Molecular Docking Studies of Phenolic Compounds from *Syzygium cumini* with Multiple Targets of Type 2 Diabetes

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ARTICLE INFORMATION

ABSTRACT

Treatment of type 2 diabetes without any side effects is still a challenge to the medical system. This leads to increasing demand for natural products with antidiabetic activity with fewer side effects. *Syzygium cumini* is a traditional herbal medicinal plant and is reported to possess a variety of pharmacological actions. It contains various types of chemical constituents including terpenoids, tannins, anthocyanins, flavonoids and other phenolic compounds. Some flavonoids and other phenolic compounds from *S. cumini* were reported in literature to have type 2 antidiabetic potential. The main objective of the current investigation was *in silico* screening of some phenolic compounds from *S. cumini* against multiple targets associated with type 2 diabetes to explore the mechanism of antidiabetic action and prediction of binding mode using molecular docking studies. *In silico* docking studies were performed for the selected molecules in the binding site of 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*, rutin showed appreciable binding with multiple targets of type 2 diabetes including α-glucosidase, dipeptidyl peptidase 4, glycogen synthase kinase 3, and glucagon receptor. Catechin was found to inhibit both α-glucosidase, and dipeptidyl peptidase 4. This information can be utilized for the design and development of potent multi-functional candidate drugs with minimal side effects for type 2 diabetes therapeutics.

1. Introduction

Diabetes mellitus (or simply diabetes) is a long-lasting disorder of food metabolism characterized by hyperglycemia, originating due to defect in insulin secretion, insulin function or both leading to tissue and vascular damage and resulting in a variety of complications (Bastaki, 2005; Cade, 2008; Grewal *et al.*, 2014; Grewal *et al.*, 2016). It is currently one of the largest global health emergencies; according to the International Diabetes Federation, in 2017 there were 425 million adults estimated to have diabetes, and the number is likely to reach 629 million by 2045 (IDF). Type 2 diabetes (T2D) affecting more than 90% of all the diabetic patients, is a long-term disordered food metabolism caused by declined insulin action (Kohei, 2010; Olokoba *et al.*, 2012). Although a variety of medicines are available for T2D therapeutics, no single drug is useful for achieving long-term control of normal blood glucose levels in majority of patients. Due to this reason, general practitioners prescribe combination of antidiabetic agents for T2D therapy and overdose of antidiabetic medicines could lead to severe hypoglycemia resulting in brutal toxic and side effects. This caused the scientific community to search for new antidiabetic drugs (Olokoba *et al.*, 2012; Osadebe *et al.*, 2014). Large numbers of plants and parts of plants were reported with their antidiabetic properties. Various types of plant-derived active principles representing several bioactive compounds have established their beneficial role for possible use in T2D therapeutics (Patil *et al.*, 2011; Ibrahim *et al.*, 2013; Kumar *et al.*, 2012). *Syzygium cumini* (Linn.) is an economically important tropical fruit tree belonging to the family Myrtaceae largely grown in Indian subcontinent along with some other parts of South Asia including Bangladesh, Sri Lanka, Nepal, Pakistan, Burma and Indonesia. It is also cultivated in some parts of Africa and South America (Swami *et al.*, 2012; Srivastava and Chandra, 2013). It is commonly known as jamun in India, black plum in Europe, jambolan in Spanish spoken countries, and Jambolac in Brazil. It is also known as java plum, Indian blackberry, Portuguese plum, Malabar plum, purple plum, Jamaica and damson plum (Ayyanar and Subash-Babu, 2012; Chagas *et al.*, 2015). Various types of secondary metabolites like flavonoids (quercetin, rutin, catechin, kaempferol, myricetin, isoquercetin,

