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Curcuma caesia. Roxb as a Potential Inhibitor of STAT3 and EGFR: a Molecular Docking Approach in Diabetic Nephropathy

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Abstract

Background*: Diabetes mellitus (DM) is a chronic disorder marked by persistent hyperglycemia, leading to various complications, including diabetic nephropathy (DN). The STAT3-EGFR signaling axis plays a crucial role in the development and progression of diabetic nephropathy, with EGFR activation leading to STAT3 phosphorylation. Curcuma caesia Roxb, rich in curcuminoids, shows promise in managing DN due to its anti-inflammatory and antioxidant properties. This study aims to predict the inhibitory potential of Curcuma caesia compounds on STAT3 and EGFR in DN using molecular docking techniques.* ***Methods****: This study utilized molecular docking to evaluate the inhibitory potential of Curcuma caesia compounds on STAT3 and EGFR. Protein structures were obtained from the RCSB database and prepared using Biovia Discovery Studio. Redocking validated the method via RMSD analysis, while docking simulations assessed binding energy (ΔG). ADMET predictions analyzed physicochemical properties and toxicity, ensuring the compounds' suitability as drug candidates.* ***Results****: Redocking process validated the method, with RMSD values indicating accuracy. Curcumin (-9.71) and ar-Curcumene (-5.02) showed the lowest binding energy for both proteins, suggesting strong interactions. Visualization revealed significant amino acid interactions, particularly involving hydrogen bonds. Additionally, pharmacokinetic and toxicity analyses indicated that most compounds are suitable drug candidates, exhibiting good absorption, distribution, and safety profiles, thus supporting Curcuma caesia's therapeutic promise in diabetic nephropathy management.* ***Conclusion****: Curcuma caesia demonstrates significant potential as a therapeutic agent for diabetic nephropathy, with favorable molecular interactions, strong binding affinity to STAT3 and EGFR, and promising pharmacokinetic and safety profiles.*

Keywords: *curcuma caesea, molecular docking, nephropathy diabetic*

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INTRODUCTION

Diabetes mellitus (DM) is a non-communicable disease characterized by persistent hyperglycemia. This chronic metabolic disorder arises from impaired insulin secretion, insulin resistance, or a combination of both, which are the primary factors contributing to the disease (Goyal et al., 2023). Persistent hyperglycemia in uncontrolled DM patients can lead to both acute and chronic complications. Common acute complications include hyperosmolar hyperglycemic state and diabetic ketoacidosis (Akalu & Birhan, 2020). Chronic complications frequently observed include diabetic neuropathy and nephropathy. Diabetic nephropathy affects approximately 40% of DM patients, causing alterations in renal hemodynamics and structural damage due to increased plasma flow and hydrostatic pressure in the glomerular capillaries (Badal & Danesh, 2014). The progression of diabetic nephropathy is driven by hemodynamic and metabolic factors within the kidney. Treatment aims to slow or halt the progression of renal damage (Badal & Danesh, 2014).

Therapeutic strategies for diabetic nephropathy focus on glycemic and blood pressure control, along with inhibition of the renin-angiotensin-aldosterone system (RAAS) and the Signal Transducer and Activator of Transcription 3 (STAT3) pathway. STAT3 plays a crucial role in the secretion of inflammatory mediators, contributing to glomerular sclerosis and tubulointerstitial fibrosis in the kidney, ultimately resulting in diabetic nephropathy (Elendu et al., 2023; Yu et al., 2023). Previous in vitro studies demonstrated that the JAK-STAT pathway is pivotal in the development of diabetic nephropathy. Recent advances in diabetic nephropathy treatment target TGF-β and NF-kB pathways and incorporate stem cell- and gene-based therapies (Zheng et al., 2019). Selective inhibition of STAT3 over 16 weeks has shown promising results in slowing the progression of advanced renal damage (Elendu et al., 2023; Varghese & Jialal, 2023). Inflammatory mediator activity induces gene transcription involved in pro- and anti-inflammatory responses, including the JAK-STAT pathway, which is activated by tyrosine kinases such as TGF-β, EGFR, and FGF (Yu et al., 2023). EGFR activation plays a significant role in the pathogenesis of diabetic nephropathy by modulating key cellular processes such as fibrosis and inflammation in renal tissues (Wang & Zhang, 2024). Through the activation of downstream signaling pathways, including TGF-β, EGFR contributes to the progression of kidney damage, making it a critical target for therapeutic intervention in diabetic kidney disease.

