RESEARCH ARTICLE

Molecular Docking Investigation of Compounds from *Sapium Ellipticum* (Hochst) Pax as Allosteric Activators of Human Glucokinase

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SUMMARY

Allosteric activators of human glucokinase (GK) had shown hypoglycaemic potential in various preclinical and clinical studies. Some of the synthetic allosteric GK activators showed some serious side effects, such as hypoglycemia and elevated levels of triglycerides. This leads to an increasing demand for natural products as allosteric GK activators with fewer side effects. *Sapium ellipticum* (Hochst) pax ethanol leaf extract (PELE) was reported to modulate GK activity in the streptozotocin-induced diabetic Wister rat model. The present study aims to evaluate *in silico* compounds found in *S. ellipticum* leaf extract to explore their binding mode and interactions with the GK enzyme. The present study is designed to evaluate *in silico* some compounds including 5 triterpenoids (lupeol, lupeol acetate, beta-amyrin, lupenone, and acetyl aleuritolic acid), 2 flavonoids (amentoflavone and luteolin-7-glucoside), 2 sterols (stigmasterol and beta-sitosterol) and 1 phenolic compound (alpha-tocopherol) found in *S. ellipticum* leaf extract in order to explore their binding mode and interactions with the GK enzyme. Lupeol, alpha-tocopherol, amentoflavone, and luteolin-7-glucoside showed analogous binding pattern in the allosteric site of GK as that of co-crystallized GK activator. These compounds displayed good binding free energy and significant binding interactions with the allosteric site residues of GK enzyme supporting the *in vitro* GK activity of *S. ellipticum* extract. This information can be utilized for the development of potent and non-toxic natural allosteric activators of human GK for the diabetes therapeutics.

Keywords: Allosteric, Diabetes, Docking, Glucokinase, Human GK, GK activators, *Sapium ellipticum*.

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INTRODUCTION

Glucokinase (GK) is a cytoplasmic enzyme expressed predominantly in pancreatic β-cells and liver hepatocyte, and catalyzes the conversion of glucose to glucose-6-phosphate with the help of adenosinetriphosphate.[1-2] In pancreatic β-cells of the pancreas, GK regulates glucose-stimulated insulin release, and in liver hepatocytes of liver, it controls the breakdown of sugars. GK acts as an emergent drug target for treatment and management of type 2 diabetes due to its key function in controlling sugar breakdown. Small molecule allosteric activators of human GK are the unique class of therapeutic candidates that allosterically activate GK and express their hypoglycemic potential.[2-4] Several GK activators had been progressed into late phases of clinical trials including AZD6370, AZD1656, MK-0941, Piragliatin and AMG151; even though strong decrease in blood sugar was observed, potential adverse reactions were also reported, such as hypoglycemia and elevated levels of triglycerides suggesting further a strong need of developing safe and potent GK activators.[5-6] Large numbers of plants and parts of the plants were reported with their anti-diabetic properties. Various types of plant-derived active principles representing several bioactive compounds have established their beneficial role for possible use in diabetes therapeutics.[7-8] This leads to increasing demand for the discovery of natural products as allosteric GK activators with fewer side effects. Recently, some plant-based compounds, including glycolipids (Glucolipsin A and B),[9] flavonoids (eupatilin, mangiferin, and kaempferol),[10-12] alkaloids (camptothecin),[13] lipid derivative (guggultetrol)[14] and steroidal derivative (coaglunide)[15] were reported as allosteric activators of human GK.