myricetin deoxyhexoside, myricetin-3-L-arabinoside, dihydromyricetin, quercetin-3-D-galactoside, myricetin 3-O-β-D-glucuronopyranoside, myricetin-4'-methylether 3-O-α-rhamnopyranoside), phenolic acids (caffeic acid, chlorogenic acid, ellagic acid, Ferulic acid, gallic acid, 3,3'-di-O-methyl ellagic acid,3,3',4-tri-O-methyl ellagic acid), tannins (nilocetin Corilagin, 3,6-HHDP glucose, 4,6-HHDP glucose, 1-galloyl glucose, 3-galloyl glucose, HHDP-galloyl glucose, trigalloyl glucose, Eugenol, and oleanolic acid), terpenes (α-pinene, α-cadinol, pinocarvone, pinocarveol, α-terpeneol, myrtenol, eucarvone, muurolol, myrtenal, cineole, geranyl acetone, β-pinene, β-terpinene, betulinic acid, eugenol, citronellol, geraniol, hotrienol, nerol, β-phenylethanol, phenylpropanal, β-siterol, and friedelin), anthocyanins (Cyanidin, delfinidin and petudinin), alkaloids (jambosine), glycosides (jamboline and antimelin), minerals (Ca, Mg, Na, K, and Cu), vitamins (thiamine, riboflavin, and nicotinic acid) are present in different parts of the plant (Veigas *et al.*, 2007; Ramya *et al.*, 2012; Ayyanar and Subash-Babu, 2012; Chagas *et al.*, 2015; Bijauliya *et al.*, 2017). *S. cumini* is known to possess wide range of pharmacological and therapeutic properties, which have been attributed to the presence of bioactive compounds in different parts of the plant (Srivastava and Chandra, 2013). A variety of various pharmacological activities were shown by *S. cumini* including anti-diabetic (Kumar *et al.*, 2008, Tripathi and Kohli, 2014), anti-cancer (Afify *et al.*, 2011), anti-oxidant (Nair *et al.*, 2013), antibacterial/antimicrobial (Prateek *et al.*, 2015), anti-inflammatory (Muruganandan *et al.*, 2001), anti-diarrhoeal (Shamkuwar *et al.*, 2012), anti-viral (Sood *et al.*, 2012), cardio-protective (Herculano *et al.*, 2014), anticonvulsant (Kumar *et al.*, 2007), antinociceptive (Avila-Pena *et al.*, 2007), gastro-protective (Chaturvedi *et al.*, 2009), anti-fertility (Rajasekaran *et al.*, 1998), chemo-protective (Goyal *et al.*, 2010), anti-allergic (Brito *et al.*, 2007), inhibition of lipid peroxidation (Veigas *et al.*, 2007), anti-histaminic (Mahapatra *et al.*, 1986), anti-pyretic (Mahapatra *et al.*, 1986), anti-plaque (Namba *et al.*, 1985), anti-hyperlipidemic (Chagas *et al.*, 2015) and hepato-protective activity (Veigas *et al.*, 2008). Some flavonoids and other phenolic derivatives obtained from *S. cumini* including quercetin, myricetin, kaempferol, ferulic acid, ellagic acid, catechin and rutin were reported in literature to have type 2 antidiabetic potential (Haraguchi *et al.*, 1998; Ohnishi *et al.*, 2004; Kamalakkannan and Prince, 2006; Liu *et al.*, 2007; Sharma *et al.*, 2008; Esmaeili *et al.*, 2009; Wein *et al.*, 2010; Bardy *et al.*, 2013; Chagas *et al.*, 2015). Currently, medicinal chemistry research is focussed on polypharmacological compounds acting on multiple targets against complex disorders including diabetes, neoplastic diseases, neurodegenerative disorders, and certain infectious disorders owing to superior efficacy, better safety profile, and ease of administration of 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; Ramsay *et al.*, 2018). In the current investigation docking studies were performed for some phenolic compounds obtained from *S. cumini* (Figure 1) in the binding site of multiple targets associated with T2D (α-glucosidase (AG), dipeptidyl peptidase 4 (DPP4), glycogen synthase kinase 3 (GSK3), glucokinase (GK) and glucagon receptor (GCR)) in order to explore the mechanism of antidiabetic action and binding modes using molecular docking studies.
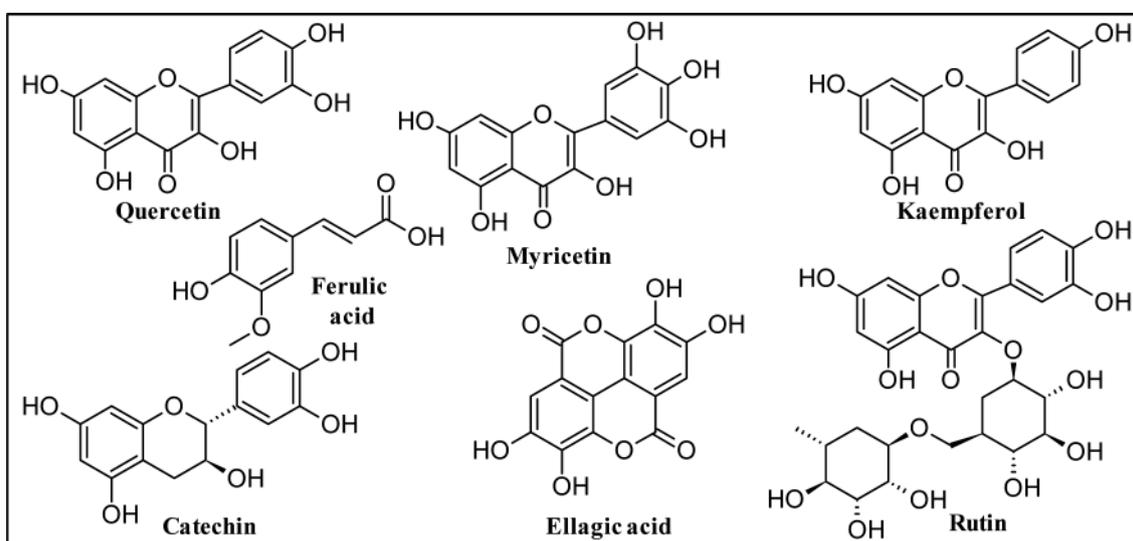
Figure 1: Phenolic compounds from *Syzygium cumini* with potential antidiabetic activity selected for *in silico* studies.

