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In-silico INVESTIGATION OF FERULIC ACID DERIVATES AGAINST MAIN PROTEASE SARS-COV

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ABSTRACT

Ferulic acid is one of the natural compounds which is prevalent in various plants. This compound has known to possess extensive biological activity to get good health and well-being. In this study, we designed 23 derivates of ferulic acid and evaluate their potency *in silico* as potential SARS-CoV Mpro inhibitors. Furthermore, *in silico* ADME profiles of designed compounds were evaluated to verify whether the ferulic acid analogs possess an acceptable pharmacokinetic profile. The molecular docking result using AutoDock 4.2.6 showed that compound FA-24, which contained dihydro benzoxazine moiety, possesses a better docking score among the designed compound. Five top compounds based on docking score (FA-16, FA-17, FA-18, FA-23, and FA-24) were then evaluated using molecular dynamics for 10 ns, followed by free binding energy evaluation using the MM-PBSA approach. The result indicated that all compounds formed stable complexes with the enzyme for 100 ns. However, MM-PBSA result showed that compound FA-16, which contained phenyl benzoate moiety, possess higher free binding energy. It is argued that this difference was due to the nature of free binding energy evaluation, which was based on molecular dynamics results. Although, both the docking score and free binding energy of the designed compound are lower than the native ligand (AZP), it is believed that further structure modification could be performed to address this shortcoming. Ultimately, all designed ferulic acid analogs possess optimal absorption and drug-likeness characteristic, while several compounds were predicted to interact with isoforms of CYP450.

Keywords: Ferulic Acid, SARS-CoV, Molecular Docking, Molecular Dynamics, MM-PBSA, good health-well-being.

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This manuscript is focusing **SDG-3**: Good Health and Well Being

INTRODUCTION

Coronaviruses are a family of RNA viruses which cause respiratory disease in humans and animals. This class of virus can incite mild illness[1] to the severe ongoing pandemic.[2] There are three coronaviruses up to this date which has caused severe symptoms in human, namely SARS-CoV[3], MERS-CoV[4], and the most recent COVID-19[5], all of which is classified into beta coronavirus genus.[6] The search for active compounds for treating coronaviruses is still of utmost importance. The natural product-based compound is one of the most attractive sources to exploit novel potential anti coronavirus agent.[7] Ferulic acid (4-hydroxy-3-methoxy cinnamic acid) (Fig.-1) is one of the most prevalent secondary metabolites found in plants, such as grains, fruits, and vegetables.[8] This compound and its derivates have been known to possess various bioactivity, namely antioxidant[9,10], anti-inflammatory[11], and antiangiogenic activity.[12] In addition, several *in silico* studies have been carried out with some positive results regarding the potential bioactivity of ferulic acid and its derivates.[13,14] In this study, we designed several ferulic acid analogs and performed *in silico* evaluation to predict the possibility of bioactivity as a SARS-CoV therapeutic agent to obtain good health and well-being. Molecular docking and molecular dynamics were used in this study to evaluate the predicted ligand's ability to bind in the receptor and form a stable complex.[15,16] Main protease enzyme (Mpro) was used as the target since it is one of the most important enzymes in SARS-CoV. Its main task is to cleave virus proteins and help them to replicate. Therefore, inhibiting this enzyme could disrupt the viral

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replication process.[17] In addition, ADME and drug-likeness profiling were also performed to predict the pharmacokinetic characteristics of the designed compound.[14]

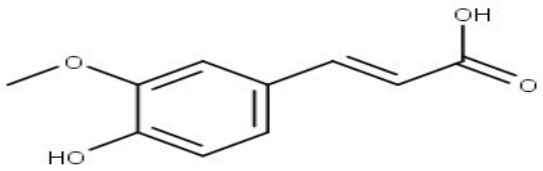


Fig.-1: Chemical Structure of Ferulic Acid

EXPERIMENTAL

Material and Methods

Drug-likeness and ADME Prediction

Ferulic acid and its 23 derivates were evaluated for their drug-likeness using Lipinski's rule of five[18] and their possible ADME properties using the Swiss-ADME webserver.[19] Several parameters were predicted namely gastrointestinal absorption[20] and cytochrome P450 inhibition.

