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Interactions of Potent A. Comosus Compounds with Thromboxane A2 Receptor: a Molecular Docking and Pharmacokinetic/Toxicity Prediction Study

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Abstract: Thromboxane A2 (TxA2) is a key signaling molecule involved in cardiovascular disease, promoting platelet aggregation, vasoconstriction, and cell proliferation. TxA2 may trigger cell proliferation in arterial walls, thereby contributing to atherosclerosis. Prior studies show that A. comosus is likely to be beneficial to the cardiovascular system by protecting cell membrane integrity and enhancing cardiac systolic and diastolic function. Using molecular docking, the target proteins of potent A. comosus chemical compounds with pharmacological activity can be precisely predicted and identified based on ligand-protein interaction scores and models generated by AutoDock 4.2 in AutoDock Tools. The results revealed that Hydroxysitosterol, 5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol, and N,N'-Bis(4-hydroxy-3-methoxycinnamoyl)-1,4-butanediamine can be potential compounds from A. comosus with alternating cardiovascular disease based on binding energy values and TxA2 inhibition interactions. These potential compounds can inhibit the activity of TxA2 by interacting with energy values of -11.35, -10.33, and -9.21 kcal/mol. Pharmacokinetic predictions revealed that the potential compounds are absorbed in the intestine, exhibit strong plasma protein binding, and are inhibitors of CYP3A4 and CYP2C9. Prediction of toxicity reveals that the potential compounds fall into the class of drug-induced acute liver failure with medium carcinogenic risk. 7alpha-Hydroxysitosterol, N,N'-Bis(4-hydroxy-3-methoxycinnamoyl)-1,4butanediamine, and 5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol are good lead compounds to synthesize as an alternative inhibitor of TxA2..

Keywords: A. comosus, Thromboxane A2, Molecular docking.

Introduction

Herbal medicines and phytotherapies have been practiced since prehistoric times, contributing to the development of novel pharmaceuticals and advancing human health. Numerous phytochemicals with established or potential biological activities have been identified. The therapeutic potential of Ananas comosus is well documented in the literature (Ahn, 2017). Ananas comosus has a longstanding role in traditional medicine, with anecdotal and folkloric reports describing its use in treating gastrointestinal disorders, arthritis, typhoid infections, hypolipidemia, inflammation, gastric pain, and malaria. Bromelain, the primary bioactive component of Ananas comosus, demonstrates efficacy against inflammation, cancer, thrombus formation, and dermatological conditions (Ajayi et al., 2022). Further studies indicate that the leaves and fruits of Ananas comosus contain a wide array of secondary metabolites. High-performance liquid chromatography with diode-array detection has identified various phenolic compounds, including hydroxycinnamic acids, hydroxycinnamoylquinic acids, phenylpropanemonoglycerides, phenylpropanediglycerides, phenylpropanoidglycosides, and flavones. Liquid chromatography-mass spectrometry analysis has revealed the presence of additional compounds, including aza-serine, isomaltose, 4-S-aminopentanoic acid, 4-hydroxy pelargonic acid, betamethasone, digoxigenin monodigitoxoside,

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methyldopate, 3,4,5-trimethoxycinnamic acid, 4-methoxycinnamic acid, eicosanedioic acid, cyclohexasiloxane, hexadecanoic acid, eicosanoic acid, and campesterol (Debnath et al., 2023).

Evidence indicates that Ananas comosus may exert beneficial cardiovascular effects. In a rat model, hydroalcoholic extracts of Ananas comosus protected the myocardium from isoproterenol-induced structural and functional damage, maintained cell membrane integrity, and improved both systolic and diastolic cardiac function. Administration of 200 mg per kg of extract reduced infarct size, coagulative necrosis, infiltration of inflammatory cells, and myocardial edema (Saxena, 2024). In the study, Sprague-Dawley rats received losartan (30 mg/kg for 10 days, orally) and varying doses of Ananas comosus (100, 250, and 500 mg/kg for 30 days, orally), followed by isoprenaline (150 mg/kg). Antioxidant activity was evaluated through histopathological and biochemical analyses. Cardioprotective effects were evidenced by elevated levels of lactate dehydrogenase and creatine kinase, as well as significant increases in superoxide dismutase and catalase enzyme activities. The observed efficacy was attributed to bromelain, which enhanced these biomarkers and was associated with the pharmacological intervention (Attuluri S, et al., 2017).