Turmeric is a plant known for its various species, one of which is black turmeric (*Curcuma caesia* Roxb.), renowned for its significant health benefits. Black turmeric is widely used as a natural herbal medicine to treat various diseases. The therapeutic potentials of *Curcuma caesia* include its effects as an antidiabetic, asthma treatment, analgesic, antimicrobial, anticancer, and thrombolytic agent (Ibrahim et al., 2023; Paudel et al., 2024). Research conducted by Udayani et al. (2024) demonstrated the ability of *Curcuma caesia* to reduce glucose levels in the body through in vivo studies. Additionally, *Curcuma caesia* can inhibit the enzymes amylase and glucosidase, which are involved in glucose metabolism and the formation of glycogen as an energy reserve (Majumder et al., 2017). Furthermore, the use of *Curcuma caesia* in the treatment of diabetic nephropathy has shown promising results, as evidenced by eGFR evaluations in in vivo studies by Aini et al. (2024). This is due to its ability to reduce oxidative stress, which mediates inflammation in the renal tubules (Grover et al., 2019). One of the active compounds in *Curcuma caesia*, curcumin, possesses anti-inflammatory and nephroprotective properties, inhibiting TLR and downregulating cadherin, thereby preventing epithelial-to-mesenchymal transition that could lead to kidney damage (Sun et al., 2014; Zhang et al., 2015).

Molecular docking studies have become a growing trend in drug development. These studies predict the binding interactions between target molecules and active compounds, enabling researchers to understand molecular-level interactions and the underlying biochemical processes. This study aims to predict the potential inhibitory activity of STAT3 and EGFR from Curcuma *caesia* and Roxb in diabetic nephropathy through a molecular docking approach.

MATERIALS AND METHODS

Validation method

STAT3 and EGFR protein structure were obtained via https://www.rcsb.org/ with PDB ID: 6NJS and 3POZ. Protein preparation uses the Biovia discovery Studio 2021 application to clean proteins from water molecules and other cofactors and separate proteins and natural ligands. The method validation process uses the redocking method using the help of the AutoDock program. The redocking process was carried out to find the root mean square deviation (RMSD) value as a method validation parameter. The RMSD value that can

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be considered valid is below 2.0 A, which shows that there is no significant change in the ligand after the docking process (Ramírez & Caballero, 2018).

The redocking process uses the Autodock application with genetics algorithm parameters which are a combination of several other parameters (Shivanika et al., 2022). The determination of the grid box in this process is the central of the ligand enabling to find the grid point number and grid point coordinates (X,Y,Z). This research uses a specific docking method, so that in the redocking process the grid box findings are very important to obtain the grid point number and grid point coordinates (Kilambi & Gray, 2017).

Docking simulation

The entire chemical structure of the active compound *Curcuma caesia was* obtained via https://pubchem.ncbi.nlm.nih.gov/. Canonical SMILES storage was used to perform ADMET predictions. The compounds obtained were then optimized in structure and minimize the energy using the Avogadro and Chemdraw 3D 2019 applications. This process provides a better compound structure with lower energy (Syahputra et al., 2022). The docking simulation process uses the same method as the redocking process, with changes to the grid point number and grid point coordinates (X,Y,Z) which adjust to the results of the redocking (Lestariningrum et al., 2024).

An analysis of the docking simulation results is found in the lowest binding energy (ΔG) value. The ΔG results of the test ligand will be compared with the natural ligand or between the docking results of the test compound and the control drug (captopril). Captopril is used in this study as a control due to its well-established role as an angiotensin-converting enzyme inhibitor, its ability to block neovascularization and modulate cellular processes in diabetic conditions makes it a relevant comparator in evaluating potential inhibitors of STAT3 and EGFR (Abdallah et al., 2015) The best ligand results were then visualized by the interaction site, binding pocket and amino acid interactions using the Biovia discovery Studio 2021 application. Analysis of the dominant amino acid interactions in each protein was carried out to find the molecular process of the compound on the target protein. All the molecular modeling and analyses in this study were performed using free and open-source software, including AutoDock and Avogadro, while ChemDraw and Discovery Biovia were used under academic licenses.

