UNIVERSITY OF SS. CYRIL AND METHODIUS IN TRNAVA

Nova Biotechnol Chim (2024) xx(x): e1782
DOI: 10.34135/nbc.1782

Nova Biotechnologica *et* Chimica

Computational study demonstrated anti-diabetic potencies of Diosgenin and Multiflorenol as peroxisome proliferator-activated receptor gamma agonist

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Article info

Article history:
Received: 14th October 2021
Accepted: 20th October 2022

Keywords:
Anti-diabetic
Diosgenin
M. charantia
Multiflorenol
PPARG

Abstract

The prevalence of diabetes mellitus continues to rise on a global basis, making this entity one of the most pressing issues facing public health nowadays. Generally, diabetes mellitus is characterized by increased blood sugar levels caused by insulin secretion or action abnormalities. Natural products have become more popular in treating various types of diseases, including diabetes mellitus, due to their minimal adverse effects. Promoting the peroxisome proliferator-activated receptor γ (PPARG) activation is an anti-diabetic strategy due to its biological function for adipocyte storage, mobilization, differentiation, and insulin sensitivity. This study aims to evaluate diosgenin and multiflorenol *in silico* as anti-diabetic drug candidates by targeting PPARG. Several analyses, such as molecular docking, protein target prediction, biological function prediction, protein-protein interaction, and pharmacokinetics analyses were carried out in this study. Computational prediction showed PPARG have involved in several activities, such as fat cell differentiation, fatty acid oxidation, fatty acid transport, and cellular response to fatty acid. The binding affinity score revealed that diosgenin and multiflorenol have a higher value than the control drug. Other characteristics, such as chemical interaction, amino acid residues, and physicochemical properties, demonstrated supportive drug development outcomes. Therefore, based on our findings, we suggested that diosgenin and multiflorenol, both of which target PPARG, would hold promise as potential candidates for an anti-diabetic drug.

Introduction

According to recent estimations, there will be approximately 463 million people living with diabetes globally in 2019. This number is expected to rise to 578 million by 2030, and it is expected that it will further increase to 700 million by 2045 (Saeedi *et al*. 2019; Akhtar *et al*. 2022). Diabetes

mellitus is defined by hyperglycemia, which is a physiologically abnormal state represented by persistently elevated blood glucose levels. Hyperglycemia is the result of abnormalities in either insulin secretion or insulin action, and it manifests in a chronic and heterogeneous manner as dysfunctions in the metabolism of carbohydrates, fats, or proteins (Banday *et al*. 2020; Dilworth *et al*. 2021).

Diabetes type 2 can lead to a wide variety of long-term consequences in a variety of human organs and systems. Consequently, it contributes to the development of various medical conditions, such as hypertension, asthma, cardiovascular diseases, blindness, sleep apnea, gynecological disorders, and limb amputations (Surani 2014; El Alami *et al*. 2022). The growth of type 2 diabetes can be attributed in large part to people living in urban areas, an aging population, unhealthy lifestyles, and an increasing body mass index. Commonly, in low-income nations, diabetes is caused by various contributing variables such as poverty, malnutrition, and illiteracy (Balcha *et al*. 2018; Rivera *et al*., 2021; Yogal *et al*. 2022).

The PPARG is a nuclear hormone receptor expressed preferentially in adipose tissue. PPARG activation results in enhanced adipocyte storage, mobilization, differentiation, and sensitivity to insulin (Janani and Ranjitha 2015; Mustafa *et al*. 2020). In light of these functions, a significant number of researchers are currently focusing their attention on the PPARG protein. Identifying the appropriate ligand for the PPARG receptor can be an approach for diabetes treatment (Villacorta *et al*. 2009; Janani and Ranjitha 2015; Yi *et al*. 2017).

Pioglitazone, which is a PPARG agonist, is one of the medications that belongs to the thiazolidinediones group, and it is now being utilized as an anti-diabetic medication. In general, the functioning of these medications is accomplished by activating PPARG, which therefore lowers oxidative stress and inflammation. However, research suggests that using these medications may result in undesirable side effects such as decreased bone density, fluid retention, and an increased risk of cardiovascular complications (Escanany *et al*. 2018). Consequently, there is a need for a new ligand candidate that is more effective while also having a less harmful effect on the body.