Scientists are keen to unravel the enigma of chemical influences on macromolecules and their targets. Identifying a substance's target and understanding its mechanism early on can help transform it into a more effective treatment. Bioinformatics can help by revealing prospective targets through structural comparisons with known chemicals in large databases. Identifying an active compound's molecular target is critical for increasing its effectiveness in the body. However, identifying these targets and understanding their relationships can be time-consuming and resource-intensive. Computer-based technologies, such as in silico experiments and molecular docking, help to accelerate and streamline the search process. Recent breakthroughs have allowed researchers to identify interesting molecules with amazing rapidity (Talele et al., 2010).

Molecular docking relies on scoring functions rooted in molecular mechanics, such as repulsion, hydrogen bonding, electrostatics, and desolvation, to assess the strength of ligand binding to its target protein. This approach sheds light on a compound's mode of action. Using this method, scientists can predict and pinpoint the target proteins of active chemicals in A. comosus, particularly those affecting the cardiovascular system, by leveraging AutoDock 4.2 scores and models. The latest docking techniques, powered by machine learning, have significantly improved the accuracy of these predictions (Forli et al., 2016). This study aimed to identify potent compounds in A. comosus with potential as Thromboxane inhibitor agents using molecular docking analysis performed with AutoDock 4.2 in the AutoDock Tools program. The effectiveness of these compounds was further evaluated through pharmacokinetic and toxicity predictions.

Materials And Methods

Preparation of macromolecules and ligands

Thromboxane (PDB ID: 6IIU) was identified through SuperPred, which is a web server that links the chemical similarity of drug-like molecules to molecular targets and treatment approaches based on the similar property principle. The macromolecule obtained the structure from PDB (https://www.rcsb.org) in .pdb format. The three-dimensional structure of chemical compounds as ligands was produced with VegaZZ in .pdb format. The ligands have been adjusted using the AutoDock 4.2 program with AutoDock Tools (ADT). ADT separates the native ligand and water molecules previous to adding hydrogen atoms.

Validation Method

Validation was performed on the native ligand to identify an appropriate conformation. The previously produced protein was redocked with the native ligand. The conformation docking results are compared with the native ligand conformation according to the crystallographic structure, which is presented as root-mean-square deviation (RMSD). If the RMSD values are less

than 2.5 Å, the structure's conformational alignment is acceptable. A value closer to 0 indicates greater alignment.

Molecular Docking

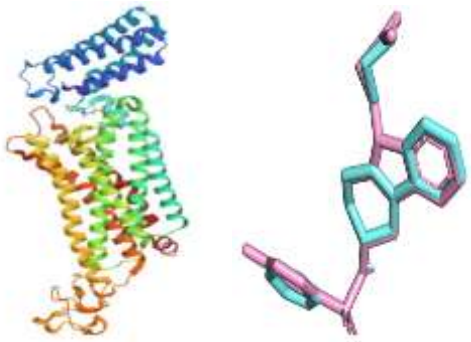
The docking is carried out using the AutoDock 4.2 program with AutoDock Tools (ADT). Setting docking with rigid macromolecular format as well as GA Runs (200) and Population Size (150). Then select the Output submenu for Lamarckian GA (4.2). The results docking all the test ligands resulted in $G_{binding}$ (kcal/mol), which was then analyzed and visualized using the Discovery Studio Visualizer Biovia to see the shape or model of the anchorage formed.

Prediction of Pharmacokinetic and Toxicity Parameters

The pharmacokinetic and toxicity parameters were predicted online using the ADMETlab 3.0 web tool (https://admetlab3.scbdd.com/server/evaluationCal). It is commonly acknowledged that probable substances' absorption, distribution, metabolism, excretion, and toxicity should be assessed for systematic as well as some physical features and medicinal chemistry compatibility. It is done by entering the SMILES code of the compounds collected from PubChem and selecting ADMET Evaluation.

Results And Discussion

The PDB ID: 6IIU represents the crystal structure of the human thromboxane A2 receptor bonded to ramatroban. This macromolecule has a crystallographic (X-ray diffraction) structure and forms a compound with ramatroban, with a resolution of 2.5 Å. Optimization of prepared macromolecules in AutoDock Tools involves determining the parameters of the grid box. The grid box represents the spatial region where native ligands or active compounds can adopt conformations when bound to a target protein. The grid box is defined to identify the coordinates of the active sites of macromolecules. The process includes setting the grid centre coordinates and grid size (Rachmania et al., 2015). In this study, the grid centre coordinates were set to x = 25.175, y = 164.914, and z = 148.502, with a grid size of 40 × 40 × 40.