ADMET Predictions

Prediction of the physicochemical and bioavailability of each test compound was using Canonical SMILES as a format for analysis with the help of tools (http://www.swissadme.ch/). Lipinski parameters are used as general parameters for oral treatment candidates in the form of molecular weight, hydrogen bond donors and acceptors, and Log-P (Abdul-Hammed et al., 2022). The pharmacokinetics of each compound were evaluated using https://biosig.lab.uq.edu.au/pkcsm/ by entering Canonical SMILES. The parameters used are absorption (GI absorption), distribution (BBB permeability), metabolism (CYP1A2), and excretion (total clearance and renal oct2 substrate) (Abdullah et al., 2021; Ononamadu & Ibrahim, 2021; Ramadhan et al., 2024). The parameters used to predict toxicity are AMES toxicity, hepatotoxicity, and LD50.

RESULTS AND DISCUSSION

Method validation

The method was validated using a redocking process for each natural ligand to the protein using the AutoDock program. The finding of the RMSD value in the STAT3 redocking process, namely 1.50, indicates good results or the method used is valid. The finding of the RMSD value in the EGFR redocking process is 1.18, indicating good results or that the method used is valid. The results of the structural deviation due to the docking process are shown in Figure 1 which shows that there is no significant difference in the ligands before (in blue) and after the docking process (in yellow). Yellow ligands are ligands resulting from the docking process, while gray ligands are natural ligands originating from proteins. Findings The area and coordinates of the STAT3 and EGFR grid boxes are shown in Table 1, the results of which will be a specific docking reference for each target.

Table 1. Grid box analysis

Native Ligand	Number Grid Points			Coordinate Grid Points			Grid Point Spacing
	X	Y	Z	X	Y	Z	
6NJS	40	56	40	13,498	54,117	0.100	0.375 A
3POZ	40	40	40	18,746	31,832	11,626	0.375 A

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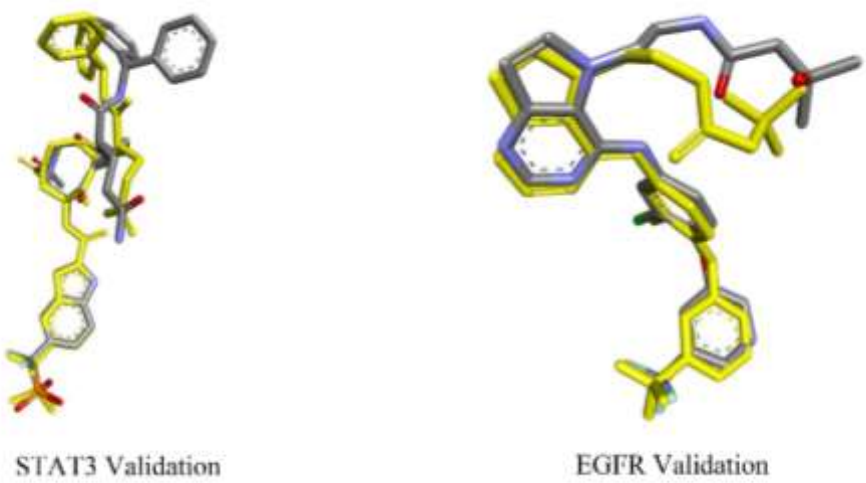

Figure 1. Ligand redocking

Docking simulation

The compounds that have been obtained are then optimized in structure and minimize the energy using the Avogadro and Chemdraw 3D 2019 applications. This process provides a better compound structure with lower energy (Syahputra et al., 2022). Each test compound is optimized and minimized energy with the aim of providing the best structural form with minimal energy. The main parameter of the docking process is the binding affinity (ΔG) between the test ligand and the protein. The lower the ΔG value indicates a good interaction, the docking results are shown in Table 2. Docking test results on *Curcuma caesia compounds* against STAT3 found that the natural ligand had the lowest ΔG, namely -10.57. ar-Curcumene has the lowest ΔG value, namely -5.04, followed by Curcumin with a ΔG value -4.87 and bornyl acetate has a ΔG value of -4.54. Captopril as a control drug in this study had a ΔG value of -4.02, where there were five Curcuma caesea compounds that had lower ΔG values. These results show the great potential of *Curcuma caesia* as an alternative treatment through inhibiting STAT3 activity in diabetic nephropathy.

