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Molecular Docking Study of α-, β-, and γ-Mangostin from Mangosteen (*Garcinia mangostana* L.) Targeting VEGFR-2 and NRP-1 for Anti-Angiogenic Therapeutics in Retinopathy Diabetic

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Abstract: To enhance the effectiveness of treatment in diabetic retinopathy patients, the development of drugs that have a combined effect of inhibiting Vascular Endothelial Growth Factor-2 (VEGFR-2) and Neuropilin-1 (NRP-1) should be conducted. This work simulates the interaction of α-mangostin, β-mangostin, and γ-mangostin (*Garcinia mangostana* L.) as a receptor against VEGFR-2 and NRP-1 as a ligand through the molecular docking approach. Redocking between receptor and native ligand (VEGFR-2, PDB ID: 4ASD and NRP-1 PDB ID: 5C7G) was performed using MGLTools 1.5.7 and Autodock Vina, then continued with PyMol2 to assure RMSD value of 0.981 Å for VEGFR-2 and 1.994 Å for NRP-1 (< 2 Å). The docking results showed that α-mangostin had the lowest binding energy to VEGFR-2 (-8.9 kcal/mol) and NRP-1 (-6.9 kcal/mol), followed by γ-mangostin with binding energy of -8.6 kcal/mol to VEGFR-2 and -6.9 kcal/mol to NRP-1, and β-mangostin with binding energy of -8.3 kcal/mol to VEGFR-2 and -6.5 kcal/mol to NRP-1. In comparison, the positive control, Sunitinib, showed binding energy of -7.9 kcal/mol to VEGFR-2 and -6.2 kcal/mol to NRP-1. This indicates that these compounds have a more lowest energy binding to VEGFR-2 and NRP-1 than Sunitinib. In addition, the docking results visualized using Biovia Discovery Studio 2021 showed that these compounds have hydrogen bonds and several other bonds to the active sites of VEGFR-2 and NRP-1. Hence, the proposed compounds have the potential to be further synthesized and evaluated in vitro and in vivo as a pathological anti-angiogenesis drug in diabetic retinopathy.

Keywords: VEGFR-2, NRP-1, Anti-angiogenic, Retinopathy diabetic

Introduction

Diabetic retinopathy (DR) is a severe microvascular complication of diabetes that can result in permanent blindness. The global prevalence of diabetic retinopathy is anticipated to rise from 126.6 million in 2010 to 191.0 million in 2030, with 30% of the population at risk of blindness (Zheng et al., 2012). Chua et al., (2017) reported that Indonesia has a significantly higher prevalence of diabetic retinopathy and vision-threatening diabetic retinopathy than other countries in the Asia-Pacific region, with rates of 43.1% and 26.3%, respectively.

Non-proliferative diabetic retinopathy (NPDR) is an early stage of diabetic retinopathy that is characterized by microaneurysms, small hemorrhages, and lipid exudates (Saravanan et al, 2013). If left untreated, NPDR may develop into Proliferative Diabetic Retinopathy (PDR), which is characterized by angiogenesis as a result of elevated reactive oxygen species (ROS) in vascular endothelial cells (Kaur et al, 2012; Giacco & Brownlee,

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2010; Reddy et al, 2014). Through inflammation and pericyte mortality, this results in irreversible cell injury (Giacco & Brownlee, 2010; Reddy et al., 2014; El-Osta et al., 2008). Localized protrusion of the capillary wall results from the loss of pericytes, which is associated with the formation of microaneurysms. Leukocyte adhesion and infiltration increase in response to inflammation, as do pro-inflammatory cytokines and chemokines such as tumor necrosis factor-α (TNF-α), interleukin-1α (IL-1α), and IL-6. Endothelial cells, neuroglial cells, and the blood-retina barrier are all damaged as a consequence (Miyamoto et al., 1999; Beltramo & Porta, 2013).

Damage to vascular endothelial cells, neuroglial cells and the blood-retina barrier leads to capillary occlusion and retinal ischemia. Hypoxia will result from these conditions, which activates Hypoxia-Inducible Factor-1α (HIF-1α) and increases the expression of Vascular Endothelial Growth Factor-A (VEGF-A) (Huang et al, 2014). VEGF-A interacts with the VEGFR-2 receptor, which can be further amplified by neuropilin-1 (NRP-1) to induce cell proliferation and migration through the mitogen-activated protein kinases (MAPKs) and phosphoinositide 3-kinase (PI3K)-Akt pathways (Shintani, et al., 2006; Koch & Claesson-Welsh, 2012; Simons et al., 2016, 2016; Zachary, 2011). This leads to the development of new blood vessels that are more susceptible to damage and vascular leakage, which exacerbates diabetic retinopathy. Additionally, the interaction between VEGF-A and VEGFR-2 disrupts the adherens and junctions of vascular endothelial cells, resulting in vascular hyperpermeability and fluid extravasation (Koch & Claesson-Welsh, 2012; Simons et al., 2016). This implies that, in diabetic retinopathy, angiogenesis is significantly influenced by VEGF-A signaling through VEGFR-2 and NRP-1.

Anti-VEGF drugs, including bevacizumab, ranibizumab and aflibercept, are commonly used in patients with diabetic retinopathy to prevent macular edema and retinal angiogenesis. Although these drugs are effective, some patients with diabetic retinopathy develop resistance and poor efficacy due to polymorphisms in the VEGF gene (El-Shazly et al, 2013). In addition, patient access to treatment has been limited by the exorbitant cost of anti-VEGF drugs (Zhao & Singh, 2018). Therefore, the research for new targets and therapies to improve the treatment efficacy in patients with diabetic retinopathy is still ongoing, one of which is the development of drugs targeting VEGFR-2. Sunitinib is one of many drugs that target VEGFR-2. It is commonly used in the treatment of renal cell carcinoma (RCC) and has been shown to be effective in inhibiting angiogenesis (Hao & Sadek, 2016). Therefore, in this study, sunitinib was chosen as a reference for the development of anti-angiogenesis drugs.