Sapium ellipticum (Hochst) Pax belonging to the Euphorbiaceae family is generally denoted as "jumping seed tree" and is broadly distributed in eastern and tropical Africa. In southwest Nigeria, especially amongst the Ilorin indigenes, this plant is prevalently called as "*aloko-ạgbọ*." Numerous therapeutic properties were traditionally linked with this plant including treatment of scurvy and stomatitis in Central

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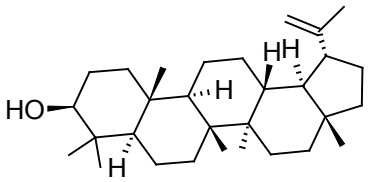
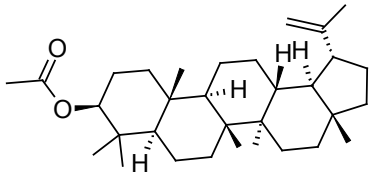
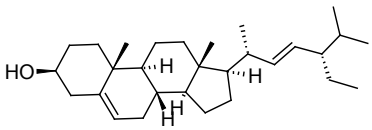
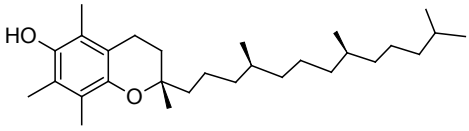
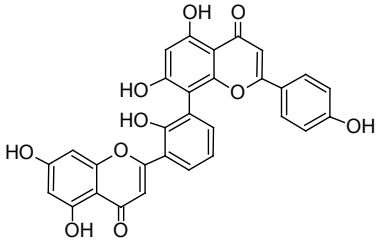
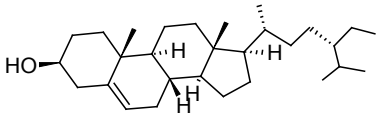
Africa; treatment of enlarged spleen in babies and used for malaria by adults in the East Africa; treatment of wounds, sore-eyes and abdominal swelling in Tanzania; treatment of eczema and as purgative in Congo; treatment of stammering in Zaire; and to relieve pains of head, chest, shoulders and back in Tanganyika.[16-18] Various types of phytoconstituents were reported in leaf extracts of *S. ellipticum* including flavonoids (amentoflavone and luteolin-7-glucoside), triterpenoids (lupeol, lupeol acetate, beta-amyrin, lupenone, and acetyl aleuritolic acid), steroidal derivatives (stigmasterol and beta-sitosterol), phenols (alpha-tocopherol), anthraquinones, alkaloids, glycosides, and cardiac glycosides.[19-21] The leaves of *S. ellipticum* showed cytotoxic activity against HeLa cervix adenocarcinoma cells, almost comparable to reference ciplastin.[22] *S. ellipticum* was used for hypertension, antenatal health, sexually transmitted infections and epigastric pain.[23] Methanol extract of *S. ellipticum* leaves showed significant free radical scavenging (antioxidant) activity in a dose-dependent fashion.[21,24,25] Dichloromethane extract of *S. ellipticum* bark showed anti-fungal activity.[26] Different extracts of S. *ellipticum* leaves showed antimicrobial activity against human pathogenic microbes.[21] Ethanol leaf extract of *S. ellipticum* was reported to maintain lipid homeostasis in streptozotocin-induced diabetic rat model.[27] Ethanol extract of *S. ellipticum* showed inhibitory effects against enzymes involved in carbohydrate metabolism including pancreatic α-amylase and intestinal α-glucosidase.[28] Recently, the ethanolic leaf extract of *S. ellipticum* was reported to increase the catalytic activity of GK and showed antidiabetic potential in streptozotocin-induced diabetic Wistar rat model.[29-31]

In the current investigation, some phytoconstituents of *S. ellipticum* leaf extract including five-triterpenoids, two-flavonoids, two-steroidal derivatives and one-phenolic compound were selected for the *in-silico* evaluation using molecular docking studies to explore their binding mode and interactions with the human GK enzyme (Table 1).

Table 1: Compounds selected for the *in-silico* molecular docking studies with human GK protein.