Docking test results on *Curcuma caesia* compounds against EGFR found that the natural ligand had the lowest ΔG, namely -11.24. Captopril as a control drug in this study had a ΔG value of -5.70, where almost all Curcuma caesea compounds had a lower ΔG value. Curcumin has the lowest ΔG value, namely -9.71, this compound has the lowest ΔG compared to other compounds. Cineole has a ΔG value - 7. 25, followed by curcumen with a value of ΔG -7.24. The compound with the highest ΔG docking result is bornyl acetate, namely -4.48. These results show the great potential of *Curcuma caesia* as an alternative treatment through inhibiting EGFR activity in diabetic nephropathy. Despite having lower binding affinities toward EGFR and STAT3 compared to the native ligands, the *Curcuma caesia* compounds still show substantial potential as alternative therapeutic agents. Their competitive binding suggests that, even with lower affinity, these compounds may effectively inhibit the target proteins due to their ability to block critical pathways in diabetic nephropathy, providing a viable therapeutic alternative.

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Table 2. Docking simulation

Compound	STAT3		EGFR	
	Energy affinity (Δ G) (kcal/mol)	**Inhibition constant (Ki)(µM)**	**Energy affinity (Δ G) (kcal/mol)**	**Inhibition constant (Ki)(µM)**
Native ligands	-10.57	17.75	-11.24	5.79
Camphor	-4.28	269.70	-6.10	5.79
Curcumin	-4.87	727.00	**-9.71**	75.82
Ocimen	-4.19	845.18	-6.36	21.81
Cineole	-4.12	957.13	-7.25	4.82
Element	-3.86	1.48	-5.80	56.02
Borneol	-3.62	2.22	-5.60	78.25
Bornyl acetate	-4.54	466.69	-4.48	521.88
ar-Curcumene	**-5.04**	203.60	-7.24	4.97
Captopril	-4.02	1.13	-5.70	66.55

Figure 2 is a visualization of protein crystals, binding pockets, and amino acid interactions resulting from docking in STAT3. The bond interactions formed between the native ligand and protein show that there are nine hydrogen bonds marked in green in the form of THR657, SER636, GLU638, GLU638, GLN644, SER 611, SER 613, and GLU612. There are seven non-hydrogen bonds formed, namely LYS658, ILE659, ARG609, ARG609, PRO639, PRO639, and VAL 637. Figure 3 show ar-Curcumene has one hydrogen bond, namely GLU638, and three non-hydrogen bonds, namely TYR640, VAL637, and TRP 623. Docking results in captopril shows that there are five hydrogen bonds in the form of ARG609, SER611, SER611, SER613, and SER613 and one non-hydrogen bond PRO639. The dominant amino acid hydrogen bond interaction in this case is GLU638, where in the three test ligands analyzed there is this amino acid group even though in captopril this group does not have a specific bond. The interaction that occurs with GLU638 will bind to oxygen during peptide ligand conformation. These findings support the interaction of STAT3 and *Curcuma caesia* which could be the basis for treatment targeting STAT3 through inhibiting the action of this protein by mediating cell apoptosis resistance and cell growth (Shao et al., 2004).