Mangosteen (*Garcinia mangostana* L.) is a tropical fruit that is extensively cultivated in Indonesia, with a particular emphasis on Sumatra, Java, Bali, and West Nusa Tenggara (Poerwanto et al., 2008). In the pericarp, there are numerous xanthones, particularly α-mangostin, β-mangostin, and γ-mangostin, which function as antioxidants, anti-inflammatory, antimicrobial, and anti-cancer compounds (Evalina et al., 2018; El-Kenawy et al., 2018). Previous research has demonstrated that xanthones can impede the proliferation and migration of T24 cancer cells (Szkaradek et al., 2019). Cell proliferation and migration can be influenced by the activity of the kinase domain on VEGFR-2, which regulates molecular pathways important for cell growth and movement and mediates intracellular signalling. However, the compounds with potential as anti-angiogenesis agents that selectively target VEGFR-2 have not been thoroughly investigated.

Molecular docking is an extensively used in silico study that is used to predict the anti-angiogenic potential of phytopharmaceuticals. This method is time-saving, cost-effective, accurate, and rapid. Furthermore, this process can also help researchers estimate the interaction between the proposed compounds (ligand) and its target (receptor) (Ananto et al., 2024). This expedites the process of developing and discovering new drugs to treat diabetic retinopathy. Thus, the objective of this research is to examine the potential interaction of α-, β-, and γ-mangostin against VEGFR-2 and NRP-1 as anti-angiogenic drug candidates in diabetic retinopathy.

Methods

Protein Preparation

The three-dimensional (3D) crystal structures of VEGFR-2 (PDB ID: 4ASD) and NRP-1 (PDB ID: 5C7G) were derived from the Protein Data Bank (PDB). The Gasteiger values were calculated and all hydrogen atoms were appended to the protein 3D crystal structures using Autodock Vina software and MGL Tools 1.5.7 (Pham et al., 2022).

Ligand Preparation

The 3D structures of α-mangostin, β-mangostin, γ-mangostin, and Sunitinib were obtained in the SDF format from Pubchem. Then, the Cactus Online SMILES Translator-NCI/CADD was employed to convert the SDF format to PDB (Nicklaus et al., 2024). The command "set number or torsions" and the command "choose torsions" were employed to torsion ligands, which were subsequently encoded in the pdbqt format.

Docking Protocol

The docking simulation was conducted on a personal computer (PC) that was run on the Windows 11 Home 64-bit operating system (10.0, Build 22631) with an 11th generation Intel® Core™ i5-1135G7 processor @2.40GHz (8 CPUs) ~2.4GHz and 8192MB of RAM. Biovia Discovery Studio 2021, PyMol2, and Autodock Vina & MGL Tools 1.5.7 were employed to visualise ligand-receptor interactions, calculate RMSD, and for docking simulation, respectively. Redocking was performed between the protein and its native ligand at the active site of the target protein to conduct docking validation. The VEGFR-2 protein was docked using a 40 Å cubic grid box with 1000 Å spacing, while the NRP-1 protein was docked using a 40 Å cubic grid box with 0.375 Å spacing. The RMSD value that was approved was less than 2 (RMSD < 2). Setting coordinates for the VEGFR-2 protein were -23.259, 0.096, and -10.064 (x, y, and z), while the NRP-1 protein's setting coordinates were 13.375, -0.413, and 10.285 (x, y, and z), with an exhaustiveness value of 16. Based on the size and position of the cubic grid box for each protein, the original ligand was substituted with α-mangostin, β-mangostin, γ-mangostin, and Sunitinib in a similar protocol. By selecting the pose with the lowest binding affinity, the interaction was visualised after 20 poses were acquired.

Results and Discussion

Binding Pocket of Receptors with Native Ligands

Figure 1 illustrates 3D (left) and 2D (right) receptor's interactions of the native ligands, sorafenib to VEGFR-2 and bicine molecule to NRP-1. Various interactions occur between the amino acids of the receptor proteins and the ligands. These interactions include hydrogen bonds, hydrophobic interactions, and other interactions, as presented in Tables 3 for sorafenib to VEGFR-2 and Table 4 for bicine molecule to NRP-1. The binding energy and the stability of the receptor-ligand complex are significantly influenced by these interactions. Sorafenib forms important hydrogen bonds with amino acid residues such as ASP1046, VAL899, and GLU885, followed by the hydrophobic interactions, including LEU1019, VAL898, ALA866, VAL848, VAL916, and LYS868, as well as other interactions (halogen, pi-sigma, pi-sulfur, pi-pi T-shaped, etc.) on VEGFR-2. Meanwhile, the bicine molecule exhibits crucial hydrogen bonds with TRP29, SER74, and THR77. Therefore, these amino acid residues are regarded as critical binding sites in the active site of the receptor protein.

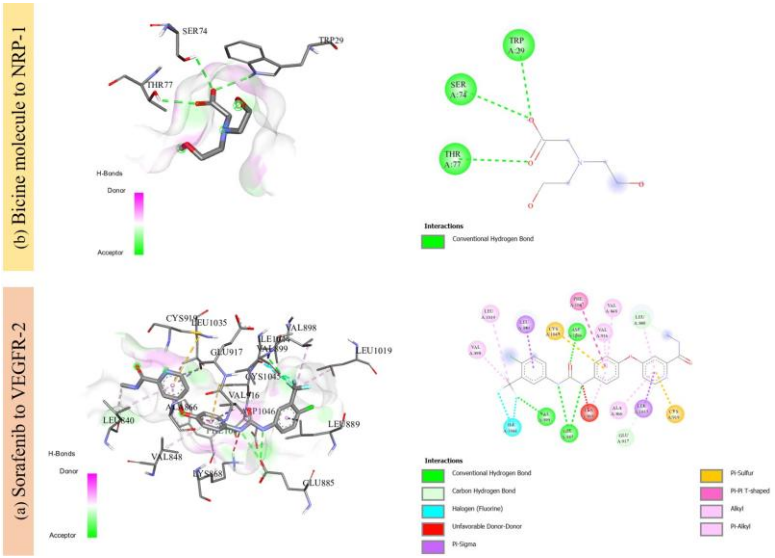

Figure 1. 3D (left) and 2D (right) visualization of native ligands: (a) Sorafenib to VEGFR-2 and (b) Bicine molecule to NRP-1.

