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In Silico Molecular Docking on Chemical Compounds from Mas Cotek (*Ficus deltoidea*) as Phosphoenolpyruvate Carboxykinase (Pepck) Inhibitor against Type-II Diabetes

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Diabetes Mellitus (DM) is an affecting disease in people of all age groups worldwide. Many synthetic medicines are available for type II diabetes mellitus in the market. The study focused to discover the strong requirement for the development of better antidiabetic compounds sourced especially from natural sources like medicinal plants by using computational approaches. The study was to determine the activity of the chemical compounds from Mas Cotek (*Ficus deltoidea*) as a potential inhibitor for the protein enzyme Phosphoenolpyruvate Carboxykinase (PEPCK) against type II diabetes. This study was conducted by *in silico* molecular docking of protein enzyme Phosphoenolpyruvate Carboxykinase (PEPCK) with Mas Cotek (*Ficus deltoidea*) chemical compounds. The physiochemical properties of the 6 compounds from *Ficus deltoidea* based on Lipinski's rule of five (RO5) were evaluated by Molinspiration software. Binding affinity as the results for isovitexin, orientin, vitexin, epigallocatechin, catechin, epicatechin, and Metformin respectively are – 10.40; – 10.30; – 10.00; –9.90; –9.70; –9.70 and –5.30. The result showed that 6 of the chemical compounds from Mas Cotek (*Ficus deltoidea*) (isovitexin, orientin, vitexin, epigallocatechin, catechin, epicatechin) have lower binding affinity and better than Metformin. However, only catechin, orientin, and, epigallocatechin passed Lipinski's rules of five and bind to the active site of the protein enzyme PEPCK. The chemical compounds from Mas Cotek (*Ficus deltoidea*) (orientin, epigallocatechin and catechin) have potential as Phosphoenolpyruvate Carboxykinase (PEPCK) inhibitors against type-II diabetes.

Key words: *In silico*, Docking; *Ficus deltoidei*; Antidiabetic; PEPCK; Metformin

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A serious metabolic condition that causes significant rates of morbidity and mortality worldwide is diabetes mellitus (DM) [1]. The International Diabetes Federation (IDF) predicts that between 2013 and 2035, the number of individuals with diabetes would rise from 382 million to 592 million as the disease has epidemic proportions in developing nations. According to the World Health Organization (WHO), there will be 415 million diabetics globally in 2015 [2], and this number is projected to increase to 642 million by 2040.[3]. Elevated plasma glucose levels, which are brought on by either inadequate insulin, insulin resistance, or both, are the hallmark of diabetes. Additionally, defects in various metabolic processes [4]. As the condition worsens, consequences include retinopathy, neuropathy, nephropathy, stroke, ischemic heart disease, peripheral vascular disease, and a number of other heterogeneous diseases [5], of which type 2 diabetes accounts for more than 95%, appear (T2D). It manifests as a result of hyperglycemia brought on by insulin resistance and pancreatic beta-cell malfunction [6]. Interestingly, there is a connection between T2D and obesity. In addition to increased cytokine production, fat accumulation in bodily tissues, and mitochondrial dysfunction, obesity also causes insulin resistance and pancreatic beta-cell malfunction [7].

Utilizing oral hypoglycemic medications is the current T2D treatment. Patients with type 1 diabetes receive their primary care from insulin replacement therapy [8]. The desire for non-harmful alternative remedies is brought on by the side effects of such medications [9]. Plant extracts have less potential for unwanted effects than synthetic antihyperglycemic medicines, making them safer, more accessible, and more economical [10]. As a result, there is an increasing interest in phytomedicine from traditional medicine.

Different civilizations all over the world have employed traditional medicinal plants for a long time to treat diabetes. The study of herbal remedies has been increasingly significant in recent years as researchers look for a fresh, efficient, and secure

