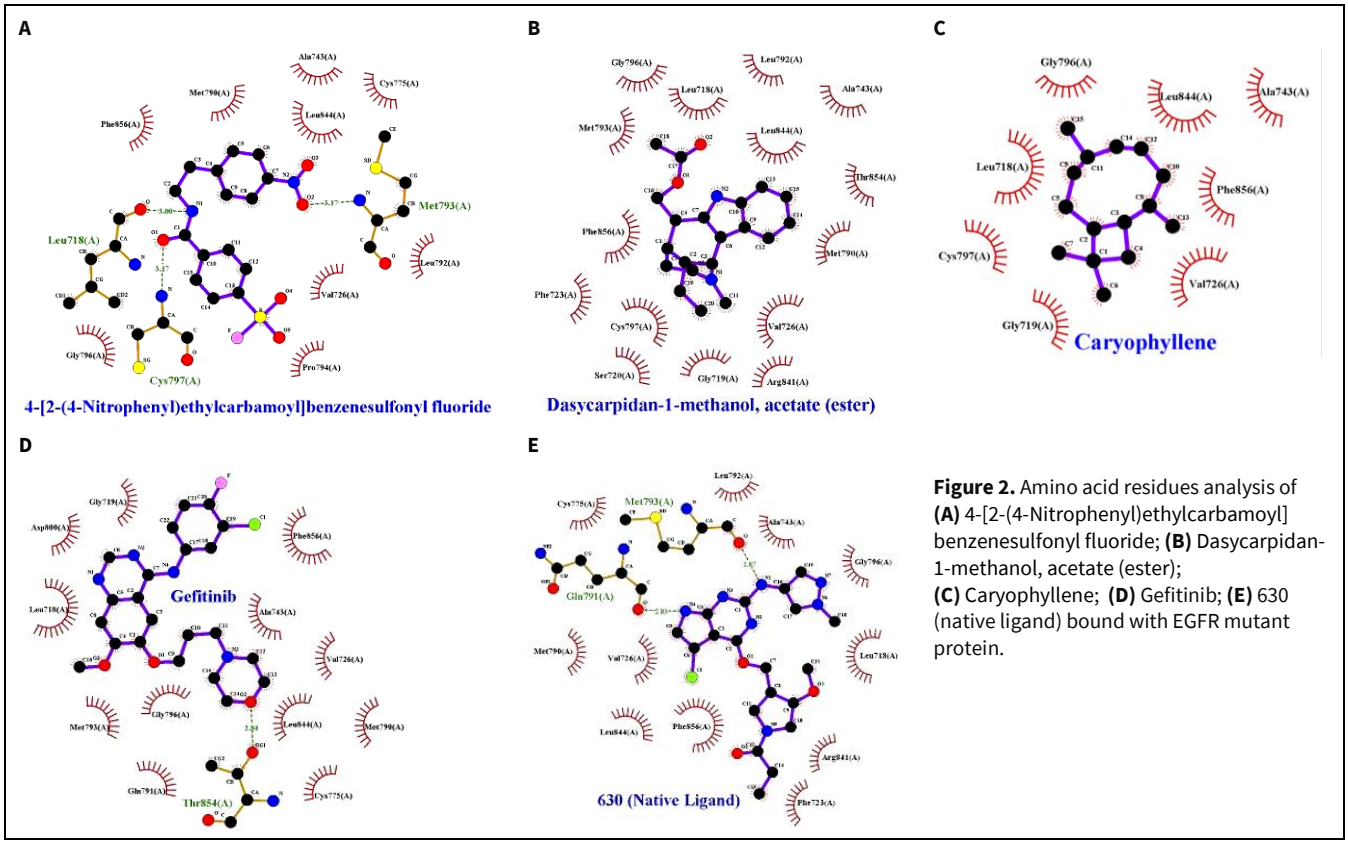

Figure 2. Amino acid residues analysis of **(A)** 4-[2-(4-Nitrophenyl)ethylcarbamoyl] benzenesulfonyl fluoride; **(B)** Dasycarpidan-1-methanol, acetate (ester); **(C)** Caryophyllene; **(D)** Gefitinib; **(E)** 630 (native ligand) bound with EGFR mutant protein.

Table 6. Molecular docking results of targeted compounds with EGFR mutant (5HG7) and wild-type EGFR (5FED).