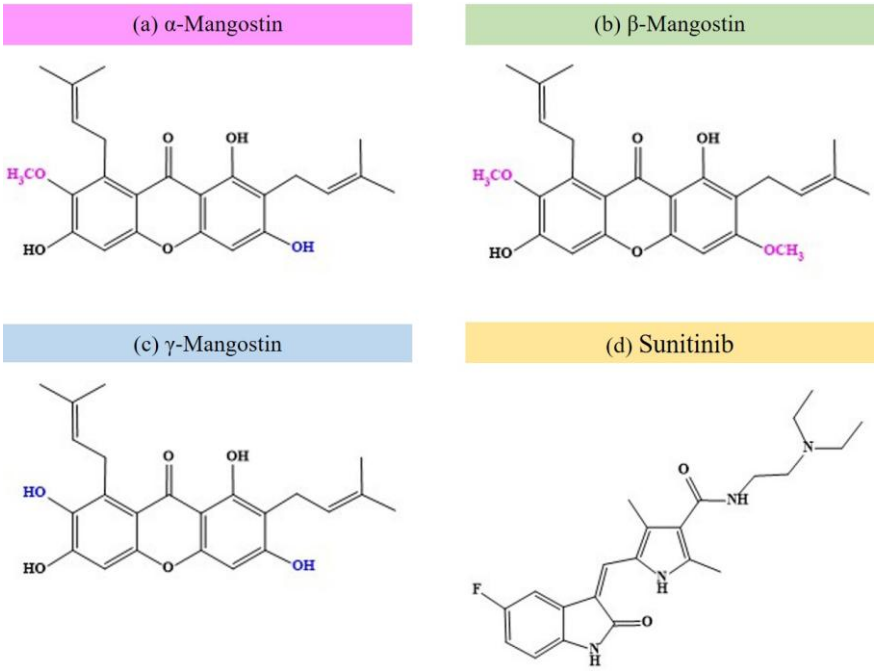

Figure 2. Proposed compounds of (a) α-mangostin, (b) β-mangostin, (c) γ-mangostin, and (d) Sunitinib as a positive control.

VEGFR-2 and NRP-1 are receptors involved in the signaling of angiogenesis in diabetic retinopathy. For this reason, there has been a recent surge in research that concentrates on their inhibition. The VEGFR-2 protein is comprised of three distinct structures: an extracellular domain, a transmembrane domain, and an intracellular domain, as reported by Go et al. (2023). Four regions form the intracellular domain: the juxtamembrane domain, kinase domain, kinase insert domain, and carboxyterminal domain (Manni et al., 2014). The juxtamembrane domain is responsible for the stabilization of the structure of VEGFR-2, whereas the kinase domain is responsible for the conformational changes of VEGFR-2 following activation (Manni et al., 2014). Both are involved in the process of signal transduction. Therefore, this protein targets the kinase domain and juxtamembrane.

NRP-1 is a transmembrane glycoprotein that functions as a co-receptor for VEGF-A and regulates the VEGFR-2 signaling pathway to improve the survival, proliferation, and chemotaxis of endothelial cells (Murga et al., 2004). NRP-1 is composed of three domains: the extracellular domain, transmembrane domain, and cytoplasmic domain (Li et al., 2011). The extracellular domain is composed of three regions: ala-2, b1-b2, and c domains (Uniewicz et al., 2014). Through interaction with the c-terminal arginine of VEGF, the b1 domain participates in the binding interaction with VEGF (Mota et al., 2018).

Structural Design of Ligands

Figure 2 shows the chemical structure of our proposed compounds, including α-, β-, and γ-mangostin, as well as sunitinib as a positive control compound. These proposed mangostin compounds as ligands consist of the xanthone nucleus as the main backbone with hydroxyl, methoxy, and isoprenyl groups as the main substituents, resulting in a variety of derivatives. The different properties exhibited by xanthones are highly dependent on the type and position of the substituents on the core ring, which is why they have been described as a 'privileged structure', as explained by Saraswathy et al. (2022). The xanthone structure and it's biological properties have generated a great deal of interest in these molecules. The hydroxyl group acts as a hydrogen acceptor, establishing hydrogen bonds with essential amino acids in VEGFR-2 and NRP-1. The xanthone backbone, methoxy and isoprenyl groups are designed to bind to the hydrophobic cavity and other interactions in the receptors.

We chose sunitinib, which is commonly used as a drug for cancer patients, as a positive control in this study. The structure of sunitinib consists of three parts, including a 5-fluoroindolin-2-one ring attached to a substituted pyrrole ring and connected to an attached amino side chain, as reported by AboulMagd and Abdelwahab (2021).

The amine and carbonyl groups of the indolin-2-one ring system can form a hydrogen bond with amino acids in VEGFR-2 and NRP-1. In addition, the indolin-2-one ring system, pyrrole ring connected to the amino side chain can lead to its incorporation into the hydrophobic and other interactions of the target protein. Therefore, this proposed compound was observed to evaluate the inhibitory activity against the target proteins VEGFR-2 and NRP-1.

Table 1. Docking validation between protein and native ligand.