Code	*Compound name*	*Structure*	*Chemical class*
SE1	Lupeol		Triterpenoids
SE2	Lupeol acetate		Triterpenoids
SE3	Stigmasterol		Sterols
SE4	Alpha-tocopherol		Phenolic compounds
SE5	Amentoflavone		Flavonoids
SE6	Beta-sitosterol		Sterols

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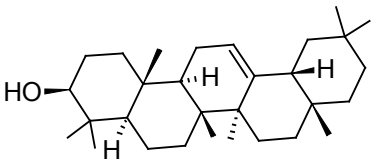
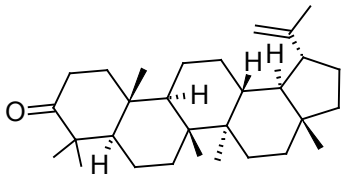
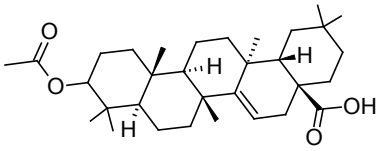
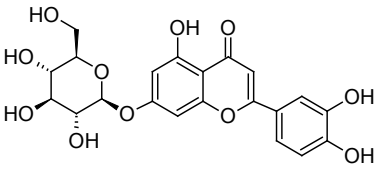
SE7	Beta-amyrin		Triterpenoids
SE8	Lupenone		Triterpenoids
SE9	Acetyl aleuritolic acid		Triterpenoids
SE10	Luteolin-7-glucoside		Flavonoids

MATERIALS AND METHODS

Prediction of pharmacokinetic parameters

All the compounds selected for molecular docking studies were evaluated for the prediction of pharmacokinetic parameters associated to absorption, distribution, metabolism, and excretion (ADME) by employing FAF-Drugs 4 server; and accessed for drug-likeness using Lipinski's rule.[32-33]

Molecular docking studies

Molecular docking investigations were performed for the selected compounds in the allosteric site of GK employing AutoDock Vina[34] and AutoDock Tools (ADT).[35] The 2D chemical structures ("SDF" format) of all the ligands were downloaded from the PubChem[36] followed by conversion to 3D ("MOL2" format) using "Frog2" server.[37] The ligands ("MOL2" format) were converted to "PDBQT" files using ADT. After assessing some co-crystallized structures for the target proteins available in the protein data bank, the best ligand-bound complex was selected (PDB ID: 3IMX) based on higher resolution and fundamental binding interactions between the GK and small molecule GK activators. The "PDB" file of GK was edited using PyMOL (The PyMOL Molecular Graphics System, Version 2.0, 2018, Schrödinger, LLC.) by removing the co-crystallized activator, all the water molecules along with other non-interacting species. The "PDBQT" file of GK protein was generated from "PDB" file using ADT.[38-41] The "Grid" tool of ADT was used to calculate the grid parameters and all the information concerning input files, grid box (grid size and geometry of the allosteric site) and out files (docked molecules and log files) were saved in "txt" file.[42] Docking was performed for all the ligands in the allosteric binding site of the GK protein using the command line on Windows. The reference ligand was docked in the allosteric binding site of the GK enzyme and compared with that of the co-crystallized GK activator for determining the accuracy of the docking protocol. The 3-D optimized ligands were docked in the allosteric binding site of the refined GK protein and scored using the scoring function. The binding free energy (ΔG, kcal/mol) for each compound was reported in log file and the binding interactions of the ligands in the allosteric site of GK were analyzed using PyMOL.[43-44]

In silico prediction of toxicity

All the compounds were evaluated for the prediction of possible toxicity of these compounds using "pkCMS" online server tool.[45-46]

RESULTS AND DISCUSSION

Prediction of ADME properties

ADME properties including molecular weight (MW), partition coefficient (log P), distribution coefficient (log D), water solubility (log S_w), topological polar surface area (tPSA), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), solubility (mg/L) and number of rotatable bonds (NRB) were calculated for the compounds chosen for the docking studies. Almost all of the compounds showed good pharmacokinetic (ADME) parameters for oral bioavailability (Table 2) and drug-likeness as contrived by using "Lipinski's rule of five."

In silico docking studies

In silico molecular docking studies were performed to explore the affinity and binding interactions of the selected compounds using AutoDock Vina in the allosteric site of the GK protein

Table 2: ADME properties predicted for the compounds selected for *in-silico* studies.