A growing trend in society is the use of medicinal plants, one of which is as a complementary treatment for diabetes. Evidence continued to mount that oral anti-diabetic medications, insulin, and diet changes were insufficient to treat diabetes effectively (Kifle *et al*. 2022). Various active chemicals in medicinal plants have pharmaceutical effects, one of which is anti-diabetic. To cure diabetes mellitus, phytochemicals with antioxidant characteristics, such as polyphenols and flavonoids, can scavenge free radicals, lower oxidative stress, ameliorate inflammation, and affect the immune system (Putra *et al*. 2019; 2023 and 2024; Putra and Rifa'i 2020; Lv *et al*. 2021). Terpenes, alkaloids, and saponins, among other secondary plant metabolites, may improve insulin secretion and control glucose uptake and utilization. Moreover, bioactive phytochemicals can have antidiabetic effects by, for example, enhancing pancreatic tissue function, which is frequently accomplished by improving insulin secretion, or decreasing intestinal glucose absorption by blocking vital enzymes involved in glucose synthesis (Kooti *et al*. 2016).

M. charantia L., often known as bitter melon or bitter gourd, is a member of the Cucurbitaceae family and is indigenous to tropical and subtropical climates. The plant has been known for centuries, and it has been incorporated into a wide variety of traditional and folk medicines (Polito *et al*. 2016) for the purpose of treating a wide variety of medical conditions, such as type 2 diabetes, high blood pressure, obesity, cancer, bacterial and viral infections (Grover and Yadav 2004). By providing nutritional and nutraceutical components, the fruits and leaves of Momordica species may have numerous health-promoting effects. Thus, in this study, we evaluated diosgenin and multiflorenol, which were widely found in the bitter melon, as potential anti-diabetic drugs through activating PPARG.

Experimental

Ligand retrieval and preparation

Diosgenin and multiflorenol, both produced from the *M. charantia* plant, were the two active

ingredients investigated (Ahmad *et al*. 2016). Pioglitazone, an anti-diabetic medication that is used for drug control, is crucial in activating the PPARG protein (Devchand *et al*. 2018; Liu *et al*. 2020). In this present study, the ligand's 2D structure was collected from the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/) using the following IDs: diosgenin (CID. 99474), multiflorenol (CID. 12312990), and Pioglitazone (CID. 4829). Then, each ligand structure was saved in sdf format, so that it was compatible for docking at a later stage (Putra *et al*. 2017; Hidayatullah *et al*. 2022; Widiastuti *et al*. 2023).

Target protein build up and preparation

The PPARG protein target was constructed through homology modeling after searching for protein sequences on Uniprot (https://www.uniprot.org). P37231-1 was the protein ID utilized in this investigation. Using the SWISS MODEL (https://swissmodel.expasy.org/), proceed with modeling the 3D structure of the target protein after acquiring its sequence. The modeling findings yielded a template protein with the code 3e00.1.B and a sequence coverage of 100 percent with the PPARG protein. Using the PyMOL software (https://pymol.org/2), the protein structure was then cleaned and optimized (Hidayatullah *et al*. 2020 and 2021; Putra *et al*. 2020 and 2021).

Molecular docking and visualization

After ligand and protein preparations were accomplished, the PyRx tool (https://pyrx.sourceforge.io/) was used to perform molecular docking. In this study, the grid box size and docking coordinates were occupied, including X: 64.2828, Y: 60.9933, Z: 44.7639 and X: 5.8594, Y: 32.9476, Z: 12.0831, respectively. Molecular docking data were visualized and analyzed using PyMOL and BIOVIA Discovery Studio software (https://www.3ds.com/). Some of the gathered data consists of binding affinity scores, positions of the binding area, types of chemical interactions, and amino acid residues.