Protein	PDB ID	Native ligand	Redocked RMSD (Å)
VEGFR-2	4ASD	Sorafenib	0.981
NRP-1	5C7G	Bicine molecule	1.994

In Silico Study: Binding Energy

In Table 1, the redocking protocol was employed to determine the RMSD values to be less than 2 Å as the docking validation, with the RMSD value in this study of 0.981 Å for the VEGFR-2 and 1.994 Å for the NRP-1. These values were generated using a specific grid box size. The RMSD is the most frequently employed method to assess the precision of the docking geometry by measuring the distance of the ligand from its reference point on the complex following the superposition of the receptor molecule (Kufareva & Abagyan, 2011). The grid box dimension of the docking method is deemed acceptable when the RMSD value is less than 2 (Wulan et al., 2023).

In Table 2, the binding energies of proposed compounds observed, with the ranges of -7.9 kcal/mol to -8.9 kcal/mol for VEGFR-2 and -6.2 kcal/mol to -6.9 kcal/mol for NRP-1. α-mangostin exhibited the lowest binding energies to VEGFR-2 and NRP-1 in comparison to sunitinib as positive control in this study. However, the binding energies of all proposed compounds did not apply equally to the VEGFR-2 when compared with the native ligand. Therefore, these proposed compounds formed a more stable complex with NRP-1 than bicine molecule. Overall, inhibitory activity of VEGFR-2 and NRP-1 is associated with compounds that have a lower binding energy and vice versa. This implies that their inhibitory activities were considerably greater than that of bicine molecule and that their interactions were more stable.

Protein-Ligand Interactions

In addition to binding energy, protein-ligand interactions important for VEGFR-2 and NRP-1 inhibition were used as screening criteria. Figure 3a-d shows the 3D (left) and 2D (right) representations of the different interactions between VEGFR-2 as receptor and the proposed compounds as ligands. In Table 3, the proposed compounds show hydrogen bond interactions between the amino acids ASP1046 and ASP814 in the VEGFR-2 protein to the O-H group on the xanthone skeleton of α-mangostin, ASP1046, LYS868 and ILE1025 to β-mangostin, ALA881 to γ-mangostin and CYS919 to the amine and carbonyl groups of the indolin-2-one ring system of sunitinib. In addition, LEU1049; ALA881; LEU882; VAL898; LEU889; VAL899; VAL916; CYS1045; ILE888; LEU1019; HIS1026; ILE1044; VAL899, ILE892; VAL898; ALA866; VAL848; LEU840; PHE1047; and LYS868 generally exhibited hydrophobic cavities with the xanthone skeleton, methoxy and isoprenyl groups of α-, β-, γ-mangostin, and formed interactions with the indolin-2-one ring system, pyrrole ring linked to the amino side chain of sunitinib. These proposed compounds also formed an additional electronic contact (pi-sigma, and carbon H-bond) with the α-, β-, γ-mangostin, with the sunitinib showed the pi-sigma, carbon H-bond, pi-sulfur, pi-pi T-shaped, and halogen.

Table 2. Binding energy of proposed compounds to VEGFR-2 and NRP-1

Compound	Binding energy (ΔG, kcal/mol)	
	VEGFR-2	NRP-1
α-mangostin	-8,9	-6,9
β-mangostin	-8,3	-6,5
γ-mangostin	-8,6	-6,9
Sunitinib	-7,9	-6,2
Sorafenib	-11,4	-
Bicine Molecule	-	-4,4