No.	Compounds	Binding Energy (kcal/mol) 5HG7	Binding Energy (kcal/mol) 5FED
1	5X4 (5FED Native Ligand)		-10.0
2	630 (5HG7 Native Ligand)	-9.0	
3	Gefitinib (First-generation of TKIs)	-7.8	-7.3
4	4-[2-(4-nitrophenyl)ethylcarbamoyl] benzenesulfonyl fluoride	-7.6	-7.5
5	Dasycarpidan-1-methanol, acetate (ester)	-7.2	-7.2
6	Caryophyllene	-7.4	-6.8
7	Methyl 3-(3-hydroxypropyl)benzoate	-6.0	-6.0
8	Z, E-2-methyl-3, 13, octadecadein-1-ol	-6.0	-5.1
9	E,E,Z-1,3,12-nonadecatriene-5,14-diol	-5.6	-5.3
10	Ethyl palmitate	-5.5	-4.7
11	Phytol	-6.3	-5.7
12	Juniperol	-6.0	-5.9
13	7-ethenylundec-5-ene	-5.7	-4.9
14	Z, Z, Z-1,4,6,9-nonadecatetraene	-5.7	-5.0

Table 7. Amino acid residues analysis of protein-ligands binding sites.

Ligands	Hydrogen bonds	Hydrophobic bonds
1-{(3R,4R)-3-[5-chloro-2-(1-methyl-1H-pyrazol-4-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxymethyl]-4-methoxy-pyrolidin-1-yl}propenone {630} **(Native ligand)**	Met793: 2.87 A Gln791: 2.83 A	Leu792, Ala743, Gly796, Leu718, Arg841, Phe723, Phe856, Leu844, Val726, Met790, Cys775
Gefitinib	Thr854: 2.84 A	Phe856, Ala743, Val726, Met790, Leu844, Cys775, Gln791, Gly796, Met793, Leu718, Asp800, Gly719
4-[2-(4-nitrophenyl)ethylcarbamoyl] benzenesulfonyl fluoride	Met793: 3.17 A Leu718: 3.00 A Cys797: 3.17 A	Gly796, Pro794, Val726, Leu792, Leu844, Cys775, Phe856, Ala743, Met790
Dasycarpidan-1-methanol, acetate (ester)	-	Met793, Gly796, Leu718, Leu792, Leu844, Ala743, Thr854, Met790, Val726, Gly719, Ser720, Cys797, Phe723, Phe856, Arg841,
Caryophyllene	-	Ala743, Leu844, Phe856, Val726, Gly796, Leu718, Gly719, Cys775

The underlined letters showed similar bonds compared with native ligands.

Amino acid residue analysis

The analysis showed that all of the potential ligands were joined to the 5FED and 5HG7 proteins at the same location as native ligands 5X4 and 630, respectively (Fig. 2). Furthermore, the top three ligands with the highest binding affinity score with the EGFR mutant (5HG7) (Fig. 2) were examined further (Table 7).

DISCUSSION

EGFR is a member of the Erb2 family from receptor tyrosine kinases (RTKs), which consists of approximately 1210 amino acids with 134 kDa molecular mass. An α-helix transmembrane, an extracellular ligand binding, a cytoplasmic tyrosine kinase, and carboxy-terminal signaling domains combination are forming EGFR structure (Amelia et al., 2022). In most cells, EGFR has a crucial role in cell homeostasis, cell proliferation, and self-regeneration (Pratama, 2015). Furthermore, EGFR activation is important in organogenesis and embryogenesis, such as placental, bone, lung, and kidney development. Impairment in this process will lead to defective organs and tissues (Chen et al., 2016).

Meanwhile, mutations at some points will lead to overexpression of EGFR and cause overproliferation in cells (Pratama, 2015). Substitution of Thr790 to methionine will cause steric hindrance in inhibition, thus leading to overexpression and resistance to first-generation TKIs, such as gefitinib. This mechanism is due to the Thr790 location which is located at the entrance of the ATP-hydrophobic pocket. Therefore, it increases the ATP affinity and prevents the inhibitors from binding. Moreover, point mutation L858R, in combination with T790M, will activate EGFR and cause overproliferation. This action results in higher resistance to cancer drugs (Pao et al., 2005).

