Molecular Docking Simulation of Antidiabetic Molecules of Libas (Spondias pinnata) Fruit and Prediction of their Pharmacokinetic Properties

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Research Article

Keywords: Spondias pinnata, diabetes mellitus, molecular docking, ADMET, drug-likeness

Posted Date: February 5th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-3915447/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at In Silico Pharmacology on June 14th, 2024. See the published version at https://doi.org/10.1007/s40203-024-00230-3.

Abstract

Diabetes mellitus is one of the chronic metabolic disorders which affects more than 16 million Filipinos. Proper education, medical intervention, and a good lifestyle can help control and manage this disease. *Spondias pinnata* is one of underutilized crops in the Philippines which is well-known for its satisfactory flavor and medicinal properties including its antidiabetic activity. A quest for natural and effective drug to manage diseases is a continuous work in progress. Drug discovery and design is a tedious and expensive process. Computer-aided drug design guides the design and makes the process more efficient and less costly. Molecular docking simulation was used to determine the potential antidiabetic compounds from the 48 reported compounds found in *S. pinnata* fruit. Seven compounds namely squalene (-9.1kcal/mol), rutin (-9kcal/mol), catechin(-8.7kcal/mol), quercetin (-8.5kcal/mol), tocopherol (-8.4kcal/mol), myricetin (-8.4kcal/mol), and ellagic acid (-8.3kcal/mol) showed comparable binding affinity with peroxisome proliferator-activated receptor gamma (PPARγ). Tocopherol and catechin showed good ADMET properties. Between the two compounds, catechin passed the four filters for drug-likeness. Thus, catechin can be a potential compound that can be used to develop antidiabetic drugs.

Introduction

Diabetes mellitus (DM) is one of the chronic metabolic disorders that involves elevation of blood glucose levels. DM has several categories including type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes (GED), neonatal diabetes, etc. Type 1 DM (T1DM), brought by defective insulin secretion, and type 2 DM (T2DM), brought by defective insulin action/production, are the main subtypes of DM [1]. T1DM is said to affect children or adolescents while T2DM affects middle-aged and older adults. T2DM is the most common type of DM, affecting 90–95% [2] of 422 million people worldwide with DM [3]. In partial and unofficial data released by the Department of Health Philippines on March 2023, more than 16 million Filipinos aged 20 years old and above were assessed to have T2DM [4].

Like any other disease, early diagnosis is important to be able to avoid the drastic health effects of T2DM. Once diagnosed, it is important to manage blood sugar levels by insulin injection or taking medications such as diguanides, sulfonylureas, or sodium-glucose-co-transporters type 2 (SGLT-2) inhibitors, meglitinides, α-glucosidase inhibitors, thiazolidinediones, glucagonlike-peptide-1 agonist, dipeptidyl peptidase IV inhibitors, and selective amylinomimetics [3]. These medicines commonly have adverse effects on patients such as hypoglycemia, gastrointestinal upset, lactic acidosis, fluid retention, upper respiratory tract infection, diarrhea, nausea, and urinary tract infections [1].

Among the medications available for DM, thiazolidinediones (TZD) are the only one that focus on improving insulin resistance of the tissues in the body [5]. TZD is a synthetic agonist of peroxisome proliferator-activated receptor gamma (PPARγ). PPARγ is an agonist-dependent nuclear hormone receptor. The binding of TZD to PPARγ causes the activation of transcription genes involved in glucose disposal. These causes improved insulin sensitivity and β cell functions [6]. However, several side effects

have been reported for the use of TZDs including weight gain, anemia, bone loss, and fractures among others [5].

Search for an alternative medication that will not or can very minimally bring side effects to patients is a continuous endeavor. The process of drug discovery and development is tedious, time-consuming, and costly. Generally, drug discovery and development involve target identification, target validation, hit discovery, lead optimization, and preclinical or clinical development. After several phases of clinical testing, the drug candidate can be submitted for approval to launch on the market [7, 8].

Computer-aided drug design (CADD) is one of the methods being used to maximize the success of drug development. It utilizes information obtained from the target and the candidate drug [7, 8]. CADD also helps guide and hasten the process with limitations in using animal models for quality and safety testing [9]. *In silico* structure-based drug design such as molecular docking can be effectively employed to investigate the interactions between a target and novel chemical compounds [8, 9]. This process of drug discovery is considered to be more productive than the traditional method of drug discovery.

Spondias pinnata commonly known as *libas* is commonly used as a souring agent in dishes such as *sinigang* and *laing* [10]. This tree is underutilized with little to no economic importance [11, 12]. However, *libas* is reported to show potential for its nutritional, medicinal, and pharmacological properties [13, 14]. Studies presented the possible use of libas as antidiabetic medication; however, the mechanism of action has not been established.

In this study, molecular docking is used to determine ligands from *libas* fruit that can be a candidate as antidiabetic drug. Molecular docking was used to identify the compounds in *libas* that can be a good ligand to PPARγ. ADMET properties and drug-likeness of the identified ligands were also determined.