2. Experimental

2.1 *In Silico Prediction of Pharmacokinetic Parameters*

All the selected molecules were analyzed for prediction of pharmacokinetic parameters related to absorption, distribution, metabolism, and excretion (ADME) by employing FAF-Drugs4 server; and evaluated using Lipinski's rule of five for drug-likeness (Miteva *et al.*, 2006; Lagorce *et al.*, 2017).

2.2 *Molecular Docking Studies*

In silico molecular docking studies were carried out for the selected molecules in the binding site of target proteins using AutoDock Vina (Trott and Olson, 2010) and AutoDock Tools (Morris *et al.*, 2009). The 2-D chemical structures of all the compounds were prepared by MarvinSketch (Marvin 15.9.21, 2015, ChemAxon) and 3-D conformations were generated using Frog2 server (Miteva *et al.*, 2010). The ligands were converted to "pdbqt" files from "mol" format using AutoDock Tools. After assessing a numbers of co-crystallized structures for target proteins available in the protein data bank (https://www.rcsb.org); the best ligand bound complexes (PDB entries: 3L4T, 4A5S, 1Q5K, 3IMX and 5EE7 for AG, DPP4, GSK3, GK and GCR,

respectively) were selected with complexes having maximum resolution and best binding interactions between ligands and proteins. An analogous docking method was used for the molecular docking of the selected derivatives as described in detail in earlier publications using AutoDock Vina and the ligand poses with most favorable docking score (binding free energy) were selected (Grewal *et al.*, 2017; Charaya *et al.*, 2018). The binding interactions of the ligands with the target proteins were analysed further for the docked poses of the ligands using PyMOL (The PyMOL Molecular Graphics System, Version 0.99rc6, Schrödinger, LLC).