Target protein, biological function, protein interaction and ADMET prediction

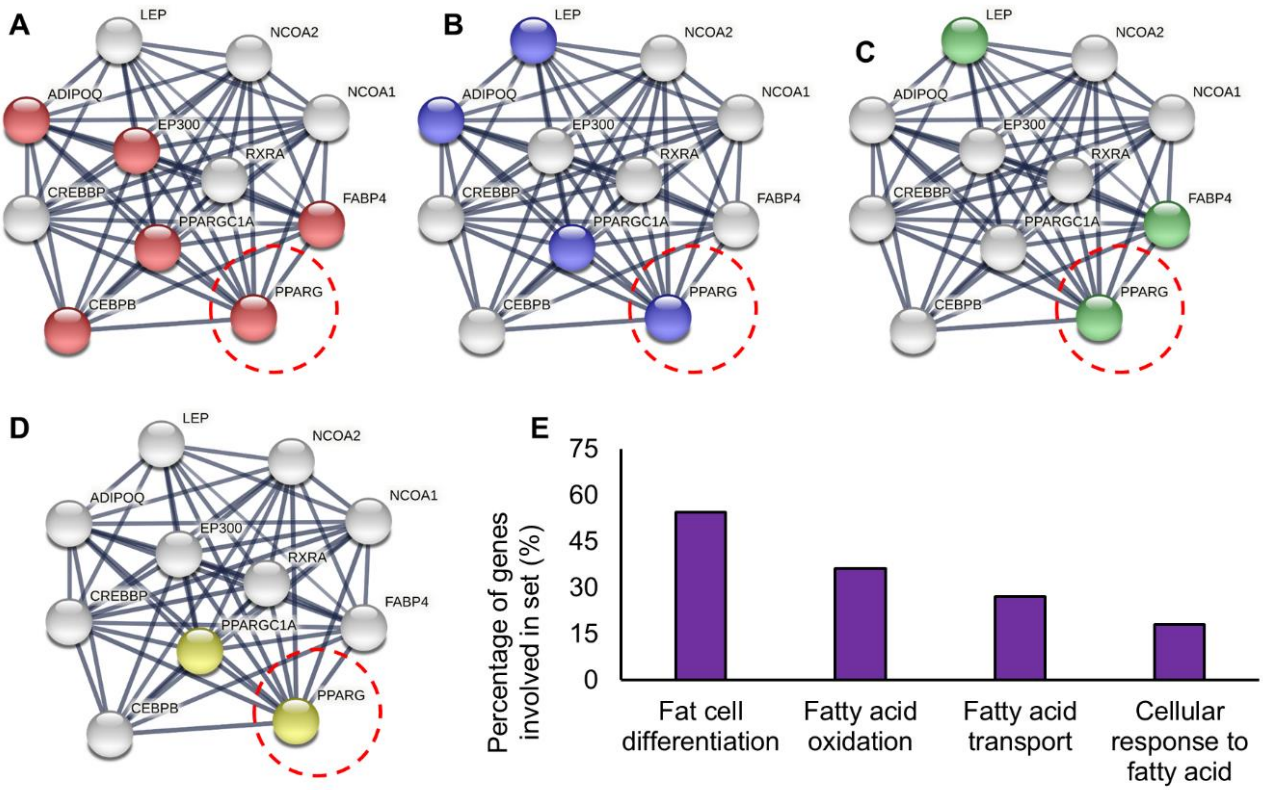
In this study, the protein targets of the active compounds used were predicted. The target protein prediction was carried out using the Swiss Target Prediction webserver (http://www.swisstargetprediction.ch/). Furthermore, the biological activities of the two active compounds were predicted through the online Way2Drug server (http://way2drug.com/passonline/index.php). After that, an analysis of protein-protein interaction was carried out via the STRING (https://string-db.org/) webserver as in our previous study (Heikal *et al*. 2021; Hidayatullah *et al*. 2021). Finally, predictions on absorption, distribution, metabolism, excretion, and toxicity are made online through the pkCSM platform (https://biosig.lab.uq.edu.au/pkcsm/).

Results and Discussion

Diabetes mellitus is a life-threatening condition and is characterized by either an insufficient production of insulin by the pancreas or an inability of the body to make decent use of insulin (Galicia-Garcia *et al*. 2020; Kifle *et al*. 2022). Targeting the PPARG protein for its activation could be one of the strategies for reducing diabetes incidence (Putra *et al*. 2020). The activation of PPARG has been reported to have specific benefits in enhancing adipocyte storage, mobilization, differentiation, and sensitivity to insulin (Janani and Ranjitha 2015; Mustafa *et al*. 2020). This evidence is similar to the computational prediction, which showed that PPARG has several activities such as fat cell differentiation, fatty acid oxidation, fatty acid transport, and cellular response to fatty acid (Fig. 1). Therefore, targeting PPARG for its activation is crucial for anti-diabetic management.

According to the molecular docking study, we further discovered that the binding positions of diosgenin and multiflorenol are identical to those of the control drug, pioglitazone. The superimposed view of all ligands indicates the bioactive compounds of *M. charantia* have a tendency to attach to the target protein's binding site as well as

the control drug. Interestingly, we found that numerous amino acid residues are present in the three protein-ligand complexes namely, Arg316(B), Leu358(B), and Ile354(B) (Fig. 2). In a similar manner, the binding affinity scores of those compounds revealed their promise value for the further drug development. Importantly, diosgenin and multiflorenol shared the same binding affinity value, which was higher than the control drug, Pioglitazone (Table 1). Together, these findings suggest that both compounds might potentially develop into anti-diabetic drug candidates. In view of the fact that the greater the negative value of the binding value, the stronger the binding that occurs between the ligand and the target protein (Putra 2018; Uzzaman *et al*. 2019; Putra *et al.* 2020; Hidayatullah *et al*. 2023).