Materials and methods

Data Collection

The 48 ligands considered in the study were based on the reported chemical composition of *S. pinnata*. Rhamnetin 3-*O*-sophoroside, caffeic acid methyl ester, lignoceric acid, β-sitosterol-D-glucoside, β-sitosterol, Δ^4 β-sitostenone, 24-methylenecycloartanol, β-amyrin, oleanolic acid, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, gallic acid, salicylic acid, ellagic acid, catechin, rutin, myricetin, quercetin, 2-methyl-2-butenal, furfural, 2(5H)-furanone, butyric acid-2-methyl-methyl ester, 5-hydroxymethylfurfural, myristic acid, limonene, o-cymen-5-ol, 1H-purine,6-methoxy, acetic acid, 4-methyl phenyl ester, palmitic acid, eicosane, stearic acid, ethyl palmitate, 10,13-octadeca-dienoic acid, methyl ester, oleic acid, (*Z*)-9,17-octadecadienal, tocopherol, linoleic acid, stigmastan-3,5-diene, eladic acid methyl ester, 3-pentadecylphenol, linolenic acid methyl ester, lignoceric acid methyl ester, cyclotetracosane, 9-hexacosene, ergosta-4,6,22-trien-3,beta-ol, squalene, ergost-5-en-3-ol, (3-beta)-, campesterol, and phytosterol[15–18] were analyzed for their interactions with receptor PPARγ [19]. Most of the 3D structures of the compounds were downloaded fromPubChem

(https://pubchem.ncbi.nlm.nih.gov/) database [20]. For those without available 3D structures, PerkinElmer Chem3D version 16.0.1.4[21] was used to manually draw the structures. All the required applications were installed: Chimera [22], AutoDockTools [23], PyRx – Virtual Screening Tool [24], AutoDock Vina [25], PyMOL [26], and LigPlot+ [27].ADMETLab 2.0 [28] was accessed using the Google Chrome browser.

Ligand and Protein Preparation

Each ligand was downloaded as sdf file. Conversion of the ligand files into pdbqt files was done using Open Babel tool in PyRx. PPARγ, the target molecule, was downloaded with a ligand attached from RCSB Protein Data Bank (https://www.rcsb.org/) [29] shown in Fig. 1. In preparation of the target molecule, Chimera was used to visualize and manipulate the target molecule and remove the ligand, and AutoDock was used to remove the water molecules and add polar hydrogens and charges. The target molecule was saved as pdbqt file. Biovia Discovery Studio Visualizer version 24.1.0.23298 [30] was also used to visualize the protein.

Molecular Docking

PyRx – Python Prescription 0.8 [24] was used to do the molecular docking between the target molecule and the ligands. PPARγ was loaded and assigned as the macromolecule. The grid box was assigned to include the binding site. The binding site of PPARγ was verified using pioglitazone. AutoDock Vina [25] in PyRx was used as a molecular docking tool. After running the software and obtaining the docking results, the attained target-ligand complex interactions were analyzed using PyMOL [26] and LigPlot+ [27].

ADMET and Druglikeness Prediction

ADMET properties and drug-likeness of the ligands were predicted using ADMET Lab 2.0 (https://admetmesh.scbdd.com/service/evaluation/index) [28]. The simplified molecular input line entry system (SMILES) of each compound was copied from PubChem and entered in ADMETLab 2.0 to calculate their ADMET properties as well as their drug-likeness.

Results and discussion

Discovery of new drugs has been a constant pursuit especially nowadays when chronic diseases are emerging and occurrence is constantly increasing. The quest for finding a new drug and having it accepted for use is tedious and expensive. CADD is attaining a good deal of attention and is now being used as an excellent alternative to conventional methods of drug design and discovery which employs extensive resources and time from screening of the compounds to hit discovery good for preclinical and clinical trials and assessment. With the use of CADD methods such as the structure-based drug design, hundreds of thousands of time and resources are being saved.

Molecular Docking

In this study, 48 compounds from *S. pinnata* were screened for their potential drug use against diabetes. Before the molecular docking method, the binding site residues of the receptor, PPARγ, were determined from literature to contain CYS285, ARG288, SER289, HIS323, ILE341, HIS449, and TYR473 [31,32]. The grid box parameter was set based on these residues and was assigned the center grid values of X = -1.9609, Y = 4.7749, and Z = -10.2850, dimensions (Å) of X = 27.4834, Y = 18.1711, and Z = 19.8376. The exhaustiveness was set to default which is 8. This controls the comprehensiveness of the Vina Wizard search [33]. Docking was then run for all 48 compounds and each run mostly gave nine different positions except for β-amyrin and oleanolic acid where two different poses were only given. The docking result includes binding affinity and lower and upper root mean square difference. Binding affinity is the strength of the binding interaction between a protein and a ligand. Binding affinity is usually measured using the equilibrium dissociation constant, K_D. The smaller the K_D value, the higher the affinity, lower the binding affinity value, thus, the stronger the interaction between the protein and the ligand [34]. Thus, the pose with the lowest binding affinity was chosen. For the docking result of pioglitazone, the best pose was the one with the binding affinity of -8.3 kcal/mol, and this was used as the reference for choosing the possible ligands that best bind with PPARγ. Figure 2 shows the PPARγ with the best pose of the ligand pioglitazone. The interactions present in the complex are hydrogen bond with CYS285, a π-sulfur interaction (electrostatic) with MET364, a π-alkyl interaction (hydrophobic) with ARG288 and LEU330, and an alkyl interaction (hydrophobic) with PHE282, HIS449, LEU453 and LEU465 (Figure 3). Although hydrogen bonds are being exploited in drug design due to their specificity in distance and geometric restrictions [35], hydrophobic interactions are a primary driving force in drug-receptor interactions [36].

From 48 compounds docked, only 7 compounds (shown in Table 1) showed binding affinity the same or lower than the binding affinity of pioglitazone. Squalene has the lowest binding affinity of -9.1 kcal/mol. Numerous hydrophobic interactions stabilize its association with PPARγ including interactions with LYS265, CYS285, ARG288, LEU330, ILE341, LEU453, LEU465, LEU469, PHE282, PHE287, PHE363, HIS449, and TYR473. Squalene and pioglitazone both have interactions with ARG288, LEU330, LEU453, LEU465, LEU469, PHE282, HIS449, and TYR473. Squalene is a triterpene with 6 isoprene that is widely present in nature. It is known to have numerous beneficial properties including as an antioxidant, aids in skin hydration, and as an emollient in adjuvants for vaccines [37-39]. A recent study showed the potential of squalene to manage some symptoms of diabetes such as decreased HDL, and elevated LDL, TC, and VLDL [40].