3. Results and Discussion

3.1 *Pharmacokinetic Parameters*

ADME properties including molecular weight (MW), partition coefficient (log P), topological polar surface area (tPSA), water solubility (log S_w), hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), solubility (mg/mL) and number of rotatable bonds were predicted for all the molecules selected for docking studies. Almost all the compounds showed good pharmacokinetic parameters and drug-like properties as contrived by Lipinski's rule of five (Table 1).

Table 1: Predicted pharmacokinetic parameters (ADME properties) of the compounds selected for docking studies.

Compound	MW[*]	log P[*]	tPSA[*]	log S_w[*]	HBA[*]	HBD[*]	Solubility	Rotatable bonds
Quercetin	302.24	1.54	131.03	-2.99	7	5	15.23	1
Myricetin	318.24	1.18	151.26	-2.85	8	6	18.42	1
Kaempferol	286.24	1.90	110.18	-3.13	6	4	12.54	1
Ferulic acid	194.18	1.51	69.59	-1.98	4	2	26.75	3
Catechin	290.27	0.51	110.38	-2.15	6	5	33.86	1
Ellagic acid	302.19	1.10	140.68	-2.83	8	4	17.84	0
Rutin	606.57	0.08	250.64	-3.41	14	10	20.06	6

3.2 *Molecular Docking Study*

The docking simulations were carried out by energy minimization and optimization of selected ligands in the binding site of target protein (PDB entries: 3L4T, 4A5S, 1Q5K, 3IMX and 5EE7 for AG, DPP4, GSK3, GK and GCR, respectively). The reference ligands was docked into the active site of target proteins; and the docked reference ligands produced a similar binding pattern and superposition on the binding mode of co-crystallized ligand validating accuracy of docking methodology. The docking score (binding free energy, ΔG, kcal/mol) of the selected compounds with various target proteins are presented in Table 2. Amongst the compounds tested *in*

silico, myricetin, catechin and rutin showed appreciable binding interactions with AG; quercetin, catechin and rutin with DPP4; rutin with GCR, kaempferol with GK; and ferulic acid and rutin with GSK3 as determined by analysing the binding interactions of the selected best docked poses and ΔG of the best docked poses. The docking studies of these molecules suggested a complimentary fit in the binding site of the target proteins. For the rest of the molecules, the molecules had a different orientation and binding pattern (flipping) in the binding site of the target protein possibly due to steric clashes of the substituents. Best docked compounds were further analyzed in details using PyMOL.

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

Ligand	Docking score (ΔG, kcal/mol)				
	AG	DPP4	GCR	GK	GSK3
Quercetin	−6.7	−8.2	−6.5	−7.2	−6.9
Myricetin	−7.4	−8.1	−6.7	−6.5	−7.2
Kaempferol	−6.8	−8.0	−6.7	−8.1	−7.0
Ferulic acid	−5.0	−5.5	−5.5	−5.7	−7.3
Catechin	−7.2	−8.3	−6.7	−6.8	−6.8
Ellagic acid	−6.5	−7.8	−6.3	−7.1	−6.4
Rutin	−8.4	−9.3	−7.3	−7.8	−7.5
Reference	−7.2	−8.5	−7.3	−9.7	−7.6

