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MOLECULAR DOCKING STUDIES OF PHENOLIC COMPOUNDS FROM *CITRUS SINENSIS* AGAINST MULTIPLE TARGETS OF TYPE 2 DIABETES

Ajmer Singh Grewal[1], Neelam Sharma[2], Sukhbir Singh[2*], Anil Bansal[2], Sakshi[2] and Supriya Kumari Singh[2]

[1]Chitkara University School of Basic Sciences, Chitkara University, Himachal Pradesh, India

[2]Chitkara College of Pharmacy, Chitkara University, Punjab, India

[*]Author for Correspondence E-mail: sukhbir.singh@chitkara.edu.in; singh.sukhbir12@gmail.com

Abstract

Treatment of diabetes deprived of any adverse action is still a menace for the health organizations. This results in growing interest for plant-derived medicines with antidiabetic potential without adverse actions. Some flavonoids and other phenolic compounds from *C. sinensis* were reported in literature to have antidiabetic potential. The main objective of the current investigation was the *in silico* screening of some phenolic compounds from *C. sinensis* against multiple targets associated with type 2 diabetes to explore the mechanism of antidiabetic action and prediction of binding mode and interactions. Molecular docking investigations were carried out for the selected molecules in the 'active site' of the multiple targets associated with type 2 diabetes (α-glucosidase, dipeptidyl peptidase 4, glycogen synthase kinase 3, glucokinase and glucagon receptor). Amongst the compounds tested *in silico*, hesperetin showed appreciable docking interactions with multiple targets of type 2 diabetes including α-glucosidase, dipeptidyl peptidase 4, glucagon receptor and glycogen synthase kinase 3. Isorhamnetin, kaempferol and sakuranetin displayed appreciable interactions three different targets of type 2 diabetes. This information can be utilized for the development of potent and safe multi-functional candidate drugs for treatment of type 2 diabetes.

Keywords: Alpha-glucosidase, *Citrus sinensis*, DPP4, Glucagon receptor, Glucokinase, GSK3, Phenolic compounds.

Introduction

Diabetes mellitus (or basically diabetes) is an enduring malady related to metabolism of nutrition characterized by increased blood glucose, originating from faulty insulin secretion, insulin action or both leading to tissue and vascular damage and resulting in a variety of serious problems. Type 2 diabetes (T2D) is prevalent amongst most of the patients suffering from diabetes (Olokoba *et al*., 2012; Grewal *et al*., 2016). Even though a number of oral antidiabetic agents are available for the management T2D, in most of the patients having T2D, no solo antidiabetic agent is advantageous in attaining durable control of plasma sugar within usual physiological range. Owing to the above reason, now-a-days doctors advise combination of hypoglycemic agents at an initial phase of T2D treatment. Additionally, overdose of hypoglycemic drugs may possibly result in serious hypoglycemia causing brutal adverse reactions, and subjects generally need immediate remedial cure. This caused the scientific community to search for safe and pharmacologically distinct antidiabetic drugs (Bastaki, 2005; Grewal *et al*., 2016a). Various types of plant-derived active principles representing several bioactive compounds have established their beneficial role for possible use in diabetes therapeutics (Kumar *et al*., 2012; Osadebe *et al*., 2014; Grewal *et al*., 2018).

Citrus sinensis (L. Osbeck), also known as sweet orange serves as the biggest citrus producer clusters grown worldwide, representing for around 70% of the entire yearly cultivation of the '*Citrus* species', and is inhabitant to Asia and is nowadays prevalent all over the Pacific as well as hot regions of the globe (Hernández *et al*., 2016). *C. sinensis* is consumed as an excellent source of vitamin C, and has been used traditionally for the treatment of disorders such as irregularity, muscle pain, stomachache, diarrhea, lungs infection, tuberculosis-infection, cough, common-cold, overweightness, menstrual illness, cardiac infarction, high blood pressure and psychological disorders (Milind and Chaturvede, 2012; Rafiq *et al*., 2018). A variety of various pharmacological activities were shown by *C. sinensis* including antidiabetic, anti-obesity, inflammation healing, bactericidal, fungicidal, anti-osteoporotic, anti-parasitic, anti-cancer, anti-oxidant, cardio-protective, hypocholesterolemic, insecticidal, relaxant, sedative, and anxiolytic activity (Hernández *et al*., 2016). Various types of secondary metabolites like flavonoids and other phenolic compounds (hesperidin, hesperetin, sinsetin, isosakuranetin, isorhamnetin, kaempferol, cyaniding-3,5-diglucoside, limocitrin, limocitrol, chrysoeriol, narirutin, naringin, naringenin, nobiletin, narirutin-4'-glucoside, pedunculin, quercetin, quercetagetin, sakuratin, sakuranetin and tangeretin), steroids (β-sitosterol and β-sitosterol-3-O- β-D-glucopyranoside), hydroxyamides (E)-N-(1,3,4,5-tetrahydroxyhexadecan-2-yl)dec-4-enamide), alkanes (tetracosane), coumarins (scoparone, limettin, sothol, xanthotoxin, bergapten, bergaptol and isopimpinellin), peptides (citrusin I, II and III), carbohydrates (sucrose, fructose, glucose and galactose), carbamates (carbofuran, carbosulfan and hydroxycarbofuran), alkyl amines (dibutyl-amine), carotenoids (zeaxanthin, zeinoxanthin, β-cryptoxanthin and lutein), volatile compounds (limonene, neral, myrcene, carvone, geranial, geraniol, α-terpinene, α-terpineol, vanillin, nerol and tyramine), and minerals (K, Mg, Ca and Na) are present in different parts of the plant (Hernández *et al*., 2016; Liu *et al*., 2012; Rafiq *et al*., 2018; Sharma *et al*., 2015; Chaudhari *et al*., 2016). Some flavonoids and other phenolic derivatives obtained from *C. sinensis* including hesperetin, isorhamnetin, kaempferol, limocitrin, limocitrol, naringenin, quercetin and sakuranetin were reported in literature to have potential benefits for T2D (Hernández *et al*., 2016; Kim *et al*., 2016; Dosoky and Setzer, 2018).