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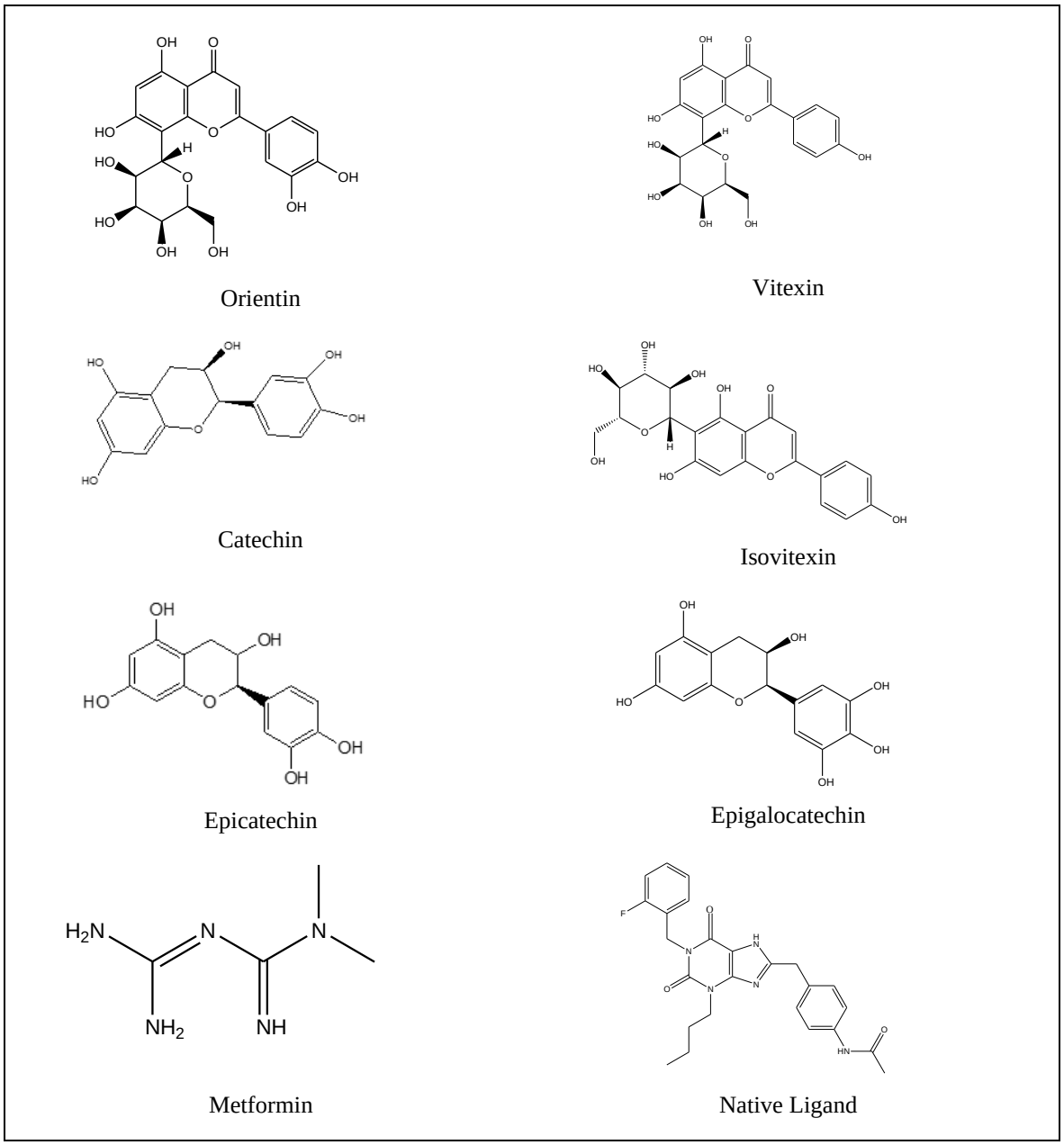


Figure 1. Chemical structure of metformin and 6 chemical compounds from Mas Cotek (*Ficus deltoidea*) (isovitexin, orientin, vitexin, epigallocatechin, catechin, epicatechin).

therapeutic agent to treat diabetes. More than 200 identified pure bioactive components from plants, including phenolics [11], flavonoids [12,13], triterpenoids, alkaloids [14–16], and carbohydrates [18], have been shown to have a reducing influence on blood sugar levels [17].

