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Molecular Docking Simulation of the antisickling activity of Naringenin-7-O-glucoside and Kaempferol-3-O-glucoside from *Uapaca heudelotii* Baill. (Phyllanthaceae) and their ADMET profile

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ABSTRACT

Introduction
Sickle cell disease is a genetic disease that affects the hemoglobin in red blood cells. The symptoms of this public health problem include anemia, painful crises, and an increased risk of infections. In the Democratic Republic of the Congo, the medicinal plant species *Uappaca heudelotii,* which has been reported to have antisickling activity in vitro constitutes a source of natural antisickling agents for potential clinical applications in sickle cell disease management.

Purpose
This study aimed to investigate the potential of two secondary metabolites (Naringenin-7-O-glucoside and Kaempferol-3-O-glucoside) from *Uappaca heudelotii* in treating sickle cell disease by targeting specific receptors (3NFY, 3WCU, 5VTB, and 7EJ1) associated with the condition.

Methods
Naringenin-7-O-glucoside and Kaempferol-3-O-glucoside from *U. heudelotii* were evaluated for their interaction with receptors associated with sickle cell disease namely 3NFY, 3WCU, 5VTB, and 7EJ1 using molecular docking simulation. Discovery Studio 2021 (Biovia) software package was used to prepare the receptor, to edit the binding site, and to visualize the results of docking. SWISS ADME and PKCSM bioinformatics tools were utilized for assessing physicochemical parameters and pharmacokinetic properties, respectively.

Results
Naringenin-7-O-glucoside and Kaempferol-3-O-glucoside exhibited significant interactions with the receptors; Both compounds formed hydrogen bonds with the receptors, indicating strong binding affinity; Naringenin-7-O-glucoside formed 4, 1, 6, and 3 hydrogen bonds with receptors 3NFY, 3WCU, 5VTB, and 7EJ1 respectively; Kaempferol-3-O-glucoside formed 5, 5, 8, and 2 hydrogen bonds with the same receptors respectively, indicating a higher number of interactions.

Conclusions
The study confirmed the potential of Naringenin-7-O-glucoside and Kaempferol-3-O-glucoside from *U. heudelotii* as effective agents against sickle cell disease. These compounds demonstrate promising antisickling properties by inhibiting hemoglobin polymerization and the Rapoport-Lübering shunt, rehydrating erythrocytes, and increasing fetal hemoglobin levels.

INTRODUCTION

Sickle cell disease affects the hemoglobin in red blood cells. The symptoms of this widespread genetic disease include anemia, painful crises, and an increased risk of infections (Jacques Elion, 2020). According to a report by the WHO, nearly 5% of the world's population carries a gene responsible for abnormal hemoglobin (Thiam et al., 2017), which has led to increased morbidity and mortality in developing countries (Yembeau et al., 2022). Most people with this disease live in sub-Saharan Africa, with prevalences varying between 10 and 40%. Various studies have been conducted to evaluate anti-sickling activities from plants, especially those from the Congo Forest basin, considering the richness of the flora, the standard of living of the population, and the important role that traditional medicine plays in the community. Some studies have focused on anti-sickling plants such as Ngunde-te-Ngunde et al., 2020 and Kitadi et al., 2020. *Uappaca heudelotii* is an evergreen, dioecious, small to medium-sized tree reaching 20(-30) m in height, with an 8 m branchless bole, normally straight and cylindrical, up to 100 cm in diameter, with stilt roots reaching 3 m in height. The bark surface is scaly, grey-brown, with inner bark ranging from pinkish to pale reddish-brown, secreting a red exudate. The crown is fairly dense and densely branched, with twigs having tufts of reddish hairs in leaf axils and conspicuous leaf scars. It is well known in various African cultures for its application in the treatment of infections and inflammatory conditions (Asante-Kwatia et al., 2022). Through *in vitro* methods, it has been found to possess anti-sickling and antibacterial activities (Ngbolua et al., 2015).

In the Democratic Republic of the Congo, *U. heudelotii* is a medicinal plant with a well-established convergence of ethno-medical use by humans and bonobos (*Pan paniscus*). Our previous study has demonstrated that this plant has a normalization rate higher than 97% and a clear reduction in methemoglobin levels in aqueous solution, demonstrating that *U. heudelotii* has anti-sickle cell and antioxidative properties *in vitro* (Kambale et al., 2013). Thus, it is important to investigate through *in silico* modelling how compounds such as Naringenin-7-O-glucoside and Kaempferol-3-O-glucoside from this plant species interact with receptors involved in the pathophysiology of sickle cell disease. The choice of flavonoids is because their anti-sickling activity has been scientifically validated *in vitro* (Gbolo et al., 2022).

METHODS

Hardware and Software

As described in numerous other studies, such as those by Mpiana et al. (2020) and Ngbolua et al. (2022), Pyrx 0.8 was utilized for molecular docking. Discovery Studio 2021 (Biovia) was employed to prepare the receptor, edit the binding site, and visualize the results of docking. Additionally, SWISS ADME and PKCSM online tools were utilized for assessing physicochemical parameters and pharmacokinetic properties, respectively.

Ligands

Two compounds with 3D structures extracted from *Uapaca heudelotii*, as reported by Achika et al. (2020), have been considered for this study: Naringenin-7-O-glucoside (PubChem ID: 92794) and Kaempferol-3-O-glucoside (PubChem ID: 5282102) (NCBI, 2024).

Figure 1:
Naringenin-7-O-glucoside

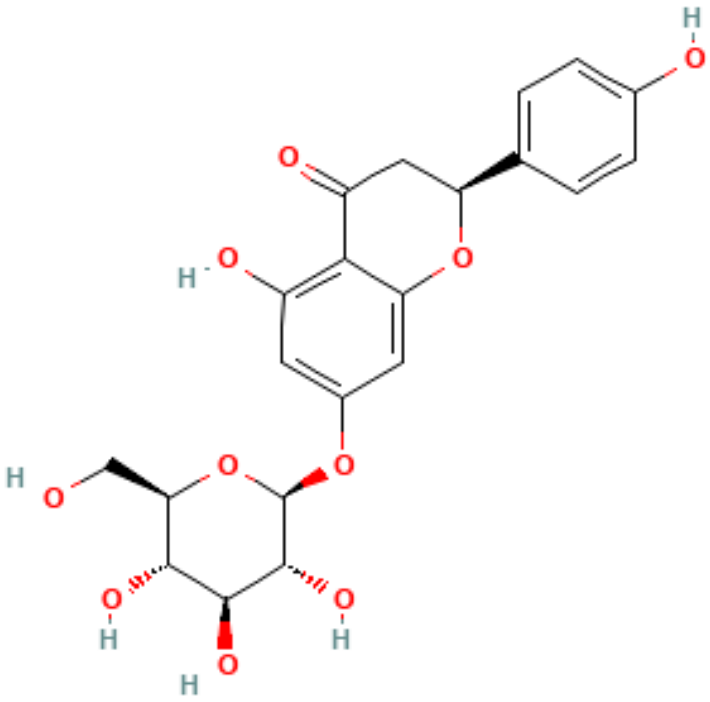
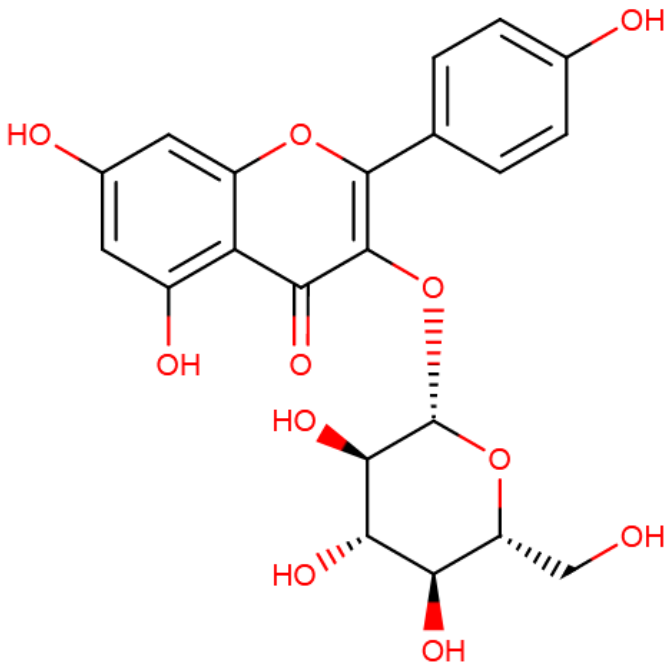