No.	Description	False Discovery Rate	Genes Involved
1	Fat cell differentiation	7.72E-09	PPARG, FABP4, PPARGC1A, CEBPB, ADIPOQ, EP300
2	Fatty acid oxidation	2.39E-06	PPARG, PPARGC1A, ADIPOQ, LEP
3	Fatty acid transport	9.42E-05	PPARG, FABP4, LEP
4	Cellular response to fatty acid	2.30E-03	PPARG, PPARGC1A

Fig. 1. The protein-protein interaction schematic figures. The involvement of PPARG and other proteins which share similar biological function as fat cell differentiation (**A**); fatty acid oxidation (**B**); fatty acid transport (**C**); and cellular response to fatty acid (**D**). The involvement of genes including PPARG in some of biological function (**E**).

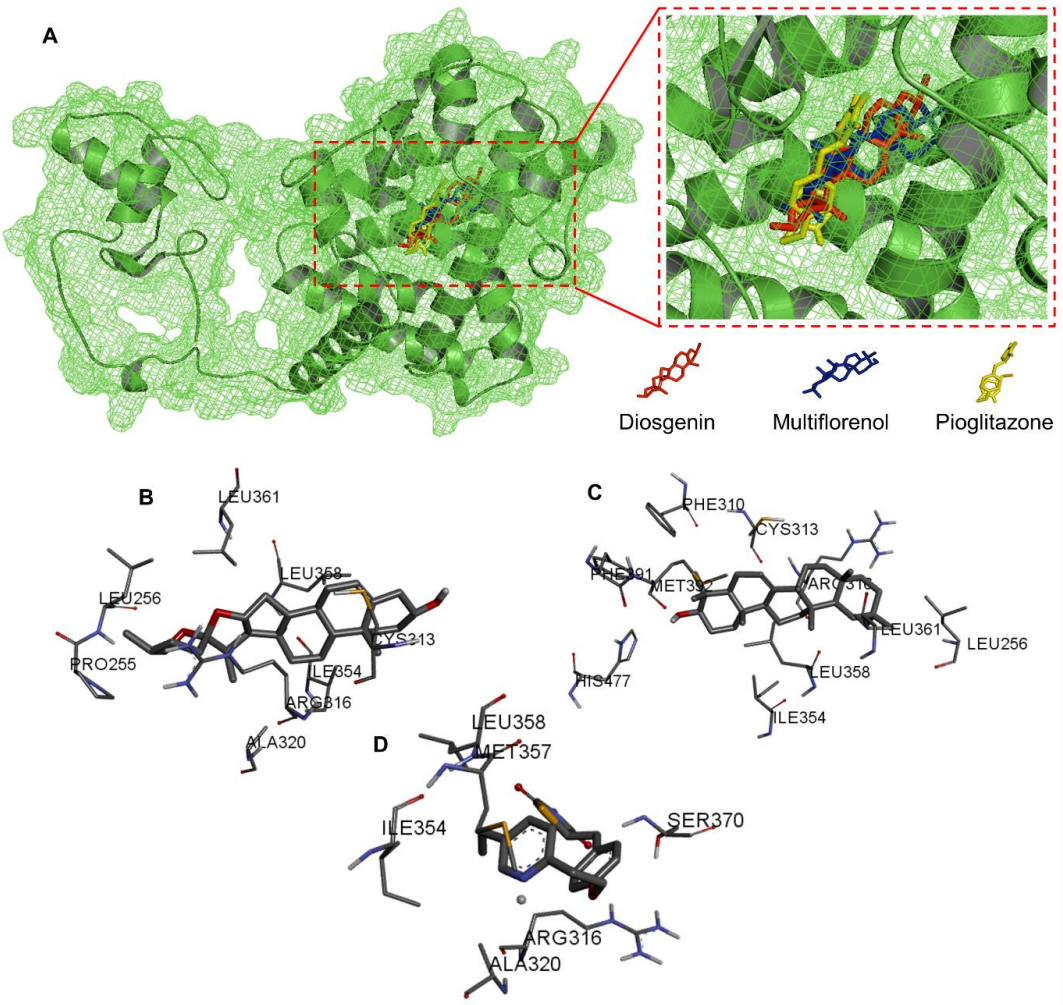


Fig. 2. Superimposed view of diosgenin, multiflorenol, and control drug toward the PPARG protein (**A**). The 2D structure and interaction visualization of diosgenin (**B**), multiflorenol (**C**), and control drug (**D**) toward the PPARG protein.

Table 1. List of binding affinity value, chemical interaction, and amino acids residue of diosgenin, multiflorenol, and control drug toward the PPARG protein.