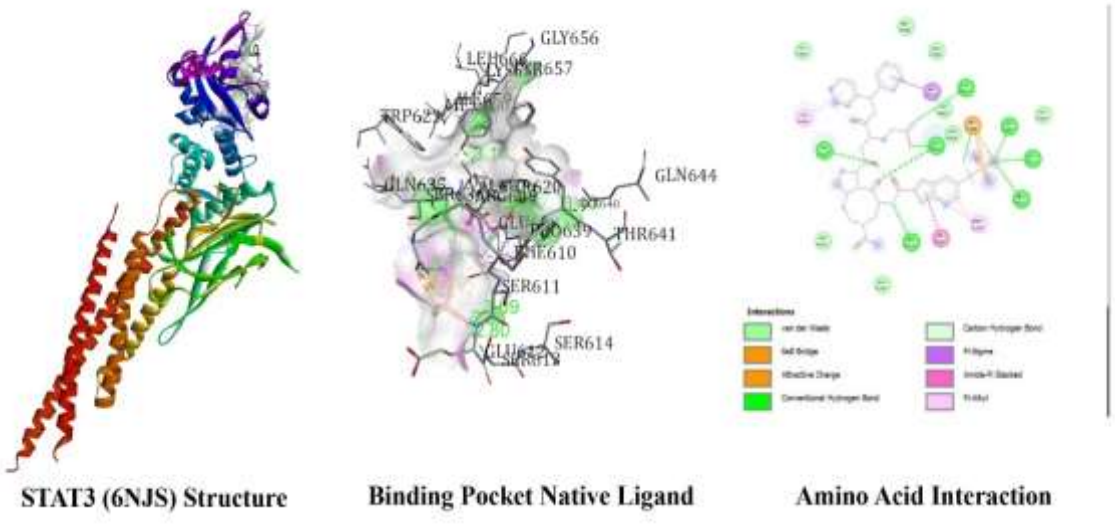

Figure 2. STAT structure and docking analysis of a native ligand

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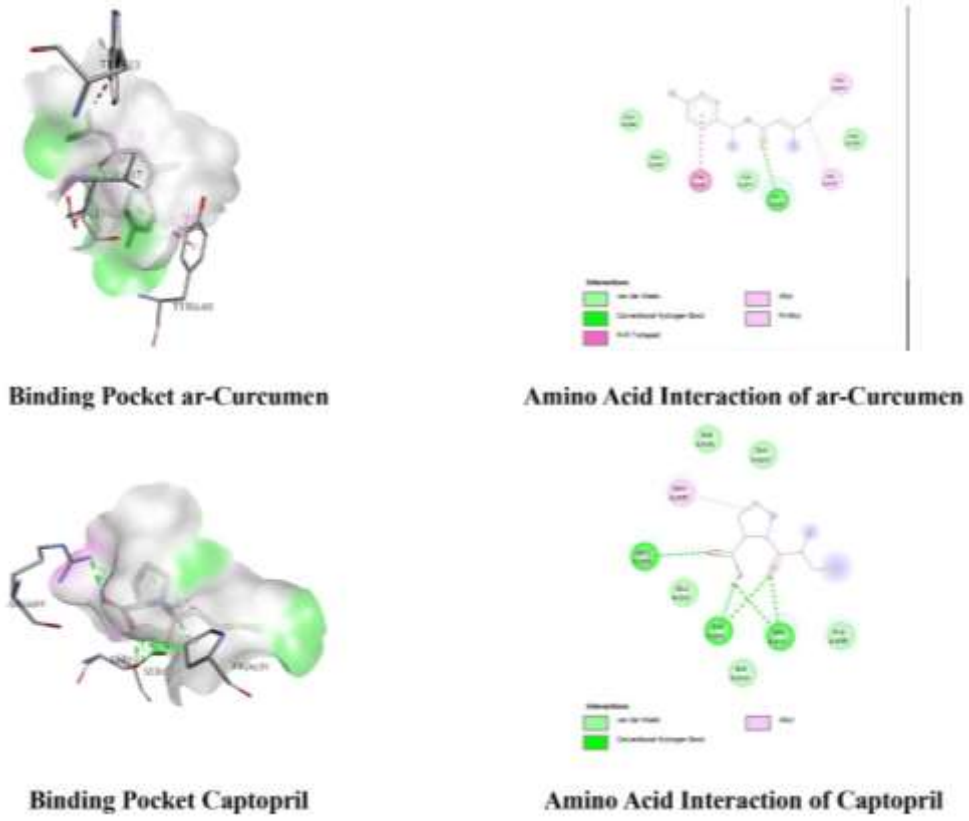

Figure 3. Visualization of the best pose docking results and amino acid interactions of ar-Curcumene and captopril