The Moraceae family plant *Ficus deltoidea*, sometimes referred to as "Mas Cotek" locally, is a novel potential medicinal herb in Malaysia. There is little information available regarding the chemical components of *Ficus deltoidea*, however, several substances have been claimed to be present, including the flavonoids isovitexin and vitexin [18,19], proantho cyanidins, flavan-3-ol monomers, and flavone glycolsides [20]. Recently, a study by Zainah and colleagues suggested that the aqueous extract of *Ficus deltoidea*, leaves may contain water-soluble insulin-secreting components with superior insulin secretion activity than the well-known hypoglycemic drug glibenclamide [21]. Fascinatingly, toxicology research on *Ficus deltoidea*, found no harmful substances in the plant [22]. The leaves of *Ficus deltoidea*, have been demonstrated to have qualities that lower blood sugar [18,19,21,23–25], are antinociceptive [26], heal ulcers [27], are anti-oxidant [18,20,28,29], are antiinflammatory [30], and are antimelanogenic [31].

The protein enzyme phosphoenolpyruvate carboxykinase (PEPCK) is highly expressed in the liver, kidney, and adipose tissue. This enzyme catalyzes the rate-limiting step in adipose tissue glyceroneo-

genesis, renal gluconeogenesis, and hepatic gluconeogenesis [32]. Consequently, is crucial to maintain glucose homeostasis [33]. The binding site and coding regions of protein enzyme Phosphoenolpyruvate Carboxykinase (PEPCK) have been sequenced from cytosolic genomic Deoxy Nucleic Acid (DNA) of subjects with type 2 diabetes mellitus [34]. The triglyceride cycle in adipose tissue and the liver is regulated in part by the protein enzyme phosphoenol-pyruvate carboxykinase (PEPCK). For the purpose of maintaining glucose homeostasis, lipid homeostasis, and disease prevention, research into the expression and control of the protein enzyme phosphoenol-pyruvate carboxykinase (PEPCK) in the triglyceride/ fatty acid cycle is required [35].

Therefore, the present study attempts to investigate the potential antidiabetic effects of 6 chemical compounds from Mas cotek (*Ficus deltoidea)* (Figure 1) by *in silico* docking. *In silico* docking is being used to uncover possible actions of chemical compounds from *Ficus deltoidea* to inhibit PEPCK, the target diabetes protein enzyme compared with metformin as the standard drug of diabetes. Meanwhile, Molinspiration software to evaluate druglikeness based on Lipinski's rules of five.

MATERIALS AND METHODS

Ligand Preparation

A total 6 chemical compounds from Mas Cotek (*Ficus deltoidea*) (isovitexin, orientin, vitexin, epigallocatechin, catechin, epicatechin) were chosen as ligands for this work. The collected Structure Data File (SDF) files of the identified chemical compounds from the PubChem database were converted into PBD format using BIOVIA Discovery Studio. The optimized ligands were saved in PDB format for use in PyRx Virtual Screening Tool to compute the Gasteiger charges. The ligands with charges were then saved in PDBQT format for molecular docking.

Protein Preparation

Phosphoenolpyruvate Carboxykinase (PEPCK) was selected as the target protein enzyme. The models of protein enzyme Phosphoenolpyruvate Carboxykinase (PEPCK) were downloaded via Protein Data Bank (PDB) with code 1NHX with the resolution 2.10 Å (http://www.rcsb.org/pdb). Water molecules and bound ligands were removed using BIOVIA Discovery Studio, before the addition of polar hydrogen atoms and Kollman charges using BIOVIA Discovery Studio. The optimized protein was then saved in PDBQT format for molecular docking.

Molecular Docking

PyRx-Virtual Screening Tool (Autodock Vina) version 8.0 was used to perform molecular docking for predicting free binding energy (Adianingsih and Kharisma, 2019). PyRx software was used for the purpose of molecular screening of 6 six and standard compounds by autodock wizard as the engine for molecular docking (Morris et al., 2008). Docking was performed on default parameters of number of generation and energy evaluation for 10 steps of run. The predicted binding affinity was calculated in kcal/mol.

Analysis and Visualization

The docked molecules were visualized using BIOVIA Discovery Studios 2019. Bonding interaction and the residues of proteins involved in the interaction with the ligands were analyzed.

Physiochemical Properties Analysis

Molinspiration tools used to analyze the physiochemical of the 6 compounds from *Ficus deltoidea* based on Lipinski's Rule of 5 (RO5) to evaluate drug likeness.

RESULTS AND DISCUSSION

Molecular Docking Studies

The protein enzyme Phosphoenolpyruvate Carboxykinase (PEPCK) with code 1NHX has the native ligand FTB. The native ligand was extracted and redocked into their original binding pockets. The root means square deviation values resulting from these overlapping between native ligands after redocking to its original binding pockets and native ligands before redocking to its original binding pockets were 1.58 Å, which was <2.0000 Å, a value typically used in evaluating the success of docking algorithms, indicating the docking methods was valid. Figure 2 shows the overlapping between native ligands after redocking.