Rutin is a bioflavonoid that is found to be present in plants. Naturally occurring flavonoids such as rutin have shown pieces of evidence of their capability to improve glucose metabolism [41]. The mechanism of the antihyperglycemic effect of rutin has been explored and is proposed to be from the decrease of carbohydrate absorption from the small intestine, inhibition of tissue gluconeogenesis, increase of tissue glucose uptake, stimulation of insulin secretion from beta cells, and protection of Langerhans islet against degeneration [42]. Rutin showed -9 kcal/mol binding affinity. Its binding with the receptor is stabilized with four hydrogen bonds with CYS285, ALA278, HIS449, and LEU340, hydrophobic interactions with PHE363, HIS449, CYS285, and LEU453, and electrostatic interaction with HIS449. Rutin

and pioglitazone both formed hydrogen bonds with CYS285 and hydrophobic interactions with LEU453 and HIS449.

The binding affinity of catechin is -8.7kcal/mol. There are two hydrogen bonds with GLU343 and GLY284. Hydrophobic interactions with GLY284, SER342, PHE264, PHE287, ILE281, CYS285, ILE341, LYS265, and ARG288 are also present. Catechin and pioglitazone both formed interaction with ARG288. Catechin, also a flavonoid, is considered as a polyphenol antioxidants family. It was reported to improve hyperglycemia and prevent complications of diabetes by improving insulin sensitivity and reducing risk factors such as obesity, hypertension, and hyperlipidemia [43,44].

Quercetin has a binding affinity of -8.5kcal/mol. Its binding is stabilized with an electrostatic interaction with HIS449, and hydrophobic interactions with CYS285, PHE363, PHE282, HIS449, LEU453, and MET364. There is an unfavorable interaction with HIS323. This kind of interaction may affect the activity and stability of the binding complex [45], however, up to two unfavorable interactions are tolerable [46]. Quercetin and pioglitazone both formed interactions with CYS285, LEU453, PHE282 and HIS449. Quercetin is another member of the flavonoid group that naturally occurs in plants. As mentioned earlier, flavonoids are known to have health benefits. Quercetin specifically contains anticarcinogenic, anti-inflammatory, and antiviral properties. Studies have also shown its effects on obesity and diabetes. Quercetin is said to act on GLUT4 to increase glucose uptake and thus, avoid hyperglycemia. It also helps to minimize oxidative damage in the pancreas and increase islets [47].

Table 1. Best binding compounds and their interactions with PPARγ binding site residues

Best binding compounds	Binding affinity (kcal/mol)	Interactions	Distance (Å)	Category
Squalene	-9.1	A:LYS265 - N:Lig	5.44	Hydrophobic
		A:CYS285 - N:Lig	4.32	Hydrophobic
		A:CYS285 - N:Lig	4.46	Hydrophobic
		A:CYS285 - N:Lig	5.44	Hydrophobic
		A:ARG288 - N:Lig	4.31	Hydrophobic
		A:ARG288 - N:Lig	4.81	Hydrophobic
		A:ARG288 - N:Lig	5.04	Hydrophobic
		A:LEU330 - N:Lig	4.74	Hydrophobic
		A:LEU330 - N:Lig	5.49	Hydrophobic
		A:ILE341 - N:Lig	4.78	Hydrophobic
		N:Lig:C - A:LYS265	4.07	Hydrophobic
		N:Lig:C - A:LEU453	4.16	Hydrophobic
		N:Lig:C - A:LEU465	4.75	Hydrophobic
		N:Lig:C - A:LEU469	5.06	Hydrophobic
		A:PHE282 - N:Lig	4.42	Hydrophobic
		A:PHE282 - N:Lig:C	5.28	Hydrophobic
		A:PHE287 - N:Lig	5.28	Hydrophobic
		A:PHE363 - N:Lig	4.57	Hydrophobic
		A:HIS449 - N:Lig	4.98	Hydrophobic
		A:HIS449 - N:Lig	5.12	Hydrophobic
		A:HIS449 - N:Lig:C	4.70	Hydrophobic
		A:TYR473 - N:Lig:C	5.07	Hydrophobic
Rutin	-9	A:CYS285:SG - N:Lig:O	3.36	Hydrogen Bond
		N:Lig:H - A:ALA278:O	3.00	Hydrogen Bond
		N:Lig:H - A:LEU340:O	2.76	Hydrogen Bond
		N:Lig:H - A:LEU340:O	1.94	Hydrogen Bond
			3.16	Hydrogen Bond
			3.42	
			4.00	

