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In silico Studies of Anti-Diabetic Potentials of Flavonoids

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Abstract

Protein Tyrosine Phosphate (PTP 1B) is regarded as a key negative regulator of insulin signalling. Thus, inhibition of PTP 1B can serve as a therapeutic target for the development of drug candidates for the treatment of type 2 diabetes mellitus. The study sought to explore flavonoids with potential inhibitory influence on the activity of PTP 1B *in silico*. Molecular Docking was conducted to predict the binding affinities of the compounds on PTP 1B and the probable binding interactions of the complexes. *In silico* tools were used to predict possible pharmokinetics (ADME) and physicochemical properties as well as the toxicity of the compounds. The result revealed that acacetin-7-O-rutinoside exhibited the highest negative binding affinity of -8.8 kcal/mol followed by Rutin, apigenin-7-O-glucoside, pectolinarin and kaempferol-7-O-glucoside with the binding energies of -8.4, -8.3, -8.3 and -8.1 kcal/mol respectively. The compounds were predicted to exhibit low acute toxicity, moderate intestinal absorption properties, and moderate clearance from the blood. However, the study predicted that the compounds were substrate for p-glycoprotein thereby affecting overall plasma bioavailability. In conclusion, the compounds showed favourable potentials for development of anti-diabetic drugs.

Keywords: PTP 1B, flavonoids, type 2 diabetes mellitus, in silico, molecular docking

Introduction

Diabetes mellitus is one of the leading cause of deaths globally and comprises of two major types – the type 1 diabetes mellitus (T1D) or insulin dependent diabetes mellitus and type 2 diabetes mellitus (T2D) or non-insulin diabetes mellitus (Dewiyanti *et al*., 2012). Type 2 diabetes mellitus is the most common form of the disorder accounting for more than 90% of the entire cases of DM affecting adults between the ages of 20 and 79 years (IDF, 2019). As Reported by IDF, 537 million people were living with diabetes in 2021 and postulated to appreciate to approximately 840 million cases by 2045 (WHO, 2024). Type 2 diabetes mellitus is characterized by an insulin resistance and/or insulin secretion deficiency developed from partially defective pancreatic beta cell (Luo *et al.,* 2020). Patients with T2D present higher risk of developing macrovascular and microvascular complications (Olatunde *et al*., 2021). Management of T2D is achieved through regulating glycaemia by the use of hypoglycaemic drugs, a sugar controlled diet and exercise (Agüero-Hernández *et al.,* 2020). However, modalities for T2D

involves the utilization of synthetic drugs that may pose concerns for health risk. This has led to a paradigm shift in interest in natural products with reduced risk.

Protein tyrosine phosphatase 1B belongs to the family of protein tyrosine phosphatases (PTP). The PTP family is widely recognised for their active role in regulating cellular activities and cell signalling (Liu *et al*., 2023). Hundreds of PTP members have been characterised and associated with either negative or positive regulatory attributes connected to signal transduction pathways (Alonso *et al.*, 2004). Protein tyrosine phosphatases 1B plays a significant role in the insulin and leptin pathway via negative regulation, thus it has been proven to be a therapeutic target for the treatment of T2DM (Lessard *et al*., 2010; Combs, 2009).

There is increased interest in search of phytochemicals with substantial PTP-1B inhibitory effects from plants and other sources. One of the classes of phytochemicals flavonoids was the centre of this research. Flavonoids are a class of polyphenolics comprising of 15 carbons and two aromatic rings linked by a three-carbon atoms. They constitute the most prevalent natural plant products and include the flavonols, athocyanins, flavanones, catechins, isoflavones and chalcone (Halbwirth, 2010). Flavonoids have shown a wide array of biological activities such as antiviral, antidiabetics, antitumor, anti-inflammatory and antioxidant properties (Almasri *et al*., 2021). Currently, there is no clinically accepted drug for targeting PTP 1B as previously developed PTP 1B inhibitors that have undergone some clinical trials were withdrawn due to their adverse side effects. Hence there is need for the identification of safe and potent PTP 1B inhibitors capable of been developed into a drug for the treatment of T2DM. This present study sought to identify potential PTP 1B inhibitors using computational studies.