No.	Compound	Binding Affinity	Chemical Interaction	Amino Acids Residue
1.	Diosgenin CID. 99474	-10.0 kcal/mol	Alkyl	Cys313(B); Ile354(B); Leu358(B); Arg316(B); Ala320(B); Pro255(B); Leu256(B); Leu361(B)
2.	Multiflorenol CID. 12312990	-10.0 kcal/mol	Alkyl/ Pi-Alkyl	Arg316(B); Leu361(B); Leu296(B); Leu358(B); Ile354(B); His477(B); Phe331(B); Met392(B); Phe310(B); Cys313(B)
3.	Pioglitazone CID. 4829	-8.0 kcal/mol	Conventional Hydrogen Bond Alkyl/ Pi-Alkyl	Ser370(B) Arg316(B); Leu358(B); Ile354(B); Met357(B); Ala320(B)

Several physicochemical properties of the protein-ligand bond complex were obtained. These properties include aromatic properties, hydrophobicity, H-bond (Fig. 3), ionizability, charge, and SAS (Fig. 4). An explanation of how the interaction between the ligand compound and the protein target takes place can be gleaned from the physico-chemical properties of the interaction between the ligand compound and the protein target. For instance, the strength of the hydrogen bonds between molecules is the most critical component that contributes to the increased binding affinity of drugs to their receptors (Uzzaman *et al*. 2021). On the other hand, an analytical method that measured the solubility of insoluble substances was called the solvent-accessible surface area, and it referred to the portion of the surface area of biomolecules that could be reached by solvents (He *et al*. 2022). These observed parameters can provide an indication of how promising a compound would be as a prospective candidate for drug development.