		A:HIS449:CE1 - N:Lig:O	4.62	Hydrogen Bond
		A:HIS449:NE2 - N:Lig	4.86 4.42	Electrostatic Hydrogen Bond
		A:CYS285:SG - N:Lig	4.40	Hydrophobic
		A:PHE363 - N:Lig	4.42	Hydrophobic
		A:PHE363 - N:Lig	3.97	Hydrophobic
		A:HIS449 - N:Lig	5.45	Hydrophobic
		N:Lig:C - A:CYS285		Hydrophobic
		N:Lig:C - A:ILE341		Hydrophobic
		N:Lig - A:CYS285		Hydrophobic
		N:Lig - A:LEU453		Hydrophobic
Catechin	-8.7	N:Lig:C - A:GLY284:O	5.07	Hydrogen Bond
		A:GLY284:CA - N:Lig	5.33 5.28	Hydrogen Bond Hydrophobic
		A:SER342:CA - N:Lig	5.30	Hydrophobic
		N:Lig:H - A:GLU343:OE2	5.09	Hydrophobic
		A:PHE264 - N:Lig	5.42	Hydrophobic
		A:PHE287 - N:Lig	4.69	Hydrophobic
		A:CYS285 - N:Lig	3.68	Hydrophobic
		A:ILE341 - N:Lig	3.92	Hydrophobic
		A:PHE264 - N:Lig	3.95	Hydrophobic
		N:Lig - A:ILE281	4.98	Hydrophobic
		N:Lig - A:CYS285	5.27	Hydrophobic
		N:Lig - A:ILE341	5.03	Hydrophobic
		N:Lig - A:LYS265	2.59	Hydrophobic
		N:Lig - A:ARG288		Hydrophobic

Continuation of Table 1. Best binding compounds and their interactions with PPARγ binding site residues

Quercetin	-8.5	A:HIS449:NE2 - N:Lig	4.05	Electrostatic
		A:HIS449:NE2 - N:Lig	3.32	Electrostatic
		A:CYS285:SG - N:Lig	3.91	Hydrogen Bond
		A:PHE363 - N:Lig	5.69	Hydrophobic
		A:PHE363 - N:Lig	4.88	Hydrophobic
		A:PHE282 - N:Lig	5.77	Hydrophobic
		A:HIS449 - N:Lig	4.59	Hydrophobic
		A:HIS449 - N:Lig	4.33	Hydrophobic
		N:Lig - A:CYS285	4.50	Hydrophobic
		N:Lig - A:LEU453	5.43	Hydrophobic
		N:Lig - A:MET364	5.12	Hydrophobic
Tocopherol	-8.4	A:SER342:HN - N:Lig	2.60	Hydrogen Bond
		A:PRO227 - N:Lig	5.12	Hydrophobic
		A:LEU228 - N:Lig	4.71	Hydrophobic
		A:ARG288 - N:Lig	4.40	Hydrophobic
		A:MET329 - N:Lig	4.88	Hydrophobic
		A:LEU330 - N:Lig	3.89	Hydrophobic
		A:LEU333 - N:Lig	4.85	Hydrophobic
		A:LEU333 - N:Lig	4.56	Hydrophobic
		N:Lig - A:ARG288	3.80	Hydrophobic
		N:Lig - A:ILE341	5.21	Hydrophobic
Myricetin	-8.4	A:CYS285:SG - N:Lig:O	3.52	Hydrogen Bond
		A:ARG288:HE - N:Lig:O	1.94	Hydrogen Bond
		N:Lig:H - A:GLU343:OE2	1.99	Hydrogen Bond
		N:Lig:H - A:GLU291:OE1	2.59	Hydrogen Bond
		N:Lig:H - A:CYS285:SG	2.79	Hydrogen Bond
		N:Lig:H - A:ARG280:O	2.36	Hydrogen Bond
		A:GLY284:CA - N:Lig	3.85	Hydrophobic
		A:SER342:CA - N:Lig	3.92	Hydrophobic
		A:GLY284:C,O;CYS285:N - N:Lig	4.08	Hydrophobic

		A:GLY284:C,O;CYS285:N - N:Lig	4.52	Hydrophobic
		N:Lig - A:ILE281	5.05	Hydrophobic
		N:Lig - A:CYS285	5.29	Hydrophobic
		N:Lig - A:CYS285	5.31	Hydrophobic
		N:Lig - A:ILE341	4.71	Hydrophobic
		N:Lig - A:ILE341	5.35	Hydrophobic
		N:Lig - A:LYS265	5.30	Hydrophobic
		N:Lig - A:ARG288	5.08	Hydrophobic
Ellagic acid	-8.3	A:LYS265:HN - N:Lig:O	2.36	Hydrogen Bond
		N:Lig:H - A:LEU340:O	2.53	Hydrogen Bond
		A:SER342:HN - N:Lig	2.96	Hydrogen Bond
		A:SER342:HN - N:Lig	3.02	Hydrogen Bond
		A:ARG288:CD - N:Lig	3.41	Hydrophobic
		N:Lig - A:ARG288	4.20	Hydrophobic
		N:Lig - A:ARG288	4.17	Hydrophobic
		N:Lig - A:ARG288	4.76	Hydrophobic
		N:Lig - A:ILE341	4.92	Hydrophobic
		N:Lig - A:ARG288	4.28	Hydrophobic
		N:Lig - A:ILE341	5.03	Hydrophobic

Tocopherol showed a binding affinity of -8.4kcal/mol. Its binding is stabilized with a hydrogen bond with SER342, and hydrophobic interactions with PRO227, LEU228, ARG288, MET329, LEU330, LEU333, and ILE341. Tocopherol and pioglitazone both formed interactions with ARG288 and LEU330. Tocopherol or vitamin E is a lipid-soluble antioxidant. It has been suggested as a strategy to correct abnormalities in carbohydrate and lipid metabolism. The effect of tocopherol in the reduction of oxidative stress benefits to LDL oxidation, isoprostanes, and anti-inflammatory effect may suggest that it can be a good therapeutic mode to control diabetes [48].

The binding affinity of myricetin was -8.4kcal/mol. Stabilization of the binding was achieved with five hydrogen bonds with CYS285, ARG288, GLU343, GLU291, and ARG280, and hydrophobic interactions with GLY284, SER342, CYS285, ILE281, ILE341, LYS265, and ARG288. An interaction with LYS265 resulted in an unfavorable interaction. Myricetin and pioglitazone both formed hydrogen bond with CYS285, and hydrophobic interaction with ARG288. Myricetin is another naturally occurring flavonoid that is also established to decrease plasma glucose in diabetes. It is also known to improve insulin resistance and

function as most flavonoids, anti-inflammatory, anti-oxidative stress, anti-aldose reductase, and anti-hyperlipidemia [49,50].