Methodology

Molecular Docking

The 3D structures of the compounds were downloaded from pubchem. The crystallographic structure of PTP 1B enzyme was obtained from protein data bank with the code 1NNY3. Hydrogen atoms were added to the protein, water molecules were removed and the ligand present was removed using discovery studio. The molecular docking simulations were performed using autodock Vina (Trott and Olson, 2010).

Biological Activity Predictions

pkCSM server was adopted to predict the absorption, distribution, metabolism, excretion/toxicity (ADME/Tox). Pharmacokinetics properties of the flavonoids such as MW (molecular weight), LogP, HBD (number of hydrogen bond donors), HBA (number of hydrogen bond acceptors), TPSA (topological polar surface area), nrtB (number of rotatable bonds), nViolation (violations of Lipinski's rule of five) were established by DruLito (drug likeness tool) and Molinspiration Online tool. Molsoft program was used to determine the drug-like properties of compounds. The lethal dose (LD_{50}) values of the flavonoids were predicted using ProTox. PROTOX server and Data Warrior software were used to determine mutagenesis, tumorigenic, reproductive effects and irritability.

Results

Virtual Screening

The binding energy predictions of the 37 flavonoids docked against PTP 1B are presented in table 1. The result revealed high binding energies with acacetin-7-o-rutinoside having the highest binding score of 8.8 kcal/mol, followed by rutin with a binding energy of -8.4kcal/mol, apigenin-7-o-glucoside, pectolinarin and kaempferol-7-o-glucoside with binding energies of -8.3kcal/mol, -8.3kcal/mol and -8.1kcal/mol respectively.

The first five compounds with high binding energy were subjected for further visualization of their binding poses as shown in figures 1-10. The result showed that the compounds do not actively interact

with the catalytic site of the enzyme but bind with the other sites of the enzyme through non-covalent bonds.

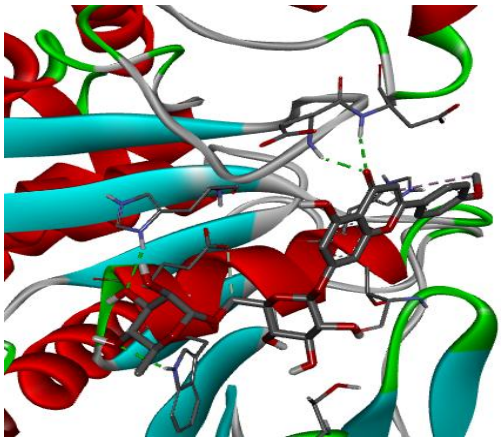

Fig. 1: Molecular Binding Mode of Acacetin-7-o-rutinoside

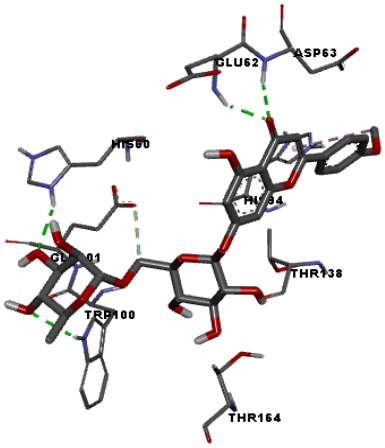

Fig. 2: A Closer View of the Interaction Between Acacetin-7-o-rutinoside and PTP 1B Interacting Amino Acids