Testing the antidiabetic effects of compounds were done by *in silico* docking between protein enzyme PEPCK with 6 chemical compounds from Mas Cotek (*Ficus deltoidea*) (isovitexin, orientin, vitexin, epigal-locatechin, catechin, epicatechin) as the test compound and metformin as the standard compound resulting the binding. Table 1 showed the binding free energy of the 6 chemical compounds from Mas Cotek (*Ficus deltoidea*) (isovitexin, orientin, vitexin, epigallocatechin, catechin, epicatechin) and standard drug metformin with the receptor protein enzyme PEPCK. Docking studies using Autodock vina wizard of PyRx software ver. 0.8 uses binding free energy calculation to find best binding mode of the ligand. This software generates protein–compound interaction profiles. Interaction profile contains electrostatic (E), hydrogen-bonding (H), and van der Waals (V) interactions. These interactions provide the basis for clustering and pharmacological post-screening analysis.

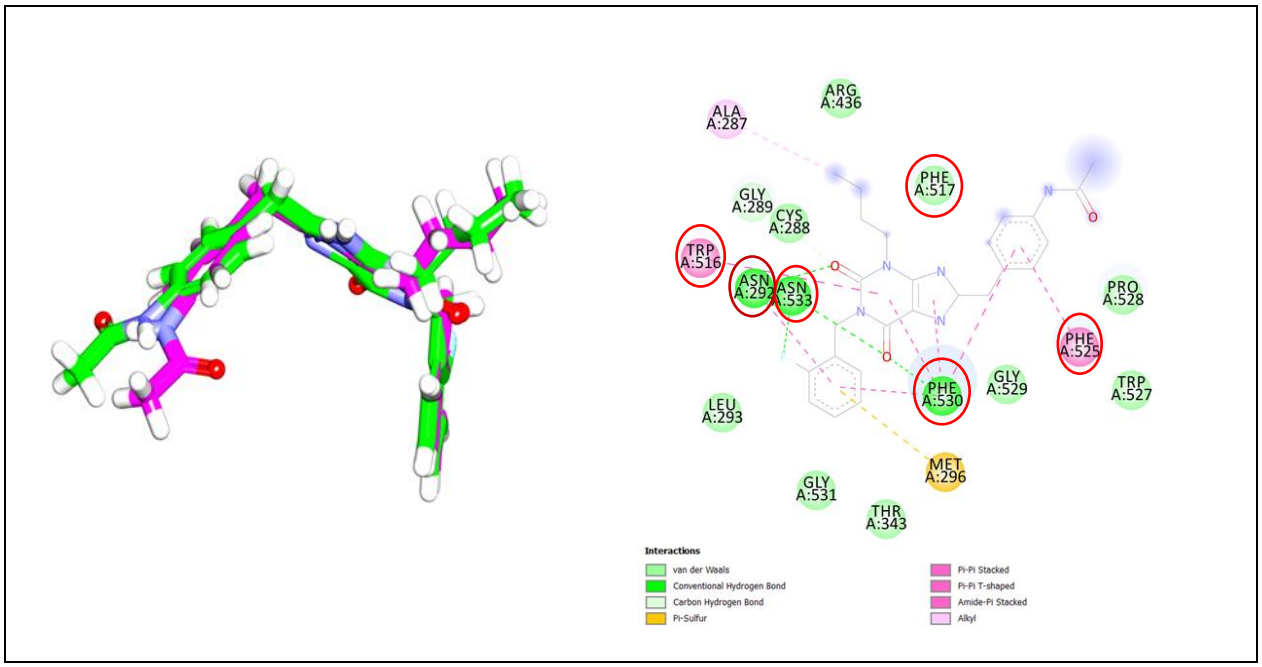


Figure 2. Overlapping between native ligands after redocking 1NHX protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) and interaction (active site) between native ligands after redocking to its original binding pockets and protein enzyme. Active site residues of PEPCK, (Trp516, Asn292, Asn533, Phe517, Phe525, Phe539) circle in red colour.