Lastly, ellagic acid has a binding affinity of -8.3kcal/mol. Three hydrogen bonds with LYS265, LEU340, and SER342 stabilized the bond, together with hydrophobic interactions with ARG288, and ILE341. Ellagic acid and pioglitazone both formed hydrophobic interaction with ARG288. Ellagic acid is hydrolysis product of ellagitannins which is found in walnuts, pomegranates and some berries. Ellagic acid shows antioxidant, anti-inflammatory, and anti-glycation properties [51]. With these properties, ellagic acid is found to normalize glucose level, maintain glucose homeostasis, thus a potential therapeutic agent in the management of DM [52].

ADMET Properties and Drug-likeness

The absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties and drug-likeness are predicted using ADMET Lab 2.0. ADMET properties provide the safety uptake, elimination, metabolic behavior, and effectiveness of a potential drug.

Absorption

Caco-2 or the human colon adenocarcinoma cell line is used as a model of human intestinal epithelium absorption and is used as a gauge for the drug's suitability as an oral drug. ADMET Lab 2.0 mentioned that a predicted value of greater than -5.15 log cm/s is a good Caco-2 permeability. Among the seven compounds, squalene and tocopherol have proper Caco-2 permeability.

MDCK or the Madin-Darby Canine Kidney cells is also an *in vitro* model for permeability screening like Caco-2 cells. Apparent permeabilities, P_{app}, are said to be gold *in vitro* standard for evaluating the uptake efficiency of drugs [53]. A $2.0x10^{-6}$ cm/s value or higher is considered to be a good permeability. All of the seven compounds have P_{app} greater than $2.0x10^{-6}$ cm/s which means a good permeability with rutin having excellent permeability while catechin has the lowest P_{app} value.

P-glycoprotein or the multidrug resistance protein-1 is one of the most studied ATP-binding cassettes which are important multidrug transporters. This can affect the efficacy of the drug for it controls the rate of cellular uptake of foreign substances such as drugs. This also includes the distribution and elimination of foreign substances [54]. All of the seven compounds are Pgp inhibitors while all are also Pgp substrates except rutin.

Human intestinal absorption or HIA is important in the apparent efficacy of the drug. HIA is also related to oral bioavailability [33]. ADMET Lab 2.0 said that an absorbance of less than 30% is considered to be poor absorption. Catechin, quercetin, and tocopherol have excellent HIA while rutin has the worst HIA.

F is the oral bioavailability of the drug which is important to consider for orally administered drugs because this is an indicator of the efficacy of the drug delivery to the circulation of the system [28]. 20%

bioavailability (F_{20}) and 30% bioavailability (F_{30}) of less than 30% are considered excellent values for bioavailability. At 20%, rutin and ellagic acid have good oral bioavailability. At 30%, all of the seven compounds do not have good oral bioavailability.

Distribution

Plasma protein binding (PPB) is a significant pharmacokinetic property of a drug. A drug with high PPB tends to bind to plasma protein and limit the distribution of the drugs into tissues where they can be metabolized. This leads to delayed onset and longer duration of action. Less than 90% PPB is an excellent value [28] which is obtained by rutin and ellagic acid.

Table 2. ADMET properties of best binding compounds predicted from ADMET Lab 2.0

ADMET Properties	Squalene	Rutin	Catechin	Quercetin	Tocopherol	Myricetin	Ellagic acid
Caco-2 Permeability	-4.912	-6.47	-5.846	-5.204	-4.753	-5.653	-5.394
MDCK Permeability	9e-06	1.9e-05	5e-06	8e-06	8e-06	6e-06	1.1e-05
Pgp-inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pgp-substrate	Yes	No	Yes	Yes	Yes	Yes	Yes
HIA	0.548	0.876	0.016	0.014	0.003	0.035	0.364
$F_{20\%}$	0.86	0.038	0.834	0.93	0.969	0.977	0.13
$F_{30\%}$	0.976	0.999	0.998	0.997	0.961	0.999	0.998
PPB	95.56%	87.11%	93.35%	95.49%	101.2%	92.76%	83.86%
VD	4.617	0.701	0.633	0.579	6.523	0.633	0.693
BBB Penetration	0.115	0.041	0.018	0.008	0.864	0.006	0.014
Fu	2.987%	17.02%	6.452%	7.423%	1.613%	10.34%	23.55%
CYP1A2 inhibitor	No	No	No	Yes	No	Yes	Yes
CYP1A2 substrate	No	No	No	No	No	No	No
CYP2C19 inhibitor	No	No	No	No	No	No	No
CYP2C19 substrate	No	No	No	No	Yes	No	No
CYP2C9 inhibitor	No	No	No	Yes	No	Yes	No
CYP2C9 substrate	Yes	No	Yes	Yes	Yes	No	No
CYP2D6 inhibitor	No	No	No	No	No	No	No
CYP2D6 substrate	No	No	No	No	No	No	No
CYP3A4 inhibitor	Yes	No	No	No	No	No	No
CYP3A4	No	No	No	No	No	No	No

substrate							
CL	4.249	1.502	17.077	8.284	7.68	7.716	3.724
$T_{½}$	0.041	0.728	0.85	0.929	0.02	0.945	0.886