(a) **(b)**

Figure 1. Human thromboxane A2 receptor (PDB ID: 6IIU) (a); Overlays of re-docking ligand (pink) and reference ligand of crystallography (blue) at 6IIU (b)

The three-dimensional structure of the test ligands was obtained by converting the Canonical SMILES line notation to .pdb format using an energy minimization approach (Helson, 2000). The preparation of the test ligands involved removing water molecules to prevent interference with the docking process, thereby facilitating mathematical calculations in molecular docking (Tjahyono and Hamzah, 2013). Furthermore, it is necessary to add hydrogen atoms to adjust the docking process to approach the pH conditions in the body and to be able to reappear hydrogen atoms in the molecule to observe the hydrogen bonds that appear in the interaction of the ligand with the target receptor (Drie, 2005). Molecular docking was performed on 3 ligands with bond energy values shown in Table 1.

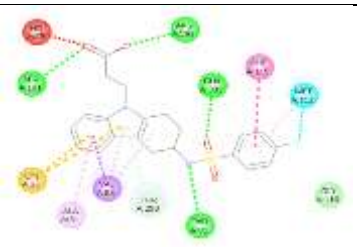
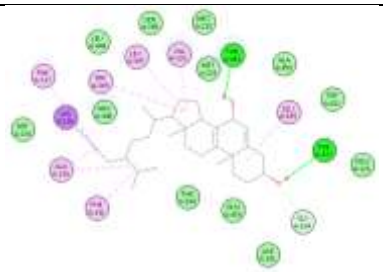
Table 1. The results of molecular docking

Ligands	Bond energy (ΔG= kcal/mol)	Inhibitory constant (Ki= nM)
Ramatroban	-12.46	0.741
7alpha-Hydroxysitosterol	-11.35	4.76
5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol	-10.33	26.80
N,N'-Bis(4-hydroxy-3-methoxycinnamoyl)-1,4-butanediamine	-9.21	177.78

Researchers analyse ligand structures to design molecules that fit more precisely into a target or receptor's binding pocket. This precision depends on the number of active torsions each ligand possesses. Ramatroban, as a native ligand, features six rotatable bonds, while 7alpha-Hydroxysitosterol, 5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol, and N,N'-Bis(4-hydroxy-3-methoxycinnamoyl)-1,4-butanediamine—the top-performing test ligands—have 8, 5, and 13 rotatable bonds, respectively. A higher number of active torsions can lengthen the search for the optimal conformation, making molecular docking more time-consuming and complex. Identifying these active torsions helps pinpoint which bonds can rotate during the docking process (Rachmania et al., 2015).

The accuracy of molecular docking is determined by the extent to which the interaction type of the experimental ligands with the macromolecule matches that of the native ligand. Table 2 presents the types of interactions observed in the experimental ligands. Hydroxysitosterol, 5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol, and N,N'-Bis(4-hydroxy-3-methoxycinnamoyl)-1,4-butanediamine had the lowest bond energy values; nevertheless, they did not have a lower binding energy value than the native ligand, which had a value of -12.46 kcal/mol as well, and the estimated inhibition constant value is particularly effective at low concentrations, which had a value of 0.741 nm.

Table 2. The visualization of bonding interactions between potential ligands and the native ligand

Ligands	Hydrogen bond Interactions	Hydrophobic bond Interactions	Visualization
Ramatroban	T81, S181, G301	T298, V85, A31, H89, F115, M112, G116	
7alpha-Hydroxysitosterol	F222, T451	F137, T289, L447, V192, L185, F141, A138, H196	

5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol	M219	A138, F137, H196, T289, L447, V192	
N,N'-Bis(4-hydroxy-3-methoxycinnamoyl)-1,4-butanediamine	T451, H196, R448, T188, C142, F141, G184	L185, M219, T289, I455, V192	

Based on physicochemical parameter screening, every one of the potential compounds had a molecular weight of less than 500 kDa. Compounds under 500 kDa typically slip more easily through cell membranes to reach their targets. Another important factor is the Synthetic Accessibility (SA) score, which measures the ease of creating a compound in the laboratory. An SA score below 6 signals that synthesis should be relatively simple and easy (Baber, 2004). Despite its enough molecular weight, 5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol boasts a high SA score, suggesting it is hard to synthesize into a drug product.