From the binding affinity data, it can be seen that chemical compounds from Mas Cotek (*Ficus deltoidea*) (isovitexin, orientin, vitexin, epigallocatechin, catechin, epicatechin) as the test compound have lower binding affinity on molecular docking to PEPCK than metformin as a standard compound for anti-diabetic to inhibit PEPCK. Lower value binding affinity on molecular docking to PEPCK of isovitexin, orientin, vitexin, epigallocatechin, catechin, and epicatechin than metformin as a standard compound for anti-diabetic to inhibit PEPCK means the strength of the binding interaction the ligand and protein, lesser the binding affinity, better is the binding of the ligand and protein.

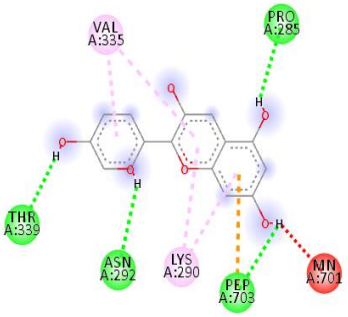
In the present study, the approach used for finding druglikeness molecules for antidiabetic inhibitor was based on the binding interaction in ligand and binding domain of the PEPCK protein. Isovitexin, orientin, and vitexin showed the best binding affinity i.e., −10.40, −10.30, and −10.00 respectively (Table 1), among the 6 different chemical compounds, and these compounds have good binding affinity compared to standard drug metformin and native ligand. However, out of 6 compounds, 3 compounds showed hydrogen bond interactions with the six amino acids (Trp516, Asn292, Asn533, Phe517, Phe530 and/or Phe525 with respect to native ligand active site (Table 1) and one compound showed unfavorable hydrogen bond interaction with amino acids in binding site (Trp516, Asn292, Asn533, Phe517, Phe530 and/or Phe525). These four compounds (catechin, orientin, epicatechin and epigallocatechin) had a minimum one interaction binding to the amino acids in active site of PEPCK meanwhile vitexin, isovitexin and standard drug metformin did not have any interaction binding to amino acids in active site.

These three compounds (catechin, orientin and epigallocatechin) are the most active and showed interaction with the target protein. Orientin is the most active ligand interacted with the Asn292 in active site of PEPCK with binding affinity -10.30 kcal/mol and was observed to make one hydrogen bond in active site. (Figure 3 (i) and (j) and Table 1). Meanwhile, epigallocatechin is the second most active ligand and interacted with the Asn292 in active site of PEPCK with binding affinity -9.90 kcal/mol. (Figure 3 (k) and (l) and Table 1). Catechin also showed interaction with the Asn292 with binding affinity -9.70 kcal/mol. However, epicatechin, vitexin, isovitexin and metformin did not bind with any active site in PEPCK. Binding affinity of these 6 compounds, standard drug and native ligand showed in Table 1. 2D and 3D images visualization of the binding interaction chemical compound (a-n) from Mas Cotek (*Ficus deltoidea*) and standard compound metformin with protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK) showed in Figure 3. The native ligands active site residues of PEPCK, (Trp516, Asn292, Asn533, Phe517, Phe525, Phe539) circle in red colour in Figure 2.

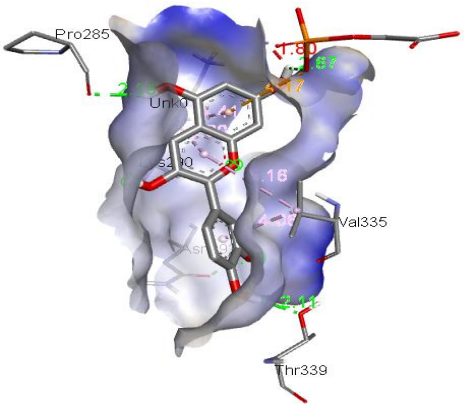
Table 1. Docking result of the chemical compounds from *Ficus deltoidea* and standard compound with the receptor protein enzyme Phosphoenolpyruvat Carboxykinase (PEPCK)