Overlay of the docked poses of myricetin, catechin and rutin with that of PDB Ligand 3L4T in the binding site of AG showed that these molecules had the similar binding and orientation pattern in the binding site of enzyme as that of co-crystallized ligand (BJ2661 *i.e.,* (1R,2S)-1-[(1S)-1,2-dihydroxyethyl]-3-[(2R,3S,4S)-3,4-dihydroxy-2-(hydroxymethyl)tetrahydrothiophenium-1-yl]-2-hydroxypropyl sulfate) (Figure 2a). The docked pose of myricetin in binding site of AG showed the H-bond interactions between carbonyl of chromen-4-one and OH of Asp203; 3-OH of chromen-4-one and NH$_2$ of Arg526; 3-OH of chromen-4-one and carbonyl of Asp542; OH of phenyl and carbonyl of Asp 327; and OH of phenyl and 'N' of His600 with H-bond distance of 3.3 Å, 3.3 Å, 3.5 Å, 2.8 Å, and 3.9 Å respectively (Figure 2b). The docked pose of catechin in binding site of AG showed the H-bond interactions between hydroxyl of chromene and NH of Arg526; hydroxyl of chromene and carbonyl of Asp542; OH of phenyl and carbonyl of Asp327; and OH of phenyl and 'N' of His 600 with H-bond distance of 3.2 Å, 3.0 Å, 2.9 Å, and 4.4 Å respectively (Figure 2c). The docked pose of rutin in binding site of AG showed the H-bond interactions between hydroxyl of glucose and 'N' of Arg526; hydroxyl of rhamnose and carbonyl of Asp203; ether 'O' and hydroxyl of Asp542; hydroxyl of rhamnose and carbonyl of Asp327; and OH of glucose and 'N' of His600 with H-bond distance of 2.8 Å, 3.3 Å, 3.3 Å, 2.7 Å, and 3.3 Å respectively (Figure 2d).
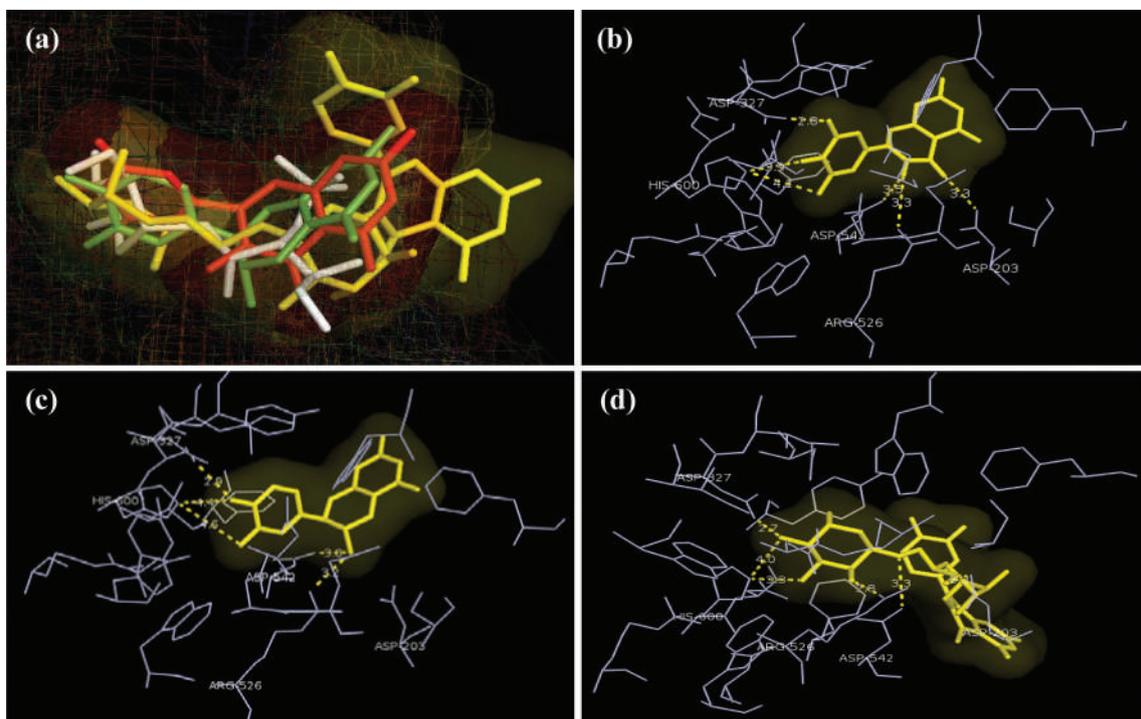

Figure 2: (a) Superimpose of myricetin (red), catechin (green) and rutin (yellow) with PDB ligand of 3L4T (white) in the binding site of AG; (b) Docked pose of myricetin; (c) catechin; (d) rutin in the binding site of AG.