Table 3. Physicochemical parameters.

Compounds	**Physicochemical parameters**						
	MW	**nHA/ nHD**	**nRot/ nRing**	**Flex**	**TPSA**	**Log P**	**SA Score**
Ramatroban	416.12	6/2	6/4	0.25	88.4	1.647	Easy
7alpha-Hydroxysitosterol	430.38	2/2	6/4	0.3	40.46	6.275	Easy
5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol	428.33	3/1	4/6	0.167	38,69	4,98	Hard
N,N'-Bis(4-hydroxy-3-methoxycinnamoyl)-1,4-butanediamine	440.19	8/4	13/2	0.812	117.12	2.181	Easy

According to pharmacokinetic predictions in Table 4, the potential compounds are absorbed in the intestine, have significant plasma protein binding, and inhibit CYP3A4 and CYP2C9. Ramatroban has a low clearance rate (5 mL/min/kg), whereas all strong chemicals have clearance rates that are greater than ramatroban's, allowing them to be quickly cleared by the body. Toxicity prediction suggests that the potential compounds are classified as Drug-induced liver injury (DILI), with a moderate carcinogenic and human hepatotoxicity risk.

Table 4. Pharmacokinetics and toxicity parameters

Compounds	Absorption		Distribution		Metabolism		Excretion		Toxicity				
	Caco-2 Perm	HIA	PPB	VD	3A4 Inh	2C9 Inh	CL	$T_{1/2}$	DILI	ROAT	Carcino-genicity	Human Hepato-toxicity	DIN
Ramatroban	-5.326	+	97.9%	0.282	yes	yes	1.602	0.99	high	moderate	high	high	high
7alpha-Hydroxysitosterol	-5.282	+	89%	-0.357	yes	yes	12.484	0.71	moderate	low	moderate	moderate	moderate
5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol	-5.274	+	98.8%	1.225	yes	yes	15.1	1.18	low	low	moderate	moderate	low
N,N'-Bis(4-hydroxy-3methoxycinnamoyl)-1,4-butanediamine	-5.235	+	96.7%	0.223	yes	yes	7.727	1.04	moderate	low	moderate	moderate	moderate

Discussion

Macromolecule preparation is the procedure of preparing an experimental protein for molecular docking by downloading the .pdb file from the Protein Data Bank. The macromolecule was chosen based on the possible drugs' ability to target Thromboxane action (TxA2 Inhibitor) using Super Prediction Anatomical Therapeutic Chemical (ATC). Macromolecular needs include crystallographic structures (X-ray diffraction) that are larger and more precise. Campbell (2002) also considers conformational resolution with a maximum RMSD value of 2.5. TxA2 inhibitor macromolecules in .pdb format contain native ligand complexes and crystallized water molecules. The native ligand and water molecule must be removed from the macromolecule so as not to interfere with the molecular docking process (Campbell, 2002).

Ramatroban, as a native ligand, is removed to obtain individual macromolecules that will be docked with the test ligand. Water molecules are removed because they can mediate the interaction between the ligands and macromolecule, which can affect the complexity of calculations in molecular docking. In addition, the removal of non-residue amino acid molecules and the addition of loading agents were also carried out to adjust the chemical environment. Residues other than amino acids are removed because they can interfere with the interaction between the ligand and amino acid residues on the active site of the macromolecule. The removal of residues other than amino acids needs to be reviewed if the macromolecule contains a chromoprotein (Zinc ion) or cofactor component that is retained in its main structure (Hypercube, 2002).

Method validation was conducted by re-docking the native ligand and macromolecule using a rigid docking approach. In this method, the macromolecule remains rigid to prevent changes in the binding site conformation during redocking, while the ligand retains flexibility (Tjahjono and Hamzah, 2013). The primary validation parameter in molecular docking is the Root Mean Square Deviation (RMSD) value, which compares the conformation of the original ligand after redocking with its crystallographic conformation (Jain and Nicholls, 2008).