Molecular Docking

The designed compounds were drawn in 2D and optimized geometrically in MarvinSketch (Marvin) (Table-1). Gasteiger charges were then assigned as a preparatory step prior to molecular docking.[21] The crystal structure of the main-peptidase receptor was used as a docking target (PDB ID: 2GTB).[22] This macromolecule was prepared by adding hydrogen and Kollman united-partial charge.[21] Afterwards the docking step was performed using AutoDock 4.2.6.[21] Validity of the process was checked by the RMSD value of the native ligand in the receptor (aza-peptide-epoxide) (AZP)[22] pre- and post-docking (Fig.-2). The docking score was used as a mean to evaluate the potential activity of designed compounds.

Molecular Dynamics

Some of the best-scoring compounds were then subjected to 100 ns molecular dynamics simulation using GROMACS 2022.[23] Ligand-protein complexes were assigned with GAFF2[24] via ACPYPE[25] and AMBER99SB-ILDN forcefield[26], respectively. The simulation was performed in a solvated condition using TIP3P water model[27] and counter-ions. The system was equilibrated in NVT and NPT condition for 100 ps using velocity rescale thermostat[28] and Berendsen barostat.[29]

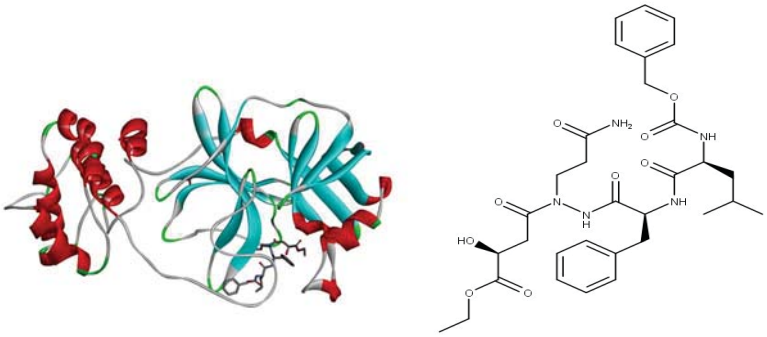


Fig.-2: Structure of SARS Coronavirus Main Peptidase (PDB ID: 2GTB) (left) and its Native Ligand (AZP) (right)

MM-PBSA Calculation

The ligand-protein complexes which underwent molecular dynamics simulation were ultimately evaluated energetically using the MM-PBSA approach. The calculation was done for the whole trajectory (100 ns) using the gmx_mmpbsa module.[30]

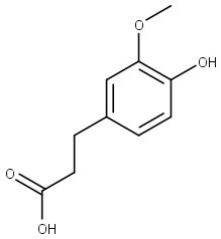
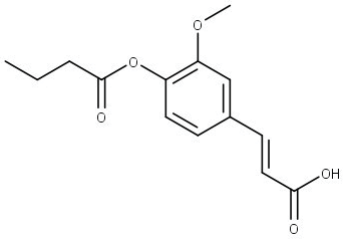
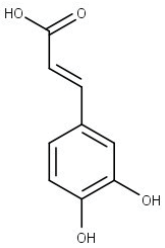
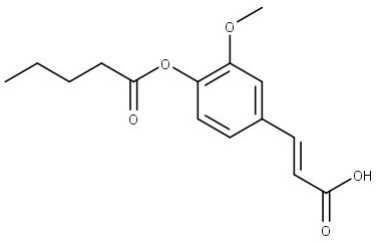
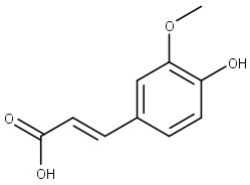
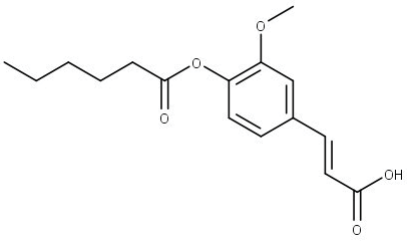
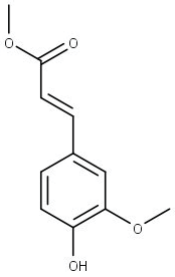
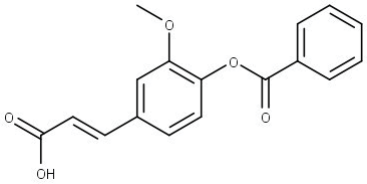
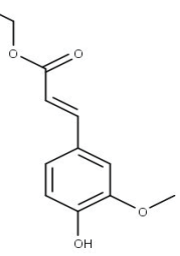
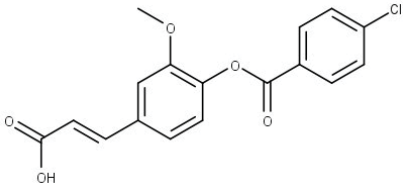
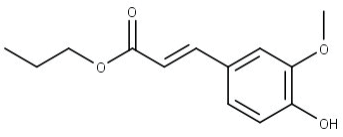
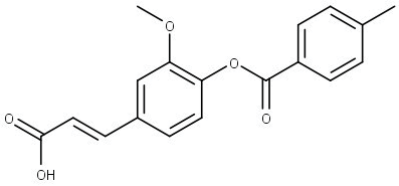
RESULTS AND DISCUSSION