In this research, EGFR mutant T790M-L858R-V948R was used. Mutation in V948 was known to reduce EGFR wild-type dimerization enzyme and stabilize the conformation of the mutant protein. It is important to have drug candidates that bind stronger to inhibit EGFR mutant rather than wild-type EGFR to reduce its adverse effects (Cheng et al., 2016).

Calophyllum inophyllum L. is a coastal plant that can be found widely in Southeast Asia, especially in Indonesia. Research conducted by Hsieh et al. (2018) stated that its seed pigment can induce cytotoxicity on lung (NSCLC) and colon cancer (DLD-1) cells detected by the MTS/MTT assay method. Meanwhile, the other parts of the plant go unnoticed, and the direct downstream effects have not been explored. *C. inophyllum*'s leaf is the most abundant part of the plant. Based on GC-MS analysis of the ethanol fraction on its leaf, it is known that there were 11 secondary metabolites inside *C. inophyllum* as listed in Table 1. In this research, virtual screening and specific docking were performed to identify the potential of *C. inophyllum*'s leaf compounds toward EGFR proteins.

Biological activity analysis showed the potential of a compound in their apoptosis agonist, anticancer, antimutagenic, and antineoplastic (lung cancer) activities. From the analysis, all the compounds with those four activities showed higher Pa values in all activities than gefitinib. Furthermore, caryophyllene has the highest result in apoptosis agonist and antineo-

plastic (lung cancer) Pa values. Meanwhile, 4-[2-(4-nitrophenyl)ethylcarbamoyl]benzenesulfonyl fluoride is the only compound that did not show any activity. Pa score higher than 0.7 showed that an experimental and computation method was performed to prove the potency of a compound. Pa score within the range of 0.5–0.7 showed that a computation experiment had been performed, but it needs further approval from the experimental method. Meanwhile, a Pa score lower 0.5 showed that a compound has low potential proven by both computation and experimental method. In some cases, a Pa score lower than 0.5 or not showing any activity might show that there was no or less previous experiment regarding that compound (Lagunin et al., 2000).

The drug's oral bioavailability was analyzed further using druglikeness analysis based on Lipinski rule parameters (Lipinski et al., 2001). Lipinski's rule consists of molecular weight <500 g/mol, partition coefficient log P, 5, hydrogen bond donor <5, hydrogen bond acceptor <10, and molar refractivity 40-130. The analysis shows that all the compounds have fulfilled Lipinski's criteria by having one maximum violation (Choy and Prausnitz, 2011). Therefore, all the compounds possess good oral bioavailability, shown by a bioavailability score of 0.55 for all the compounds (Joanna et al., 2020). The ability of a compound to enter through cell membranes (Matsson and Kihlberg, 2017), become soluble (Jacek et al., 2012), and flexible (Jagannathan, 2019) is the definition of oral bioavailability. The previous study shows that 60 out of 82 medications listed in the IMS-health Institute meet Lipinski's criteria (Gimenez et al., 2010). In particular, oral medicines that passed phase II clinical status are linked with compounds that fulfill Lipinski's criteria (Lipinski, 2004).

Toxicity class, toxicity endpoints, and organ toxicity were analyzed in toxicity analysis using the Protox-II web server. One of the purposes of this analysis was to examine the hepatotoxicity of a compound. It is important since absorbed drugs will be metabolized in the liver (Gimenez et al., 2010). Other than hepatotoxicity, carcinogenicity, and mutagenicity endpoints were analyzed. The globally harmonized system (GHS) was used to rank toxicity classes, and confidence estimation probability was used to score organ toxicity and toxicity endpoints (Banerjee et al., 2018). An estimation score below 0.70 is considered below the threshold and considered safe (Tungary et al., 2022). From the analysis result, all the compounds have toxicity classes 4-5 and are considered safe in other toxicity analyses (organ toxicity and toxicity endpoints). An interesting result was shown in gefitinib, a first-generation TKIs. It showed that gefitinib can induce hepatotoxicity by having a hepatotoxicity probability value of 0.73 (active). A previous study stated that long-term oral administration of gefitinib can cause hepatotoxicity as an adverse effect. An increase in aminotransferase (28.7%), bilirubin (9.9%), and ALP (3.0%) were found in patients who consumed gefitinib orally (Wang et al., 2021).