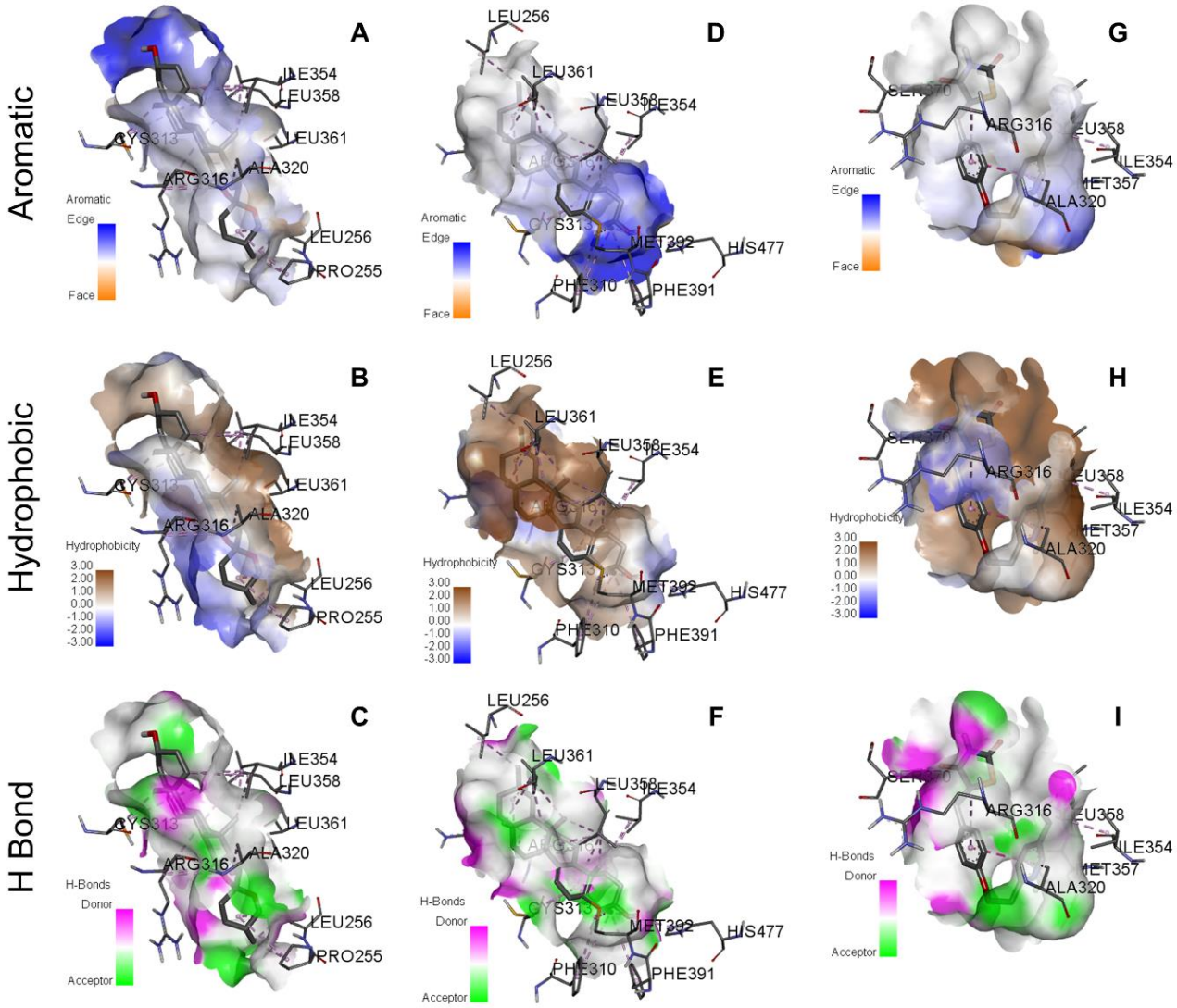


Fig. 3. The physicochemical properties of diosgenin, multiflorenol, and control drug toward the PPARG protein. Upper panel indicates aromatic properties; middle panel indicates hydrophobic properties, and lower panel indicates H-bond properties. **A – C**: Diosgenin; **D – F**: Multiflorenol; **G – I**: Pioglitazone.

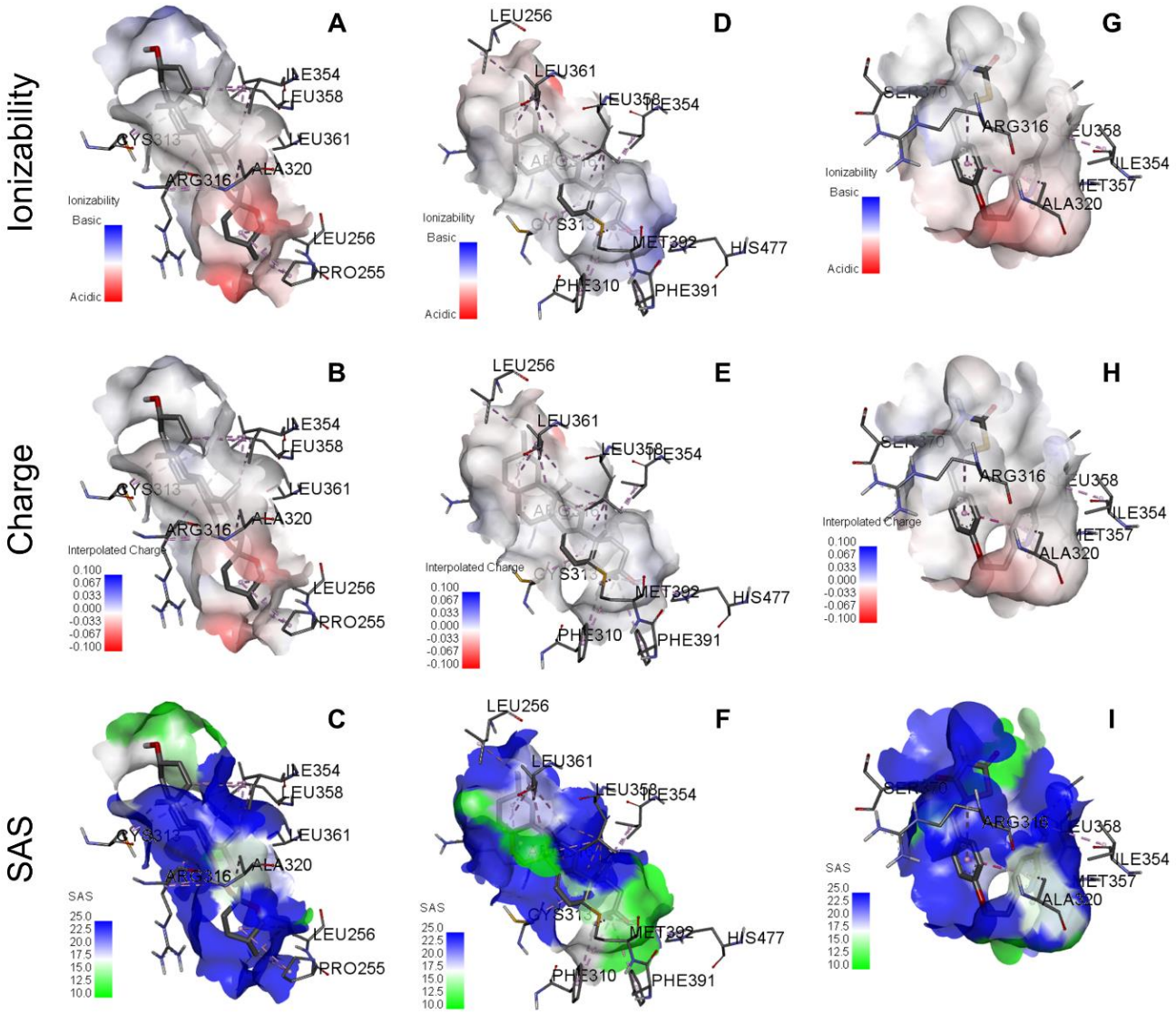


Fig.4. The physicochemical properties of diosgenin, multiflorenol, and control drug toward the PPARG protein. Upper panel indicates ionizability properties; middle panel indicates charge properties, and lower panel indicates SAS properties. **A – C**: Diosgenin; **D – F**: Multiflorenol; **G – I**: Pioglitazone.