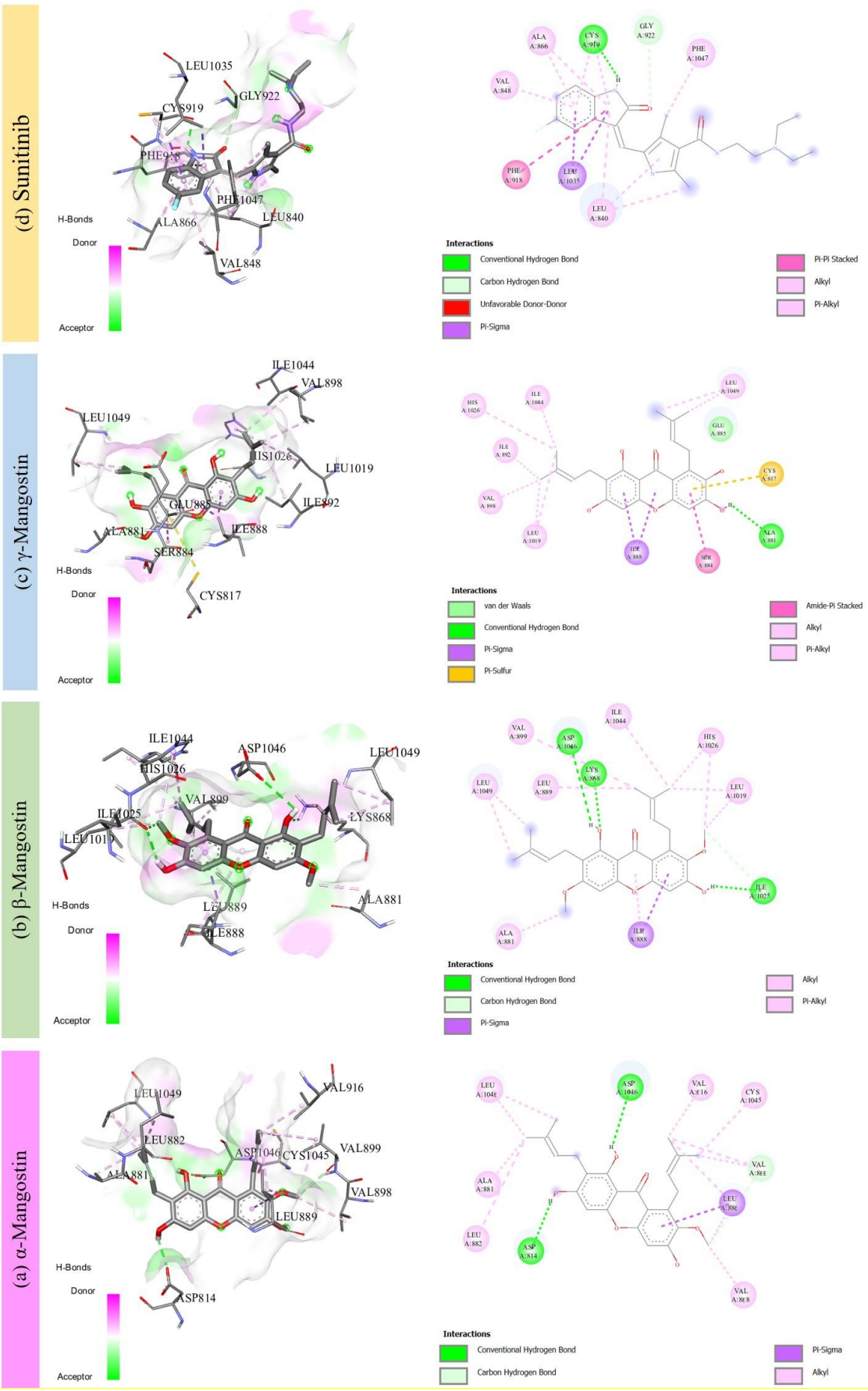

Figure 3. 3D (left) and 2D (right) visualization of (a) α-mangostin, (b) β-mangostin, (c) γ-mangostin, and (d) Sunitinib to VEGFR-2.

Table 3. Protein-ligan interaction of the proposed compound against VEGFR-2

Compound	Types of interaction		
	H-bond	Hydrophobic	Others
α-mangostin	ASP1046 (2.66 Å); ASP814 (2.29 Å)	LEU1049; ALA881; LEU882; VAL898; LEU889; VAL899; VAL916; CYS1045	Pi-sigma: LEU889 (3.71 Å) Carbon H-bond: VAL899 (3.40 Å)
β-mangostin	ASP1046 (2.88 Å) LYS868 (2.97 Å) ILE1025 (2.42 Å)	LEU1049; ALA881; ILE888; LEU1019; HIS1026; ILE1044; VAL899; LEU889	Pi-sigma: ILE888 (3.77 Å) Carbon H-bond: ILE1025 (3.33 Å)
γ-mangostin	ALA881 (2.30 Å)	ILE1044; HIS1026; ILE892; VAL898; LEU1019; LEU1049	Pi-sigma: ILE888 (3.91 Å; 3.87 Å) Pi-sulfur: CYS817 (5.75 Å)
Sunitinib	CYS919 (2.43 Å)	ALA866; VAL848; LEU840; PHE1047	Pi-sigma: LEU1035 (3.84 Å; 3.87 Å) Carbon H-bond: GLY922 (3.22 Å)
Sorafenib	ASP1046 (1.95 Å) VAL899 (2.89 Å) GLU885 (2.92 Å; 3.35 Å)	LEU1019; VAL898; ALA866; VAL848; VAL916; LYS868	Pi-sigma: LEU889 (3.61 Å); LEU1035 (5.74 Å) Pi-sulfur: CYS1045 (5.13 Å); CYS919 (5.33 Å) Pi-Pi T-shaped: PHE1047 (4.87 Å) Halogen: ILE1044 (3.16 Å; 3.70 Å) Carbon H-bond: LEU840 (5.39 Å); GLU917 (3.40 Å)

In Table 4, the proposed compounds show interactions with amino acid residues on NRP-1. α-mangostin formed three hydrogen bonds with TYR25, THR44 and TRP29, as well as a hydrophobic interaction with TYR25. In addition, the Pi-Pi T-shaped interactions formed at amino acids TYR25 and TRP29 indicated an interaction between the aromatic ring of the ligand and aromatic residues on the receptor. β-mangostin interacts with TRP29 and ILE143 via hydrogen bonding. TYR25 and TYR81 are involved in the Pi-Pi stacked interaction, which shows the interaction between the two aromatic ring systems of the ligand and the tyrosine residue. This interaction helps to increase binding stability through hydrophobic effects. TYR25 exhibits a Pi-Pi T-shaped interaction, which is a type of aromatic interaction that can increase the affinity of the ligand to the receptor through electrostatic interactions.

Table 4. Protein-ligan interaction of the proposed compound against NRP-1

Compound	Types of interaction		
	H-bond	Hydrophobic	Others
α-mangostin	TYR25 (2.72 Å); THR44 (2.51 Å) TRP29 (2.50 Å)	TYR25	Pi-Pi stacked: TYR25 (4.26 Å; 4.40 Å; 5.71 Å); TYR81 (4.90 Å); TRP29 (6.43 Å)
β-mangostin	TRP29 (2.83 Å) ILE143 (3.07 Å)	TYR25	Pi-Pi stacked: TRP29 (6.44 Å); TYR25 (5.51 Å; 4.37 Å; 4.45 Å); TYR81 (4.55 Å) Carbon H-bond: ASP48 (5.16 Å)
γ-mangostin	TYR25 (2.75 Å) THR44 (2.47 Å) TRP29 (2.51 Å)	TYR25	Pi-Pi stacked: TYR25 (4.27 Å; 4.41 Å; 5.72 Å); TYR81 (4.88 Å); TRP29 (6.43 Å)
Sunitinib	TYR81 (2.60 Å) THR77 (2.85 Å)	LYS79	Pi-Pi stacked: TRP29 (5.89 Å); TYR25 (5.41 Å) Pi-sigma: TYR25 (3.88 Å) Carbon H-bond: TRP29 (2.68 Å); LYS79 (3.68 Å)
Bicine molecule	TRP29 (2.78 Å) SER74 (2.75 Å) THR77 (2.67 Å)	-	-