A molecular docking process with a specific docking method was performed to examine the binding affinity of compounds with EGFR protein. The position of each protein's native ligands was used to determine the grid size. To ensure accuracy, a redocking process was performed by using 5X4 (5FED native ligand) and 630 (5FHG native ligand). The molecular docking results showed that all compounds have a higher binding affinity score than the native ligand (5X4 & 630). A lower binding affinity score is considered a strong interaction (Saputri et al., 2016). The result shows that overall compounds docked with EGFR mutant consistently have lower binding affinity than wild-type EGFR. In particular, it is shown that all of *C. inophyllum*'s leaf compounds bind more specifically and strongly to the EGFR mutant. Therefore, it explains how those compounds will result in lower side effects than other anticancer drugs (Cheng et al., 2016). The top three compounds with the lowest binding affinity with both EGFR proteins are 4-[2-(4-nitrophenyl)ethylcarbamoyl]benzenesulfonyl fluoride, dasycarpidan-1-methanol, acetate (ester), and caryophyllene. Besides possessing the lowest binding affinity score, those three compounds showed "moderately soluble" to "soluble" in the solubility parameter. Soluble molecules are greatly preferred in drug formulation since they will be easily handled and formulized (Daina et al., 2017).

Further amino acid residue analysis was performed to analyze its binding site in EGFR mutant inhibition (Table 7). Amino acid residue analysis showed that 630 formed two hydrogen bonds at Met793 and Gln791 with EGFR mutant. The same hydrogen bond was found in 4-[2-(4-nitrophenyl) ethylcarbamoyl] benzenesulfonyl fluoride, specifically at Met793 (Amelia et al., 2022; Hor et al., 2023). The hydrogen bond was known to possess a stronger bond with 4-6 kcal/mol (Deshmukh and Gadre, 2009). In the hydrophobic interaction result, it is shown that all of the compounds were bound at Ala743, Gly796, Leu718, Phe856, Leu844, and Val726. Based on the literature study, the tyrosine kinase domain was located at 706-979. In this range of amino acid residue, there were some residues located at ATP binding pockets, such as Leu718, Val726, Ala743, Met793, and Leu844. These residues form a core hydrophobic and conserved binding pocket (Amelia et al., 2022). When a specific ligand binds to a receptor, in this case, EGFR protein, it will cause an alteration in the struc-

ture to become a dimer. This conformational change will activate the tyrosine kinase domain. ATP was used to phosphorylate on the tyrosine kinase domain to fully activate the protein. Once the protein fully activates, it will lead to a protein cascade, resulting in cell proliferation. Therefore, various mutations lead to ATP over-affinity towards the tyrosine kinase domain, thus causing overproliferation. Inhibiting ATP binding at these specific sites will prevent the ATP from phosphorylating further and stop the mutant cells from proliferating (Abourehab et al., 2021).

First-generation anti-lung cancer drugs, such as gefitinib, relied solely on reversible affinity (Luthfiana et al., 2023). Meanwhile, irreversible affinity has been recently used since it can sustain target engagement even when numerous ATP is present inside the cells. Its mechanism relies on conformational changes of kinase protein to inhibit the signaling pathways of cell proliferation (Siak et al., 2023). Native ligand 630 was known for its ability to inhibit EGFR mutants by relying on its irreversible affinity (Cheng et al., 2016). The analysis result showed that 4-[2-(4-nitrophenyl) ethylcarbamoyl] benzenesulfonyl fluoride has the same action mechanism as the native inhibitor of EGFR mutant (5HG7) protein. Furthermore, this compound possesses high GI absorption compared to the other two compounds and is not involved in CYP3A4 inhibition. CYP3A4 is an isoenzyme that plays a role in drug elimination. It prevents unwanted drug-drug interactions and the accumulation of drugs or their metabolites (Daina et al., 2017). Therefore, based on the overall analysis, non-toxic compounds with potential as EGFR mutant inhibitors are 4-[2-(4-nitrophenyl)ethylcarbamoyl] benzenesulfonyl fluoride. Meanwhile, *in vitro* and *in vivo* analyses need to be performed to confirm this result.