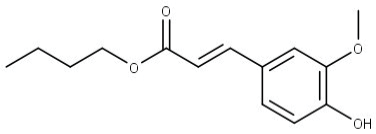
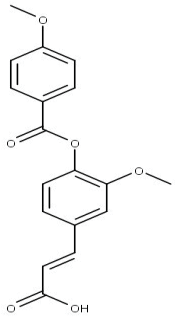
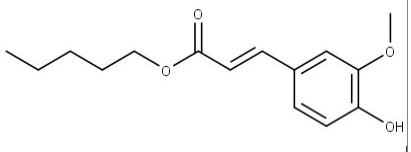
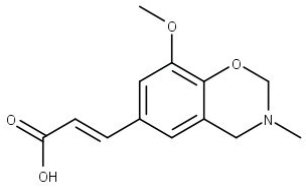
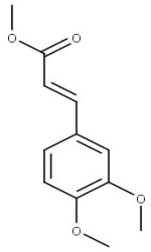
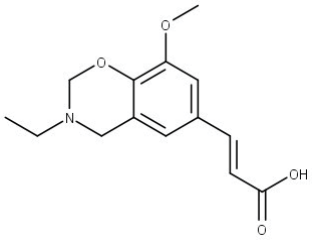
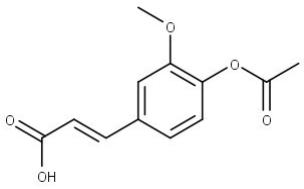
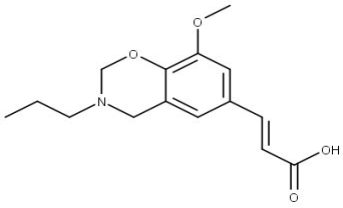
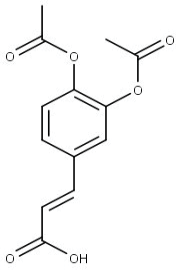
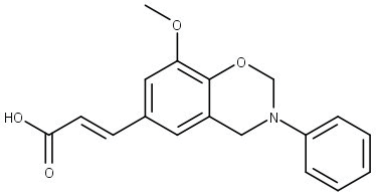
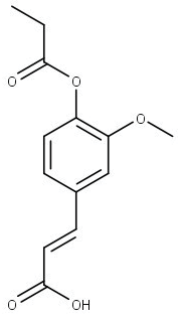
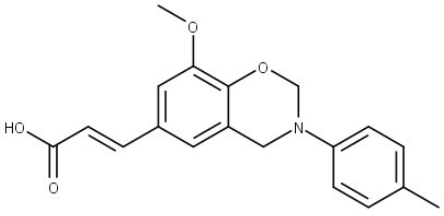
Drug-likeness and ADME Prediction

Drug-likeness evaluation is one of the important parts of the early stage of drug discovery. This concept lies on the assumption that approved drugs have specific physicochemical descriptors which differentiate

them from non-drug compounds.[31] Here we implemented 'Rule of Five'[18] to evaluate the drug-likeness of designed compounds.