Figure 2:
Kaempferol-3-O-glucoside



Receptors

Four receptors were utilized for this study: the structure of Erythrocyte-specific bisphosphoglycerate mutase (PDB ID: 3NFY), the structure of deoxygenated giant hemoglobin (PDB ID: 3WCU), the structure of the transcription factor Beta Cell lymphoma/leukemia 11A (PDB ID: 5VTB), and the structure of the voltage-gated potassium channel KV1.3 (PDB ID: 7EJ1).

1. ***Docking protocol:*** The protocol employed is the one outlined by Ngbolua et al. (2022) and Kitete et al. (2022). Molecular docking was conducted, taking into account the binding site parameters of each receptor. Betulinic acid (PubChem ID: 64971) and Cromolyn (PubChem ID: 2882) were utilized as controls.
2. ***Assessment:*** We have considered cases where the binding affinity (ΔG) values are lower than 0 and where one or more hydrogen bonds have been formed. Ultimately, we compared the distance between two chemical elements linked from the receptor and ligand with the sum of their van der Waals radii. If the distance is shorter than the sum, it indicates a strong interaction.
3. ***Evaluation of molecular optimization property of the hits compounds:*** The molecular optimization properties of the hit compounds have been calculated. The following have been assessed: ligand efficiency, fit quality, fit quality scaled ligand efficiency, and ligand efficiency dependent on lipophilicity, as previously reported by Bembenek et al. (2009), Kirsch et al. (2019), and Shultz (2013).

$FQ = \frac{\text{LE}}{\text{LE\_Scale}}$ (1) Where FQ = fit quality.

$LE = \frac{|\Delta G|}{\text{HA}}$ (2) Where LE = ligand efficiency, HA = number of heavy atoms, ΔG = Gibbs free energy binding.

$\text{LE}_{\text{\_Scale}} = 0.0715 + \frac{7.5328}{HA} + \frac{25.7079}{HA*HA} + \frac{361.4722}{HA*HA*HA}$ (3) Where LE_Scale = Fit quality scaled ligand efficiency.

$LLE = \frac{|\Delta G|}{\text{Log P}}$ (4) Where LLE = Ligand Lipophilic Efficiency.

$LELP = \frac{\text{Log P}}{\text{LE}}$ (5) Where LELP = Ligand efficiency dependent lipophilicity, Log P = Partition coefficient.

$\Delta G = -RTlnKi$ (6) Where R=Perfect gas constant, T=Temperature, Ki = Inhibition constant

$LE = \frac{1.4(\text{pIC50})}{\text{HA}}$ (7) Where pIC_{50}= -log of inhibitory concentration 50.

FQ = fit quality, LE = ligand efficiency, HA = number of heavy atoms, ΔG = Gibbs free energy binding, LLE = Ligand Lipophilic Efficiency, LELP = Ligand efficiency dependent lipophilicity, Log P = Partition coefficient.

RESULTS

After docking and assessment, the results are presented in the following table highlighting the receptors as candidates:

Binding affinity and interactions

Each compound that underwent docking against the four receptors, including the two controls, has exhibited interactions. Details regarding the substrate, type of linkage, and the distance between two bonded atoms (which is crucial for assessing the strength of the interactions) are important for clarity. It should be noted that the lower the distance between two bonded atoms compared to the sum of their van der Waals radii, the stronger the integration. Conversely, when the sum is higher, the interaction is weaker. The hydrogen bonds that were formed are summarized in the following table.

Table 1:
Binding affinities and interactions

Receptor	Compound	H Bounds	Substrate	Distance	Sum of van der Waals radii
3NFY	Cromolyn	6	ASP A:250	2,2	2,72
			ARG A:116	2,31	2,72
			ARG A:116	2,52	2,72
			ARG A:100	2,59	2,72
			ARG A:100	2,69	2,72
	Betulinic acid	3	ARG A:10	2,5	2,72
			GLU A:37	2,38	2,72
			LYS A:247	1,88	2,72
	Naringenin-7-O-glucoside	4	GLN A:44	1,9	2,72
			ASN A:17	1,94	2,72
			ASN A:17	1,78	2,72
			ASN A:190	2,66	2,72
			ASN A:190	1,91	2,72
	Kaempferol-3-O-glucoside	5	ARG B:193	2,57	2,72
			ARG B:193	3,05	2,72
			VAL B:248	2,08	2,72
			ASP B:250	2,15	2,72
			ASP B:250	2,52	2,72
3WCU	Cromolyn	2	GLN C:98	1,96	2,72
			GLN B:94	1,82	2,72
	Betulinic acid	3	ARG C:53	2,18	2,72
			SER C:77	2,65	2,72
			ASN A:73	3	2,72
	Naringenin-7-O-glucoside	1	ARG A:97	2,24	2,72
	Kaempferol-3-O-glucoside	5	VAL C:71	2,78	2,72
			GLN B:94	2,24	2,72
			ASN C:73	2,56	2,72
			ASN C:73	2,06	2,72
			SER C:77	2,01	2,72
5VTB	Cromolyn	6	ARG A:131	1,28	2,72
			GLN A:322	2,28	2,72
			GLN A:48	2,1	2,72
			TRP A:235	2,13	2,72
			HIS A:236	2,8	2,72
	Betulinic acid	1	GLN A:324	2,42	2,72
			SER A:184	2,21	2,72
			SER A:381	2,4	2,72
	Naringenin-7-O-glucoside	6	TYR A:132	2,35	2,72
			TYR A:132	2,26	2,72
			TRP A:185	1,82	2,72
			ASP A:232	2,32	2,72
			LEU A:279	2,1	2,72
	Kaempferol-3-O-glucoside	8	TRP A:325	2,64	2,72
			TRP A:382	2,47	2,72
			SER A:381	1,91	2,72
			GLN A:48	2,17	2,72
			GLN A:48	2,29	2,72
			ASP A:323	2,35	2,72
			VAL A:333	2,2	2,72
			GLN A:324	1,96	2,72
7EJ1	Naringenin-7-O-glucoside	3	GLU H:309	2,27	2,72
			GLU H:225	2,33	2,72
			SER H:247	1,96	2,72
	Kaempferol-3-O-glucoside	2	GLU F:309	2,59	2,72
			GLU F:225	2,21	2,72

The two compounds found in *Uappacca heudelotti* are forming strong interactions with 3WCU. Naringenin-7-O-glucoside forms 1 hydrogen bond (H-O) with a substrate, ARG A: 97, with a distance lower than the sum of the van der Waals radii between H-O and ARG A: 97. Kaempferol-3-O-glucoside forms 5 hydrogen bonds with 4 substrates: VAL C: 71, GLN B: 94, ASN C: 73 and SER C: 77, involving three types of bonds (H-O, H=O and O=H). All interactions are deemed strong.