CONCLUSION

EGFR is a protein that has a crucial role in cell regeneration and proliferation. Meanwhile, its mutations can lead to cancer development, such as Non-Small Cell Lung Cancer (NSCLC). During drug development, some resistance has been found towards anti-lung cancer because of those mutations. Various secondary metabolites have potential as anticancer drugs. One of them is *Calophyllym inophyllum* L., a coastal plant from Southeast Asia. An exploration of *C. inophyllum*'s leaf secondary metabolites would be a novel approach toward anti-lung cancer drug development. Based on overall analysis, 4-[2-(4-nitrophenyl)ethylcarbamoyl]benzenesulfonyl shows a potential as an EGFR mutant inhibitor. However, research about EGFR mutant inhibitors from secondary metabolite compounds needs to be updated to confirm this result.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

The authors acknowledge the University of Surabaya for supporting this research. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Contribution	Silvia P	Ongko J	Antonius Y
Concepts or ideas	x		
Design	x	x	
Definition of intellectual content	x		
Literature search	x		
Experimental studies	x		
Data acquisition	x	x	x
Data analysis	x	x	x
Statistical analysis	x		x
Manuscript preparation	x	x	x
Manuscript editing	x	x	x
Manuscript review	x	x	x

Citation Format: Silvia P, Ongko J, Antonius Y (2024) Epidermal growth factor receptor mutant T790M-L858R-V948R inhibitor from *Calophyllum inophyllum* L. leaf as potential non-small cell lung cancer drugs. J Pharm Pharmacogn Res 12(5): 881–891. https://doi.org/10.56499/jppres23.1740_12.5.881

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Volume 12, Issue 5

J Pharm Pharmacogn Res 12(5), (Sep-Oct) 2024

assessment: The Index of Internal Effort framework for pharma innovations. | [Salvan
las distancias en la evaluación de patentes: El marco del Índice de Esfuerzo Interno pa
las innovaciones farmacéuticas]. J Pharm Pharmacogn Res 12(5): 852-86
https://doi.org/10.56499/jppres23.1859_12.5.852 FREE PDF [672 Kb] [ABSTRACT]

5.- Original Article

Poppy Anjelisa Zaitun Hasibuan, Jane Melita Keliat, Muhammad Fauzan Lubis (202
**Combination of cisplatin and ethyl acetate extract of *Vernonia amygdalina* Del
induces cell cycle arrest and apoptosis on PANC-1 cells via PI3K/mTOR.** | [Combinaci
de cisplatino y extracto de acetato de etilo de *Vernonia amygdalina* Delile induce
detención del ciclo celular y la apoptosis en células PANC-1 vía PI3K/mTOR]. J Phar
Pharmacogn Res 12(5): 870-880. https://doi.org/10.56499/jppres23.1748_12.5.870 FRI
[695 Kb] [ABSTRACT]

6.- Original Article

Precella Silvia, Jeremi Ongko, Yulanda Antonius (2024) **Epidermal growth factor recept
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Binh Quoc Pham, Ngan Kim Thi Nguyen, Su Quoc Pham, Cuong Duy Nguyen, Lam Vu Trir
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Paween Kunsorn, Witchuda Payuhakrit, Nasapon Povichit, Prasit Suwannalert (202
**Piceatannol-rich extract from *Passiflora edulis* Sims seeds attenuates morphologic

Pharmacogn Res 12(5): 900-910. https://doi.org/10.56499/jppres23.1717_12.5.900 PDF [5
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9.- Review

Julio C. Romero-Gamboa, Melissa Pinella-Vega, Pablo A. Millones-Gómez, John Gallego-Ramírez, Alejandro Valencia-Arias (2024) **Research trends in the study biofilms related to periodontal disease: A bibliometric analysis.** | [Tendencias investigación en el estudio de las biopelículas relacionadas con la enfermed periodontal: Un análisis bibliométrico]. J Pharm Pharmacogn Res 12(5): 911-92 https://doi.org/10.56499/jppres23.1877_12.5.911 FREE PDF [913 Kb] [ABSTRACT]

10.- Original Article

Yasmiwar Susilawati, Raden Bayu Indradi, Aiyi Asnawi, Ellin Febrina (2024) **Molecul docking and dynamics studies of 8,9-dimethoxy ellagic acid contained in *Peperom pellucida* (L.) Kunth against various diabetes mellitus receptors.** | [Estudios acoplamiento y dinámica molecular del ácido 8,9-dimetoxielágico contenido *Peperomia pellucida* (L.) Kunth frente a varios receptores de diabetes mellitus]. J Phar Pharmacogn Res 12(5): 929-942. https://doi.org/10.56499/jppres23.1936_12.5.929 FRE PD [912 Kb] [ABSTRACT]

