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Bioactive Compounds Found in *Cucumis sativus* Demonstrate Optimal Binding Affinity to PTP1B

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Abstract

Diabetes mellitus is a group of cardiometabolic disorders defined by elevated blood sugar levels. The majority of people affected by this disease reside in rural areas of low- and middle-income countries. The PTP1B inhibitory enzyme is involved in the control of leptin and insulin signaling. The Cucumis sativus plant, which includes several phytochemical constituents, has been shown to have antidiabetic properties. This study examines the in silico inhibitory potential of bioactive compounds obtained from Cucumis sativus against a potentially diabetogenic enzyme, PTP1B. The analysis resulted in scores for the first five compounds (isoorientin, chlorogenic acid, isovitexin, caffeic acid, and ferullic acid) ranging from -8.60 to -6.44 kcal/mol. The Molecular Mechanics/Generalized Born Surface Area (MM-GBSA) of each ligand is expressed as follows: -56.46, -51.13, -51.63, -53.06 and -52.65 ΔGbind. Researchers are looking for plants that can be used as stable treatments with few side effects, although many drugs are already used to treat diabetes. As a result, the MM-GBSA and properties of the lead compound ADMET were determined.

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Keywords: *Diabetes mellitus, Protein tyrosine phosphatase 1B (PTP1B), Cucumis sativus, Computational biology.*

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List of Abbreviations

CYP: Cytochrome P
MW: Molecular weight
HBA: Hydrogen bond acceptor
HBD: Hydrogen bond donor
TPSA: Topological polar surface area
PTP1B: Protein tyrosine phosphatase 1B
MM-GBSA: Molecular mechanics generalized born surface area
PDB: Protein database
ADME-Tox: Absorption, distribution, metabolism, excretion and toxicity

Introduction

A group of metabolic illnesses known as diabetes mellitus are characterized by a persistent rise in blood glucose levels brought on by problems with insulin secretion, insulin action, or both. If diabetes is not managed, it can cause coma, stupor, and, occasionally, death from non-ketotic hyperosmolar syndrome or ketoacidosis if left untreated (ADA, 2014), (Craig et al., 2009; Galtier, 2010).

Insulin resistance, metabolic syndrome, pre-diabetes, and more severe illnesses including cardiovascular disease (CVD) and type 2 diabetes (diabetes mellitus) are all included in the term "cardio metabolic disease" (Guo et al., 2014). Because they share risk factors such being overweight or obese, dyslipidemia, and high blood pressure, these illnesses are included under the general phrase "cardio metabolic disease" (Vasudevan and Ballantyne, 2005). Chronic diseases like diabetes, obesity, and hypertension have significantly

increased in recent years not just in affluent nations but also in developing nations with emerging economies (Malik et al., 2013; Han et al., 2010).

The prevalence and incidence of cardio metabolic problems have also increased in tandem with the rise in obesity, diabetes, and hypertension (Springer et al., 2013; Kuklina et al., 2012). Inactivity, an unhealthy lifestyle, and an unhealthy food are the main risk factors for cardio metabolic illnesses, which are primarily brought on by smoking (James, 2008; Yusuf et al., 2001; Deaton et al., 2011; World population ageing, 2002). The American Diabetes Association (ADA) created a classification of diabetes in 1997 that includes type 1 (insulin-dependent diabetes mellitus), type 2 (non-insulin-dependent diabetes mellitus), other types, and gestational diabetes mellitus (GDM). This classification is still the most widely used and endorsed by the ADA (ADA, 2014).

Type 1 Diabetes Mellitus

According to Pihoker et al., (2005), autoimmune loss of pancreatic beta-cells is the cause of autoimmune type 1 diabetes (Atkinson and Eisenbarth, 2001). Although it is unclear how these autoantibodies contribute to the etiology of the disease, the presence of autoantibodies against pancreatic islet cells is a marker of type 1 diabetes. Islet cell autoantibodies, glutamic acid decarboxylase (GAD, GAD65) and insulin autoantibodies, zinc transporter protein (ZnT8A) and protein tyrosine phosphatase (IA2 and IA2) autoantibodies are some of these autoantibodies (Vermeulen et al., 2011). These pancreatic autoantibodies, which are used to identify type 1 diabetes in individuals, may have been present in their serum for months or even years prior to the beginning of the condition (Couper and Donaghue, 2009).