Overlay of the docked poses of quercetin, catechin and rutin with that of PDB Ligand 4A5S in the binding site of DPP4 showed that these molecules had the similar binding and orientation pattern in the binding site of enzyme as that of co-crystallized ligand (6-[(3S)-3-Aminopiperidin-1-yl]-5-benzyl-4-oxo-3-(quinolin-4-ylmethyl)-4,5-dihydro-3h-pyrrolo[3,2-d]pyrimidine-7-carbonitrile) (Figure 3a). The docked pose of quercetin in binding site of DPP4 showed the H-bond interactions between ether 'O' of chromen-4-one and NH of Tyr631; and hydroxyl of chromen-4-one and carboxyl 'OH' of Glu205 with H-bond distance of 3.8 Å, and 4.5 Å respectively (Figure 3b). The docked pose of catechin in binding site of DPP4 showed the H-bond interactions between ether 'O' of chromen-4-one and NH of Tyr631; hydroxyl of chromen-4-one and aromatic OH of Tyr662; and hydroxyl of chromen-4-one and carboxyl 'OH' of Glu205 with H-bond distance of 4.5 Å, 3.1 Å, and 4.6 Å respectively (Figure **3c**). Docked pose of rutin in binding site of DPP4 showed the H-bond interactions between phenyl hydroxyl and carbonyl of Glu205; and hydroxyl of phenyl ring and aromatic OH of Tyr662 with H-bond distance of 4.5 Å, 3.1 Å, and 4.6 Å respectively (Figure 3d).
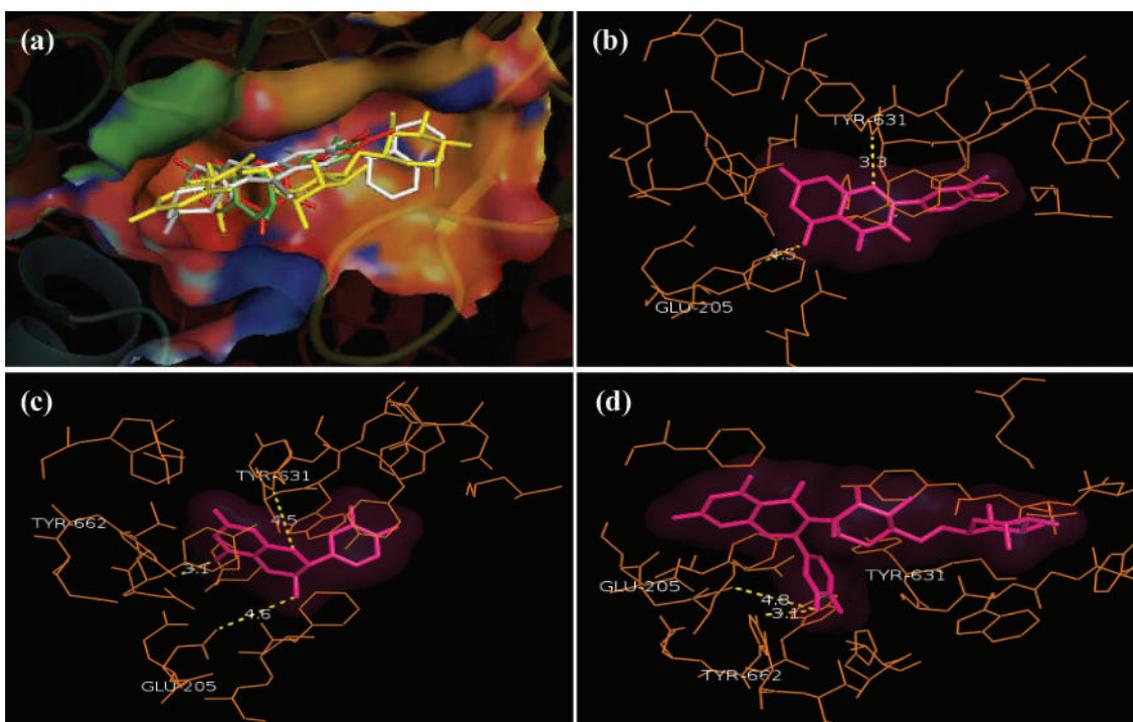