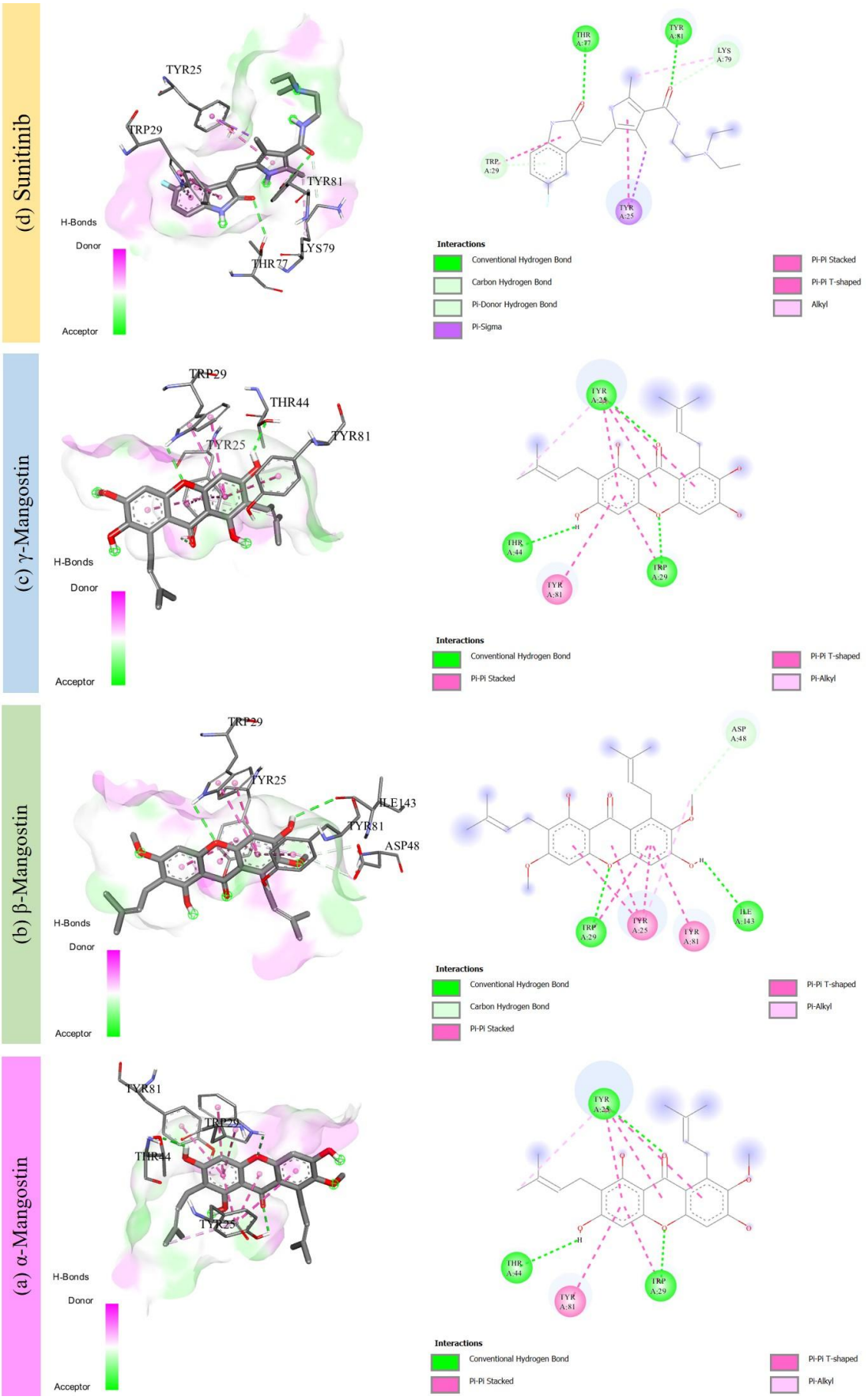

Figure 4. 3D (left) and 2D (right) visualization of (a) α-mangostin, (b) β-mangostin, (c) γ-mangostin, and (d) Sunitinib to NRP-1.

TYR25 also exhibits a Pi-Alkyl interaction, which involves the interaction of the aromatic ring of the ligand with the hydrocarbon side chain of a tyrosine residue. This interaction is hydrophobic in nature and helps to stabilise the ligand within the active site. γ-mangostin shows three hydrogen bonds with THR44, TYR25 and TRP29 and a hydrophobic interaction with TYR25. TYR81 and TYR25 form a pi-pi stacking interaction with the aromatic ring of the ligand. This interaction is important in stabilising the binding. TYR25 is also involved in Pi-Pi T-shaped interactions, which increase the stability of the complex through electrostatic interactions. Meanwhile, sunitinib forms two hydrogen bonds with TYR81 and THR77. Pi-Sigma and Pi-Pi stacked interactions with TYR25 played a role in binding stability, while alkyl interactions with LYS79 showed a hydrophobic contribution. Compared to sunitinib, α-mangostin showed the strongest interaction among other ligands.

This study shows that functional interactions in ligand-receptor complexes are strongly influenced by the presence of polar and hydrophobic amino acid residues interacting with ligands in the receptor active site. These interactions play an important role in stabilising the ligand-receptor complex and in determining the binding affinity of the ligand to the receptor. Therefore, compounds or ligands that are able to interact specifically with these key residues have the potential to inhibit the biological activity of the receptor protein and can therefore be developed as effective inhibitor candidates.

Conclusion

This study supports the hypothesis that α-, β- and γ-mangostin compounds derived from mangosteen fruit have potential as more potent inhibitors of VEGFR-2 and NRP-1 receptors compared to sunitinib. Molecular interaction analysis showed that the three compounds have a higher binding affinity to the active site of the receptor, and thus may be more effective in inhibiting VEGFR-2 and NRP-1 activity. With promising pharmacological properties, α-, β- and γ-mangostin can be developed as lead compounds in the design and optimization of VEGFR-2 and NRP-1 inhibitors for anti-angiogenesis therapy.