Table-1: Chemical Structure of 24 Ferulic Acid Analogs

Compound Name	2D Structure	Compound Name	2D Structure
FA-1		FA-13	
FA-2		FA-14	
FA-3		FA-15	
FA-4		FA-16	
FA-5		FA-17	
FA-6		FA-18	

FA-7		FA-19	
FA-8		FA-20	
FA-9		FA-21	
FA-10		FA-22	
FA-11		FA-23	
FA-12		FA-24	

The results showed that all compounds comply with the criteria, suggesting that all of them possess drug-like characteristics (Table-2). Meanwhile, ADME prediction is also necessary to be conducted in the early phase of drug discovery. This is done to spot some compounds which could be problematic in the late stage

of drug candidate evaluation.[32] Using Swiss-ADME webserver[19], the process was performed to check several ADME parameters. The results showed that all compound is predicted to be highly absorbed in the gastrointestinal tract. However, several compounds are predicted to inhibit CYP450 isoforms, notably 1A2, 2C9, and 2C19 (Table-2). Since these interactions could lead to unwanted drug-drug interactions, thus care must be taken about this finding even if it is an *in-silico* prediction.[33]

Molecular Docking

A molecular docking step was performed to predict the binding energy of ferulic acid derivates against the MPro receptor (PDB ID: 2GTB).[22] This method confirmed its validity by re-docking its native ligand with an RMSD value of 1.75 Å. The results showed that none of the designed ligands yield a better docking score and predicted Ki value against the receptor, compared to the native ligands. The docking score for designed compounds is observed between -5.13 to - 7.46 and Ki values between 3.41 to 172.28 μM. In addition, ligand-protein interaction was also observed using BIOVIA Discovery Studio Visualizer 2021 (Table-2). It can be seen that several compound-bearing phenyl benzoate moieties (*e.g.*, FA-16, FA-17, and FA-18) and compounds with dihydro benzoxazine moieties (*e.g.*, FA-23 and FA-24) are predicted to inhibited SARS-Cov MPro receptor.

Table-2: CYP450 Inhibition, Docking Score, Predicted Ki, and Ligand-Residue Interaction Profile of Ferulic Acid Analogs *in silico*

Compound	CYP Inhibitors	Docking Score	Predicted Ki (μM)	Ligand-Residue Interaction
FA-1	No	-5.5	93.6	LEU141(Amide-π), ASN142, GLY143, SER144, CYS145, GLU166 (Hydrogen Bond)
FA-2	No	-5.49	95.05	LEU141, MET165(Amide-π), SER144(Unfavorable), ASN142, HIS172 (van der Waals), PHE140, LEU141, GLU166 (Hydrogen Bond)
FA-3	No	-5.42	107.07	LEU141, MET165(Amide-π), LEU141(van der Waals), PHE140, LEU141, GLY143, CYS145, GLU166 (Hydrogen Bond)
FA-4	No	-5.79	56.8	LEU141, MET165(Amide-π), LEU141, ASN142(van der Waals), GLY143, SER144, CYS145, GLU166(Hydrogen Bond)
FA-5	1A2	-5.47	97.78	LEU141, MET165(Amide-π), HIS41, MET165(π-Alkyl), GLU166(π-Anion), LEU141, GLU166(van der Waals), GLY143, SER144, CYS145,

				GLU166(Hydrogen Bond)
FA-6	1A2,2C19	-5.82	54.15	HIS141, CYS145(π-Alkyl), CYS44, CYS145(Alkyl-Alkyl), SER144(Unfavorable), SER144(Hydrogen Bond)
FA-7	1A2,2C19	-5.50	92.37	HIS41, HIS172(π-Alkyl), CYS44, MET49(Alkyl-Alkyl), CYS145(π-Sulfur), HIS163(van der Waals), LEU141, GLY143, CYS145(Hydrogen Bond)
FA-8	1A2,2C19	-6.10	33.88	HIS41, HIS172(π-Alkyl), CYS44, MET49, PRO52, MET165, ARG188(Alkyl-Alkyl), HIS163(π-π), CYS145(π-Sulfur), SER144(Unfavorable), HIS163(van der Waals), LEU141, SER144(Hydrogen Bond)
FA-9	1A2,2C19	-5.24	144.21	CYS145(π-Alkyl), CYS145(Alkyl-Alkyl), MET165(S-O), ASN142, HIS163(van der Waals), GLY143(Hydrogen Bond)
FA-10	No	-5.13	172.28	MET165(π-Alkyl), MET165(Alkyl-Alkyl), MET165(S-O), CYS145(π-Sulfur), GLN189(van der Waals), SER144(Unfavorable), GLN189(van der Waals), LEU141, GLY143, CYS145(Hydrogen Bond)
FA-11	No	-5.63	75.10	MET165, PRO168(π-Alkyl), MET165(van der Waals), GLU166, GLN189(Hydrogen Bond)
FA-12	No	-5.6	78.59	MET165(π-Alkyl), MET165(S-O), CYS145(π-Sulfur), SER144(Unfavorable),