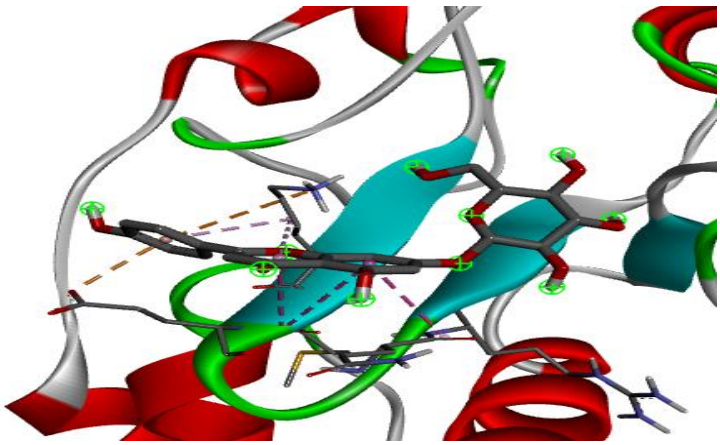

Fig. 3: Molecular Binding Mode of Apigenin-7-o-glucoside

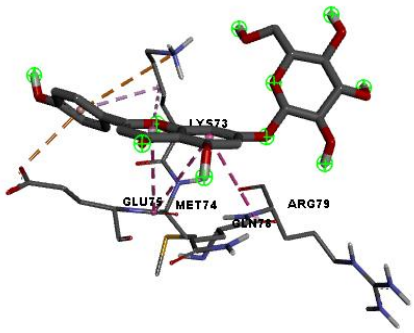

Fig. 4: A Closer View of Apigenin-7-O-glucoside and Interacting Amino Acids

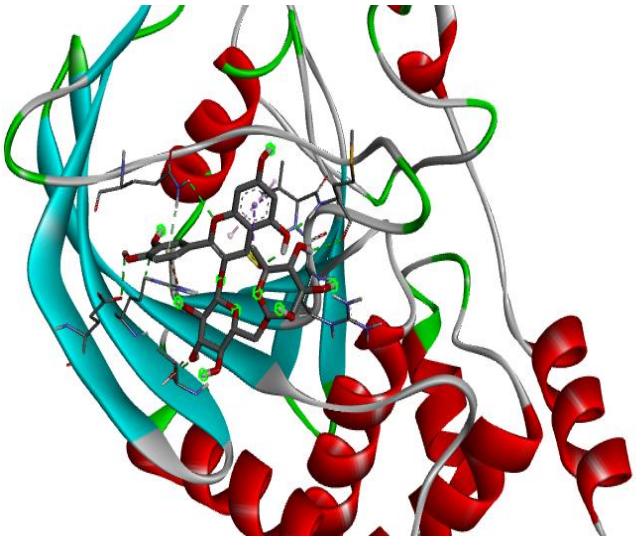

Fig. 5: Molecular Binding Mode of Rutin

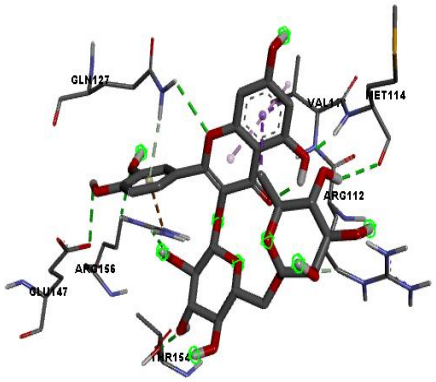

Fig. 6: A Closer View of Rutin and Interacting Amino Acids of PTP 1B

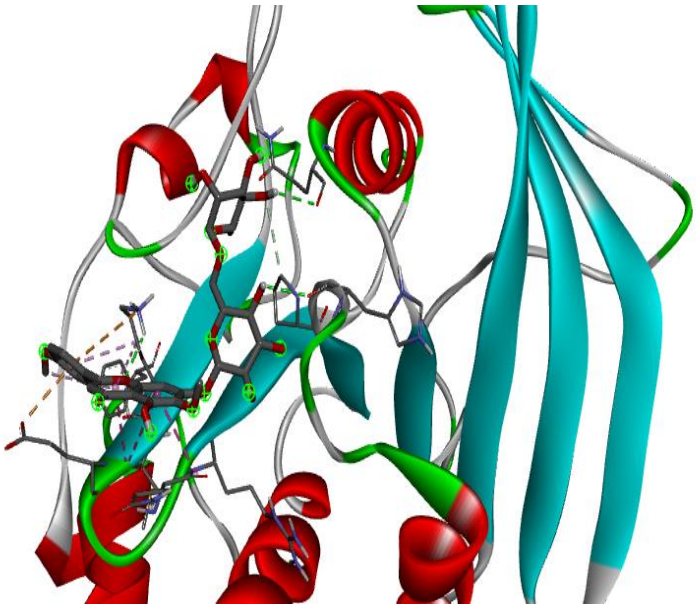

Fig. 7: Molecular Binding Mode of Pectolarinin

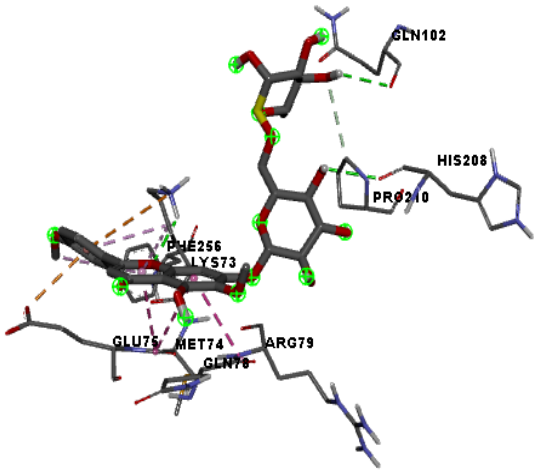

Fig. 8: A Closer View of Pectolarinin and Interacting Amino Acids

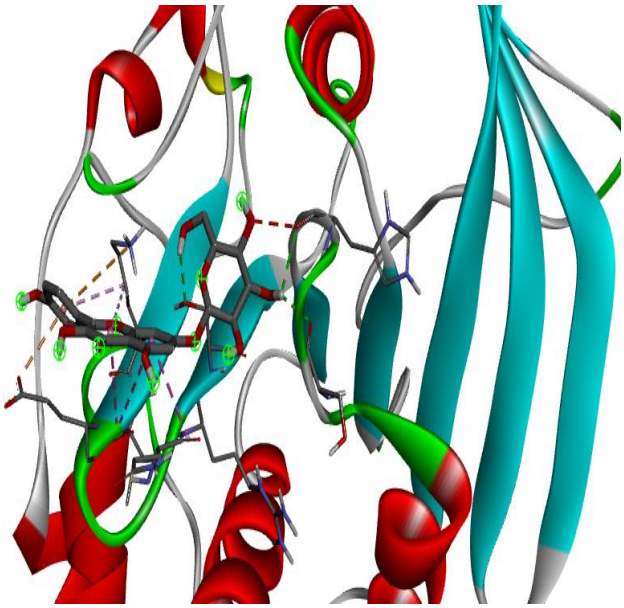

Fig. 9: Molecular Binding Mode of Kaemferol-7-o-glucoside

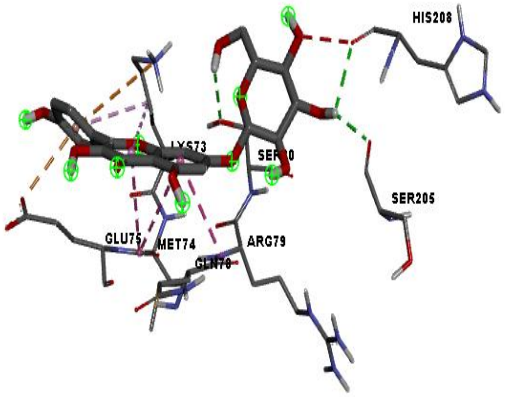

Fig. 10: A Closer View of Kaemferol-7-O-glucoside and Interacting Amino Acids

Pharmacokinetic Properties

Tables 2 -6 indicate the pharmacokinetic properties and toxicity behaviour of the acacetin-7-o-rutinoside, rutin, apigenin-7-o-glucoside, pectolinarin and kaempferol-7-o-glucoside. The result showed that each of the compound violated one of the Lipinski's rule of five (table 2). The compounds had low toxicity (LD_{50} of 5000mg/kg respectively) thus placing them in toxicity class of 5. They exhibited no toxic fragment or induce toxicity via a toxic target. Furthermore, they were found to be non-irritant or prompt teratogenic effect as shown in table 3. However, kaempferol-7-o-glucoside and pectolinarin were found to have mutagenic and tumorigenic effect respectively.

Table 4 revealed the adsorption profile of the compounds. The five compounds showed low water solubility property, low to moderate intestinal absorption, low skin permeability. The compounds were found to be substrates of p-glycoprotein and none served as an inhibitor 1 or 2 to p-glycoprotein. Table 5 shows the distribution and excretion profile of the compounds. the compounds were predicted to have a moderate VDss, impermeable through the blood-brain barrier, as well as the central nervous system. The compounds were shown to have low total clearance rate and none was a substrate of renal OCT2. The compounds were predicted to be neither substrates or inhibitors of CYP450 enzymes as depicted in table 6.