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Ho Anh Hien, Nguyen Minh Tam, Dirk Devroey, Stefan Heytens, Vo Tam, Tran Binh Thang, Nu Hong Duc, Dang Thi Thanh Nha, Doan Pham Phuoc Long, Nguyen Vu Phong, Huynh V Minh, Hoang Anh Tien (2024) **Hypertension knowledge and its associated factors amo hypertensive patients in primary care settings in Central Vietnam: A cross-sectio study.** | [Conocimiento de la hipertensión y sus factores asociados entre pacient hipertensos en entornos de atención primaria en el centro de Vietnam: Un estu transversal]. J Pharm Pharmacogn Res 12(5): 943-95 https://doi.org/10.56499/jppres24.1955_12.5.943 FREE PDF [509 Kb] [ABSTRACT]

12.- Review

Jonathan Christianto Sutadji, Dian Anggraini Permatasari Musalim, David Setyo Bu Jennifer Susanto, Fanny Gunawan, Chaq El Chaq Zamzam Multazam, Citrawati Dy Kencono Wungu (2024) **SS-31 protects diabetic nephropathy progression: A systema review of *in vivo* and *in vitro* studies.** | [El SS-31 protege la progresión de la nefropa diabética: Una revisión sistemática de estudios *in vivo* e *in vitro*]. J Pharm Pharmaco

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Suleiman Zakari, Wisdom D. Cleanclay, Mercy Bella-Omunagbe, Hajara Zakari, Celesti O. Ogbu, Daniel Ejim Uti, Olubanke O. Ogunlana (2024) **The role of SRC-3 in prosta cancer progression and implications for therapeutic targeting: A systematic review** [El papel de SRC-3 en la progresión del cáncer de próstata y las implicaciones para orientación terapéutica: Una revisión sistemática]. J Pharm Pharmacogn Res 12(5): 99 1007. https://doi.org/10.56499/jppres23.1916_12.5.994 FREE PDF [741 Kb] [ABSTRACT]

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Health Professions
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Asociacion Academica de Ciencias Farmaceuticas de Antofagasta (ASOCIFA)

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PUBLICATION TYPE

Journals

ISSN

07194250

COVERAGE

2013-2023

INFORMATION

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editor@jppres.com

SCOPE

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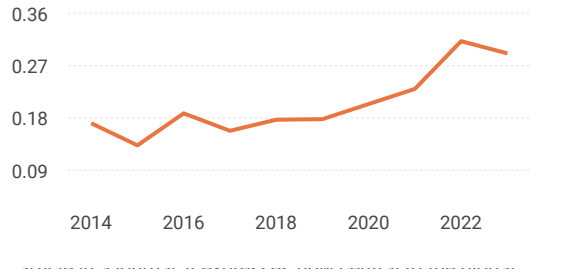

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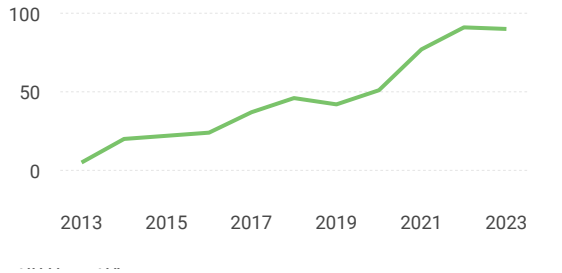

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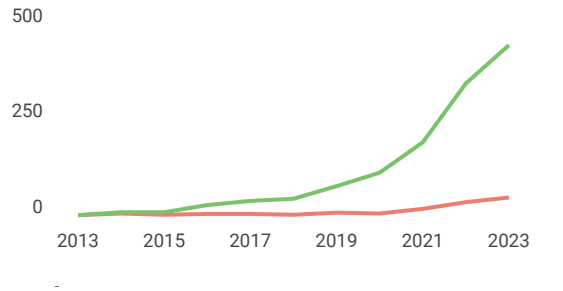