From the table, it is evident that the two compounds present in Uappacca heudelotti are establishing strong interactions with 3NFY. Naringenin-7-O-glucoside forms 4 hydrogen bonds with 2 substrates: ASN A: 17 and ASN A: 190, involving 2 types of bonds (O=H and H-O). Kaempferol-3-O-glucoside forms 5 hydrogen bonds with 3 substrates: ARG B: 193, VAL B: 248 and ASP B: 250, involving 3 types of bonds (H-O, H=O and O=H). The interaction involving H=O exhibits a distance higher than the sum of the van der Waals radii.

Interactions with 5VTB are also robust. Naringenin-7-O-glucoside forms 6 hydrogen bonds with 5 substrates: SER A: 381, TYR A: 132, TRP A: 185, ASP A: 232, and LEU A: 279, with bond types O-H and O=H. The distances are lower than the sum of the van der Waals radii. Kaempferol-3-O-glucoside forms 8 hydrogen bonds with 4 substrates: TRP A: 325, TRP A: 382, SER A: 381 and GLN A: 48, as well as ASP A: 323 and GLN A: 324, involving 2 types of bonds (H=O, H-O, and O=H). All interactions are robust.

Kaempferol-3-O-glucoside and Naringenin-7-O-glucoside also form bonds with 7EJ1. The former is bonded to 3 substrates: GLU H: 309, GLU H: 225 and SER H: 247, utilizing 2 types of bonds (O=H and H-O). Naringenin-7-O-glucoside is bonded to GLU F: 309 and GLU F: 225 using O=H bonds.

The interaction overview is represented in 2D and 3D that all compounds are active against 3NFY fig. 1–4, 3WCU fig. 8–8, 5VTB fig 9–12 and 7EJ1 fig 13–14.

ADMET profile

The ADMET characteristics of Kaempferol 3-O-glucoside and Naringenin-7-O-glucoside were predicted using two database SWISS ADME and PkCSM. Their canonical SMILES were utilized for this purpose.

Table 2:
ADMET profile of Kaempferol 3-O-glucoside and Naringenin-7-O-glucoside

Compounds	C1	C2	R.V
LOGP	-0.244	-0.017	-2–6.5
Intestinal absorption (human)	48.052	36.035	Above 30
BBB permeability	-1.514	-1.261	Less than -1
Renal substrate	No	No	No
Carcinogenicity	No	No	No
Hepatotoxicity	No	No	No

(R.V: Recommended value; C1: Kaempferol 3-O-glucoside; C2: Naringenin-7-O-glucoside; Log P: Lipophilicity; BBB: Blood-brain barrier).

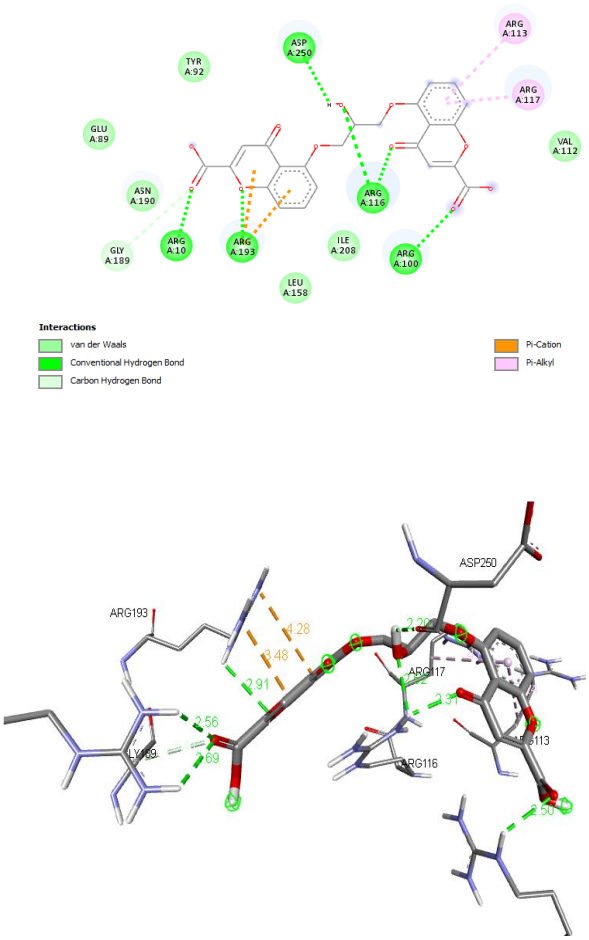
From **Table 2**, it can be observed that the two compounds are non-hepatotoxic and non-carcinogenic. They exhibit good intestinal absorption and lipophilicity. Their BBB permeability values are less than -1, indicating that they fall within a favorable range.

Receptor-ligands interactions

3NFY

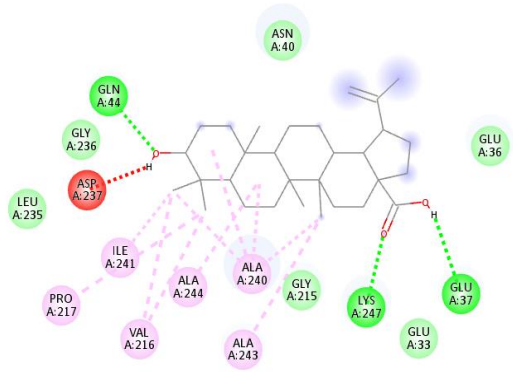
1. Cromolyn

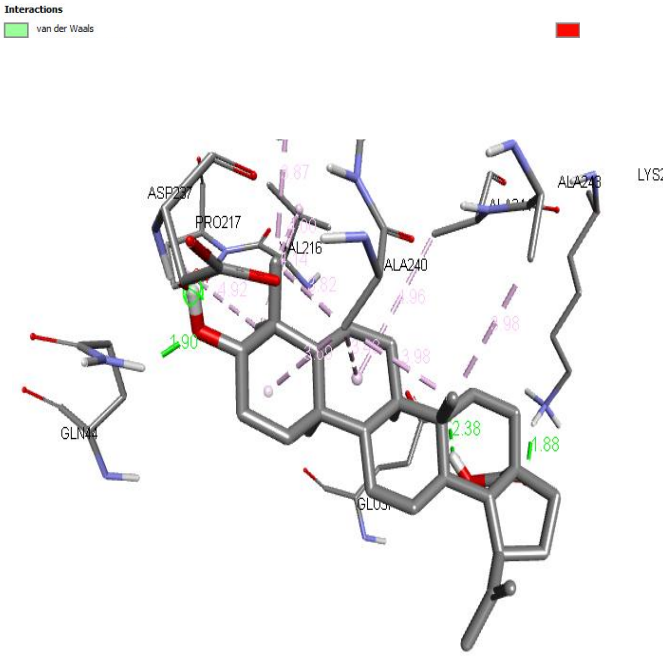
Figure 3:
2D and 3D interactions between cromolyn and 3NFY