Type 1 diabetes can strike anyone at any age, but it most frequently affects kids and teenagers. While adults generally maintain enough insulin secretion to prevent ketoacidosis for many years, children and adolescents typically have a rapid rate of beta-cell death and also display it (Zimmet et al., 1994). This kind of diabetes frequently manifests rapidly and can cause symptoms like polyuria, enuresis, polydipsia, lack of energy, weariness, polyphagia, hazy vision, rapid weight loss, poor wound healing, and recurring infections (International Diabetes Federation, 2013). Idiopathic type 1 diabetes is an uncommon and less serious variant of the disease than autoimmune type 1. The majority of patients with this type are from Africa or Asia, and they experience varying degrees of insulin insufficiency as well as sporadic ketoacidosis (Abiru et al., 2002).

As an unique kind of diabetes that was first identified in 2000 and is non-immune mediated, fulminant type 1 diabetes shares some characteristics with idiopathic type 1 diabetes (Imagawa et al., 2000). Ketoacidosis, high glucose levels (288 mg/dL), and undetectable serum C-peptide levels, a marker of endogenous insulin production, are used to identify it (Imagawa and Hanafusa, 2011). The condition has been influenced by genetic and environmental factors, including viral infection. When there are no known autoantibodies against pancreatic beta cells, the antiviral immune response may accelerate the demise of pancreatic beta cells (Imagawa and Hanafusa, 2011). (Imagawa and Hanafusa, 2006). Additionally, fulminant type 1 diabetes and pregnancy have been linked (Shimizu et al., 2006).

Type 2 Diabetes Mellitus

Insulin resistance and a relative lack of insulin production are features of this form of diabetes (DeFronzo, 1988; DeFronzo, 1997). Although referring to the severity of insulin resistance, the plasma insulin concentration (both fasting and meal-stimulated) is typically increased in despotic terms; the plasma insulin concentration is insufficient to maintain normal glucose homeostasis (DeFronzo, 2004; Abdul-Ghani and DeFronzo, 2008). Beta cell loss progresses over time, and the risk of insulin insufficiency increases (DeFronzo, 2009).

According to Miyazaki et al. (2002), the majority of people with type 2 diabetes exhibit intra-abdominal (visceral) obesity, which is a type of ectopic fat deposition that is closely related to the existence of insulin resistance (Zimmet et al., 1994). Additionally, these people frequently exhibit hypertension, vascular endothelial dysfunction (Cersosimo and DeFronzo, 2006), dyslipidemia (high triglyceride and low HDL-cholesterol levels; postprandial hyperlipemia), and higher PAI-1 levels. The term "metabolic syndrome" or "insulin resistance syndrome" refers to this set of disorders (Reaven, 1988; DeFronzo and Ferrannini, 1991).

These anomalies enhance the risk of atherosclerotic cardiovascular disease (ASCVD) with major vascular consequences in those with type 2 diabetes mellitus (myocardial infarction and stroke). It is unclear what hereditary factors contribute to the common variety of type 2 diabetes. Type 2 diabetes mellitus has been linked to a large number of genes, however they only account for a small portion of the disease's heritability (Skyler et al., 2017; DeFronzo 1997; Van Tilburg et al., 2001).

Regular urination, unexplained weight loss, and increased thirst are among the typical signs of type 2 diabetes mellitus (National Institute of Diabetes and Digestive and Kidney Diseases 2014). Along with increased appetite, exhaustion, and unhealing wounds, the symptoms may also include (National Institute of Diabetes and Digestive and Kidney Diseases 2014). Strokes, heart disease, kidney failure, diabetic retinopathy, which can cause blindness, and inadequate blood flow in the limbs, which may lead to amputations are long-term effects of hyperglycemia (World Health Organization 2011).