Continuation of Table 2. ADMET properties of best binding compounds predicted from ADMET Lab 2.0

hERG Blockers	**No**	**No**	**No**	**No**	**No**	**No**	**No**
H-HT	Slight	No	No	No	No	No	Yes
DILI	No	Yes	No	Yes	No	Yes	Yes
AMES Toxicity	No	Yes	Yes	Slight	No	Slight	No
Rat Oral Acute Toxicity	No	No	Slight	No	No	No	No
FDAMDD	Slight	Good	Good	Slight	Good	Slight	Slight
Skin Sensitization	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Carcinogenicity	No	No	No	No	No	No	No
Eye Corrosion	Slight	No	No	No	No	No	No
Eye Irritation	Yes	Slight	Yes	Yes	Slight	Yes	Yes
Respiratory Toxicity	No	No	No	No	No	No	No

The volume of distribution (VD) is defined as the relationship between the concentration of a drug in the plasma to the concentration of the drug in the body. Although VD is not mostly optimized, it is important to understand the VD of a drug to determine effective doses, dosing regimen, and therapeutic window of the drug [55]. The VD of all seven compounds is predicted to be suitable.

Blood-brain barrier (BBB) penetration is significant in drugs that need to act in the central nervous system [28]. However, for peripheral drugs, BBB penetration is not required. All of the compounds have good BBB penetration values except for tocopherol.

The unbound fraction (Fu) of a drug is the portion that employs a therapeutic or pharmacologic effect for it is not bound to plasma proteins [56]. A Fu of 5% or more is an acceptable Fu. Rutin, catechin, quercetin, myricetin, and ellagic acid have good Fu.

Metabolism

Metabolism of drugs is mediated by cytochrome P450 enzymes [57] CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 are isoforms of cytochrome P450 which are responsible for 90% of drug metabolism [13]. Being a substrate or inhibitor of these isoforms is important in understanding whether the drug is metabolized or not. The predicted CYP2C19 substrate is tocopherol, and for CYP2C9 are

squalene, catechin, quercetin, and tocopherol. CYP1A2 and CYP2C9 inhibitors are quercetin, myricetin, and additionally, ellagic acid for CYP1A2. CYP3A4 has squalene as an inhibitor. These inhibitors may cause drug-drug interactions when indicated with drugs that are metabolized by these enzymes. The effects of these drug-drug interactions may be a reduction in clearance of the drug which may cause toxicity, or decreased pharmacologic effect [33].

Excretion

Drug clearance is calculated as the rate the drug is removed from plasma divided by the concentration of the drug in the plasma. This is defined together with the half-life and frequency of drug dosing [58]. Catechin, quercetin, tocopherol, and myricetin have acceptable drug clearance which means that they are easily removed out of the body.

The half-life of a drug is the time the original amount of the drug in the body is cut in half. Although it is estimated, that the half-life is related to the ability of the body to process the drug [59]. The plasma half-life of a drug is inversely proportional to the total clearance of the drug [60]. From here, squalene and rutin are expected to have a good and average $t_{½}$, respectively. However, tocopherol has good $t_{½}$.

Toxicity

The human ether-a-go-go (hERG) gene is responsible for the encoding of the delayed rectifier potassium channel. It is the one that activates cardiac repolarization. When blocked, this can cause long QT syndrome and sudden death in people with cardiac ischemia [61]. All of the seven compounds are not hERG blockers.

Human hepatotoxicity (H-HT) is the toxicity or adverse effect of drugs on the liver, and DILI is the drug-induced liver injury [28]. Squalene is slightly hepatotoxic while ellagic acid is hepatotoxic. Rutin, quercetin, myricetin, and ellagic acid are predicted to cause DILI.

Ames test is designed by Bruce Ames that aims to assess the potential carcinogenic effect of a compound [62]. For the AMES toxicity, the mutagenicity of the drug is being predicted. Rutin and catechin are positive for AMES toxicity while quercetin and myricetin are slightly mutagenic.

ADMET Lab mentioned that rat oral acute toxicity is considered as one of the most important safety evaluations of a drug candidate because this involves evaluation in mammals. Only catechin showed slightly rat oral acute toxicity.

FDA's maximum daily recommended dose gives an estimate of the possible toxic dose threshold of the candidate drug in humans [28]. Rutin, catechin, and tocopherol have good FDAMDD which means that the high value, and less toxic compounds for humans.

Skin sensitization is an initial indication of the effect of a substance on the immune system [63]. All of the seven compounds are skin sensitizers. Sensitization may result in as mild reactions to severe and

fatal reactions.

Carcinogenicity is a serious effect of a substance to cause a change in the normal metabolic process that can cause cancers. It is believed that carcinogenic substances may have the ability to damage the genome or disrupt cellular metabolic processes. None of the seven compounds are carcinogenic.

Eye corrosion and irritation are important considerations in assessing the safety of a candidate drug. There are known eye irritants that directly affect the cornea of the eye. The effect may be mild to severe as it can cause eye damage [64]. Squalene is predicted to cause eye corrosion while all of the compounds are mild to severe eye irritants.

Respiratory toxicity is one of the major reasons for the withdrawal of drugs from the market. Drug-induced respiratory injuries are sometimes asymptomatic. Respiratory sensitization and interstitial lung diseases are the common types of drug-induced respiratory injuries [65]. All of the seven compounds were predicted not to cause respiratory toxicity.

Drug-likeness

With respect to the bioavailability of candidate drugs, drug-likeness is the assessment of the probability of the compound being an oral drug [66]. ADMET Lab 2.0 includes four drug-likeness parameters which are complementary rules, the Lipinski rule, the Pfizer rule, the GSK rule, and the Golden Triangle.