The accuracy of molecular docking is determined by the extent to which the interaction type of the experimental ligands with the macromolecule matches that of the native ligand. Table 2 presents the types of interactions observed in the experimental ligands. Hydroxysitosterol, 5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol, and N,N'-Bis(4-hydroxy-3-methoxycinnamoyl)-1,4-butanediamine exhibited the lowest bond energy values. Ramatroban inhibits Thromboxane (TxA2) through the mechanism described below.

Ramatroban was originally developed as a thromboxane prostanoid (TP) antagonist for the treatment of thrombosis and coronary artery disease. It was later identified as an inhibitor of thromboxane A2 (TXA2)-induced bronchoconstriction. The carboxylic acid group of ramatroban is positioned toward the extracellular surface and forms strong polar interactions with

helices II and VII. These include two salt bridges with residues H89 and R295 and a hydrogen bond with S181. The nitrogen atom in the sulfonamide group forms a hydrogen bond with the side chain of T81. The oxygens of the sulfonamide group form two hydrogen bonds with the side chain of Q301 and the main chain of L78. The phenyl ring of the benzenesulfonamide group participates in multiple hydrophobic interactions with residues M112, F115, G116, W258, and L294. The 1,2,3,4-tetrahydrocarbazole ring inserts into a cavity formed by helices I, II, III, and VII, making hydrophobic contacts with A31, F34, V85, M112, L294, and T298. These molecular interactions may inhibit receptor function by restricting conformational changes associated with activation (Fan et al., 2019). Ramatroban possesses antagonistic effects against the thromboxane A2 (TXA2) receptor, with an IC50 value of 8.4 nM and a binding affinity measure or inhibition constant of 0.58 nM (Ulven, 2005).

Drug-likeness evaluates a compound's suitability for clinical trials by assessing its physicochemical properties. Rotatable bonds influence molecular flexibility and bioavailability, with higher counts generally leading to reduced absorption. Lipinski's rule of five recommends fewer than 10 rotatable bonds for optimal oral absorption. Among the lead phytochemicals, N, N'-Bis(4-hydroxy-3-methoxycinnamoyl)-1,4-butanediamine had the highest number of rotatable bonds at 13. Hydrogen bond donors (HBD) and acceptors (HBA) are key descriptors for predicting oral bioavailability. Blood-brain barrier penetration depends on lipophilicity, molecular size, and the number of HBD and HBA. Higher HBD and HBA counts reduce BBB permeability. Lipinski's rule of five recommends no more than 5 HBD and 10 HBA for optimal bioavailability. All potent compounds in this study met these criteria, with more HBA than HBD (Janicka et al., 2024).

The total polar surface area (TPSA) influences drug permeability and absorption. A TPSA below 140 Å² favors intestinal absorption, while a TPSA below 90 Å² supports blood-brain barrier penetration. Higher TPSA values reduce permeability. All potent compounds in this study had TPSA values consistent with potential drug leads. Lipophilicity, measured by the n-octanol-water partition coefficient (LogP), reflects compound hydrophobicity. Compounds with LogP values above 5 often have poor solubility, tissue accumulation, and rapid metabolism. Lipinski's guidelines recommend a LogP of 5 or less. Among the compounds studied, 7alpha-Hydroxysitosterol had the highest LogP (Lipinski et al., 2012).

Based on physicochemical parameter screening, every one of the potential compounds had a molecular weight of less than 500 kDa. Compounds under 500 kDa typically slip more easily through cell membranes to reach their targets. Another important factor is the Synthetic Accessibility (SA) score, which measures the ease of creating a compound in the laboratory. An SA score below 6 signals that synthesis should be relatively simple and easy (Baber, 2004). Despite its enough molecular weight, 5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol boasts a high SA score, suggesting it is hard to synthesize into a drug product.

Human Intestinal Absorption (HIA) quantifies the extent of intestinal absorption based on the ratio of bioavailability to excretion. HIA is categorized as adequate at 20–70% (+) and good at 70–100% (++). The Caco2 assay predicts drug permeability through intestinal epithelial cells derived from human colon adenocarcinoma, utilizing multiple in vitro transport pathways. Caco-2 permeability is classified as high (>70 nm/s), medium (4–70 nm/s), or low (<4 nm/s) (Cheng *et al*., 2013). Plasma Protein Binding (PPB) reflects the degree to which a drug molecule binds to plasma proteins; values below 90% indicate weak binding, while higher values indicate strong binding. The volume of distribution relates drug concentration in blood plasma to the total amount of drug in the body, with an optimal range of 0.04–20 L/kg (Xiangya, 2021).