2. Betulinic acid

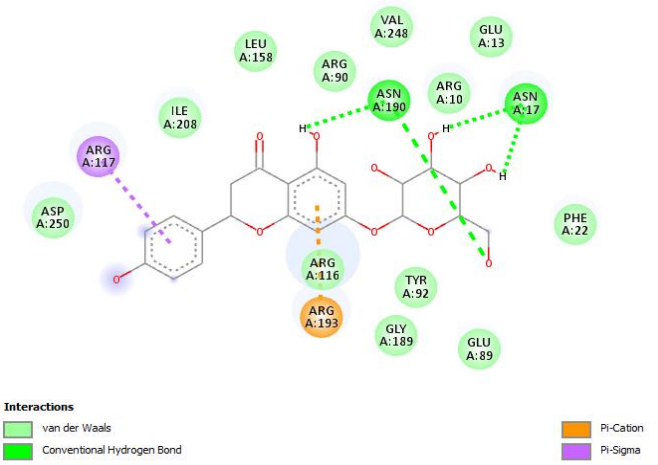
Figure 4:
2D and 3D interactions between betulinic acid and 3NFY





3. Naringenin-7-O-glucoside

Figure 5:
2D and 3D interactions between Naringenin-7-O-glucoside and 3NFY



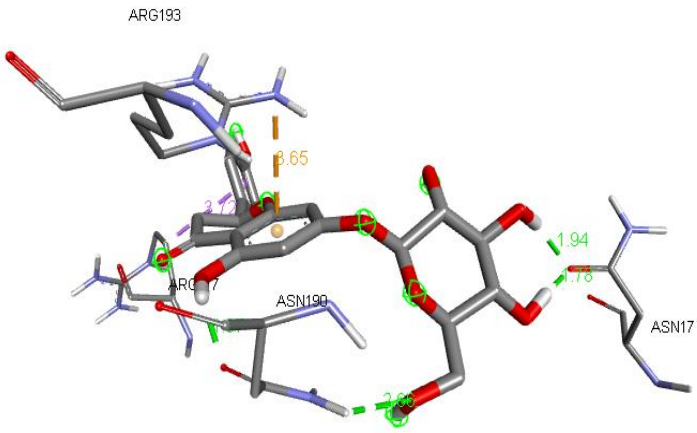
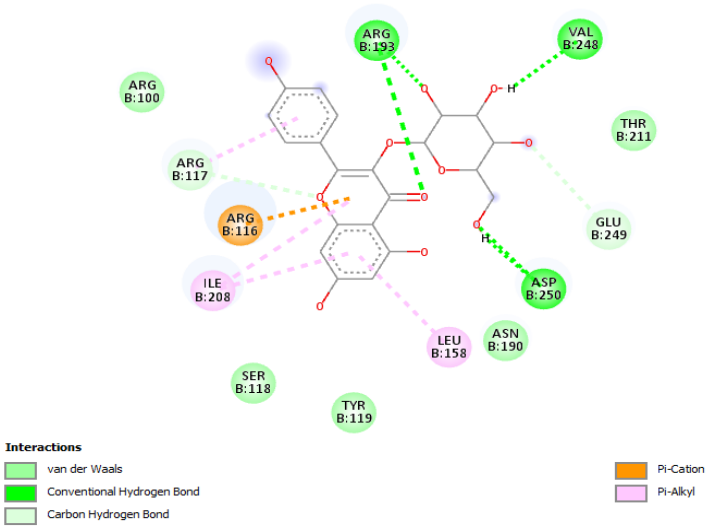
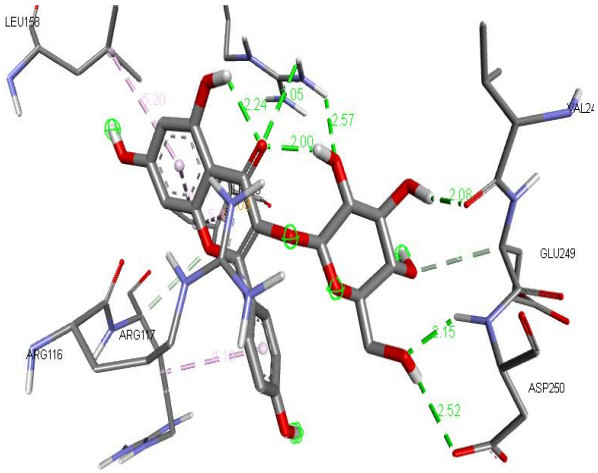