Table 3. Drug-likeness of the best binding compounds predicted from ADMET Lab 2.0

Best binding compounds	Lipinski	Pfizer	GSK	Golden Triangle
Squalene	Yes	No	No	No
Rutin	No	Yes	No	No
Catechin	Yes	Yes	Yes	Yes
Quercetin	Yes	Yes	Yes	Yes
Tocopherol	Yes	No	No	No
Myricetin	Yes	Yes	Yes	Yes
Ellagic acid	Yes	Yes	Yes	Yes

Lipinski rule of five looks at these five things: a molecule with less than 500 Da molecular mass, less than 5 hydrogen bond donors, less than 10 hydrogen bond acceptors, and an octanol-water partition coefficient of log P not more than 5. The Pfizer rule 3/75 relates the log P>3 and tPSA < 75Å^2 with the adverse effect of a drug candidate. The GlaxoSmithKline (GSK) rule 4/400 looks at those with logP >4 and M>400 Da have a less favorable safety profile [67]. The Golden Triangle creates the rule that when

200 ≤ MW ≤ 50, and -2 ≤ logD ≤ 5, the substance has the chance of having good ADMET properties [68].

Table 3 shows the drug-likeness of the best binding compounds. Catechin, quercetin, myricetin, and ellagic acid are the compounds that satisfy all of the four drug-likeness filters. Squalene, rutin, and tocopherol did not satisfy three out of four drug-likeness filters.

Conclusion

CADD methods such as the structure-based drug design is a useful method to explore the potential of compounds as a drug. The molecular docking simulation enables the investigation of the interaction of the compounds from *S. pinnata* fruit. From the 48 compounds found in *S. pinnata* fruit only seven compounds were found to have similar or better binding affinity with the drug pioglitazone, a known ligand of PPARγ namely squalene, rutin, catechin, quercetin, tocopherol, myricetin, and ellagic acid. ADMET properties and drug-likeness revealed the compounds that behave properly inside the body. Catechin and tocopherol showed good ADMET properties except for distribution for tocopherol. Catechin passed the four filters for drug-likeness. The result of molecular docking, together with the ADMET properties and drug-likeness of catechin makes it a potential compound to be developed as a drug that targets PPARγ.

Declarations

Supplementary Information

The online version contains the supplementary materials and results.

Acknowledgements

The author wants to extend her profound gratitude to Dr. Sheryl Lozel B. Arreola for her thoughtful insights on the conduct of this study, and to the Commission on Higher Education Region IV through the Staff and Instructors' Knowledge Advancement Program for the scholarship.

Funding

No funding was received for the conduct of the research.

Data availability

All data and materials are available in the supplementary information.

Competing interest

The author has no competing interests to declare that are relevant to the content of this article.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