Cucumis Sativus (Cucumber)

Cucumis sativus (cucumber) (Figure 1) belongs to the genus Cucumis of the family Cucurbitaceae and is an economically important fruit vegetable (Sebastian et al., 2010). Considered an annual, cucumbers come in three main varieties, sliced, pickled and seedless, of which several varieties have been created. Cucumbers are native to South Asia, but are now grown on most continents, so some types of cucumbers are traded on the world market (Silvertown, 1985). Today, Cucumis sativus is widely grown in temperate and tropical regions of the world (Vora, 2014).

Figure 1: Cucumbers growing on vines (Tui garden).

Cucumbers grown for fresh consumption are known as cut cucumbers. The main slicer cultivar ripens on vines with large leaves that provide shade (Dublin, 2016). Pickling with sugar, brine, spices, and vinegar creates a variety of flavored products from pickles and other foods (Avi, 2014). Cucumbers that are sweeter than other cucumbers and have thin skins are called burpless cucumbers. They are easily digestible and have a pleasant taste. It also grows up to 60 cm in length, is almost seedless, and has a delicate skin. These cucumbers are sold as seedless or burpless. Other types of cucumber seeds and peels are said to give gas to some people (Jordan-Reilly, 2013).

Cucumber with its water-rich phytochemical composition has various uses for therapeutic, culinary and cosmetic purposes (Mukherjee et al., 2013). This plant is a creeping climbing plant that roots into the ground and forms a trellis that wraps around the support with thin spiral tendrils (Mariod et al., 2017). The fruits of typical cultivars of cucumber are nearly cylindrical, but narrow at the tip and can be 62 cm (24 in) long and 10 cm (4 in) in diameter (Zhang et al., 2019). Epidemiological and nutritional studies have shown many benefits of cucumbers. And it's a staple in salads, soups, and smoothies. This plant is also an excellent hydrator and contains phytochemicals with various health benefits including weight loss, atherosclerosis, treatment of some eczema diseases, constipation, high blood pressure, anti-inflammatory, and anti-cancer property (Oboh et al., 2017). Recent studies have shown that kaempferol in Cucumis sativus is an important antidiabetic agent (Ibitoye et al., 2018). Additionally, cucumbers are popular for natural beautification and skin treatment (Fiume et al., 2014).

Protein-Tyrosine Phosphatase 1B (Ptp1B)

Protein tyrosine phosphatase (PTP; EC 3.1.3.48) is a large family of enzymes that separate phosphate groups from proteins phosphorylated by tyrosine. Regulation of cell growth, proliferation, and transformation are essential roles for these enzymes. Among the protein tyrosine phosphatase (PTP) family, protein tyrosine phosphatase 1B (PTP1B) is a classical or purified enzyme, also known as non-receptor type 1 protein tyrosine phosphatase (Barrett et al., 1999). It is widely expressed in human tissues such as liver, muscle, adipose tissue and brain (Zabolotny et al., 2008).

After years of research, protein tyrosine phosphatase 1B has been shown to be involved in various diseases. In previous reports, the protein-tyrosine phosphatase 1B enzyme was mainly used as a target for the treatment of diabetes or obesity. Palpable evidence suggests that the protein-tyrosine phosphatase 1B enzyme is involved in the regulation of insulin and leptin signaling. In the insulin signaling pathway, protein tyrosine phosphatase 1B dephosphorylated the IR or insulin receptor 1 (IRS-1) substrate, thereby further shutting down signaling or reducing insulin sensitivity. Thus, protein-tyrosine phosphatase 1B inhibitors have emerged as a new and potential drug target for the treatment of obesity and type 2 diabetes mellitus (Cho, 2013).

Multiple reports indicate that protein-tyrosine phosphatase 1B is an established regulator of metabolism in mammals and a pharmacological target for type 2 diabetes. During the fusion of insulin and its receptor, protein-tyrosine phosphatase 1B can catalyze the dephosphorylation of insulin receptor (IR) and insulin receptor (IRS) substrates, balancing the process phosphorylation and dephosphorylation of tyrosine residues, leading to regulation of insulin signaling (Salmeen et al., 2000). In addition, protein-tyrosine phosphatase 1B can dephosphorylate activate JAK2 and STAT3 and avoid leptin signaling (Figure 2) (Lund et al.; 2005). Elevated expression of protein-tyrosine phosphatase 1B affects PTK activity (He et al., 2014), leads to insulin failure to bind to insulin receptors (IR), causes insulin and leptin resistance and cause type 2 diabetes and obesity. (Barr, 2010).