Figure 6:
2D and 3D interactions between Kaempferol-3-O-glucoside and 3NFY

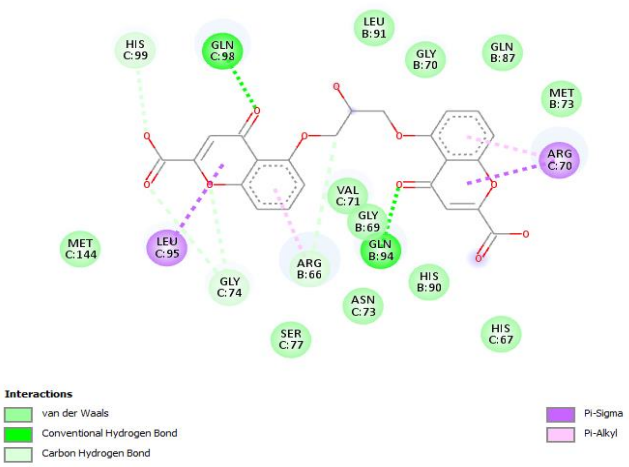




3WCU

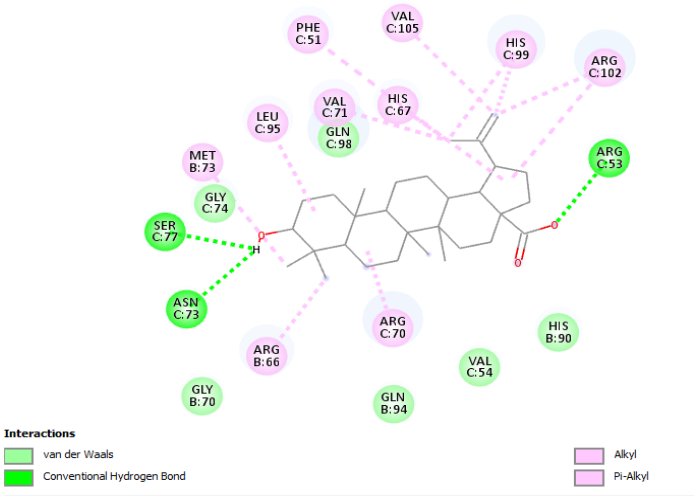
5. Cromolyn

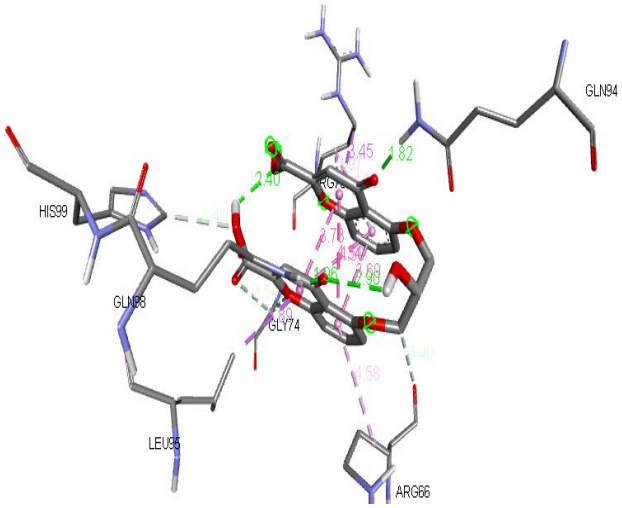
Figure 7:
2D and 3D interactions between Cromolyn and 3WCU

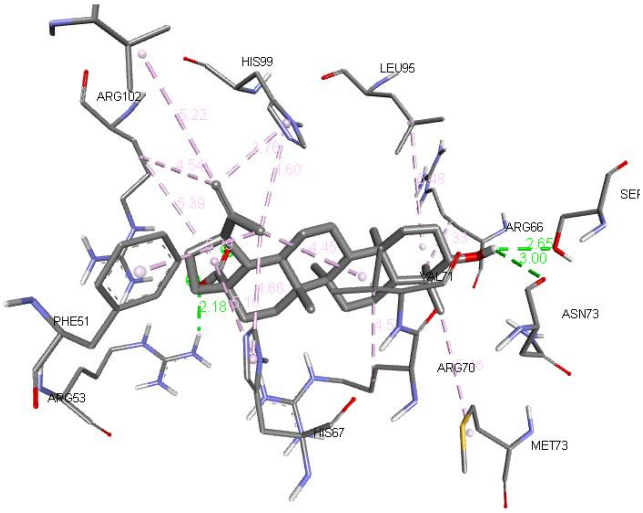


6. Betulinic acid

Figure 8:
2D and 3D interactions betulinic acid and 3WCU



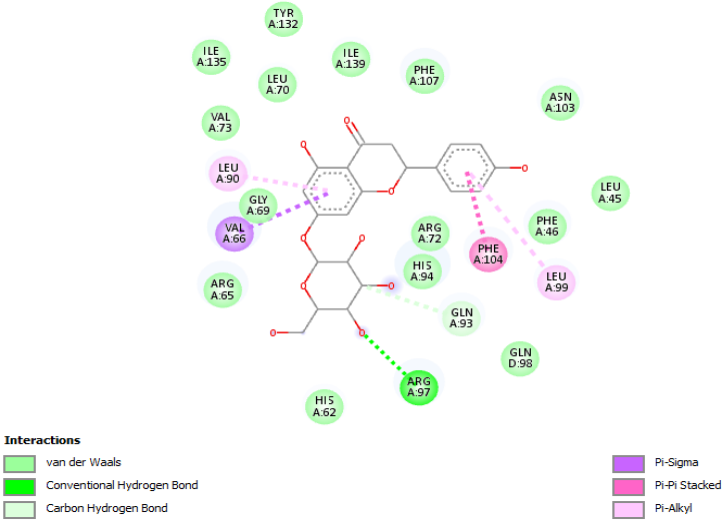


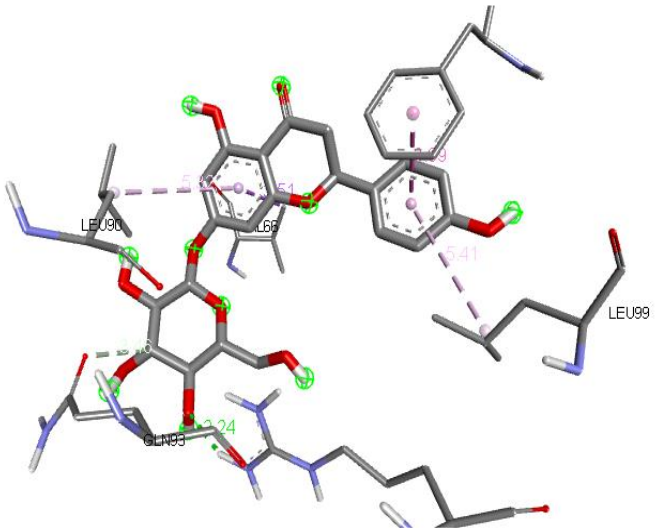


 https://dx.doi.org/10.4314/orapj.v5i2.11

7. Naringenin-7-O-glucoside

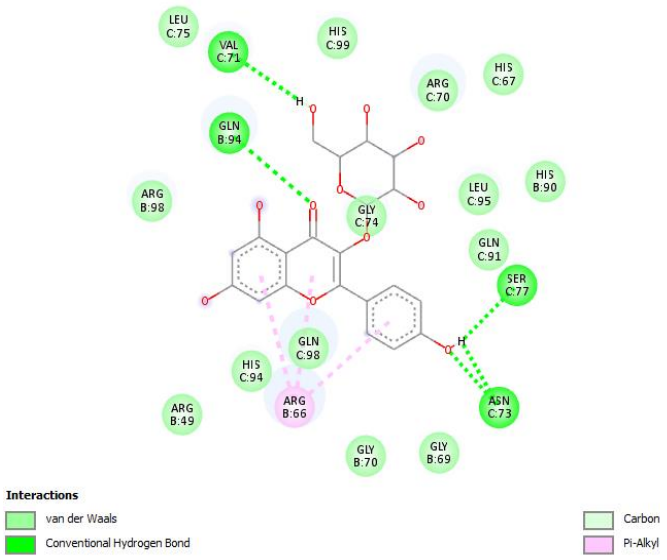
Figure 9:
2D and 3D interactions Naringenin-7-O-glucoside and 3WCU