Table 1: Binding Energies of Compounds (Flavonioids) Against PTP 1B

Compounds	Binding energy (kcal/mol)
Acacetin-7-o-rutinoside	-8.8
Apigenin 7-o-glucoside	-8.3
Apigenin	-7.5
Astragalin	-7.4
chamaejasmin	-7.8
Bacekup	-7.3
Fiscetin	-6.0
epigallocatin gallate	-7.5
Diosmetin	-7.2
delphinidin-3 rutinoside	-7.8
Chrysin	-7.4
isokaemferide	-7.0
isorhamnetin	-7.1
isoquercetin	-7.4
kaempferol	
hyperoside	-7.7
Kaemferol	-6.6
Kaempferol-7-o-glucoside	-8.1
Luteolin	-7.3
Myricetin	-7.2
Myricetin-3-rhamnoside	-7.8
Myricetin rhamnosylgalactoside	-7.9
Naringerin	-7.8
Nobiletin	-6.2
Oroxylin A	-7.2
Pectolinarin	-8.3
Puriocembrin	-7.1
puerarin	-7.0
Querctagetin	-7.2
Quercetin	-7.9
Quercetin-3-rhamnoside	-7.6
Reynoutrin	-7.7
Rutin	-8.4
Tangeretin	-6.4
vitexin	-1.2
Vitexin-2-o-rhamnoside	-7.5
Vitexin-2-o-xyloside	-7.6
Woginin	-7.2

Table 2: Physiochemical Properties of Predicted PTP 1B Inhibitors

Compounds	MW	HBD	HBA	LogP	Drug likeness	TPSA	violation	nrtB
Acacetin-7-o-rutinoside	592.18	7	14	-0.68	2.46	214.06	1	7
Apigenin 7-o-glucoside	432.11	6	10	-0.16	-3.25	166.14	1	4
Kaempferol-7-o-glucoside	448.37	7	11	0.18	-3.71	55.77	1	4
Pectolinarin	622.19	7	15	-0.44	2.46	223.29	1	8
Rutin	610.51	10	16	-0.74	1.93	265.52	1	6

Table 3: Toxicity Profile of PTP 1B Inhibitors

Compounds	LD_{50} (mg/kg)	Toxicity class	Toxicity fragment	Toxicity targets	Mutagenic	Tumorogenic	Reproductive effect	Irritant
Acacetin-7-o-rutinoside	5000	5	none	none	inactive	none	None	none
Apigenin 7-o-glucoside	5000	5	none	none	inactive	none	None	none
Kaempferol-7-o-glucoside	5000	5	none	none	active	none	None	none
Pectolinarin	5000	5	None	none	inactive	high	None	none
Rutin	5000	5	None	None	None	None	None	None

Table 4: Adsorption Profile of PTP 1B Inhibitors

Compounds	Water solubility (log mol/l)	Intestinal absorption (%absorption)	Skin permeability (log Kp)	P-glycoprotein substrate	P-glycoprotein inhibitor 1	P-glycoprotein inhibitor 2
Acacetin-7-o-rutinoside	-2.96	36.67	-2.74	yes	No	No
Apigenin 7-o-glucoside	-2.56	37.61	-2.74	yes	No	No
Kaempferol-7-o-glucoside	-2.76	30.72	-2.74	yes	No	No
pectolinarin	-2.99	41.85	-2.74	yes	No	No
Rutin	-2.89	23.44	-2.74	yes	No	No

Table 5: Distribution and Excretion Profile of PTP 1B Inhibitors

Compounds	VDss (logl/kg)	Fraction unbound (FU)	BBB permeability (logBB)	CNS permeability (log PS)	Total clearance (log ml/min/kg)	Renal OCT2 substrate
Acacetin-7-o-rutinoside	0.91	0.12	-1.64	-4.67	0.10	No
Apigenin 7-o-glucoside	0.34	0.22	-1.39	-3.75	0.54	No
Kaempferol-7-o-glucoside	1.02	0.24	-1.47	-3.91	0.46	No
pectolinarin	0.68	0.12	-1.86	-4.79	0.03	No
Rutin	1.66	0.19	-1.89	-5.18	0.37	No

Table 6: Metabolic Profile of PTP 1B Inhibitors

Compounds	CYP2D6 substrate	CYP3A4 substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
Acacetin-7-o-rutinoside	no	No	no	no	no	no	no
Apigenin 7-o-glucoside	no	No	no	no	no	no	no
Kaempferol-7-o-glucoside	no	No	no	no	no	no	no
pectolinarin	no	No	no	no	no	no	no
Rutin	no	No	no	no	no	no	no

Discussion

Virtual Screening

The current study sought to screen and predict the mechanistic influence of flavonoids on the activity of protein tyrosine phosphate 1B (PTP1B). This was achieved by employing molecular docking tool to reveal the favourable binding mechanism between the enzyme (PTP 1B) and the flavonoids.