Recommendations

The docking results showed that α-, β- and γ-mangostins have high binding affinity towards VEGFR-2 and NRP-1. However, structural optimisation, such as side-chain modification, can be used to further increase the affinity and selectivity of the compounds towards the target receptors. Further validation is required to establish the pharmacological potential of these compounds, including molecular dynamics simulations to assess the stability of ligand-receptor complexes in a more realistic biological environment, experimental binding assays to determine the dissociation constant (Kd) of the ligand against VEGFR-2, and cell-based assays to assess the efficacy of angiogenesis inhibition. This study may be the first step in the development of α-, β- and γ-mangostin as anti-angiogenesis therapeutic candidates for patients with diabetic retinopathy.

Credit Authorship Contribution Statement

Melina Ayu Widiastuti: Writing – original manuscripts, Conceptualization, Methodology, Investigation, Data curation, Docking simulation, Funding acquisition, Project administration. **Supanji**: Writing – review & editing, Supervision, Formal analysis, Validation. **Ganjar Andhulangi**: Writing – review & editing, Docking Software, Visualization, Illustration, Formal analysis, Data curation, Resources, Validation.

Scientific Ethics Declaration

* The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

Conflict of Interest

* No potential conflict of interest was declared by the authors.

Data Availability

* The authors affirm that the data that substantiates the results of this study is included in the paper. If raw data files are required, they can be obtained from the corresponding author upon a reasonable request.

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References

AboulMagd, A. M., & Abdelwahab, N. S. (2021). Analysis of sunitinib malate, a multi-targeted tyrosine kinase inhibitor: A critical review. *Microchemical Journal*, *163,* 105926.

Ananto, A. D., Pranowo, H. D., Haryadi, W., & Prasetyo, N. (2024). Exploring the inhibition of SARS-COV-2 PLPRO: Docking and molecular dynamics simulation of flavonoid in red fruit papua and its derivatives. *Molekul*, *19*(3), 581.

Beltramo, E., & Porta, M. (2013). Pericyte loss in diabetic retinopathy: Mechanisms and consequences. *Current Medicinal Chemistry*, *20*(26), 3218–3225.

Chua, J., Lim, C. X. Y., Wong, T. Y., & Sabanayagam, C. (2017). Diabetic retinopathy in the Asia-Pacific. *Asia-Pacific Journal of Ophthalmology*, *7*(1), 3-16.

El-Kenawy, A. E., Hassan, S. M., & Osman, H. H. (2018). *Mangosteen* (*Garcinia mangostana* L (Vol.18,pp. 313–319). LWT.

El-Osta, A., Brasacchio, D., Yao, D., Pocai, A., Jones, P. L., Roeder, R. G., Cooper, M. E., & Brownlee, M. (2008). Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. *The Journal of Experimental Medicine*, *205*(10), 2409–2417,

El-Shazly, S. F., El-Bradey, M. H., & Tameesh, M. K. (2013). Vascular endothelial growth factor gene polymorphism prevalence in patients with diabetic macular oedema and its correlation with anti-vascular endothelial growth factor treatment outcomes. *Clinical and Experimental Ophthalmology*, *42*(4), 369–378.

Evalina, G. M., Bambang, P., Bambang, S. S., Wahyu, W., & Arbi, D. (2018). Microstructural characterization of the *Garcinia mangostana* fruit at different maturity level. *Journal of Natural Remedies*, *18*(2), 63–70.

Giacco, F., & Brownlee, M. (2010). Oxidative stress and diabetic complications. *Circulation Research*, *107*(9), 1058–1070.

Go, Y. J., Kalathingal, M., & Rhee, Y. M. (2023). Elucidating activation and deactivation dynamics of VEGFR-2 transmembrane domain with coarse-grained molecular dynamics simulations. *PLoS ONE*, *18*(2), e028178.

Hao, Z., & Sadek, I. (2016). Sunitinib: The antiangiogenic effects and beyond. *Oncotargets and Therapy*, *9*, 5495–5505.

Huang, H., He, J., Johnson, D., Wei, Y., Liu, Y., Wang, S., Lutty, G. A., Duh, E. J., Carmeliet, P., & Semba, R. D. (2014). Deletion of placental growth factor prevents diabetic retinopathy and is associated with AKT activation and HIF1α-VEGF pathway inhibition. *Diabetes*, *64*(1), 200–212.

Kaur, A., Kumar, R., & Sharma, A. (2024). Diabetic retinopathy leading to blindness- a review. *Current Diabetes Reviews*, *20*(9), e240124225997.

Kooi, C. W. V., Jusino, M. A., Perman, B., Neau, D. B., Bellamy, H. D., & Leahy, D. J. (2007). Structural basis for ligand and heparin binding to neuropilin b domains. *Proceedings of the National Academy of Sciences*, *104*(15), 6152–6157.

Kufareva, I., & Abagyan, R. (2011). Methods of protein structure comparison. *Methods in Molecular Biology, 857*, 231–257.

Li, J., Zhou, N., Luo, K., Zhang, W., Li, X., Wu, C., & Bao, J. (2014). In silico discovery of potential VEGFR-2 inhibitors from natural derivatives for anti-angiogenesis therapy. *International Journal of Molecular Sciences*, *15*(9), 15994–16011.

Li, X., Luo, F., Wang, S., Ni, E., Tang, X., Lv, H., Chen, X., Chen, L., & Yan, J. (2011). Monoclonal antibody against NRP-1 b1b2. *Hybridoma, 30*(4), 369–373.

Manni, S., Kisko, K., Schleier, T., Missimer, J., & Ballmer-Hofer, K. (2014). Functional and structural characterization of the kinase insert and the carboxy terminal domain in VEGF receptor 2 activation. *The FASEB Journal*, *28*(11), 4914–4923.