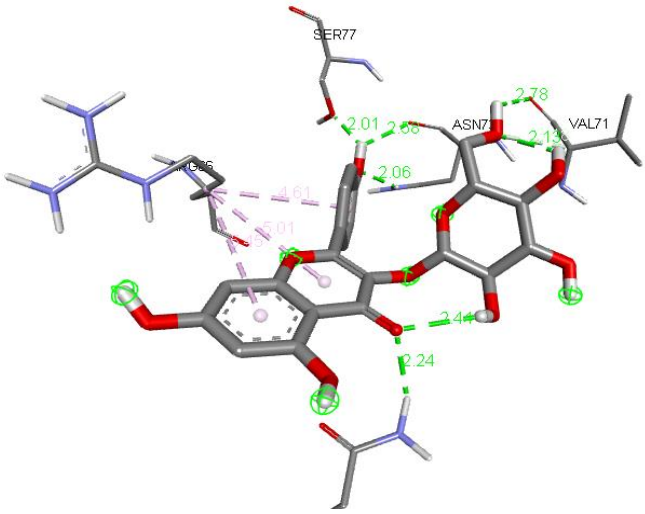




8. Kaempferol-3-O-glucoside

Figure 10:
2D and 3D interactions Kaempferol-3-O-glucoside and 3WCU

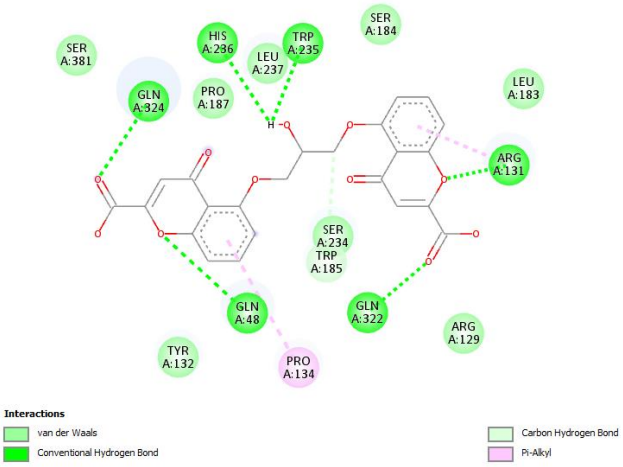




5VTB

9. Cromolyn

Figure 11:
2D and 3D interactions Cromolyn and 5VTB



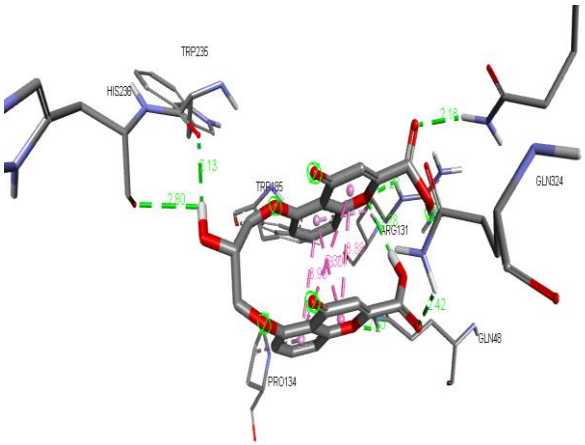
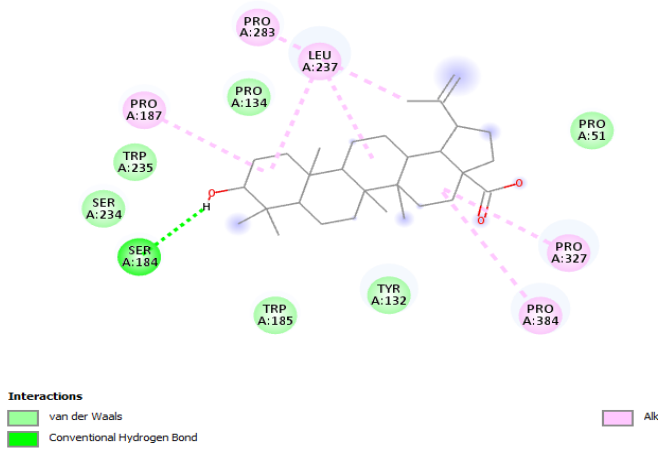
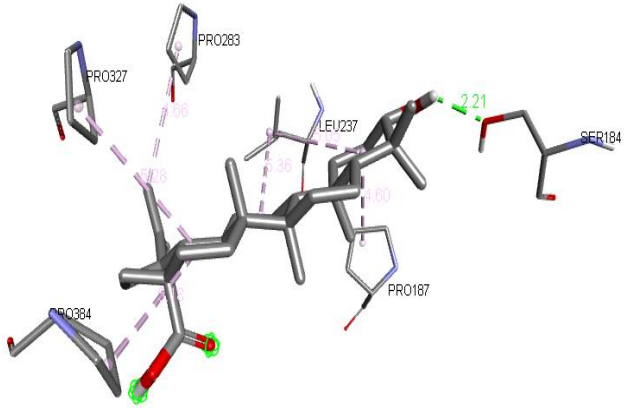


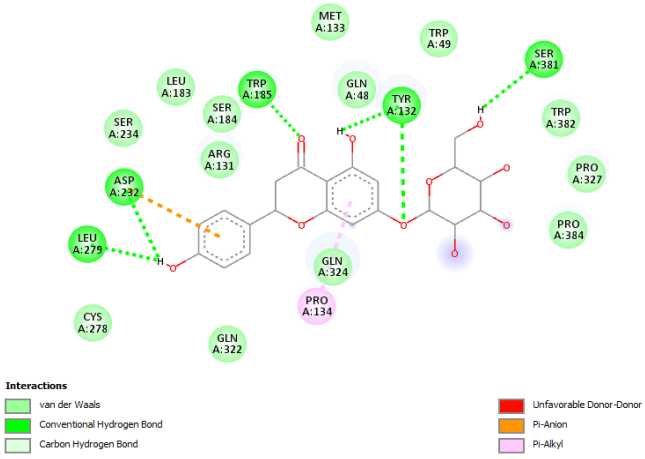
Figure 12:
2D and 3D interactions betulinic acid and 5VTB

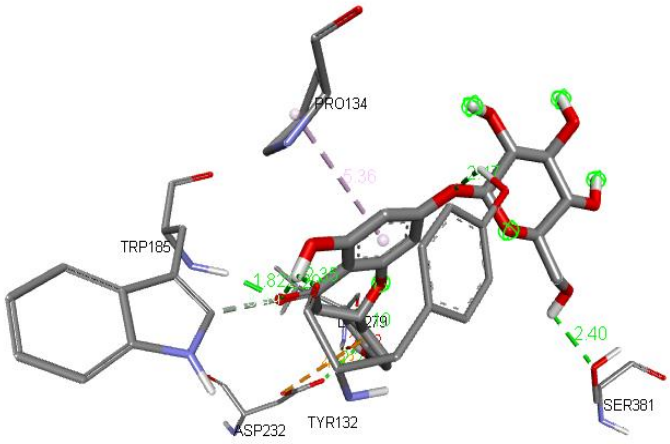




11. Naringenin-7-O-glucoside

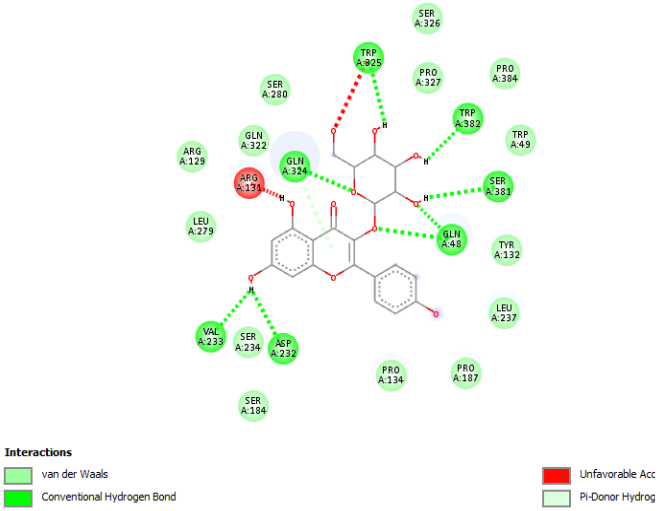
Figure13:
2D and 3D interactions Naringenin-7-O-glucoside and 5VTB