The flavonoids that exhibited lowest binding energies where identified as the lead compounds and subjected to elucidation of their binding interactions. The relative high binding energy of the compounds may be attributed to the structure of the compounds. Flavonoids are characterized with the presence of multiple cyclic structures, methoxyl and hydroxyl groups (Almasri et al., 2021). In addition, observation of the structures of the five compounds indicates the presence of sugar moieties attached to the flavonoid nucleus. The presence of these sugar moieties may play significant influence in the mechanism of inhibition of the compounds against PTP 1B.

The binding modes of the compounds against the enzyme are shown in figures 1-10. Molecular interactions including hydrogen bonding, hydrophobic interactions, van der Waal forces, and other interactions, responsible for strengthening the interactions between protein and ligand, are frequently observed in docked complexes (Shah *et al*., 2016). The oxygen groups of the two rutinosides interacted with Thr 138, His 60 and Trp 100 through hydrogen bonding. The carbonyl group of the C ring was capable of interacting with two neighbouring amino acids (Asp 63 and Glu 62) via hydrogen bonding. The other oxygen group on ring B contributed to the formation of ligand-protein complex through forming a π-akyl bond with His 94. On the other hand the glycoside bond between the two sugars formed a carbon hydrogen bond with the polar and charged amino acid Glu 101. Interestingly, the binding mode of acacetin-7-o-rutinoside (fig 1-2) showed that the compound neither interacts with the active site of the enzyme or to the established allosteric site (Zhang *et al*., 2017), however, it was predicted to interact with the less prominent amino acid residue (Glu 101) in the WPD. This may indicate that the compound is neither a competitive nor an allosteric inhibitor.

Met 114 of the R-loop of PTP 1B was favourably stabilized by forming hydrogen bonding with the hydroxyl group of the sugar and the O group of C6 of the A ring in rutin (fig 5-6). Similarly, Arg 156 was held by hydrogen bonds from the hydroxyl group of the sugar and the O group of C5' of the C ring and a pi cation bond with phenyl ring C. Glu 147 interacted through a hydrogen bond with OH group of C-4 of the C ring. π-akyl and π-sigma bonds were formed between the ring C and ring A. The O of the glycosidic bond donated a carbon hydrogen bonding to Arg 112- an amino acid that is part of the E loop. Van der Waal interactions with Thr 177 an amino acid in the WPD loop, Ile 149, Gln 123, Leu 144, and His 175 contributed to the overall binding energy. This may suggest that rutin binds close to the catalytic site of the enzyme inducing a conformational changes in the active thus weakening enzyme's activity.

The binding mode of kaempferol-7-o-glucoside (fig 9-10) shows favourable interactions with PTP 1B through hydrogen bonding with Ser 205, His 208 and Ser 80. Amide-pi-stacked bond was formed between the phenyl rings A and C with Gln 78 and Met 74. The O group of C-2 was involved in forming π -akyl bond with Lys73. The ring B interestingly formed both pi-cation and pi-anion bonds with Lys 73 and Glu 75 respectively. Van der Waals forces were formed with Arg 79, Pro 206, Gly 209, Pro 210 and Leu 71. Ser 205, His 208 and Pro 206 form part of the S-loop of the enzyme while Arg 79, Ser 80 are part of the WPD loop. The S-loop is essential for the WPD loop mobility which in turn influences substrate binding and catalytic activity (Patel, 2014). The compound stabilized the WPD loop and the S-loop leading to a decrease in binding affinity of the compound.

The OH group of the glycoside present in pectolarinin (fig 7-8) stabilizes the S-loop by interacting with His 208 through hydrogen bond, in addition, hydrogen bonds were formed with Gln 102 and Lys 73 with another OH group of the glycoside and O group of the C ring. Additionally, Lys 73 formed multiple bonds including pi-cation bond with the B ring, and pi-akyl bond with the C ring. The methoxyl group on C-4 on the B ring formed another pi-akyl bond with Phe 256 while the phenyl ring for a pi-cation and pi-anion bond with Lys 73 and Glu75 residues respectively. The residues Met 74 and Gln 78 formed an amide-pi stacked bond with the phenyl group of A ring. van der Waals were observed to exist with Arg 79. This indicates that pectolarinin did not interact with the catalytic amino acids but with neighbouring amino acids that resulted in the high binding energy. Hence, pectolarinin may be predicted to be a non-competitive inhibitor.