				LEU141, GLY143, CYS145(Hydrogen Bond)
FA-13	1A2	-6.01	39.32	CYS44, MET49, PRO52, MET165(Alkyl-Alkyl), MET165(S-O), LEU141, CYS145(Hydrogen Bond)
FA-14	1A2	-6.19	28.88	CYS44, MET49, PRO52, TYR54, MET165(Alkyl-Alkyl), MET165(π-Alkyl), CYS145(π-Sulfur), GLU166(van der Waals), ASN142, GLY143, SER144, CYS145(Hydrogen Bond)
FA-15	1A2, 2C19	-5.98	41.15	CYS145, MET165, HIS163, HIS172(π-Alkyl), GLU166, ARG188(van der Waals), MET49, GLY143, CYS145(Hydrogen Bond)
FA-16	1A2	-6.76	11.00	HIS41, MET49, MET165(π-Alkyl), MET165(Alkyl-Alkyl), CYS44, MET165(π-Sulfur), GLU166(van der Waals), ASN142, GLY143, SER144, CYS145(Hydrogen Bond)
FA-17	1A2,2C19, 2C9	-6.59	14.84	MET165, LEU167, PRO168, PHE185(π-Alkyl), GLU166(van der Waals), ASN142, GLY143, SER144, CYS145(Hydrogen Bond)
FA-18	1A2, 2C19	-7.03	7.03	HIS41(π-σ), MET165(π-Alkyl), MET165, LEU167(Alkyl-Alkyl), SER144, GLN189(Unfavorable), GLU166(van der Waals), LEU141, GLY143, CYS145(Hydrogen Bond)
FA-19	1A2,2C19, 2C9	-6.34	22.69	HIS41, MET165(π-Alkyl), MET165,

				PRO168(Alkyl-Alkyl), SER144(Unfavorable), LEU141, GLY143, SER144, CYS145(Hydrogen Bond)
FA-20	No	-5.53	88.75	SER144(Unfavorable), PHE140, GLU166(van der Waals), LEU141, GLY143, CYS145(Hydrogen Bond)
FA-21	No	-5.45	100.89	HIS41(π-σ), HIS41(π-π), MET165(π-Alkyl), MET165(π-Sulfur), SER144, GLN189(Unfavorable), LEU141, GLY143, CYS145(Hydrogen Bond)
FA-22	No	-5.42	105.98	HIS41(π-σ), HIS41(π-π), CYS44, MET49, PRO52, ARG188(Alkyl-Alkyl), MET165(π-Sulfur), GLN189(van der Waals), LEU141, GLY143, CYS145(Hydrogen Bond)
FA-23	2C19,2C9	-6.80	10.39	MET165(π-Alkyl), SER144(Unfavorable), GLU166, GLN189(van der Waals), LEU141, GLY143, CYS145(Hydrogen Bond)
FA-24	1A22C19,2C9	-7.46	3.41	MET165, LEU167, PRO168(π-Alkyl), SER144(Unfavorable), LEU141, GLY143, SER144, CYS145(Hydrogen Bond)
AZP		-8.33	0.78	HIS41(π-π), CYS44, MET49, PRO168(π-Alkyl), MET165(π-Sulfur), ASN142(van der Waals), ASN142, GLY143, HIS164, GLU166, GLN189(Hydrogen Bond)