Currently, medicinal research is focussed on polypharmacological compounds acting on multiple targets against complex disorders including diabetes, cancer,

neurodegenerative diseases, and certain infectious diseases owing to greater efficacy, improved safety profile and ease of administration of the multi-target drugs. Molecular docking is one of the most widely used techniques for the design of multi-target drugs (Espinoza-Fonseca, 2006; Scotti *et al*., 2017). Various types of proteins and enzymes are involved in the pathogenesis of T2D including α-glucosidase (AG), dipeptidyl peptidase 4 (DPP4), glucagon receptor (GCR), glucokinase (GK) and glycogen synthase kinase 3 (GSK3) (van de Laar, 2008; Duez *et al*., 2012; Scheen, 2012; Godoy-Matos, 2014; Grewal *et al*., 2014; Singh *et al*., 2017; Grewal *et al*., 2019; Grewal *et al*., 2019a; Henriksen and Dokken, 2006; MacAulay and Woodgett, 2008). In the current investigation docking studies were performed for some phenolic compounds found in various parts of *C. sinensis* (Figure 1) in the binding site of the multiple targets associated with T2D in order to explore the mechanism of antidiabetic action and binding modes of these compounds using molecular docking studies.

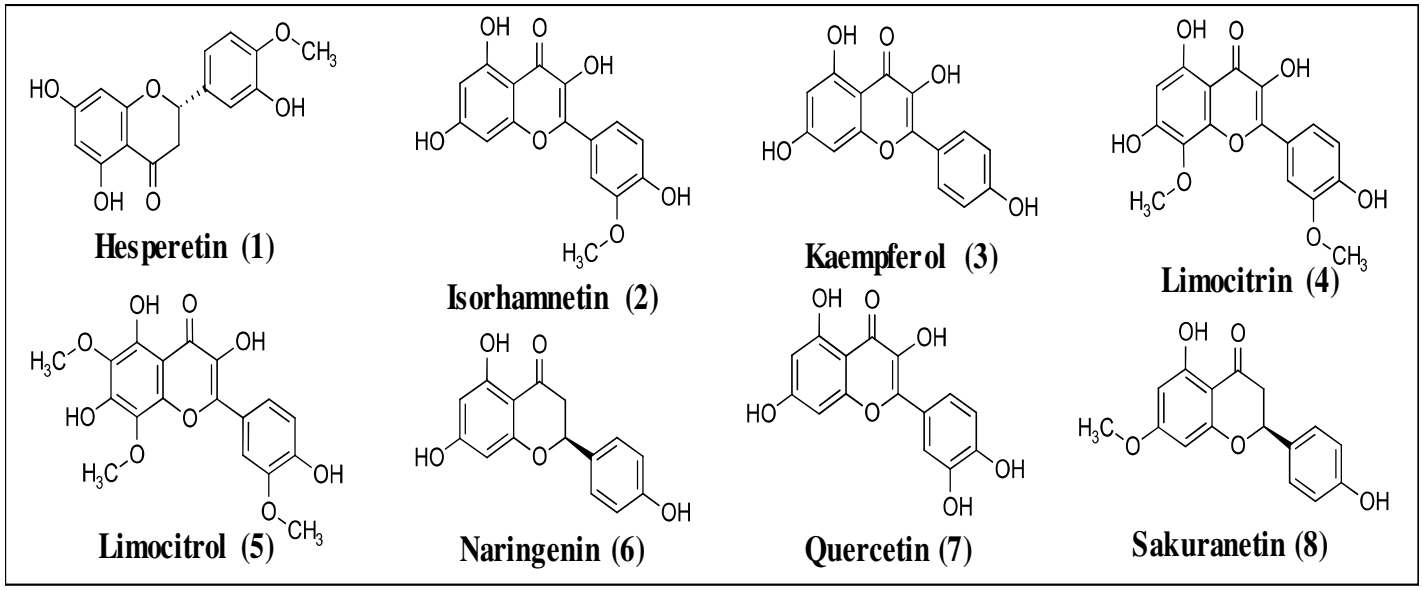

Fig. 1: Chemical structures of the phyto-constituents chosen for molecular docking investigations *in silico*.