Comp.	*MW*	*log P*	*log D*	*log Sw*	*tPSA*	*HBA*	*HBD*	*Solubility*	*NRB*
SE1	426.7	9.8	7.5	-8.6	20.2	1	1	75.6	1
SE2	468.8	9.4	7.8	-9.1	26.3	2	0	50.7	3
SE3	412.7	8.6	7.4	-7.5	20.2	1	1	237.2	5
SE4	430.7	9.7	8.9	-8.5	29.4	2	1	86.4	12
SE5	538.5	5.0	3.1	-6.5	181.1	10	6	759.4	3
SE6	414.7	9.3	7.8	-7.9	20.2	1	1	153.8	6
SE7	426.7	9.1	7.4	-8.2	20.2	1	1	111.5	0
SE8	424.7	9.6	8.0	-8.4	17.1	1	0	92.7	1
SE9	498.7	8.4	4.4	-8.0	66.4	4	1	162.9	3
SE10	448.4	0.7	0.1	-3.0	190.3	11	7	21372.5	4

(PDB ID: 3IMX). The reference GK activator produced an analogous binding pattern and overlay on binding mode of co-crystallized GK activator (PDB ID: 3IMX) with ΔG of -9.0 kcal/mol validating accuracy of the docking procedure. Based on the lowest binding free energy (ΔG) and docking interactions in the allosteric site of GK protein, lupeol, alpha-tocopherol, amentoflavone and luteolin-7-glucoside were further investigated in minutiae using PyMOL for exploring binding interactions of these compounds with the allosteric site residues of GK (Table 3).

Super-imposing of the docked poses of lupeol (SE1), alpha-tocopherol (SE4), amentoflavone (SE5) and luteolin-7-glucoside (SE10) with that of the co-crystallized GK activator (PDB entry: 3IMX) ((2R)-3-cyclopentyl-N-(5-methoxy[1,3] thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(4-methylpiperazin-1-yl) sulfonyl]phenyl}propanamide) in the allosteric binding site of the GK enzyme demonstrated that the selected molecules had the similar binding and orientation pattern in the allosteric binding site of GK enzyme as that of the co-crystallized GK activator (Figure 1).

The docked pose of lupeol showed H-bond interaction between 'OH' of 4-hydroxyphenyl group and backbone 'carbonyl' of Arg63 residue with bond length of 4.0 Å and hydrophobic interactions with Pro66, Trp99, Ile211, Tyr214, Tyr215 and Val455 residues of the allosteric site of GK. Alpha-tocopherol showed H-bond interaction (between phenolic 'OH' and backbone 'carbonyl' of Arg63 residue with bond length of 2.8 Å) with GK protein. The phenolic ring of alpha-tocopherol projected into the hydrophobic cavity displaying interactions with Val62, Ile211, Tyr214, His218, Leu451, and Val455 residues and side-chain protruded in the hydrophobic pocket comprising of Val91, Trp99, Tyr215 and His 218 residues in an allosteric site of GK. Amentoflavone showed H-bond interactions between phenolic 'OH' and backbone carbonyl of Arg63 residue (bond length 2.6 Å), and 'OH' of the flavone moiety and 'OH' of Ser69 residue (bond length 4.2 Å) of GK. The phenolic moiety of amentoflavone projected in hydrophobic pocket showing interactions with Ile211 and Val455 residues, flavone moiety showed hydrophobic interactions with Pro66, Tyr214 and His218 residues in an allosteric site of GK. Luteolin-7-glucoside showed H-bond interactions between alcoholic 'OH' and backbone carbonyl of Arg63 residue (bond length 3.1 Å), and 'OH' of the flavone moiety and 'OH' of Ser69 residue (bond length 3.4 Å) in the allosteric site of GK. The 3,4-dihydroxy phenyl moiety of luteolin-7-glucoside protruded in the hydrophobic cavity displaying interactions with Val455 and Lys459 of the R13 helix, along with Pro66 of the connecting region I and Ile159, flavone moiety packs between Ile211, Tyr214, Val455 and Ala456 residues of an allosteric site of GK (Figure 2).