Inhibition of the CYP2C19 and CYP2C9 enzymes can increase plasma protein concentrations, potentially leading to adverse effects (Van Booven *et al*., 2010). CYP2D6 is primarily responsible for the metabolism of a wide range of drugs and chemical compounds (Bertilsson *et al*., 2002). This enzyme is distributed across various tissues, with the highest expression

in the liver (Ali et al., 2013). CYP3A4 plays a central role in hepatic metabolism by catalyzing the oxidation of small organic molecules, thereby facilitating their elimination from the body (Dai et al., 2001; Oyesakin *et al*., 2018).

Clearance (CL) is used to determine the maintenance dose required to achieve a target plasma or therapeutic concentration. High clearance is defined as values greater than 15 mL/min/kg, while low clearance is defined as values less than 5 mL/min/kg. The half-life ($T_{1/2}$) estimates the time needed for the drug concentration in plasma to decrease by half during elimination. A short half-life is less than 3 hours, whereas a long half-life exceeds 3 hours. All tested ligands exhibit short half-lives (Xiangya, 2021).

Drug-induced liver injury (DILI) refers to acute liver failure resulting from drug exposure and is associated with direct dose-dependent hepatotoxicity. Hepatotoxicity is categorized as either high risk or no risk. All potential compounds identified in A. comosus are classified as having a risk of hepatotoxicity and are considered moderately carcinogenic (Xiangya, 2021).

Acute rat oral toxicity (ROAT) is important in understanding hazard identification and drug risk management. This toxicity is often measured by the 50% lethal dose (LD_{50}), the amount of chemical that is expected to cause death in 50% of treated animals in a period of time. An LD50 of 500 mg/kg indicates a substance is slightly toxic or moderately toxic to humans and animals, depending on the specific classification system used. Generally, a substance with an LD50 of 500 mg/kg is considered moderately toxic by some standards, or on the cusp of being slightly toxic by others (Deora et al., 2010). Drug-induced nephrotoxicity (DIN) happens when some drugs harm the kidneys and is a significant cause of acute kidney injury, particularly in hospitalized patients. Common drugs include NSAIDs, antibiotics, blood pressure meds, and chemotherapeutic treatments. Mild cases may be asymptomatic, while severe cases can cause lethargy, edema, abnormal urine, or confusion (Kramer and Karpa, 2017). The result of DIN screening indicates the risk that potent compounds may cause mild kidney damage.

Conclusions

Molecular docking analysis indicates that compounds from A.comosus may regulate TxA2 activation by binding with Gibbs free energy values of -11.35, -10.33, and -9.21 kcal/mol. Pharmacokinetic predictions showed that the potential compounds are absorbed in the intestine, have significant plasma protein binding, and inhibit CYP3A4 and CYP2C9. The toxicity parameters indicated that the potential compounds are classified as Drug-induced liver injury (DILI), with a moderate carcinogenic and human hepatotoxicity risk. 7alpha-Hydroxysitosterol, N,N'-Bis(4-hydroxy-3-methoxycinnamoyl)-1,4butanediamine, and 5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol are promising compounds for synthesis as alternative TxA2 inhibitors.

Conflict of Interest: The author declares that there are no conflicts of interest concerning the publication of this article.

References

Ahn, K., 2017. The worldwide trend of using botanical drugs and strategies for developing global drugs. BMB.Rep.50(3),111–116.doi:10.5483/bmbrep.2017.50.3.221.

Ajayi, A.M., Coker, A.I., Oyebanjo, O.T., Adebanjo, I.M., Ademowo, O.G., 2022. Ananas Comosus (L.) Merr. (pineapple) Fruit peel extract demonstrates antimalarial, anti-nociceptive, and anti-inflammatory activities in experimental models. J. Ethnopharmacology. 282, 114576.doi: 10.1016/j.jep.2021.114576.

Attuluri S, et al. Potency evaluation of combined therapy of losartan and Ananas comosus during isoprenaline-mediated cardiac dysfunction in rats. World Journal of Pharmacy and Pharmaceutical Sciences. 2017;6(8).

Baber JC, Feher M. Predicting Synthetic Accessibility: Application in Drug Discovery and Development. Mini Rev Med Chem. 2004; 4:681–692. doi: 10.2174/1389557043403765.