Ligand	Binding Affinity (kcal/mol)	Interaction and Residues	Distance (Å)
Catechin	-9.70	**H Bond**	
		Thr339	2.11
		Asn292	2.49
		Pro285	2.19
		Pep703	2.67
		π Bond	
		Lys290	4.80, 4.41
		Val335	4.06, 5.10
Epicatechin	-9.70	**H Bond**	
		Cys288	2.54
		Gly289	1.84
		Thr339	2.41
		π Bond	
		Ftb704	5.43
		Lys290	4.94, 4.53
		Val335	4.99, 4.05
		Pep703	4.08
Orientin	-10.30	**H Bond**	
		Pro285, Pro 337	2.37, 2.29
		Thr339	2.61
		Asn292	2.50
		π Bond	
		Lys290	4.77, 4.32
		Val335	4.24, 5.12
		Ftb704	5.38
Vitexin	-10.00	**H Bond**	
		Gly48	2.19, 2.15
		Asn330	2.58
		Arg171	2.56
		Glu421	2.43
		π Bond	
		Pro409	4.02
		Ile172	5.05

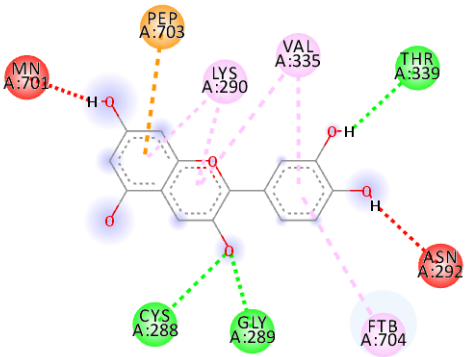
Ligand	Docking Score (kcal/mol)	Interaction and Residues	Distance (Å)
Isovitexin	-10.40	**H Bond**	
		Phe284	2.00
		Pro285	2.09, 2.51
		π Bond	
		Pro337	3.73, 5.02
		Val335	3.46, 3.94
		Ftb704	4.84
Epigallocatechin	-9.90	**H Bond**	
		Asn292	2.45
		Pro337	1.96
		Cys288	2.44
		Pep703	2.45
		π Bond	
		Val335	4.07, 5.16
		Lys290	4.44, 4.80
Metformin	-5.30	**H Bond**	
		Phe333	2.74, 2.59
		Asp310	2.51