Prediction of toxicity and safety

The possible toxicity (mutagenicity, carcinogenicity, cardiotoxicity, hepatotoxicity, and skin irritation) for the selected compounds was accessed using the "pkCSM" online server tool, which depends on the "graph-based signatures." As

Table 3: Binding interactions and docking score (ΔG) of selected compounds with human GK enzyme.

	H-bond interactions			
Comp.	*Residue(s)*	*Distance (Å)*	*Residues involved in hydrophobic interactions*	*ΔG*
SE1	Arg63	4.0	Pro66, Trp99, Ile211, Tyr214, Tyr215, Val455	-8.2
SE2	Ser69	4.6	Pro66, Ile211, Tyr214, Val455	-7.6
SE3	Arg63	3.7	Pro66, Tyr214, Tyr215, Val455	-7.7
SE4	Arg63	2.8	Val62, Val91, Ile211, Tyr214, His218, Leu451, Val455	-8.6
SE5	Arg63	2.6	Pro66, Ile211, Tyr214, His218, Leu451, Val455	-9.3
	Ser69	4.2		
SE6	Ser69	3.1	Pro66, Tyr214, His218, Val455	-7.7
SE7	Arg63	3.2	Pro66, Tyr214, His218, Leu451, Val455	-7.4
SE8	Arg63	3.9	Pro66, Ile211, Tyr214, Leu451, Val455	7.6
SE9	Arg63	3.1	Pro66, Ile211, Tyr214, His218, Val455	7.2
SE10	Arg63	3.1	Val62, Pro66, Ile159, Ile211, Val452, Val455, Ala456, Lys459	-8.7
	Ser69	3.4		