Materials and Methods

Prediction of pharmacokinetic parameters

All the compounds selected for molecular docking studies were analyzed for the prediction of pharmacokinetic parameters related to absorption, distribution, metabolism, and excretion (ADME) by employing FAF-Drugs4 server; and accessed using 'Lipinski's rule of five' for drug-likeness (Lagorce *et al*., 2017).

Molecular docking studies

Molecular docking investigations were carried out for the selected compounds in the 'binding site' of the proteins involved in pathogenesis of T2D (AG, DPP4, GCR, GK, and GSK3: PDB IDs 3L4T, 4A5S, 5EE7, 3IMX, and 1Q5K; respectively) using 'AutoDock Vina' (Trott and Olson, 2010) and 'AutoDock Tools' (Morris *et al*., 2009). The 2D chemical structures of all the ligands were prepared by MarvinSketch (Version 18.5.0, 2018, ChemAxon) followed by conversion to 3D with Frog2 server (Miteva *et al*., 2010). All the ligands were converted to "pdbqt" files using AutoDock Tools. After assessing a number of co-crystallized structures for the target proteins available in the protein data bank; the best ligand bound complexes were selected. The PDB files of the proteins were edited using PyMOL (Schrödinger, LLC.) by removing the co-crystallized ligands, entire water units together with every non-bonded species. The "pdbqt" files of target proteins were generated from the "pdb" files using AutoDock Tools. The grid specifications were computed by means of "Grid" tool of 'AutoDock Tools' and saved in "txt" file. Docking was performed using command line. Reference ligands (co-crystallized ligands of respective PDBs) were docked in the binding/active/allosteric site of the intended proteins and compared with that of the co-crystallized structures for determining accuracy of docking protocol. The binding free energy (ΔG, kcal/mol) for each ligand was reported in log file and the docking interactions of the ligands in binding site of the target proteins were analysed using PyMOL (Grewal *et al*., 2017; Rathee *et al*., 2018; Charaya *et al*., 2018; Rathee *et al*., 2019; Grewal *et al*., 2019b).

In silico prediction of toxicity

All the compounds were evaluated for the *in silico* prediction of possible toxicity of these compounds using pkCSM online platform (Pires *et al*., 2015).

Results and Discussion

Prediction of ADME parameters

ADME parameters including molecular weight (MW), partition coefficient (log P), distribution coefficient (log D), water solubility (log S_w), 'topological polar surface area' (tPSA), H-bond acceptors (HBA), H-bond donors (HBD), solubility (mg/L) and 'number of rotatable bonds' (NRB) were predicted for all the phytoconstituents chosen for the molecular docking investigations. All of the molecules chosen for the *in silico* investigations showed good pharmacokinetic parameters for oral bioavailability (Table **1**) and drug-like properties as contrived by 'Lipinski's rule of five' (i.e., MW < 500 Da; log P < 5; HBA ≤ 10 and HBD: ≤ 5).

Table 1: Predicted ADME properties of the compounds selected for molecular docking studies.

Ligand	Ligand name	MW	log P	log D	log S_w	tPSA	HBA	HBD	Solubility	NRB
1	Hesperetin	302.2	2.60	2.56	-3.47	96.22	3	6	9436.2	2
2	Isorhamnetin	316.3	1.87	1.19	-3.19	120.03	4	7	13083.6	2
3	Kaempferol	286.2	1.90	1.35	-3.13	110.80	4	6	12543.7	1
4	Limocitrin	346.3	2.46	1.40	-3.64	129.26	4	8	9069.3	3
5	Limocitrol	376.3	2.43	0.84	-3.72	138.49	4	9	9161.7	4
6	Naringenin	272.2	2.52	2.72	-3.33	86.99	5	8	9773.4	3
7	Quercetin	302.2	1.54	1.01	-2.99	131.03	5	7	15228.1	1
8	Sakuranetin	286.3	2.85	2.98	-3.53	75.99	2	5	8371.4	2

*Optimum range (for drug-likeness or oral bioavailability): MW: < 500 Da; log P: < 5; log D: < 5; log S_w: ≤ -5; tPSA: < 140 Å; HBA: ≤ 10; HBD: ≤ 5; Solubility: > 100 mg/L; NRB: ≤ 10.

In Silico docking investigations

In silico molecular docking investigations were performed to explore the affinity as well as binding interactions of the phenolic compounds using AutoDock Vina in the 'binding site' of the intended proteins (AG, DPP4, GCR, GK and GSK3). The docked reference ligands (co-crystallized ligands of respective PDBs) produced an analogous binding pattern and overlapping on the binding manner of the x-ray crystallized ligands (PDB structures) authenticating accuracy of the methodology using in docking investigations. Docking score (also known as binding free energy, ΔG) of the top ranked docked conformations of the selected compounds with the target proteins are presented in Table 2.

Table 2: Docking score of the selected compounds for docking in the 'binding site' of AG, DPP4, GCR, GK and GSK3.