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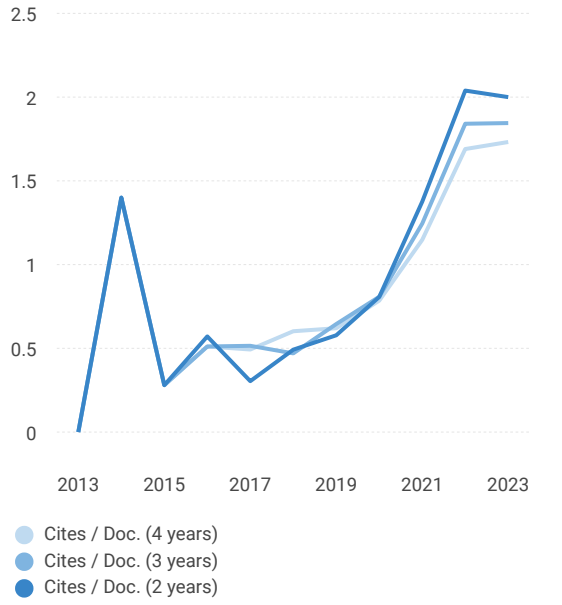

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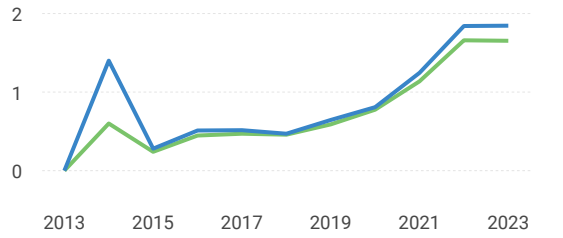

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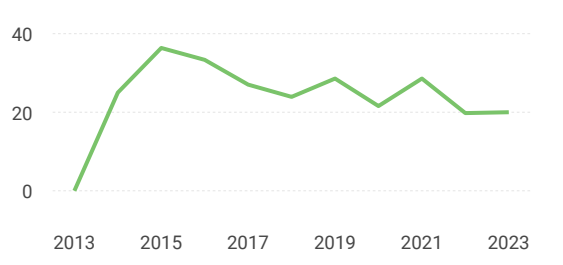

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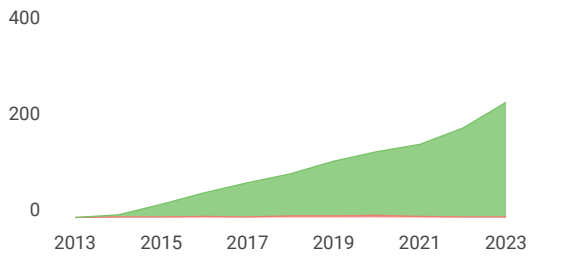

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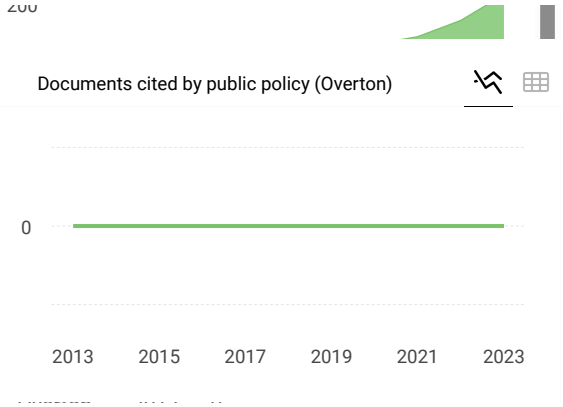

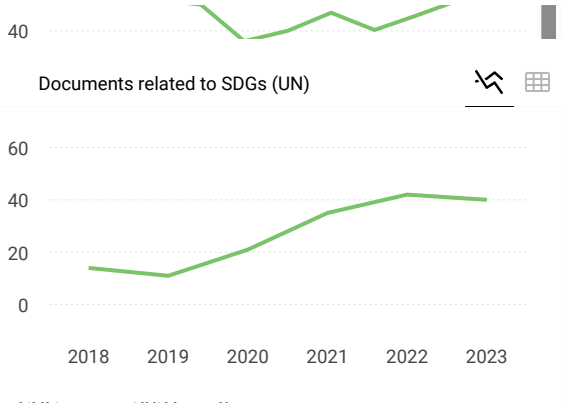

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