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Figures

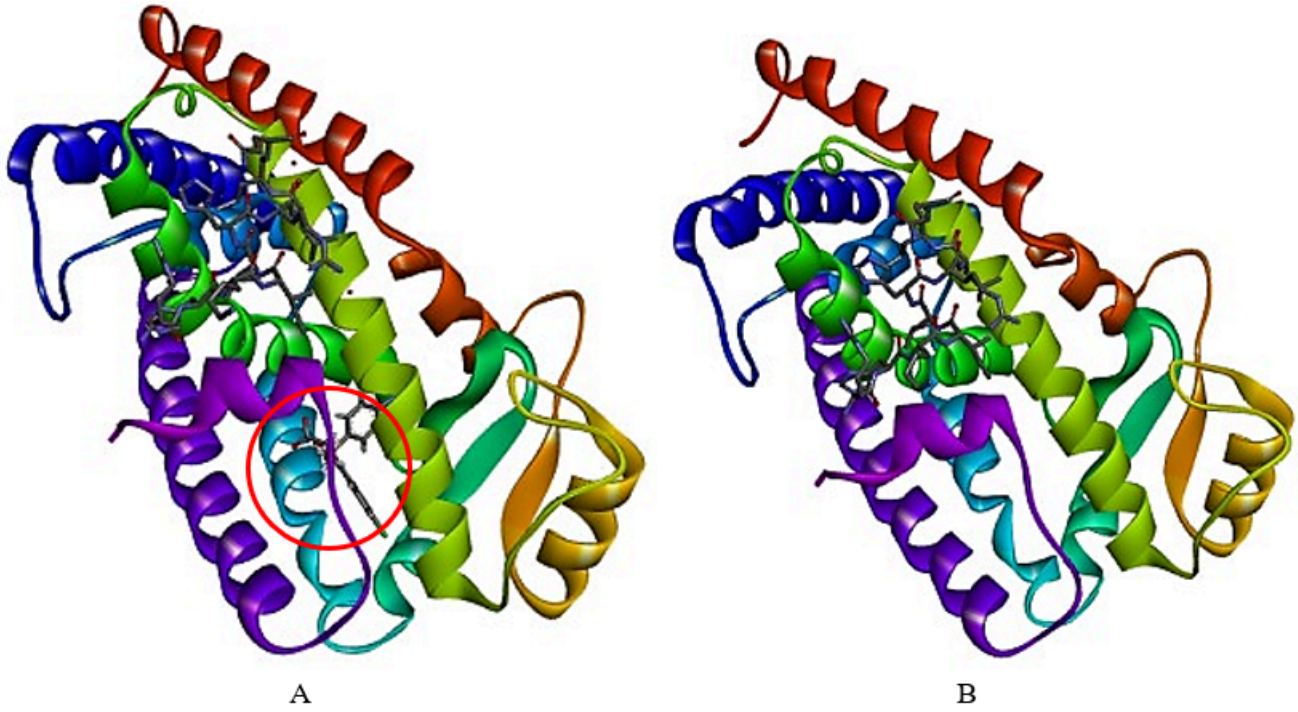

Figure 1

(A) human PPARγ in complex with lanifibranor (encircled), (B) PPARγ used in

molecular docking

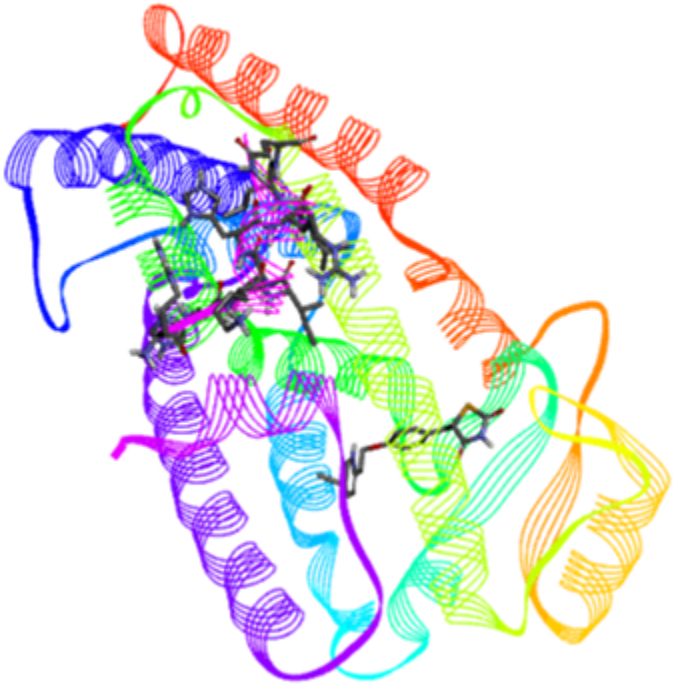

Figure 2

PPARγ-Pioglitazone complex showing the best pose of the Pioglitazone using Discovery Studio Visualizer

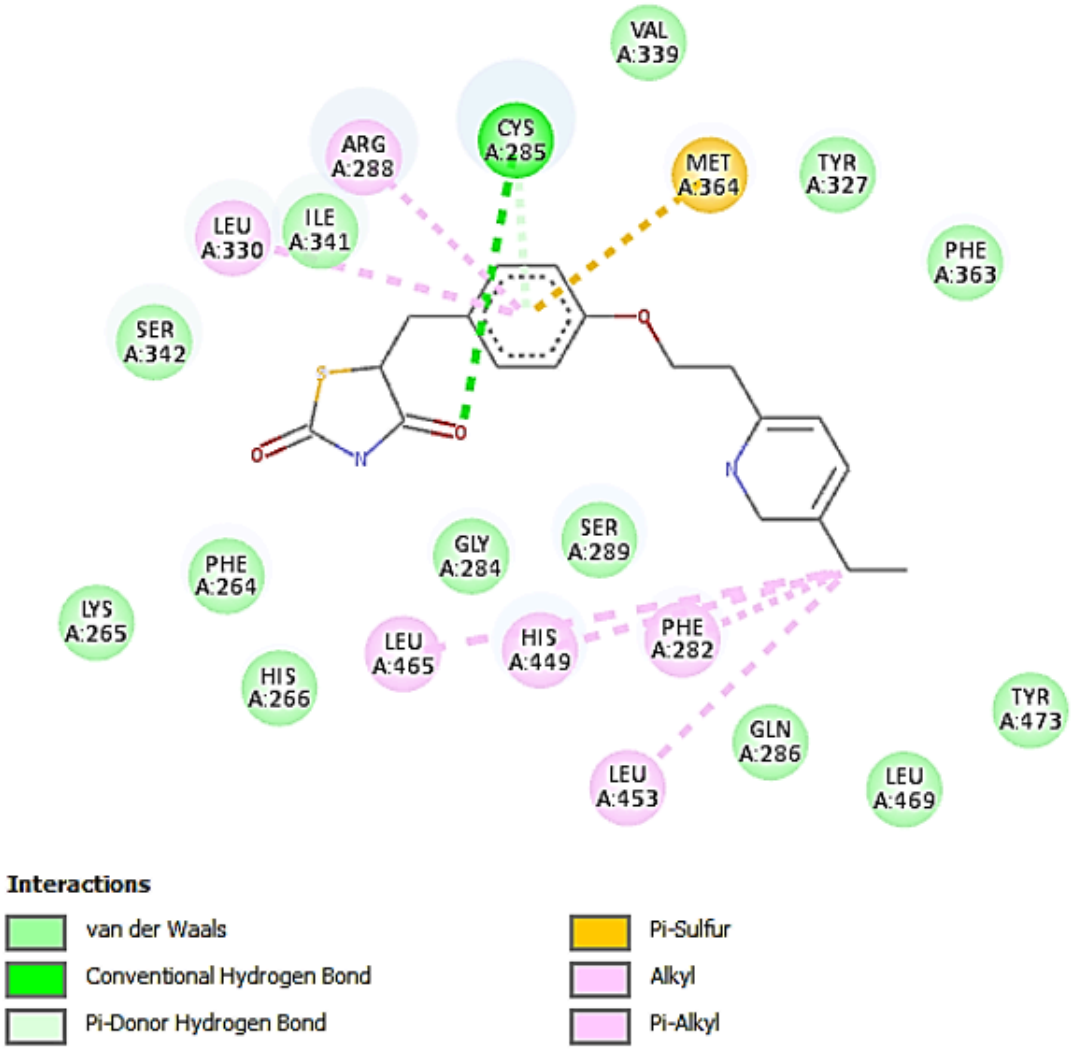

Figure 3

Interactions between PPARγ and Pioglitazone as visualized in Discovery Studio Visualizer

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Dockingresults.csv
- SupplementarymaterialJEKDiacos.pdf