Ligand No.	Ligand name	ΔG (kcal/mol)				
		AG	DPP4	GCR	GK	GSK3
1	Hesperetin	-7.5	-8.2	-8.6	-7.1	-7.9
2	Isorhamnetin	-7.0	-7.2	-7.6	-8.1	-7.6
3	Kaempferol	-7.0	-8.3	-7.4	-7.2	-7.6
4	Limocitrin	-6.7	-7.4	-6.9	-8.0	-6.4
5	Limocitrol	-6.1	-7.6	-6.7	-8.3	-7.2
6	Naringenin	-6.1	-7.9	-7.9	-8.9	-7.0
7	Quercetin	-6.5	-7.1	-7.8	-7.5	-7.9
8	Sakuranetin	-7.2	-7.8	-8.3	-7.2	-7.0
Reference*		-7.6	-7.9	-8.5	-8.4	-7.6

*Co-crystallized ligands of the respective PDB IDs.

Docking with AG

Based on ΔG and docking interactions; compounds 1, 2, 3 and 8 were then again studied in minutiae by means of PyMOL for exploring the binding connections of these analogues with binding site residues of AG protein (Table 3).

Table 3: Binding interactions of compounds 1, 2, 3 and 8 with AG (PDB ID: 3L4T).

Ligand	H-bond interactions	Hydrophobic interactions (residues)
	Residues and Distance (Å)	
1	Asp327 (3.1, 2.9), His600 (4.2)	Trp406, Phe575
2	Asp327 (2.9), Arg526 (3.3), Asp542 (3.4), His600 (4.0)	Trp406, Phe575
3	Asp327 (2.8), Arg526 (3.2), Asp542 (), His600	Trp406, Phe575
8	Asp203 (3.2), Asp542 (3.6)	Trp406, Phe575

Superimposes of the docked conformations of 1, 2, 3 and 8 with the with that of PDB ligand 3L4T (BJ2661) in the binding site of AG disclosed that these molecules had an analogous binding and orientation manner in the 'binding site' of AG as that produced by co-crystallized inhibitor (Figure 2).

The docked poses of 1, 2, 3 and 8 showed appreciable H-bond interactions with binding site residues (Asp203, Asp327, Arg546, Asp542 and His600) of AG protein. These compounds projected in the hydrophobic cavity revealing bonding to Trp406 and Phe575 residues in the 'binding site' of AG (Figure 3).

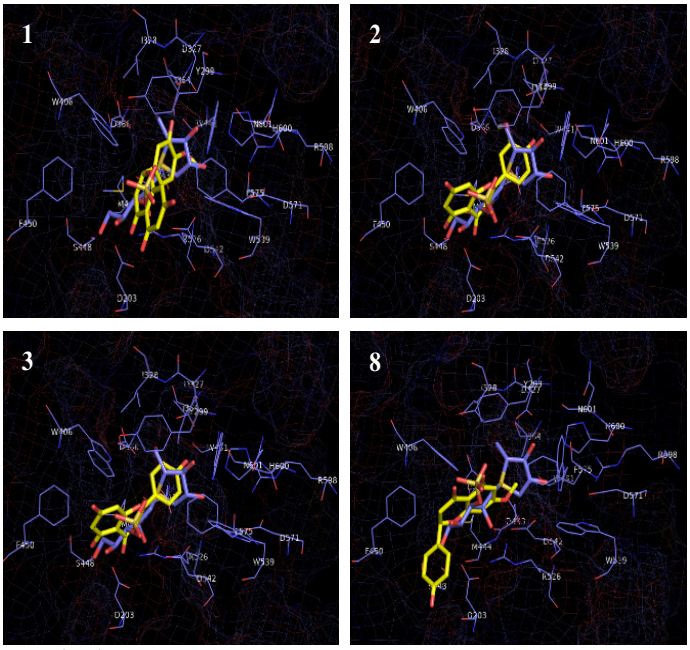

Fig. 2: Superposition of the docked postures of 1, 2, 3 and 8 (yellow) with that of PDB ligand 3L4T (purple) in the 'binding site' of AG.

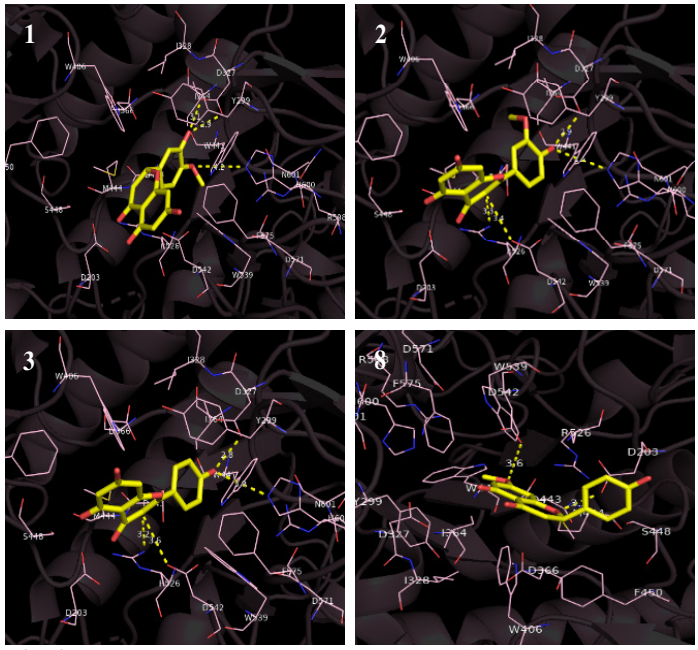

Fig. 3: Docked pictures presenting H-bonds of 1, 2, 3 and 8 with the residues in 'binding site' of AG.