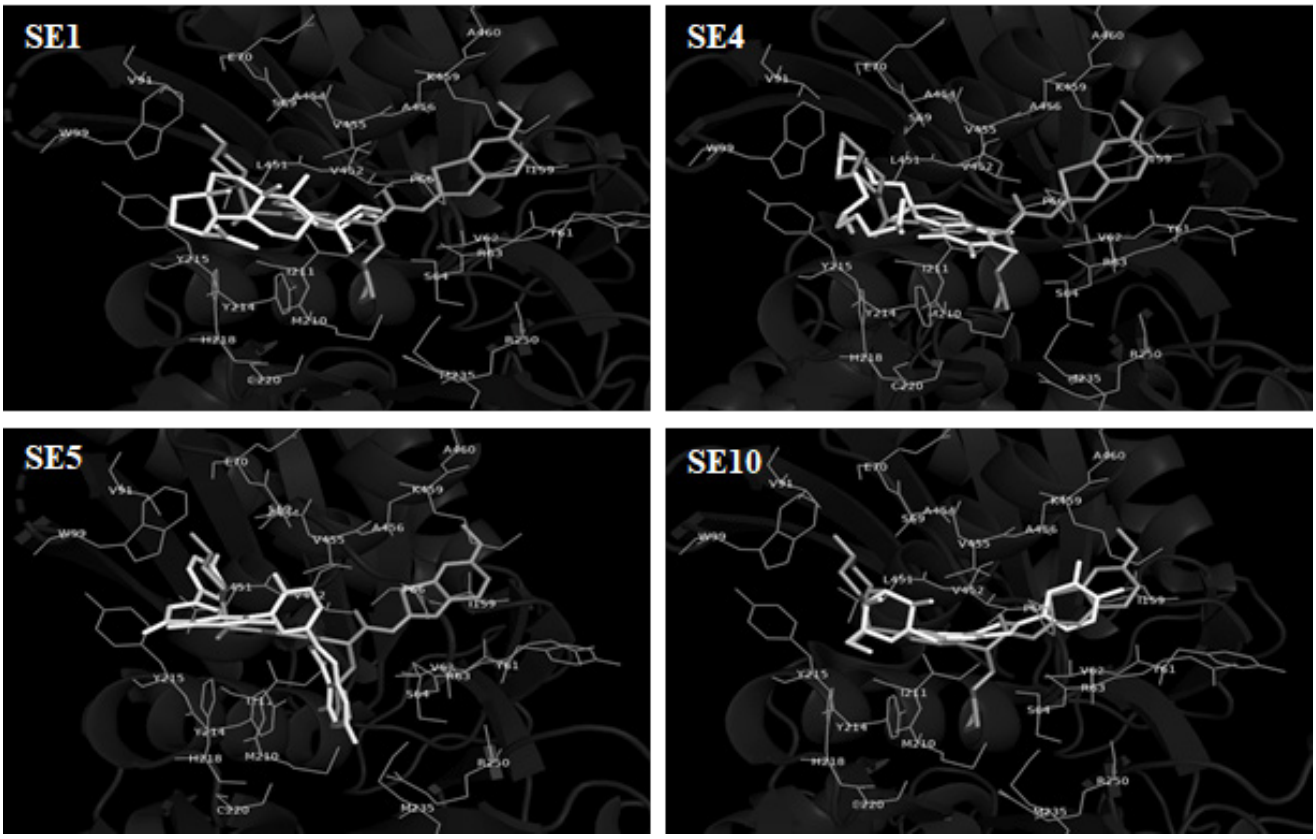


Figure 1: Super-positioning of the docked poses of lupeol (SE1), alpha-tocopherol (SE4), amentoflavone (SE5), and luteolin-7-glucoside (SE10) (white sticks) with that of PDB ligand 3IMX (grey sticks) in the allosteric site of GK.