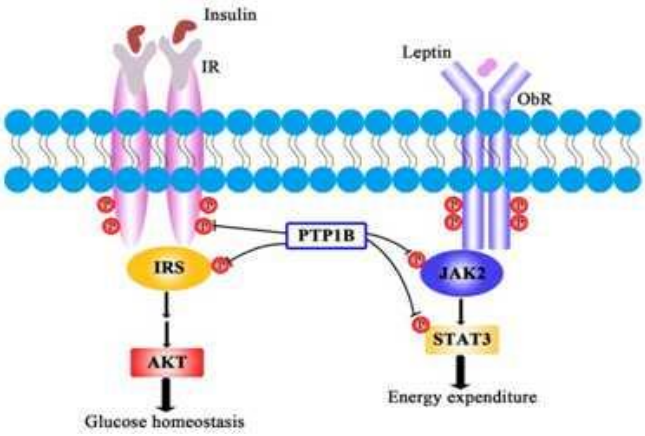

Figure 2: The physiological signal pathways involving PTP1B (Medcrave, 2016).

Protein tyrosine phosphatase 1B inhibitors may potentially improve insulin resistance and normalize plasma glucose and insulin levels without inducing hypoglycemia (lowering blood glucose excessively) (Liu, 2003). A number of pharmaceutical companies have presented several protein tyrosine phosphatase 1B inhibitors, including ertiprotafib, ISIS 113715, ISIS-PTP1BRx, and trodusquemin, as potential treatments for type 2 diabetes in recent clinical trials (Henry et al., 2012). However, several new synthetic protein tyrosine phosphatase 1B inhibitors such as thiazolidinediones,

benzothiophene biphenyls, benzofurans, aminobenzoic acids, and vanadium complexes have been reported (Koyama et al., 2003).

Organisms in nature have synthesized a variety of novel structures and secondary metabolites during their biological development. Secondary metabolites contain structural diversity and superior medicinal properties, and many pharmaceuticals are derived directly or indirectly from natural products. In addition, secondary metabolites continue to serve as novel drugs. Natural products are therefore considered to be an essential source of new drugs for protein tyrosine phosphatase 1B inhibitors (Koehn and Carter, 2005). A wide variety of natural products with protein tyrosine phosphatase 1B inhibitory activity have been reported, including morphinan alkaloids, terpenoids, and flavonoids (Bustanji et al., 2006).

Methodology

Molecular Screening and Docking Study

A total of 118 phytochemicals were obtained from the PubChem online database. Schrödinger Suite and Maestro 12.8 software were employed for computer-based drug screening (Schrödinger, 2021). This library of compounds associated with Cucumis sativus was sourced from an online database and docked into the active site of protein-tyrosine phosphatase 1B (PTP1B) to predict compounds with inhibitory potential, aiming to identify the most effective mechanism for blocking PTP1B activity in diabetes treatment. The standard principles of molecular docking were followed, involving the generation and preparation of ligands. Two-dimensional (2D) structures of secondary metabolites from Cucumis sativus were retrieved in SDF format from the PubChem online database, known for their antidiabetic activities (Kim et al., 2016; WebMD, Department of Therapeutic Research, 2020). These structures were then converted into three-dimensional (3D) representations using the Ligprep tool (Schrödinger, 2021). This conversion process included adding hydrogen atoms, ionizing at pH 7.2 ± 0.2, and removing salt components using Epik (Shelley et al., 2007; Schrödinger, 2021). The OPLS4 force field (Harder et al., 2016) was utilized for ionization and generating tautomeric states, resulting in 123 structures with one stereoisomer per ligand.