Molecular Dynamics and MM-PBSA Calculation

The top five ligand-protein complexes (FA-16, FA-17, FA-18, FA-23, and FA-24) were further evaluated for their stability and free binding energy using MD simulation and MM-PBSA calculation, respectively

(Fig.-3). Molecular docking simulation result for 100 ns indicated that all ligand complex is relatively stable. Most of the ligand shows flexibility as shown by relatively high RMSD value during simulation, where compound FA-16, FA-18, and FA-24 yield slightly higher torsional flexibility than the rest of the tested ligand with an RMSD value of 0.8 Å. Furthermore, MM-PBSA calculation was performed based on the following equation

$$\Delta G_{binding} = \Delta E_{MM} + \Delta G_{polar\ solv.} + \Delta G_{non\text{-}polar\ solv.} - T\Delta S$$

Where ΔE_{MM} represents the sum of van der Waals and electrostatic energy, $\Delta G_{polar\ solv}$ and $\Delta G_{non\text{-}polar\ solv.}$ refers to polar and non-polar solvation, respectively. Since the conformational entropy difference value is minimal, it can be ignored.[34] This method can be complemented with molecular docking results since it takes conformational dynamics and solvation into account.[16] It showed different result from the docking score, notably for compound FA-16 which possess the lowest free binding energy score, compared to its docking score. On the contrary, the top two compounds according to molecular docking results possess low free binding energy values (Table-3). It is argued that ligand flexibility during the molecular dynamics simulation caused this result.

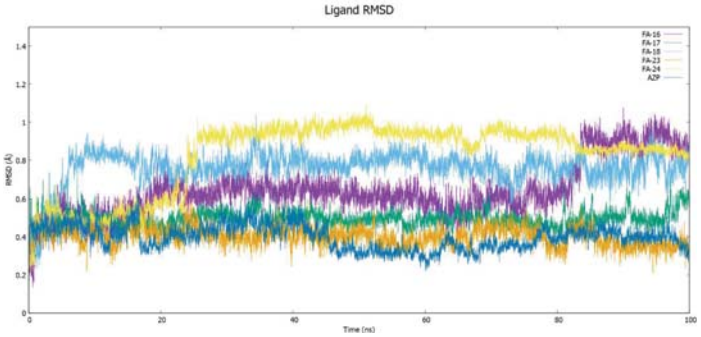


Fig.-3: Ligand RMSD Fluctuation During 100 ns Simulation (FA-16: Violet; FA-17: Green; FA-18: Cyan; FA-23: Orange; FA-24: Yellow; AZP: Blue)

Table-3: Free Binding Energy Score of Several Ferulic Acid Analogs and AZP using MM-PBSA Approach

Compounds	ΔG (MMPBSA)
FA-16	-8.42 ± 0.35
FA-17	-6.39 ± 2.11
FA-18	-5.00 ± 1.14
FA-23	-6.24 ± 1.13
FA-24	-5.81 ± 1.86
AZP	-11.83 ± 1.92

CONCLUSION

The results showed that some designed ferulic acid derivates are predicted to be potential inhibitors of the SARS-CoV MPro receptor. The lack of *in silico* potency compared to native ligands (AZP) suggests that further structure modification is needed in order to improve their potential activity.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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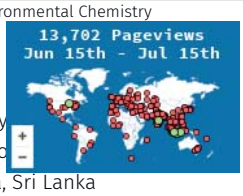

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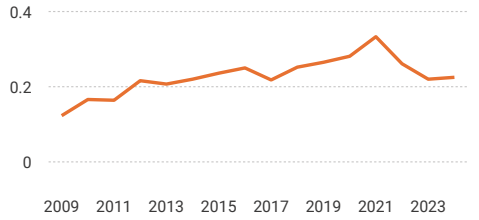

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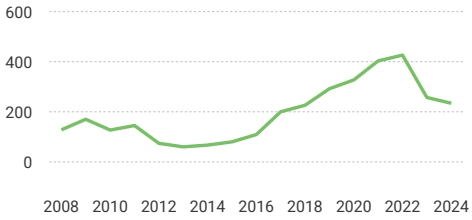