In addition, according to the *in silico* prediction that we carried out, we discovered that diosgenin predominantly targets proteins such as nuclear receptors (20 %) and voltage-gatedion channel and kinase (13.3 %). On the other hand, multiflorenol has targeted proteins such as nuclear receptor (26.7 %), cytochrome p450 (20 %), and hydrolase, or electrochemical transporter (13.3 %). Interestingly, the predicted biological properties showed that diosgenin acts as UDP-glucuronosyltransferase substrate, cholesterol antagonist, glyceryl-ether mono-oxygenase inhibitor, hypolipemic, dolichyl-diphosphooligosaccharide-protein glycol-transferase inhibitor, 27-hydroxycholesterol 7 alpha-monooxygenase inhibitor, alkenyl-glycerophosphocholine hydrolase inhibitor, and galactolipase inhibitor. Besides, the predicted biological properties of multiflorenol including insulin promoter, lipid metabolism regulator, lipid peroxidase inhibitor, hypolipemic, alkenylglycerophosphocholine hydrolase inhibitor, alkylacetylglycerophosphatase inhibitor, acylcarnitine hydrolase inhibitor, and phospholipase C inhibitor (Fig. 5). Accumulating evidence demonstrated that both diosgenin and multiflorenol exert anti-diabetic abilities (Table 2).