Miyamoto, K., Khosrof, S., Bursell, S., Rohan, R., Murata, T., Clermont, A. C., Aiello, L. P., Ogura, Y., & Adamis, A. P. (1999). Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition. *Proceedings of the National Academy of Sciences*, *96*(19), 10836–10841.

Mota, F., Fotinou, C., Rana, R. R., Chan, A. W. E., Yelland, T., Arooz, M. T., O'Leary, A. P., Hutton, J., Frankel, P., Zachary, I., Selwood, D., & Djordjevic, S. (2018). Architecture and hydration of the arginine-binding site of neuropilin-1. *FEBS Journal*, *285*(7), 1290–1304.

Murga, M., Fernandez-Capetillo, O., & Tosato, G. (2004). Neuropilin-1 regulates attachment in human endothelial cells independently of vascular endothelial growth factor receptor-2. *Blood*, 105(5), 1992–1999.

Nicklaus, M. C., Sitzmann, M., Filippov, I. V., Oellien, F., Bienfait, B., Voigt, J. H., & Sun, G. (2024, February 9). *Online SMILES translator*. Retrieved from https://cactus.nci.nih.gov/translate/.

Pham, Q. M., Le, T. T. H., Pham, T. H. M., Tran, Q. T., Lam, T., DO, Vu, T. T. L., & Pham, Q. L. (2022). Molecular docking tutorial using Autodock 4.2.6 on SARS-Cov-2 main protease for beginner. *Vietnam Journal of Science and Technology/Science and Technology*, *60(*6), 929–947.

Poerwanto, R., Efendi, D., Sobir, & Suhartanto, R. (2008) Improving productivity and quality of Indonesian mangosteen. *Acta Horticulturae*, *769*, 285-288.

Rahimi, N., & Costello, C. E. (2014). Emerging roles of post-translational modifications in signal transduction and angiogenesis. *Proteomics*, *15*(2–3), 300–309.

Rampogu, S., Baek, A., Park, C., Son, M., Parate, S., Parameswaran, S., Park, Y., Shaik, B., Kim, J. H., Park, S. J., & Lee, K. W. (2019). Discovery of small molecules that target vascular endothelial growth factor receptor-2 signalling pathway employing molecular modelling studies. *Cells*, 8(3), 269,

Reddy, M. A., Zhang, E., & Natarajan, R. (2014). Epigenetic mechanisms in diabetic complications and metabolic memory. *Diabetologia*, 58(3), 443–455.

Roth, L., Nasarre, C., Dirrig-Grosch, S., Aunis, D., Crémel, G., Hubert, P., & Bagnard, D. (2007). Transmembrane domain interactions control biological functions of neuropilin-1. *Molecular Biology of the Cell*, *19*(2), 646–654.

Saraswathy, S. U. P., Lalitha, L. C. P., Rahim, S., Gopinath, C., Haleema, S., SarojiniAmma, S., & Aboul-Enein, H. Y. (2022). A review on synthetic and pharmacological potential of compounds isolated from *Garcinia mangostana* linn. *Phytomedicine Plus*, 2(2), 100253.

Saravanan, V., Venkatalakshmi, B., & Rajendran, V. (2013). Automated red lesion detection in diabetic retinopathy. *IEEE Conference on Information & Communication Technologies (ICT)*, 6558096, 236–239,

Shintani, Y., Takashima, S., Asano, Y., Kato, H., Liao, Y., Yamazaki, S., Tsukamoto, O., Seguchi, O., Yamamoto, H., Fukushima, T., Sugahara, K., Kitakaze, M., & Hori, M. (2006). Glycosaminoglycan modification of neuropilin-1 modulates VEGFR2 signaling. *The EMBO Journal*, 25(13), 3045–3055.

Shintani, Y., Takashima, S., Kato, H., Komamura, K., & Kitakaze, M. (2009). Extracellular protein kinase CK2 is a novel associating protein of neuropilin-1. *Biochemical and Biophysical Research Communications*, *385*(4), 618–623.

Simons, M., Gordon, E., & Claesson-Welsh, L. (2016). Mechanisms and regulation of endothelial VEGF receptor signalling. *Nature Reviews Molecular Cell Biology*, *17*(10), 611–625.

Szkaradek, N., Sypniewski, D., Żelaszczyk, D., Gałka, S., Borzdziłowska, P., Marona, H., & Bednarek, I. (2019). Influence of new synthetic xanthones on the proliferation and migration potential of cancer cell lines in vitro. *Anti-Cancer Agents in Medicinal Chemistry*, *19*(16), 1949–1965.

Uniewicz, K. A., Ori, A., Ahmed, Y. A., Yates, E. A., & Fernig, D. G. (2014). characterisation of the interaction of Neuropilin-1 with heparin and a heparan sulfate mimetic library of heparin-derived Sugars. *PeerJ*, 2, e461.

Wulan, F. F., Wahyuningsih, T. D., Astuti, E., & Prasetyo, N. (2023). Towards targeting EGFR and COX-2 inhibitors: Comprehensive computational studies on the role of chlorine group in novel thienyl-pyrazoline derivative. *Journal of Biomolecular Structure and Dynamics*, *42*(19), 9857–9872,

Zachary, I. C. (2011). How neuropilin-1 regulates receptor tyrosine kinase signalling: the knowns and known unknowns. *Biochemical Society Transactions*, *39*(6), 1583–1591.

Zhao, Y., & Singh, R. P. (2018). The role of anti-vascular endothelial growth factor (Anti-VEGF) in the management of proliferative diabetic retinopathy. *Drugs in Context*, *7*, 1–10.

Zheng, Y., He, M., & Congdon, N. (2012). The worldwide epidemic of diabetic retinopathy. *Indian Journal of Ophthalmology*, *60*(5), 428,

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