Docking with DPP4

Based on ΔG and docking interactions; compounds 1, 4, 5, and 8 were examined again in minutiae by means of PyMOL for exploring binding connections of these analogues with binding site residues of DPP4 (Table 4).

Table 4: Binding interactions of compounds 1, 4, 5, and 8 with DPP4 (PDB ID: 4A5S).

Ligand	H-bond interactions Residues and Distance (Å)	Hydrophobic interactions (residues)
1	Glu205 (3.2), Glu206 (3.0), Tyr662 (2.9)	Trp629, Ser630, Tyr662
4	Glu205 (3.5), Glu206 (2.7), Tyr631 (5.3), Tyr662 (3.7)	Gly628, Trp629, Ser630
5	Glu205 (4.0), Glu206 (4.3), Tyr631 (4.2), Tyr662 (2.8)	Trp629, Ser630, Tyr662
8	Glu205 (3.3), Glu206 (2.9), Tyr662 (3.0)	Tyr547, Gly628, Ser630

Superimposes of the docked postures of 1, 4, 5, and 8 with that of PDB ligand 4A5S in the 'binding site' of DPP4 disclosed that these analogues had an analogous binding and orientation manner in the 'binding site' of DPP4 as that produced by the x-ray crystallized inhibitor (Figure 4).

The docked poses of 1, 4, 5, and 8 showed appreciable H-bond interactions with binding site residues (Glu205, Glu206, Tyr631, Tyr662) of DPP4 protein. These compounds projected in the hydrophobic cavity demonstrating bonding with Gly628, Trp629, Ser630 and Tyr662 residues in binding site of DPP (Figure 5).

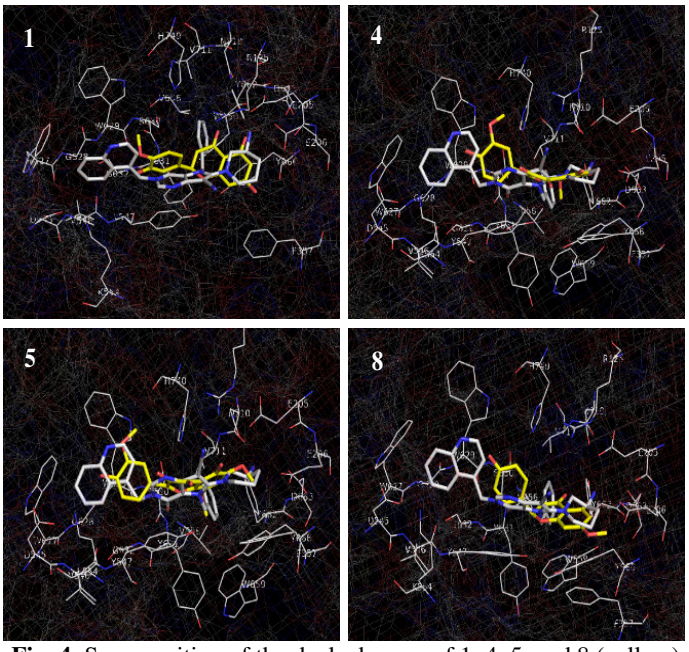

Fig. 4: Superposition of the docked poses of 1, 4, 5, and 8 (yellow) with that produced by the PDB ligand 4A5S (grey) in the 'binding site' of DPP4.

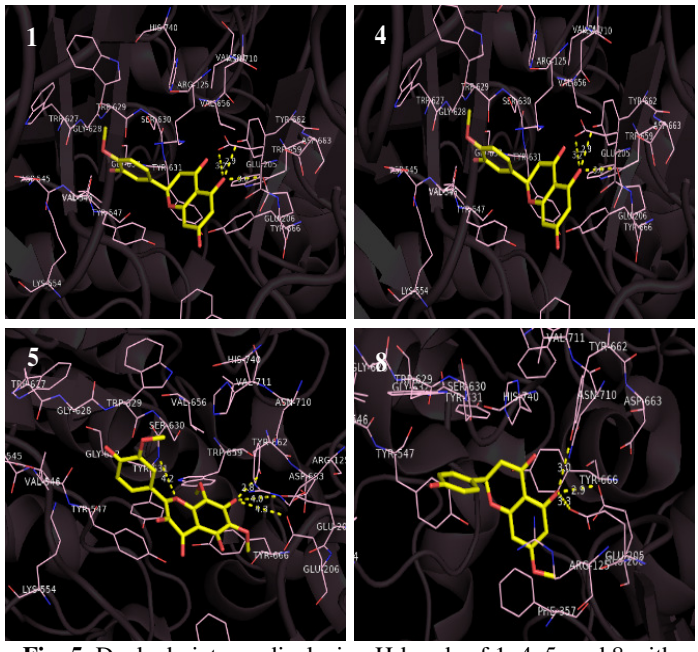

Fig. 5: Docked pictures displaying H-bonds of 1, 4, 5, and 8 with the 'binding site' residues of DPP4.