Apigenin-7-o-glucoside (fig 3-4) exhibited few molecular interactions with the amino acid residues of PTP 1B. π-cation and pi-anion bonds were formed between the phenyl structure of the B ring and Lys 73 and Glu 75 respectively, moreover, Lys 73 formed interaction with the C ring through a pi-akyl bond. Met 74 and Gln 78 both formed amide-pi stacked bonds with the C and B rings. Apigenin-7-o-glucoside was predicted to form no bonds with the catalytic amino acid residues or the allosteric site of PTP 1b hence, it can be suggested to be a non-competitive or uncompetitive inhibitor.

The pharmacokinetic properties of the compounds were evaluated to assess their oral bioavailability. Their properties were aligned to the Lipinski's rules known as the rule of five which include the molecular weight, logP (the logarithm of octanol/water partition coefficient), number of hydrogen bond donors and acceptors. The rule serves to determine the drug-likeness or examine whether a compound will have a good oral bioavailability to buttress its biological activity. The rule stipulates that for a compound to behave as a drug the molecular weight must be ≤500, number of hydrogen bond acceptors ≤10, number of hydrogen bond donors ≤5 and logP ≤5. Compounds that violate more than one of these rules tend to have low oral bioavailability (Rao *et al*., 2012). Table 2 shows that one of the rules were violated by each of the molecules.

The results of absorption, distribution, metabolism and excretion (ADME) evaluations are shown in Tables 2-6. These properties are important in drug development as they determine if a drug have good pharmacokinetic properties in terms of absorption, distribution, metabolism and excretion (Silva *et al*., 2014). Analysis of the absorption properties showed that the compounds have moderate intestinal absorption values with rutin having the lowest (23.44%) and pectolinarin having the highest value (41.85%). Skin permeability property is important for assessing compounds for drug transdermal administration. The five compounds exhibited low skin permeability value indicating that they are not agents for transdermal administration.

The distribution test of the compounds showed high volume distribution (VDss) values which suggests that they could be evenly distributed between in the blood plasma. Moreover, the test showed a low BBB permeability and CNS permeability. This indicates that the compounds do not penetrate into the brain or the central nervous system. These parameter seeks to limit the unwanted side effects of compounds in the brain.

Total Clearance and Renal Organic Cation Transporter 2 (OCT2) are important parameters to determine a compound's excretion property. The analysis showed a high total clearance values of the compounds which suggest high rate of removal of the compound from the system. The compounds were predicted to be non-substrates of renal organic cation transporter.

The metabolism test in table 7 showed that the compounds are neither substrates nor inhibitors of cytochrome P450 a key enzyme in the detoxification of drugs and other foreign substances. This suggests that the compounds are not metabolized by phase 1 elimination system.

The toxicological status of the compounds were analysed to ascertain the safety of the compounds which is essential for drug development. The evaluation of the lethal dose 50 (LD_{50}) showed that the five molecules had LD_{50} of 5000mg/kg and placed in toxicity class 5 suggesting that the molecules are relatively safe. Also, they exhibited no toxic fragment in their structure. The test also showed that they are not teratogenic and non-skin irritants. Mutagenicity and tumorigenicity assessment showed that kaempferol-7-o-glucoside and pectolinarin were predicted to be mutagenic and tumorigenic respectively.

Conclusion

Molecular docking simulations of 37 flavonoids against PTP 1B activity predicted five most potent inhibitors. These inhibitors were predicted to have no interactive with the amino acid residues present in the active site. Favourable interactions were predicted to be involved in the stabilization of the interactive binding structure existing between the protein and the inhibitors. Moreover, the structure activity relationship explored suggested that sugar units found in flavonoids could contribute to the overall high binding energy. The pharmacokinetic and toxicity analysis showed that the compounds exhibited satisfactory properties for development of oral PTP 1B inhibitors. However, the compounds were found to violate one of the Lipinski's rule each. Pectolarinin and Kaempferol-7-o-glucoside were found to be tumorigenic and mutagenic respectively**.** Hence, the other three compounds could serve as lead for further studies and drug development.

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