Figure 3: (a) Superimpose of quercetin (red), catechin (green) and rutin (yellow) with PDB ligand of 4A5S (white) in the binding site of DPP4; (b) Docked pose of quercetin; (c) catechin; (d) rutin in the binding site of DPP4.
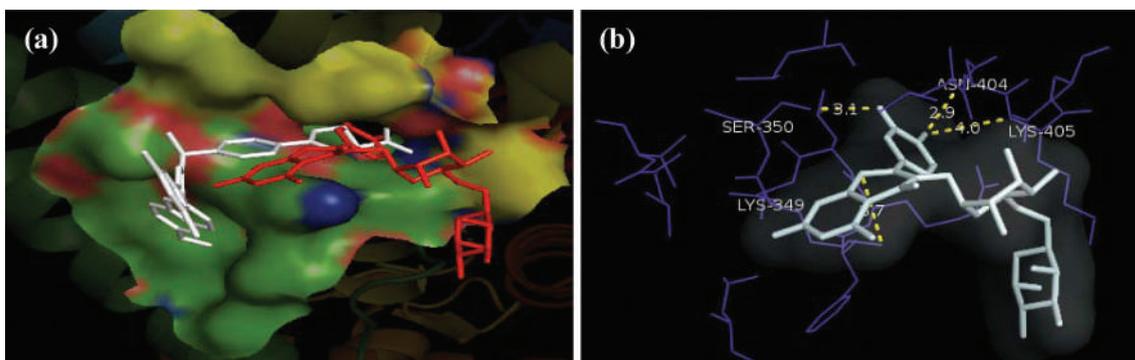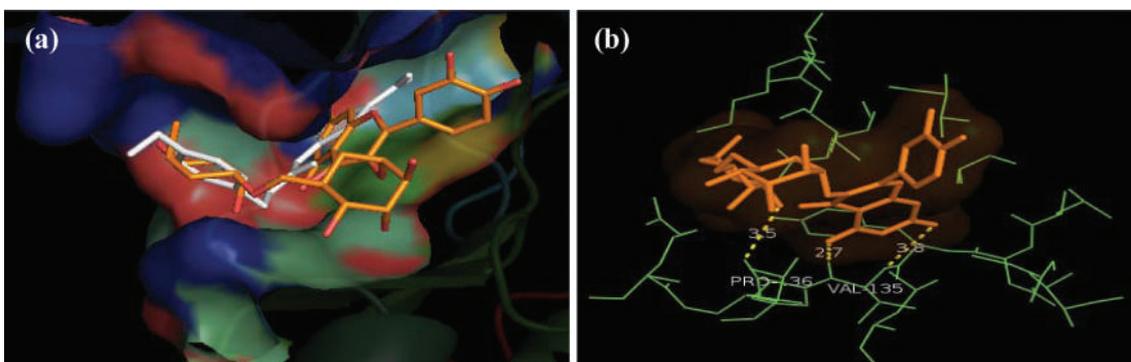

Figure 4: (a) Superimpose of rutin (red) with PDB ligand of 5EE7 (white); (b) Docked pose of rutin in the binding site of GCR.

Overlay of the docked pose of rutin with that of PDB Ligand 5EE7 in the binding site of GCR showed that it had the similar binding and orientation pattern in the binding site of enzyme as that of co-crystallized ligand (MK-0893 i.e., 3-[[4-[(1{S})-1-[3-[3,5-bis(chloranyl)phenyl]-5-(6-methoxynaphthalen-2-yl)pyrazol-1-yl]ethyl]phenyl]carbonylamino] propanoic acid) (Figure 4a). The docked pose of rutin in binding site of GCR showed the H-bond interactions between ether 'O' of chromen-4-one and NH of Lys349; hydroxyl of phenyl and carbonyl of Ser350; hydroxyl of phenyl and amide NH of Asn404; and phenyl hydroxyl and amide NH of Lys405 with H-bond distance of 3.9 Å, 3.1 Å, 2.8 Å, and 3.8 Å respectively (Figure 4b).