Docking with GCR

Based on ΔG and docking connections; compounds 1 and 8 were examined again in minutiae by means of PyMOL for exploring docking connections of these analogues with 'binding site' residues of the GCR (Table 5).

Table 5: Binding interactions of compounds 1 and 8 with GCR (PDB ID: 5EE7).

Ligand	H-bond interactions Residues and Distance (Å)	Hydrophobic interactions (residues)
1	Arg346 (4.0), Lys349 (3.2), Ser350 (3.5), Asn404 (2.9), Lys405 (4.1)	Lys349, Leu403
8	Arg346 (4.0), Lys349 (3.3), Ser350 (3.3), Asn404 (3.0), Lys405 (4.1)	Lys349, Leu403

Superimposes of the docked postures of 1 and 8 with the with that of PDB ligand 5EE7 (reference ligand) in the 'binding site' of GCR disclosed that these analogues had an analogous binding and alignment manner as that produced by the co-crystallized antagonist of GCR (Figure 6).

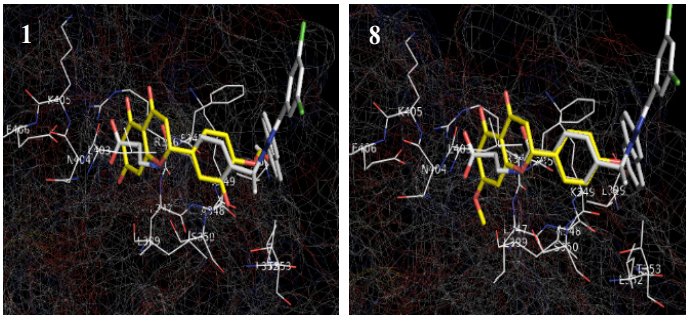

Fig. 6: Superposition of the docked postures of 1 and 8 (yellow) with that of PDB ligand 5EE7 (grey) in the binding site of GCR.

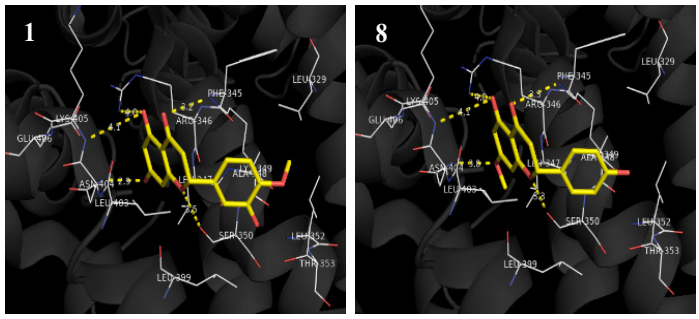

Fig. 7: Docked pictures displaying H-bonds of 1 and 8 with the 'binding site' residues of GCR.

The docked pictures of 1 and 8 disclosed significant H-bonds with 'binding site' residues (Arg346, Lys349, Ser350, Asn404 and Lys405) of GCR. These compounds projected in the hydrophobic cavity displaying bonding with Gly628, Trp629, Ser630 and Tyr662 residues in binding site of GCR (Figure 7).

Docking with GK

Based on ΔG and docking connections; 2, 4, 5 and 6 were examined again in minutiae by means of PyMOL for exploring docking connections of these molecules with the 'allosteric site' residues of GK (Table 6).

Table 6: Binding interactions of compounds 2, 4, 5 and 6 with GK (PDB ID: 3IMX).

Ligand	H-bond interactions Residues and Distance (Å)	Hydrophobic interactions (residues)
2	Arg63 (2.7), Ser69 (3.6)	Ile159, Ile211, Tyr214, Met210, Val455, Lys459
4	Arg63 (3.0), Ser69 (2.7)	Ile159, Ile211, Tyr214, Met210, Val455, Lys459
5	Arg63 (4.1), Ser69 (2.9)	Ile159, Ile211, Tyr214, Met210, Val455, Lys459
6	Arg63 (3.2), Ser69 (3.2)	Ile159, Ile211, Tyr214, Met210, Val455, Lys459

Superimposes of the docked postures of 2, 4, 5 and 6 with that of PDB ligand 3IMX in the 'allosteric site' of GK demonstrated that these analogues had an analogous binding and alignment manner as that produced by the co-crystallized activator (Figure 8).

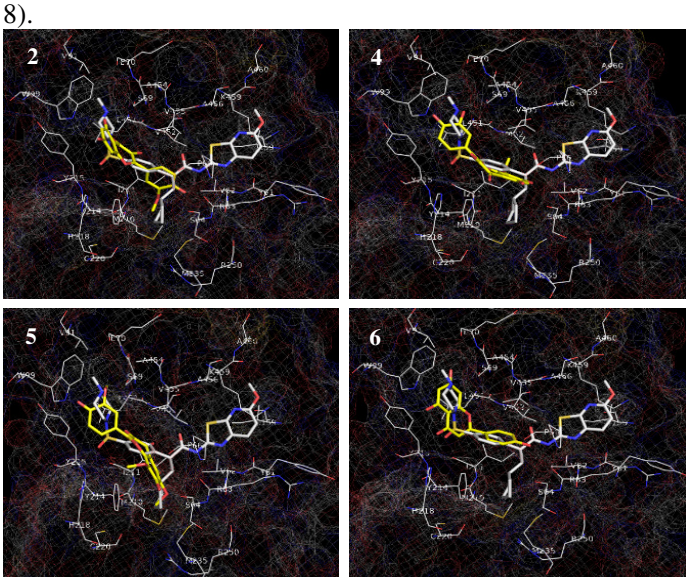

Fig. 8: Superposition of the docked postures of 2, 4, 5 and 6 (yellow) with that of PDB ligand 3IMX (grey) in the 'allosteric site' of GK.