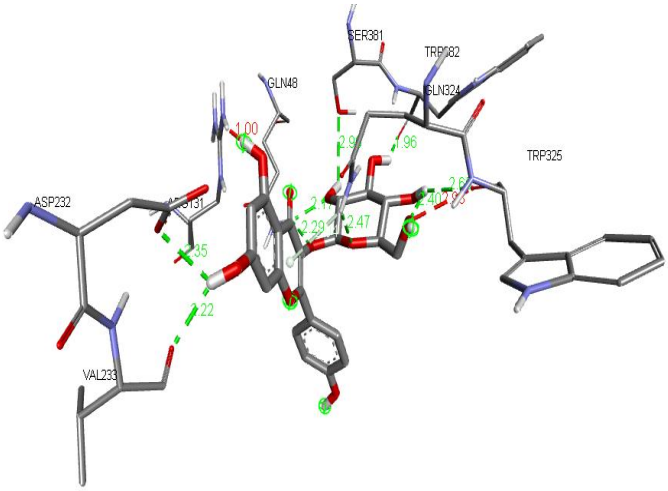




12. Kaempferol-3-O-glucoside

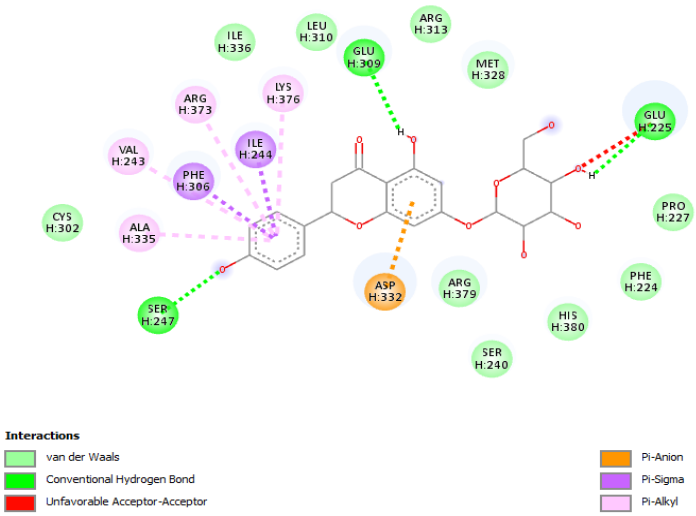
Figure 14:
2D and 3D interactions Kaempferol-3-O-glucoside and 5VTB

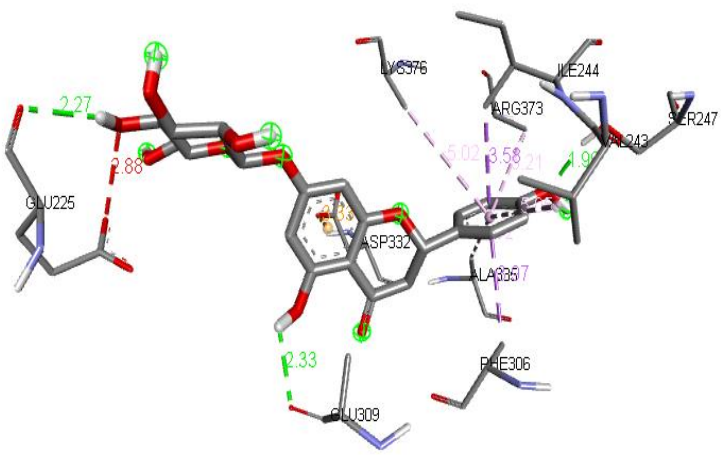




13. Naringenin-7-O-glucoside

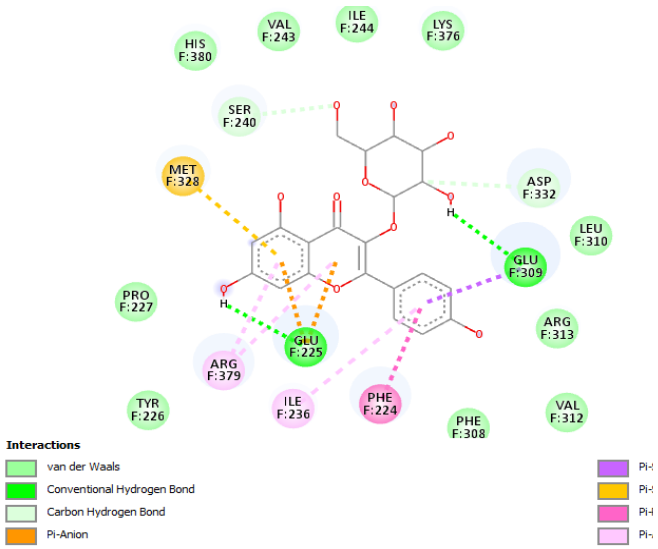
Figure 15:
2D and 3D interactions Naringenin-7-O-glucoside and 7EJ1

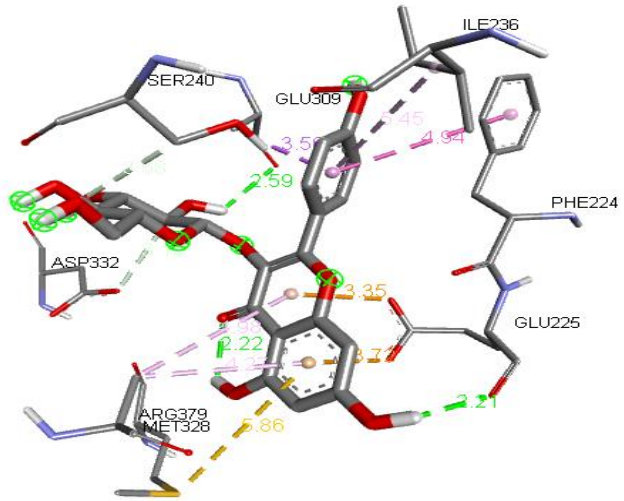




14. Kaempferol-3-O-glucoside

Figure 16:
2D and 3D interactions Kaempferol-3-O-glucoside and 7EJ1





3NFY

Table 3:
Binding affinity and other parameters

Parameters	CS1	C1	CS2	C2
Docking score in ***absolute value*** kCal/mol	8,1±0.31	8.5±0.6	8.4±0.1	8.6±0.41
Heavy atoms	34	32	33	31
LogP	2.11	-0.24	7.09	-0.34
Ligand efficiency	0,24	0,27	0,25	0,28
Ligand Lipophilic efficiency	0.26	-0.03	0.84	-0.04
Ligand Efficiency Scale	0.31	0.32	0.31	0.33
Fit Quality	0.78	0.83	0.81	0.84
KI	0.9968	0.9966	0.9967	0.9966
PIC_{50}	5.7857	6.0714	6	6.1428

(CS1: Cromolyn; C1: Kaempferol-3-O-glucoside; CS2: Betulinic acid; C2: Naringenin-7-O-glucoside)

From the Table above, it can be observed that the two compounds found in *Uappaca heudelotii* exhibit favorable docking scores compared to the positive controls (CS1 & CS2). Naringenin-7-O-glucoside scored 8.6 kcal/mol, and Kaempferol-3-O-glucoside scored 8.5 kcal/mol, while Cromolyn and Betulinic acid scored 8.1 kcal/mol and 8.4 kcal/mol, respectively. Additionally, they demonstrate higher ligand efficiency values and lower ligand lipophilic efficiency compared to the controls. The values of ligand efficiency are very similar.