Visualization of protein crystals, binding pockets, and amino acid interactions resulting from docking of test ligands against EGFR is shown in Figure 5. It was found that there were dense amino acid bond interactions in the native ligand, there were four hydrogen bonds and 20 non-hydrogen bonds. The hydrogen bonds formed in the native ligand are LYS745, THR845, THR845, **THR790**, and GLN791. Meanwhile, the non-hydrogen bonds formed in the native ligand are LUE788, VAL726, LYS745, LYS745, **MET766**, PHE856, PHE856, ARG776, ARG776, CYS775, CYS775, CYS775, ILE853, MET793, MET793, ALA743, ALA743, LEU844, L EU844, and LEU 718. Figure 5 show the results of bond interactions in curcumin found seven hydrogen bonds, namely PHE858, ASP855, LYS745, GLN791, LEU792, **THR790**, and MET793. There are five non-hydrogen bonds formed in the form of **MET766**, LEU777, LEU788, ALA743, and LEU844. Captopril as a control ligand has four hydrogen bonds, namely THR854, **THR790**, ALA743, and LEU788. Two amino acid bonding interactions were found in captopril in the form of PHE856 and **MET766**.

The most dominant hydrogen bonding interaction of amino acids in this analysis is THR790. The same findings were shown in research on curcumin as an anticancer drug. This shows that curcumin analogs can be an alternative treatment through EGFR inhibition (Afzal et al., 2022). Mutations in EGFR at the THR790 MET site help the development of Non Small Cell Lung Cancer (NSCLC) cancer cells by inhibiting this mutation; curcumin can be useful as an anti-cancer NSCLC (Lu et al., 2024)). The most dominant non-hydrogen bonding interaction of amino acids in this analysis is MET766. The interaction of MET766 with EGFR can be anti-proliferative, which can help in the recovery of renal tubules in diabetic nephropathy sufferers (Ibrahim et al., 2020).

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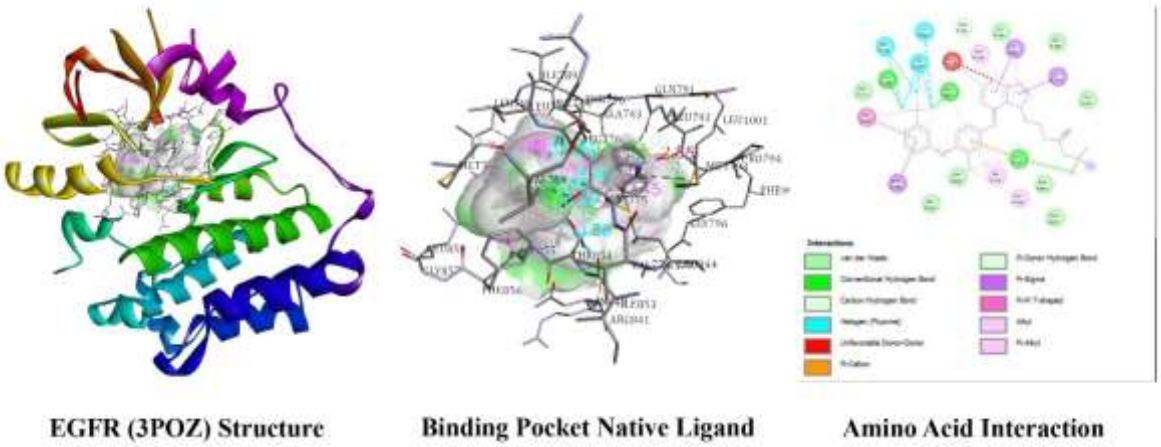