Overlay of the docked pose of kaempferol with that of PDB Ligand 3IMX in the allosteric site of GK showed that it had the similar binding and orientation pattern in the allosteric binding site of GK enzyme as that of co-crystallized activator ((2R)-3-cyclopentyl-N-(5-methoxy[1,3]thiazolo[5,4-b]pyridin-2-yl)-2-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl} propanamide) (Figure **5a**). Kaempferol was found to bind to an allosteric pocket of GK protein, which is about 20Å remote from the glucose binding site. The docked pose of kaempferol showed the H-bond interaction between hydroxyl and carbonyl group of chromene-4-one with backbone carbonyl and amide NH of Arg63 on GK protein with H-bond distance of 4.9 Å and 4.7 Å respectively (Figure 5b).
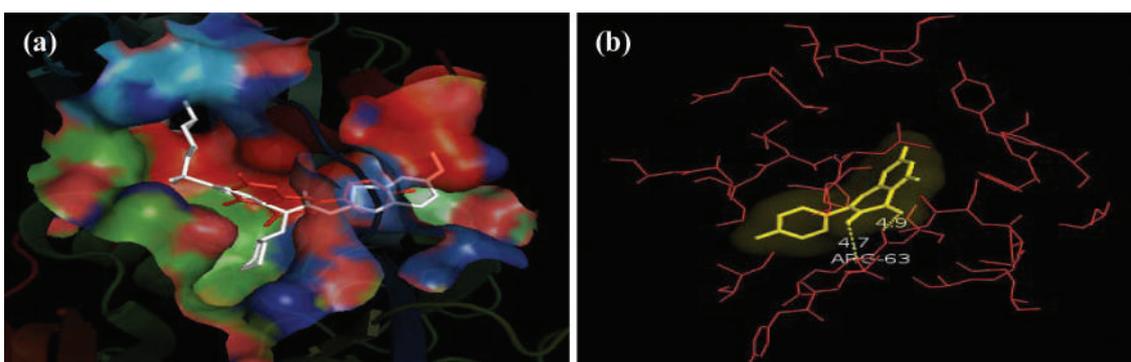
Figure 5: (a) Superimpose of kaempferol (red) with PDB ligand of 3IMX (white); (b) Docked pose of kaempferol in the allosteric site of GK.

Figure 6: (a) Superimpose of rutin (red) with PDB ligand of 1Q5K (white); (b) Docked pose of rutin in the binding site of GSK3.

Overlay of the docked pose of rutin with that of PDB Ligand 1Q5K in the binding site of GSK3 showed that it had the similar binding and orientation pattern in the binding site of GSK3 enzyme as that of co-crystallized ligand (N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl) urea) (Figure 6a). The docked pose of rutin in binding site of GSK3 showed the H-bond interactions between 'OH' of glucose and carbonyl of Pro136; 'OH' of oxychromen-4-one and carbonyl of Val135; and carbonyl of oxychromen-4-one and amide 'NH' of Val135 with H-bond distance of 2.7 Å, 3.5 Å, and 3.8 Å respectively (Figure 6b).

4. Conclusion

Molecular docking studies using AutoDock vina and AutoDock Tools was performed to explore the binding mechanism of the selected natural phenolic compounds from *S. cumini* with multiple targets associated with T2D. In current in silico docking study, results clearly demonstrated that amongst the compounds tested *in silico,* rutin showed appreciable binding with multiple targets of T2D including α-glucosidase, dipeptidyl peptidase 4, glycogen synthase kinase 3, and glucagon receptor. Catechin was found

to inhibit both α-glucosidase, and dipeptidyl peptidase 4. Myricetin was found to inhibit AG and quercetin was found to inhibit DPP4. Kaempferol was found to activate allosterically GK protein. *In silico* study is actually an added advantage to screen the type 2 antidiabetic agents and natural phenolic compounds may serve as useful leads for the synthesis of clinically useful and safe type 2 antidiabetic agents. 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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