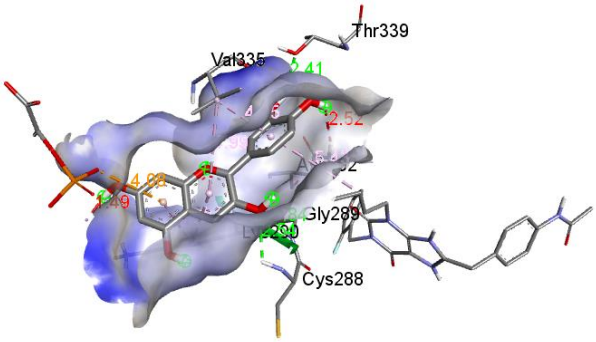
a) 2D image catechin



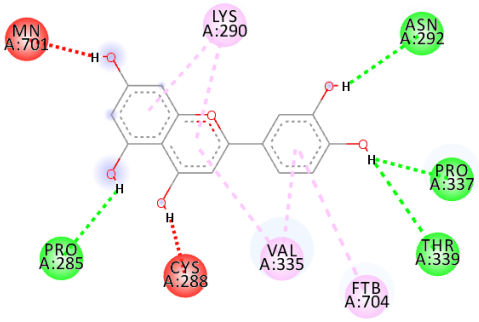
b) 3D image catechin



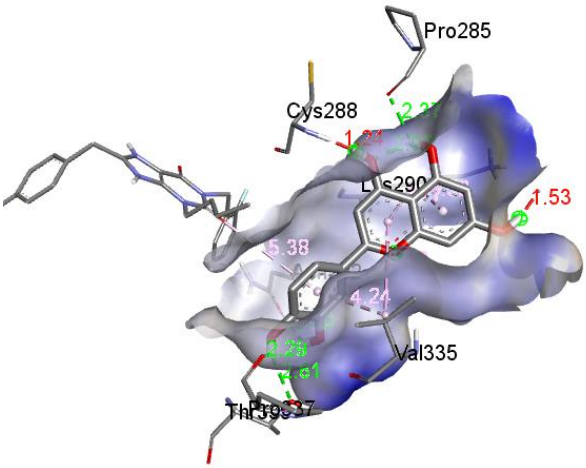
c) 2D image epicatechin



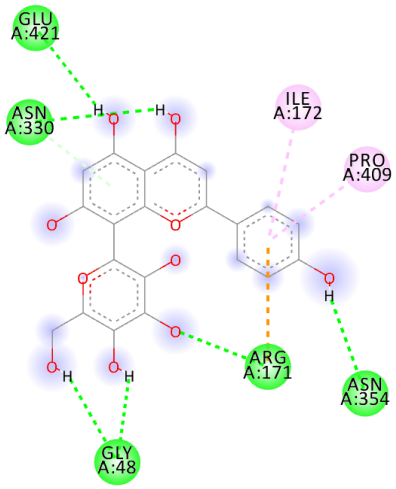
d) 3D image epicatechin



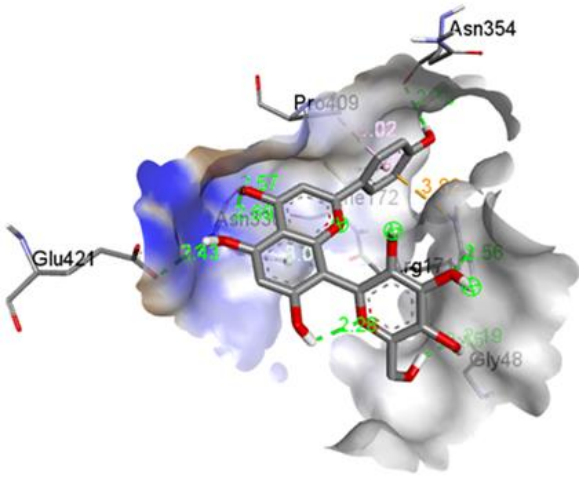
e) 2D image orientin



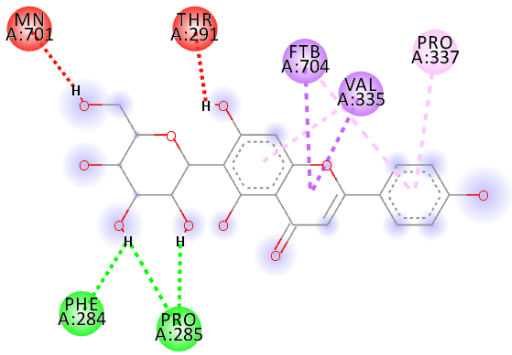
f) 3D image orientin



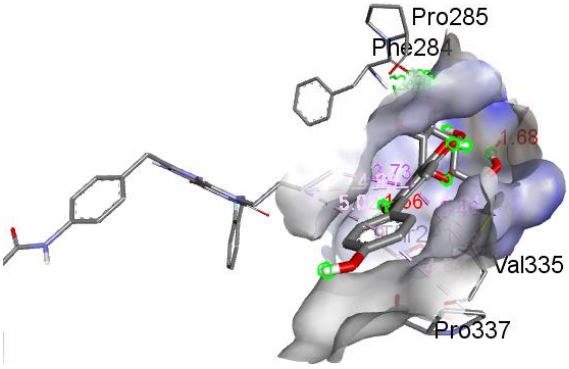
g) 2D image vitexin



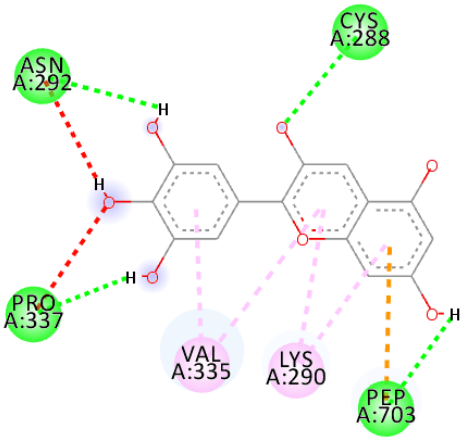
h) 3D image vitexin



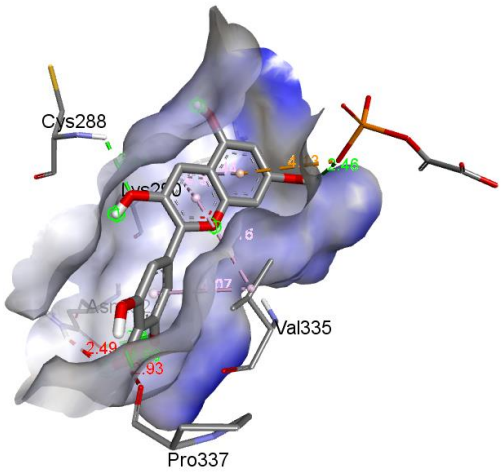
i) 2D image isovitexin



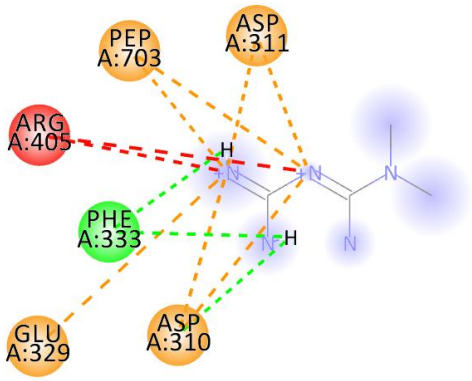
j) 3D image isovitexin



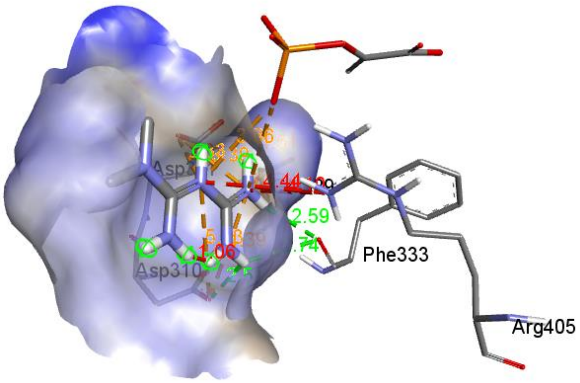
k) 2D image epigallocatechin



l) 3D image epigallocatechin



m) 2D image metfromin



n) 3D image metfromin

Figure 3. 2D and 3D images visualization of the binding interaction chemical compound (a-n) from Mas Cotek (*Ficus deltoidea*) and standard compound metformin with enzyme Phosphoenolpyruvat Carboxykinase (PEPCK).

Table 2. Predicted Physicochemical Properties and Drug Likeness of Designed Compounds

Compound/Drug	LogP	TPSA	HBA	HBD	MW	Lipinski Rule
Metformin	1.26	91.50	5	5	126	YES:0 violation
Catechin	1.37	110	6	5	290	YES:0 violation
Epicatechin	1.37	110	6	5	290	NO:0 violation
Orientin	0.03	120	7	5	448	YES:0 violation
Vitexin	0.52	181	10	7	432	NO:1 violation
Isovitexin	0.52	181	10	7	432	NO:1 violation
Epigallocatechin	1.08	130	7	5	306	YES:1 violation

Physiochemical Properties Analysis