Figure 4. EGFR structure and docking analysis a native ligand

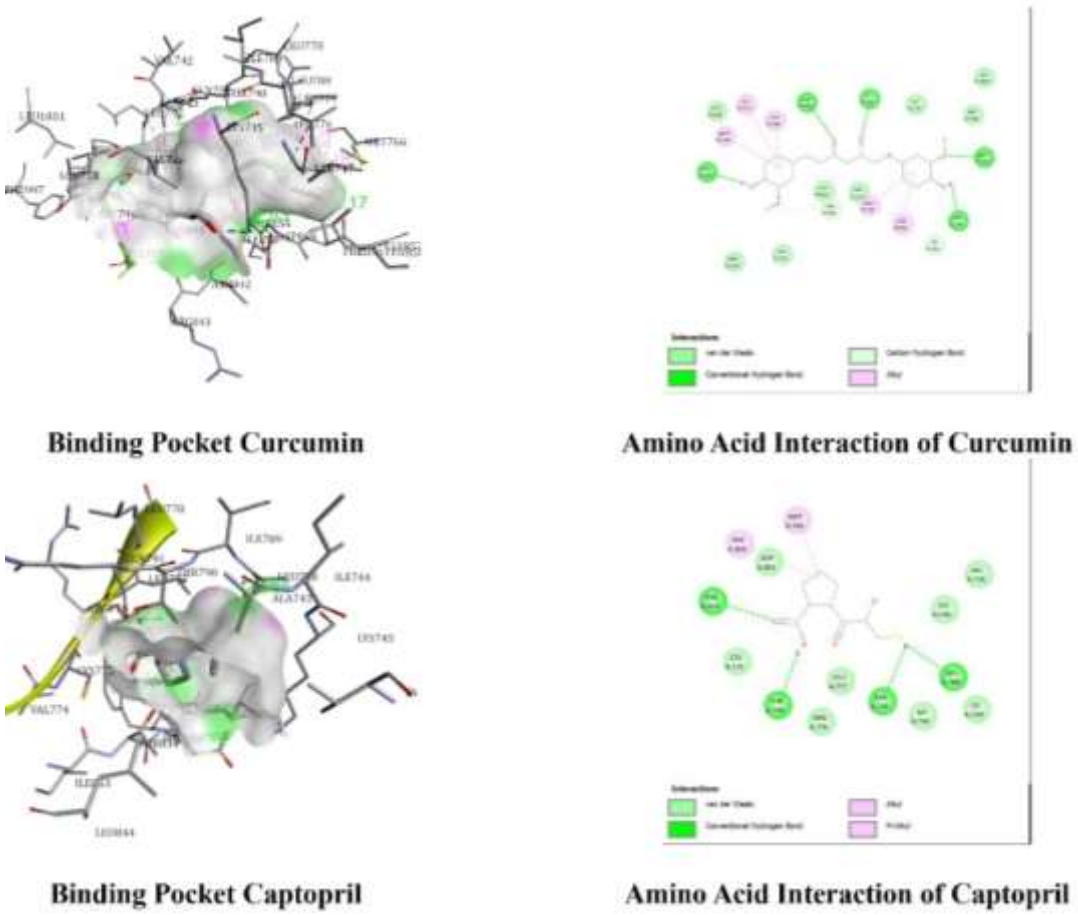

Figure 5. Visualization of the best pose docking results and amino acid interactions of ar-Curcumene and captopril

The results of this study show the potential for using *Curcuma caesia* as an alternative treatment for diabetic nephropathy patients. Research conducted by Machado et al/ (2022) showed good results in early treatment in diabetic rat renal injury with improvements in renal oxidative repercussion and hemodynamics profile (Machado et al., 2022). Aini et al.(2024) showed that there was a decrease in serum creatinine and microalbumin in the urine of mice affected by diabetic nephropathy by administering *Curcuma caesia extract* . *Curcuma caesia* can reduce the expression of KIM-1, NGAL, and reduce toxic oxidative stress in renal tissue of mice with diabetic nephropathy (Ghasemi et al., 2019). Lee et al. (2019) showed that there was a

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reduction in kidney damage by administering a curcumin analog (Dibenzoylmethane) which could reduce the risk of developing diabetic nephropathy in mice . The benefits of *Curcuma caesia* as antidiabetic, anti-inflammatory, promoting-autophagy, and antioxidant strengthen the results of this research which shows great potential in the treatment of diabetic nephropathy (Zhu et al., 2022). The role of curcumin and ar-curcumene as the active compounds in *Curcuma caesia* is significant, as they show promising binding affinities with EGFR and STAT3. However, the study could further emphasize the findings related to other species of *Curcuma*, such as *C. longa, C. phaecocaulis, C. wenyujin, C. aromatica,* and *C. kwangsiensis* which may also contain similar bioactive compounds and contribute to a broader understanding of the therapeutic potential of the *Curcuma* genus in treating diabetic nephropathy (Chen et al., 2023).