The docked poses of 2, 4, 5 and 6 showed appreciable H-bond interactions with binding site residues (Arg63 and Ser69) of the GK protein. These compounds projected in the hydrophobic cavity displaying bonding with Ile159, Ile211, Tyr214, Met210, Val455, Lys459 residues of the 'allosteric site' of GK (Figure 9).

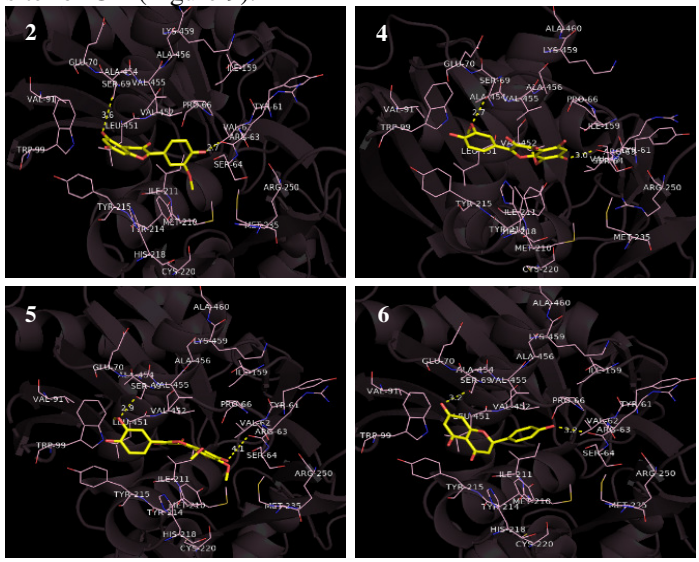

Fig. 9: Docked pictures displaying H-bonds of 2, 4, 5 and 6 with the 'allosteric site' residues of GK.

Docking with GSK3

Based on ΔG and docking interactions; compounds 1, 2, 3 and 7 were examined again in minutiae by means of PyMOL for exploring docking connections of these molecules with the allosteric site residues of GSK3 (Table 7).

Table 7: Binding interactions of compounds 1, 2, 3 and 7 with GSK3 (PDB ID: 1Q5K).

Ligand	H-bond interactions	Hydrophobic interactions (residues)
	Residues and Distance (Å)	
1	Val135 (3.2, 3.6), Pro136 (3.8)	Ile62, Arg141
2	Val135 (3.0, 4.3), Pro136 (3.5)	Ile62, Arg141
3	Val135 (3.0, 3.4, 4.2), Pro136 (3.1)	Ile62, Arg141
7	Val135 (3.0, 4.3), Pro136 (3.5)	Ile62, Arg141

Superimposes of the docked postures of 1, 2, 3 and 7 with the with that of PDB ligand 1Q5K in the binding site of GSK3 enzyme disclosed that these analogues had an analogous binding and orientation manner in the 'binding site' of protein as that produced by the co-crystallized inhibitor of GSK3 (Figure 10).

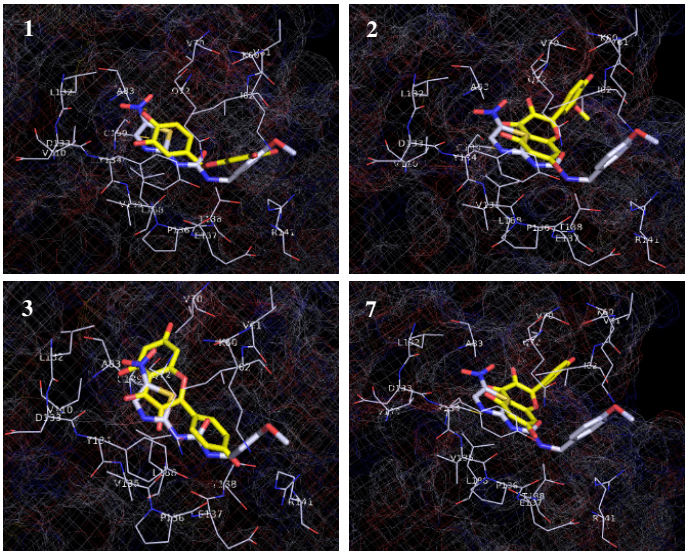

Fig. 10: Superposition of the docked postures of 1, 2, 3 and 7 (yellow stick) with that produced by PDB ligand 1Q5K (grey stick) in the 'binding site' of GSK.

The docked postures of 1, 2, 3 and 7 displayed appreciable H-bonds with binding site residues (Val135 and Pro136) of the GSK3 protein. These compounds projected in the hydrophobic cavity displaying connections with Ile62 and Arg141 residues of the binding site of GSK3 (Figure 11).