The physicochemical evaluation of the selected ligands is very important in deciding the drug-likeness of a particular chemical compound to be developed into a potential drug. The physicochemical descriptor of ligands was computed by an online web server mol-inspiration. Molecular analysis of the properties of potential drug candidates is very essential in the early stage of drug discovery. According to Lipinski and his team, drug-like compounds must obey the rule of five (RO5) i.e. molecular weight (MW) ≤ 500 Da, number of hydrogen bond donor (HBD's) ≤ 5, number of hydrogen bond acceptor (HBAs) ≤ 10 and octanol–water partition coefficient (Log P) ≤ 5 and no more than one violation is allowed. As shown in Table 2, all selected ligands have those properties mostly within the range of druglikeness values, except for epicatechin, vitexin and isovitexin. (Table 2).

CONCLUSION

In conclusion, molecular docking was made to recognize the binding interactions of these reported compounds with the protein enzyme. We examined the interaction of inhibitors with that of our target protein enzyme. The molecular docking study indicates a good binding affinity and binding mode and thus showed the therapeutic potential of these compounds as anti-diabetic agents. The compounds were tested for physicochemical properties by Molinspiration. All the six chemical compounds from Mas Cotek (*Ficus deltoidea*) of isovitexin, orientin, vitexin, epigallocate-chin, catechin, and epicatechin showed lower binding affinity values on molecular docking to PEPCK than metformin as the standard PEPCK inhibition drug. However, only catechin, orientin, and, epigallocate-chin passed Lipinski's rules of five and bind to the active site of the protein enzyme PEPCK. Catechin, orientin, and epigallocatechin can be suggested that these 3 compounds should be further explored to develop as a potent antidiabetic drug.

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