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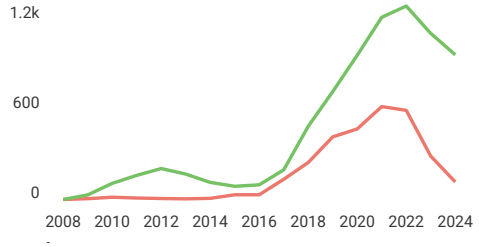

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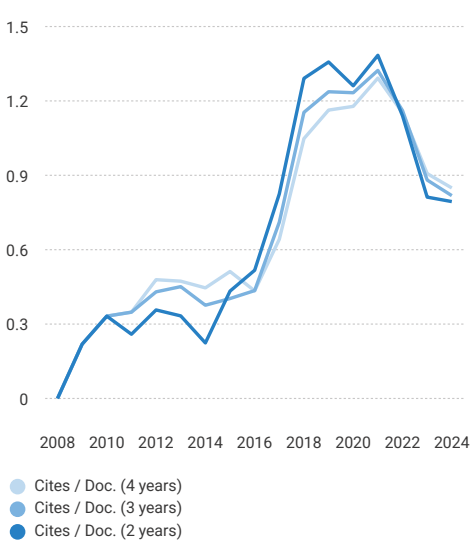

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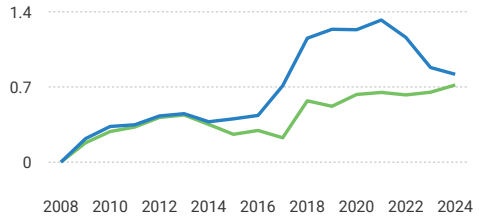

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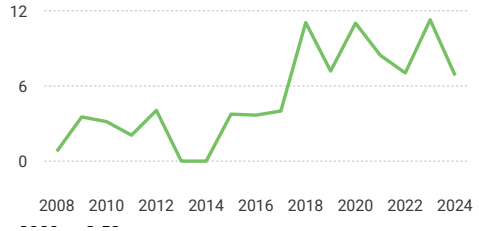

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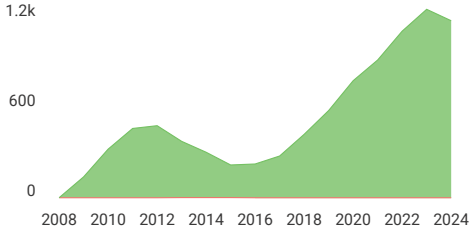

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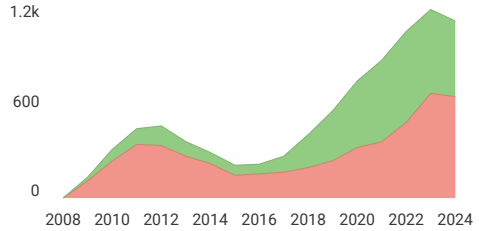

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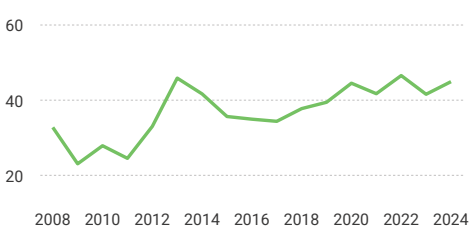
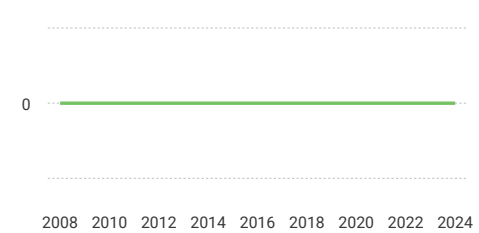
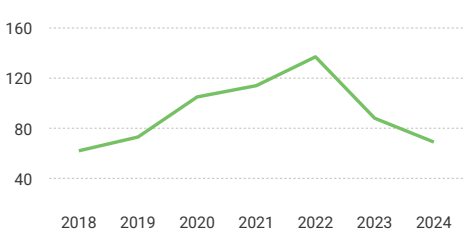


Documents cited by public policy (Overton)



Documents related to SDGs (UN)



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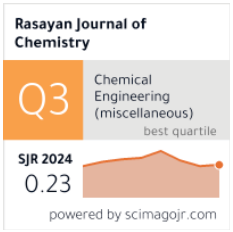
Estimated financial value

etr



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