ADMET predictions

The similarity analysis of eight black turmeric compounds (Table 3) against existing drugs indicates that seven of them meet the criteria outlined by Lipinski's rules. Only elemene exhibits a non-compliance issue, with a LogP value exceeding 4.15. Compounds with high LogP values can demonstrate poor solubility in aqueous environments, which may lead to slow absorption and irregular bioavailability, thereby causing problematic kinetic profiles in the body (Dong et al., 2018). Overall, most black turmeric compounds show good potential as drug candidates.

The pharmacokinetic and toxicity analysis of the active compounds in black turmeric shows promising results, making them suitable candidates for drug development (Table 4). All compounds have an absorption value greater than 30%, indicating good absorption capabilities. Regarding distribution, all compounds demonstrate positive results, although they have difficulty crossing the blood-brain barrier with values below -1. The cytochrome P450 enzyme, which plays a role in metabolism, shows a tendency to be inhibited only by curcumin. CYP1A2 plays a crucial role in the metabolism of many drugs, and its inhibition may result in decreased clearance rates and prolonged drug action, which could potentially lead to accumulation and increased therapeutic effects or side effects (Bayoumi et al., 2024). Additionally, all compounds exhibit good excretion values. Toxicity analyses, including the Ames test and hepatotoxicity assessments, reveal no toxic properties in any of the compounds, further supporting the idea that black turmeric can be considered a safe and effective drug candidate.

Table 3. Lipinski analysis

Compound	Molecular Weight	Hydrogen Bond donors	Hydrogen Bond acceptors	Log-P	Violations
Camphor	152.23 g/mol	0	1	2.30	-
Curcumin	368.38 g/mo	2	6	1.47	-
Ocimen	154.25 g/mol	0	1	2.30	-
Cineole	154.25 g/mol	0	1	2.45	-
Elemene	204.35 g/mol	0	0	**4.53**	LOGP>4.15
Borneol	154.25 g/mol	1	1	2.45	-
Bornyl acetate	196.29 g/mol	0	2	2.76	-
ar-Curcumene	218.33 g/mol	0	1	3.37	-

Table 4. ADMET analysis

Compound	GI Absorption	BBB Permeability	CYP1A2	Total Clearance	Renal Oct2 Substrate	AMES Toxicity	Hepatotoxicity
Camphor	95.968%	0.612	No	0.109	No	No	No
Curcumin	82.19%	-0.562	Yes	-0.002	No	No	No
Ocimen	95.898%	0.436	No	1.272	No	No	No
Cineole	96.505%	0.491	No	1.009	No	No	No
Element	94.359%	0.809	No	0.251	No	No	No
Borneol	93.439%	0.646	No	1.035	No	No	No
Bornyl acetate	95.366%	0.553	No	1.029	No	No	No
ar-Curcumene	95.626%	0.66	No	1.543	No	No	No
requirement	>30%	<-1	No	Higher is batter	No	No	No

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CONCLUSION

This study shows that *Curcuma caesia* compounds with good ability, can even surpass control drugs against STAT3 and EGFR. While ar-curcumin with STAT3 has a binding energy of -5.04 and curcumin with EGFR has a binding energy of -9.71 which shows the best ΔG value in the docking test; these results are based on computational analysis and may not fully represent their therapeutic potential in vivo. Future in vitro and in vivo studies will provide deeper insights into the actual effectiveness and safety of these compounds, thus allowing for a more accurate evaluation of their potential as therapeutic alternatives for diabetic nephropathy.

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AUTHOR CONTRIBUTIONS

Conceptualization, M.F., S.A.M., S.R.; Methodology, M.F., S.A.M.; Software, M.F.; Validation, M.F., S.A.M.; Formal Analysis, S.A.M., S.R.; Investigation, M.F., S.R.; Resources, S.A.M., S.R.; Data Curation; M.F.; Writing - Original Draft, M.F., S.A.M., S.R.; Writing - Review & Editing, M.F., S.A.M., S.R.; Visualization, S.A.M., S.R.; Supervision, S.R.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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