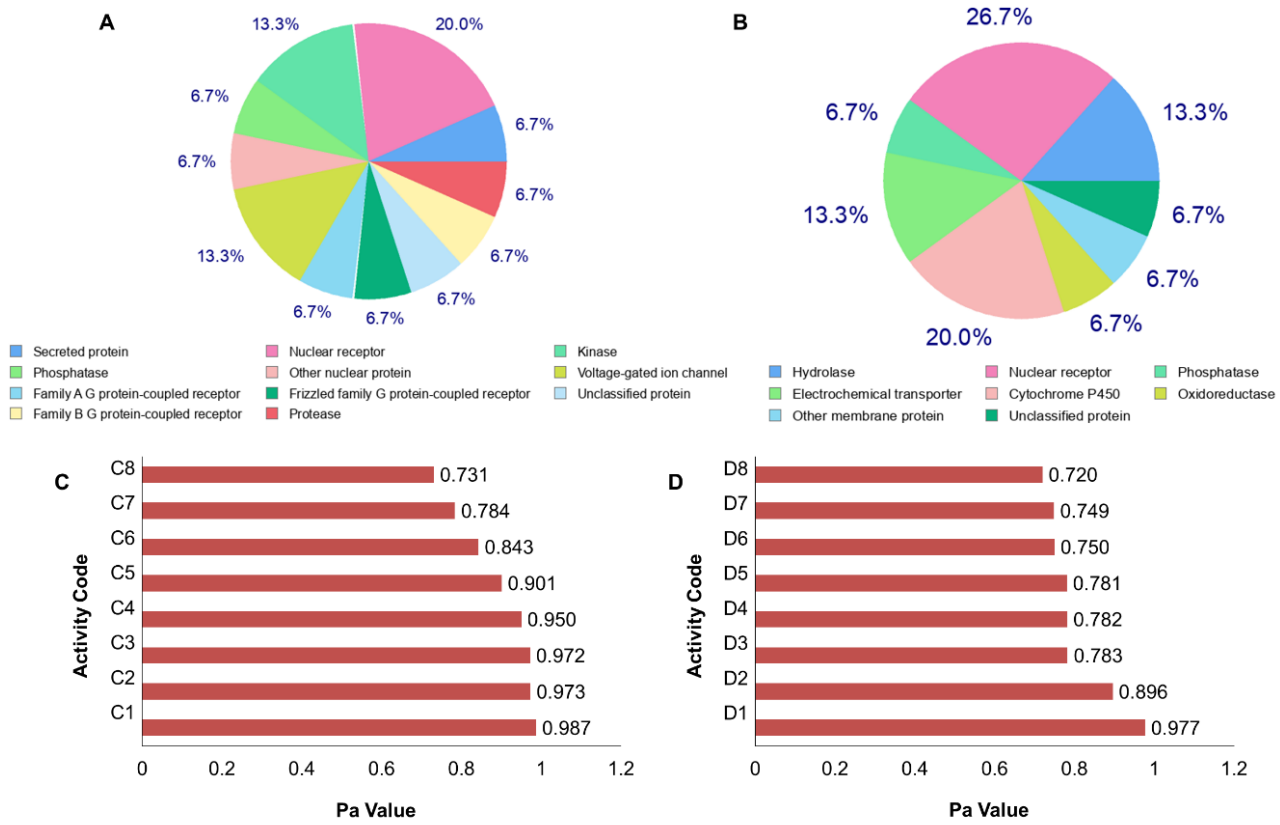


Fig. 5. The predicted target protein and predicted biological properties of diosgenin (**A** and **C**) and multiflorenol (**B** and **D**). The predicted biological properties of diosgenin including C1: UDP-glucuronosyltransferase substrate; C2: Cholesterol antagonist; C3: Glyceryl-ether mono-oxygenase inhibitor; C4: Hypolipemic; C5: Dolichyl-diphosphooligosaccharide-protein glycol-transferase inhibitor; C6: 27-Hydroxycholesterol 7alpha-monooxygenase inhibitor; C7: Alkenyl-glycerophosphocholine hydrolase inhibitor; and C8: Galactolipase inhibitor. The predicted biological properties of multiflorenol including D1: Insulin promoter; D2: Lipid metabolism regulator; D3: Lipid peroxidase inhibitor; D4: Hypolipemic; D5: Alkenylglycerophosphocholine hydrolase inhibitor; D6: Alkylacetylglycerophosphatase inhibitor; D7: Acylcarnitine hydrolase inhibitor; and D8: Phospholipase C inhibitor.

Table 2. The anti-diabetic properties of diosgenin and multiflorenol.

Compounds	Anti-diabetic properties	References
Diosgenin	↓ activity of α-Amylase and α-	Ghosh *et al*. 2014
	↓ glucagon-induced HGPa	Nagy *et al*. 2013
	↓ activity of intestinal disaccharidases in	McAnuff *et al*. 2006
	↓ activity of glucose transport in	McAnuff *et al*. 2005
	↓ activity of SGLT-1	Al-Habori *et al*. 2001
Multiflorenol	Control gut glucose absorption and	Tripathy *et al*. 2021
	Possess lipid-reducing effects	Srivastava *et al*. 2020
	Block α2A - adrenergic receptor to	Lehner *et al*. 2020

There are several mechanisms how diosgenin and multiflorenol decrease the negative effects of diabetes mellitus. For example, diosgenin could reduce the activity of several biomarkers related to diabetes mellitus such as α-amylase, α-glucosidase (Ghosh *et al*. 2014), and SGLT-1 (Al-Habori *et al*. 2001). Similarly, multiflorenol regulates the glucose level by controlling gut absorption, promoting glucose uptake in muscle (Tripathy *et al*. 2021), and blocking the α-2A adrenergic receptor (Lehner *et al*. 2020). In this present study, we provided about 15

predictors of ADMET results from the PkCSM webserver for diosgenin and multiflorenol (Fig. 6). The qualities of a compound, including its absorption, distribution, metabolism, excretion, and toxicity, play an essential part in drug discovery and development. Failure to meet ADMET criteria is a common cause of drug candidate attrition (Guan *et al.* 2019; Venkatraman 2021). Consequently, determining the ADMET value for potential drug candidates is an important step.

Property	Model Name	Predicted Value		Unit
		Diosgenin	Multiflorenol	
Absorption	Water solubility	-5.539	-6.39	Numeric (log mol/L)
Absorption	Caco2 permeability	1.293	1.216	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	96.565	94.239	Numeric (% Absorbed)
Distribution	VDss (human)	0.426	0.233	Numeric (log L/kg)
Distribution	BBB permeability	0.2	0.661	Numeric (log BB)
Distribution	CNS permeability	-2.885	-1.911	Numeric (log PS)
Metabolism	CYP2D6 substrate	No	No	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	Yes	Yes	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitior	No	No	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitior	No	No	Categorical (Yes/No)
Excretion	Total Clearance	0.328	-0.045	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	Yes	No	Categorical (Yes/No)
Toxicity	Max. tolerated dose (human)	-0.559	-0.637	Numeric (log mg/kg/day)
Toxicity	Oral Rat Acute Toxicity (LD50)	1.921	2.348	Numeric (mol/kg)
Toxicity	Hepatotoxicity	No	No	Categorical (Yes/No)

Fig. 6. The chemical absorption, distribution, metabolism, excretion, and toxicity properties of diosgenin and multiflorenol.

Promoting PPARG activation is a crucial strategy to overcome diabetes. Based on in silico study, we found that diosgenin and multiflorenol have great potency as anti-diabetic drug candidates due to their binding affinity, chemical interaction, physicochemical properties, predicted biological activity, and ADMET analysis.

Acknowledgements

Authors thank Universitas Negeri Malang and the Computational Laboratory, Brawijaya University Malang for support this study.

Conflict of Interest

The authors declare that they have no conflict of interest.

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