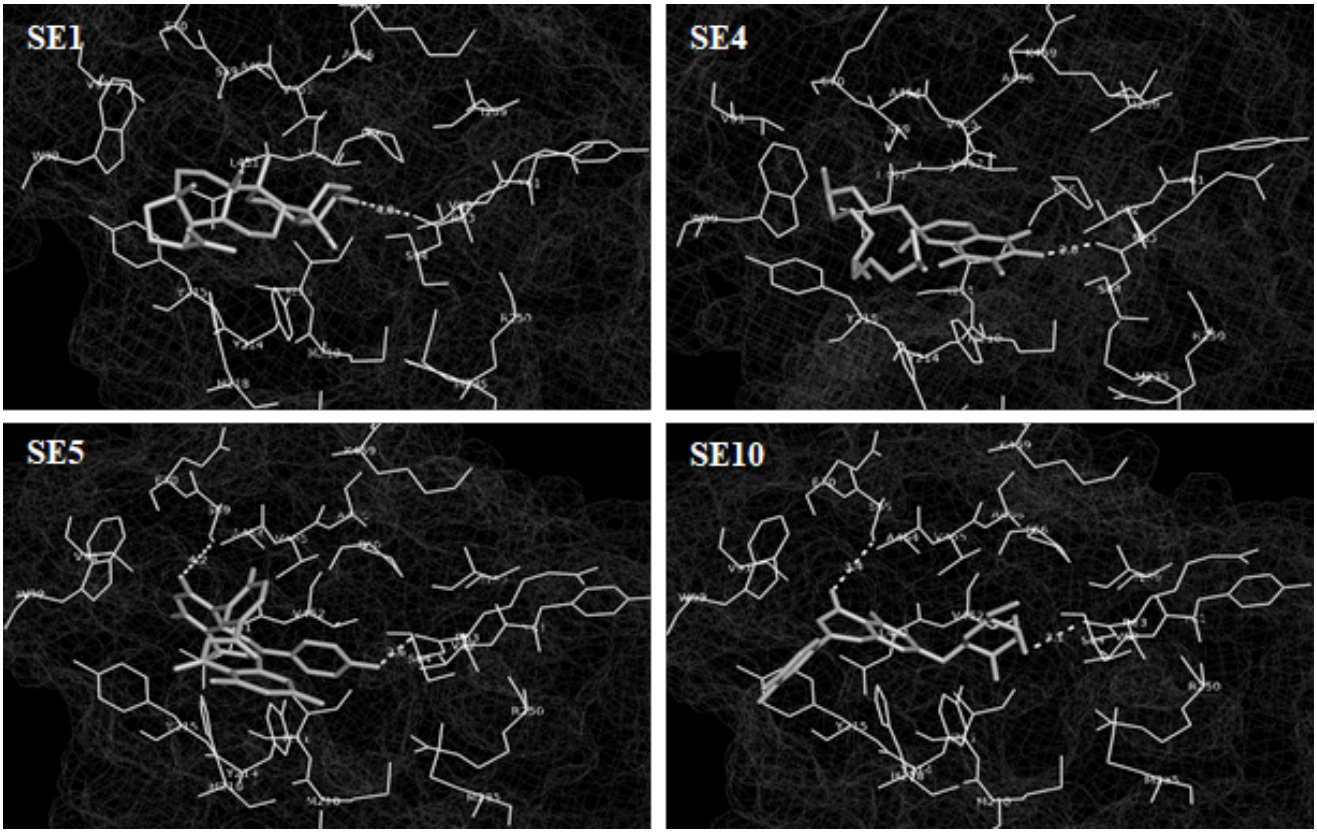


Figure 2: Best docked poses of lupeol (SE1), alpha-tocopherol (SE4), amentoflavone (SE5), and luteolin-7-glucoside (SE10) showing H-bond interactions with the allosteric site residues of GK.

Table 4: Toxicity prediction for the selected compounds using "pkCMS" online server.

Comp.	*Muta-genicity*[a]	*Cardio-toxicity*[b]	*Acute toxicity*[c]	*Chronic toxicity*[d]	*Max. tolerated dose*[e]	*Hepato-toxicity*	*Skin irritation*
SE1	No	No*	2.616	0.967	0.067	No	No
SE2	No	No*	2.364	2.212	0.649	No	No
SE3	No	No*	2.433	0.848	0.604	No	No
SE4	No	No*	2.055	2.903	0.656	No	No
SE5	No	No*	2.489	3.219	0.425	No	No
SE6	No	No*	2.332	0.845	0.431	No	No
SE7	No	No*	2.267	0.987	0.022	No	No
SE8	No	No*	2.353	1.015	0.541	No	No
SE9	No	No#	2.794	1.834	0.326	No	No
SE10	No	No*	2.432	4.383	1.165	No	No

[a]Mutagenicity was accessed using AMES test; [b]Cardiotoxicity was accessed using hERG-I and hERG-II inhibition; [c]Acute toxicity: Oral rat acute toxicity (*i.e.*, LD_{50} in mol/kg); [d]Chronic toxicity: Oral rat chronic toxicity (log mg/kg_bw/day); [e]Max. tolerated dose (Human): log mg/kg/day; *Compound showed inhibition of hERG-II only (i.e., partially safe); #Compound not inhibited both hERG-I and hERG-II (i.e., no cardiotoxicity).

per the results displayed in Table 4, all the selected compounds displayed little toxicity possibility.

In summary, some compounds found in *S. ellipticum* were evaluated *in silico* using molecular docking studies for exploring binding interactions of these compounds with allosteric binding site residues of the human GK enzyme. Amongst these compounds, lupeol, alpha-tocopherol, amentoflavone, and luteolin-7-glucoside displayed appreciable binding interactions with allosteric site residues of GK supporting the *in vitro* GK activity of *S. ellipticum* leaf extract reported by Ighodaro *et al*., (2017). Structural modifications and further studies on these phytoconstituents could be done to develop safe and potent allosteric activators of the human GK enzyme for the treatment of diabetes.

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