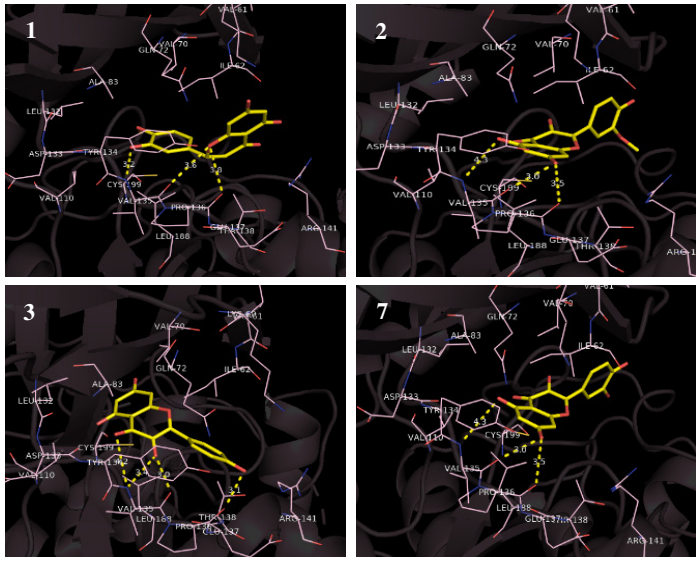

Fig. 11: Docked pictures displaying H-bonds of 1, 2, 3 and 7 with the 'binding site' residues of GSK.

Overall, molecular docking studies of the selected phenolic compounds from *C. sinensis* in the multiple targets associated with pathogenesis of T2D showed that some of the compounds (hesperetin, isorhamnetin, kaempferol and sakuranetin) evaluated *in silico* had shown good binding interactions and binding free energy with the multiple proteins involved in the pathogenesis of T2D. Amongst the compounds evaluated *in silico*, hesperetin had shown appreciable docking interactions (both H-bond and hydrophobic interactions) with AG, DPP4, GCR and GSK3 proteins. Isorhamnetin displayed good docking interactions with AG, GK and GSK3 proteins. Kaempferol showed appreciable docking interactions with AG, DPP4 and GSK3. Limocitrin displayed appreciable docking interactions with DPP4 and GK proteins. Limocitrol and naringenin showed good docking interactions with DPP4 and GK. Quercetin showed good docking interactions and GSK3 enzyme. Sakuranetin showed significant docking interactions with AG, DPP4 and GCR proteins.

***In silico* prediction of toxicity**

The possible toxicity (mutagenic, cardiotoxicity, acute toxicity, hepatotoxicity, skin irritation and chronic toxicity) for the optimized compounds was accessed using pkCSM platform (online computer program). Conferring to the outcomes shown in Table 8; all the molecules displayed little toxicity possibility (no cardio-toxicity and hepato-toxicity was predicted for all the selected compounds). For all the compounds accessed *in silico* for the prediction of toxicity using online computer program, only mutagenicity was predicted for the three compounds analyzed (hesperetin, limocitrin and naringenin). Oral rat acute toxicity ($LD_{50,}$ mol/kg) for the selected compounds was predicted in range 1.7 to 2.4 mol/kg and oral rat chronic toxicity (log mg/kg_bw/day) was predicted in the range 1.4 to 3.4 log mg/kg_bw/day. In this perspective, the initial evaluation carried out *in silico*, could counterpart forthcoming investigations on the toxicity profile of these compounds.

Table 8: Toxicity prediction for the optimized compounds obtained using pkCSM.

Sr. No.	Muta-genicity[a]	Cardio-toxicity[b]	Acute Toxicity[c]	Chronic Toxicity[d]	Hepato-toxicity	Skin Irritation	Max. Tolerated Dose[e]
1	Yes	No	2.411	1.661	No	No	0.456
2	No	No	1.757	2.359	No	No	1.106
3	No	No	2.301	2.699	No	No	0.910
4	Yes	No	1.818	2.672	No	No	1.107
5	No	No	1.974	3.464	No	No	0.617
6	Yes	No	2.189	1.994	No	No	0.402
7	No	No	1.944	3.169	No	No	1.159
8	No	No	2.204	1.495	No	No	0.593

[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 (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" (low $\leq$ 0.477 and high $\geq$ 0.477).

Conclusions

Docking studies were performed to explore the binding mechanism of the selected natural phenolic compounds from *C. sinensis* with multiple targets associated with T2D. In current molecular docking studies, results clearly demonstrated that amongst the compounds evaluated *in silico*, hesperetin showed significant binding interactions with multiple targets of T2D including AG, DPP4, GCR and GSK3. Isorhamnetin, kaempferol and sakuranetin showed good interactions three protein targets of T2D. All the analogues displayed drug-like characteristics as elaborated by means of 'Lipinski's rule of five'. *In silico* investigation is essentially an extra benefit to screen the antidiabetic agents and natural phenolic compounds might behave as valuable leading hits for the identification of clinically suitable and safe type 2 antidiabetic drugs. However, structural modifications and further studies on these natural phenolic compounds are required to develop safe and potent natural type 2 antidiabetic agents.

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Conflict of interest

The authors declare that there is no conflict of interests.

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