3WCU

Table 4: Binding affinity and other parameters

Parameters	CS1	C1	CS2	C2
Docking score in ***absolute value*** kCal/mol	8±0.63	8,4±0.28	9,3±0.11	10,1±0.42
Heavy atoms	34	32	33	31
LogP	2,11	-0,2	7,09	-0,34
Ligand efficiency	0,24	0,26	0,28	0,33
Ligand Lipophilic efficiency	0,26	-0,03	0,76	-0,03
Ligand Efficiency Scale	0,31	0,32	0,31	0,33
Fit Quality	0,77	0,82	0,90	0,99
KI	0,9969	1	1	0,9961
PIC_{50}	5,7143	6	6,64	7,2143

(CS1: Cromolyn; C1: Kaempferol-3-O-glucoside; CS2: Betulinic acid; C2: Naringenin-7-O-glucoside)

From Table 4, it is evident that Naringenin-7-O-glucoside, a compound found in *Uappaca heudelotii*, exhibits a superior docking score compared to the two positive controls. Naringenin-7-O-glucoside scored 10.1 kcal/mol, whereas Kaempferol-3-O-glucoside scored 8.5 kcal/mol, while Cromolyn and Betulinic acid scored 8.1 kcal/mol and 8.4 kcal/mol, respectively. Additionally, they demonstrate higher ligand efficiency values and lower ligand lipophilic efficiency compared to the controls. The values of the ligand efficiency scale are very similar.

5VTB

Table 5:
Binding affinity and other parameters

Parameters	CS1	C1	CS2	C2
Docking score in ***absolute value***	8.86±0.25	9.9±0.13	8.4±0.11	9.3±0.14
Heavy atoms	34	32	33	31
LogP	2.11	-0.24	7.09	-0.34
Ligand efficiency	0.26	0.31	0.25	0.30
Ligand Lipophilic efficiency	0.24	-0.02	0.84	-0.04
Ligand Efficiency Scale	0.31	0.32	0.31	0.33
Fit Quality	0.85	0.96	0.81	0.91
KI	0.9965	0.9961	0.9967	0.9964
PIC_{50}	6.3286	7.0714	6.0000	6.6429

(*CS1: Cromolyn; C1: Kaempferol-3-O-glucoside; CS2: Betulinic acid; C2 : Naringenin-7-O-glucoside)*

From Table 5, it is evident that Kaempferol-3-O-glucoside and Naringenin-7-O-glucoside, two compounds found in *Alpaca heudelotii*, have demonstrated better docking scores than the two controls. Kaempferol-3-O-glucoside scored 9.9 kcal/mol, and Naringenin-7-O-glucoside scored 9.3 kcal/mol, while Cromolyn and Betulinic acid scored 8.86 kcal/mol and 8.4 kcal/mol, respectively. Additionally, they exhibit higher ligand efficiency values and lower ligand lipophilic efficiency compared to the controls. The values of the ligand efficiency scale are very similar.

7EJ1

Table 6:
Binding affinity and other parameters

Parameters	CS1	C1	CS2	C2
Docking score in absolute value	6.13±0.73	7.16±0.71	8.06±0.82	7.96±0.92
Heavy atoms	34.00	32.00	33.00	31.00
LogP	2.11	- 0.24	7.09	- 0.34
Ligand efficiency	0.18	0.22	0.24	0.26
Ligand Lipophilic efficiency	0.34	- 0.03	0.88	- 0.04
Ligand Efficiency Scale	0.31	0.32	0.31	0.33
Fit Quality	0.59	0.70	0.78	0.78
KI	0.9976	0.9972	0.9969	0.9969
PIC_{50}	4.3786	5.1143	5.7571	5.6857

(*CS1: Cromolyn; C1: Kaempferol-3-O-glucoside; CS2: Betulinic acid; C2 : Naringenin-7-O-glucoside)*

From Table 6, it is apparent that betulinic acid exhibits a binding affinity of 8.06 kcal/mol, which is the highest score compared to Naringenin-7-O-glucoside and Kaempferol-3-O-glucoside, two compounds found in *Uappaca heudelotii*, which respectively have scores of 7.96 kcal/mol and 7.16 kcal/mol. These two compounds have higher values than Cromolyn, which had a score of 6.13 kcal/mol. The values of the ligand efficiency scale are very similar.

CONCLUSIONS

DISCUSSION

This study is of critical importance for the poor countries, especially the Democratic Republic of the Congo. Indeed, sickle cell disease, and common genetic diseases in these regions, have significant public health problems due to serious complications and social and economic burdens.

Consequently, this study provides a new perspective on the search for treatments for sickle cell disease by studying the anti-sickle properties of naturally occurring compounds extracted from indigenous plants. This research, which identified potential molecules with anti-inflammatory activities, paved the way for the development of new, affordable, and accessible drugs for the population in need. Furthermore, the Silica approach used in this study enables an effective and cost-effective preliminary assessment of the feasibility of the compounds under consideration.

Using computational methods, molecular interactions, potential toxicity, and other drug kinetic parameters can be predicted before *in vivo* testing is carried out, thereby reducing drug development costs and timelines. This *in silico* approach, especially for the Democratic Republic of the Congo, where resources are limited and research infrastructure precarious, provides an opportunity to contribute significantly to the fight against sickle cell disease. The study also identified promising compounds from indigenous plants, highlighting the potential for the discovery of drug products from natural resources in the country, which could have a positive long-term economic impact.

CONCLUSIONS

Sickle cell disease remains one of the most complex diseases of this century due to its genetic origin, which prevents it from being completely cured. The results obtained from this study, which aimed to investigate the antisickling properties of compounds isolated from *Uappaca heudelotii* using *in silico* approaches, confirm that Naringenin-7-O-glucoside and Kaempferol-3-O-glucoside exhibit antisickling properties. These findings justify the traditional use of this plant for treating sickle cell anemia and suggest its potential use as a medicinal food. Furthermore, the study revealed that *U. heudelotii* could inhibit both the polymerization of hemoglobin S and the Rapoport-Lübering shunt, rehydrate erythrocytes, and elevate fetal hemoglobin levels.

Applications of Results

Development of novel therapies for sickle cell disease using Naringenin-7-O-glucoside and Kaempferol-3-O-glucoside; Utilization of *U. heudelotii* as a potential source for natural antisickling agents; Further research into the mechanisms of action and potential clinical applications of these compounds in sickle cell disease management.

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Conflicts of Interest: None declared.

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