Bertilsson, L., Alm, C., De Las Carreras, C., Widen, J., Edman, G., Schalling, D. (1999). Debrisoquine hydroxylation polymorphism and personality. Lancet 333, 555.

Campbell, N.A. 2002. Biologi Edisi Kelima Jilid 1. Jakarta: Erlangga.

C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney. 2012. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev., 64 (1) (2012), pp. 4-17, https://doi.org/10.1016/S0169-409X(96)00423

Dai, D., Tang, J., Rose, R., Hodgson, E., Bienstock, R.J., Mohrenweiser, H.W., dan Goldstein, J.A. 2001. Identification of variants of CYP3A4 and characterization of their abilities to metabolize testosterone and chlorpyrifos. *J. Pharmacol. Exp. Ther*. 299: 825–831.

Debnath, B., Singh, W.S., Manna, K., 2023. A phytopharmacological review on Ananas comosus.Adv.Tradit.Med. 23(2), 291–298.

Deora PS, Mishra CK, Mavani P, Asha R, Shrivastava B, Rajesh KN. Effective alternative methods of LD50 help to save a number of experimental animals. J Chem Pharm Res. 2010;2(6):450–453.

Drie, JH. 2005. Pharmacophore-based virtual screening: a practical perspective. Boca raton: Taylor and Francis group, 157-205.

Fan H, Chen S, Xiaojing, ShuoHan, Zhang, Weiliang, et al., 2019. Structural basis for ligand recognition of the human thromboxane A2 receptor. Nature Chemical Biology: VOL15, JANUARY 2019. 27-33: https://doi.org/10.1038/s41589-018-0170-9.

Jain, A. N., Nicholls, A. 2008. Recommendations for evaluations of computational methods. *J. Compt. Aided Mol.* 22: 133-139.

Janicka, M. Sztanke, K. Sztanke. 2024. Modeling the blood-brain barrier permeability of potential heterocyclic drugs via biomimetic IAM chromatography technique combined with QSAR methodology. Molecules, 29 (2) (2024), p. 287, 10.3390/molecules29020287.

Kramer R, Karpa K. Drug-Induced Acute Kidney Injury: A Standardized Patient Case for Clerkship Students. *MedEdPORTAL*. 2017;13:10553.

Oyesakin Y.M., George D.E., Fadare R.Y., Idris A.Y., dan Fadare O.A. 2018. Molecular Docking and In-Silico ADME Prediction of Substituted (E)- 4-Styryl-7,8-dihydroquinazolin-5(6H)- ones and 5-((E)-Styryl)pyrimidine[4,5-d]pyrimidine-2,4(1H,3H)-diones as Potential SERT Inhibitors and Antidepressants. *American Journal of Pharmacological Sciences*. 6(1): 25- 32.

Rachmania RA, Supandi, Christina FA. (2016). Analisis Penambatan Molekul Senyawa Flavonoid Buah Mahkota Dewa pada Reseptor α-Glukosidase Sebagai Antidiabetes. Pharmacy 13(2): 239-251.

Saxena P, Panjwani D. Cardioprotective potential of hydro-alcoholic fruit extract of Ananas comosus against isoproterenol-induced myocardial infarction in Wistar Albino rats. Journal of Acute Disease. 2024;6(3):228-34.

Tjahjono DH, and Hamzah N. 2013. Studi Hubungan Kuantitatif Struktur-Aktivitas, Fitur Farmakofor dan *Docking* Molekuler Senyawa Turunan Pirazolo-Pirimidin Sebagai Inhibitor Mer Torsin Kinase. *Acta Pharmaceutica Indonesia* 38(1): 1-10.

Ulven T, Kostenis E: Minor structural modifications convert the dual TP/CRTH2 antagonist ramatroban into a highly selective and potent CRTH2 antagonist. J Med Chem. 2005 Feb 24;48(4):897-900. doi: 10.1021/jm049036i.

Van Booven, D, Marsh, S, McLeod, H, Carrillo, M.W., Sangkuhl, K, Klein, TE, and Altman, R.B. 2010. Cytochrome P450 2C9-CYP2C9. Pharmacogenetics. Genomics. 20: 277–281.

Xiangya School of Pharmaceutical Sciences. 2021. ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties. Nucleic Acids Res, 2021, 49(W1): W5-W14. PMID:33893803.