Preparation of Target Protein

The X-ray crystal structure of the complex with the inhibitor (PDB ID: 2FJN) was obtained from the Protein Data Bank (Asthana et al., 2014; Berman et al., 2000). This structure, previously used as a target receptor in diabetic studies (Shahenda et al., 2019), was prepared using the Protein Preparation Tool in the Maestro Schrödinger Suite. Bond orders were assigned, hydrogen atoms were added, zero-order metallic bonds were generated, disulfide bonds were formed, water molecules were removed, and a het state was created, employing Epik at pH 7.0 ± 0.2 during protein preparation. Further optimization included H-bond assignment and fluid force field-optimized potentials (OPLS4) to refine the protein.

Generation of Receptor Grid

The receptor grid, representing the interaction area between ligands and proteins, was created using the receptor grid dialog box and was based on the binding site of the protein. The active site of 2FJN, including all relevant amino acid residues, was automatically encompassed in a cubic grid box. The three-dimensional coordinates of the generated grid were X=36.71, Y=45.14, and Z=52.40.

Molecular Docking

Molecular docking was performed using Maestro 12.8 (Schrödinger, 2021) and the Glide tool (Friesner et al., 2004). Extra Precision (XP) docking techniques were employed to screen the 118 synthesized compounds against the crystal structure of PTP1B (2FJN) to identify molecules with the most favorable docking scores. In the docking experiment, the protein was treated as a rigid body, while the ligand's rotatable bonds were allowed to be flexible.

ADME/Tox Screening

Pharmacokinetic profiles, toxicity, and drug-likeness of the identified compounds were assessed using the SwissADME (http://www.swissadme.ch) and Pro-Tox II online servers (https://tox-new.charite.de/protox II).

MM/GBSA

The Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) continuum solvent model was utilized to determine the binding free energy of the docked protein-ligand complexes. This involved employing rotamer search techniques from Prime, in conjunction with the OPLS4 force field and the VSGB solvent model, to complete the project.

Results and Discussion

Elevated blood glucose levels are a hallmark of diabetes, a metabolic disorder. Protein tyrosine phosphatase 1B (PTP1B) and Dipeptidyl peptidase IV (DPP-IV) have been recognized as promising drug targets for managing Type-2 diabetes mellitus (Zhang and Lee, 2003; Singh, 2014). In-silico screening of natural compounds for drug development has emerged as a cost-effective and efficient alternative to labor-intensive laboratory procedures. Computational analyses have significantly reduced the risk of late-stage drug failures (Rifaioglu et al., 2019). Cucumis sativus has also been associated with maintaining the optimal functioning of organs like the kidneys, lungs, and heart. Its phytonutrients (ligands) are believed to contribute to heart disease, osteoporosis, and cancer prevention (Mary, 2020).

Furthermore, this study explores the in-silico impact of phytochemicals present in Cucumis sativus on protein tyrosine phosphatase 1B (PTP1B), a key negative regulator of insulin and leptin signaling. Inhibiting PTP1B activity enhances the effectiveness of both insulin and leptin, potentially curbing obesity and diabetes. Consequently, pharmacological agents that inhibit PTP1B activity hold promise as therapeutics for treating Type 2 diabetes and obesity (Ahmad et al., 1995). The study involved docking the protein tyrosine phosphatase 1B (PTP1B) protein with a library of compounds generated from Cucumis sativus. The results reveal that five compounds, namely Isoorientin, chlorogenic acid, Isovitexin, Caffeic acid, and Ferulic acid, exhibit inhibitory potential against PTP1B, shedding light on their molecular interactions, binding orientations, and potential therapeutic efficacy.

Ramachandran plot

The Ramachandran plot is a graphical representation that illustrates the statistical distribution of feasible values for the Phi and Psi dihedral angles in an Ala-X-Ala tripeptide where 'X' represents an unidentified amino acid (Ramachandran et al., 1963). In Figure 3, a visual representation of the Ramachandran plot was saved following the preparation of the protein. This plot, as depicted in Figure 3, provides valuable information for predicting the Psi and Phi angles, which, in turn, are instrumental in describing the secondary structure of the protein PTP1B. The determination of whether the protein adopts an alpha helix or beta sheet conformation relies on the positive or negative values of these torsional angles, determined by the sequential arrangement of amino acids within the protein.

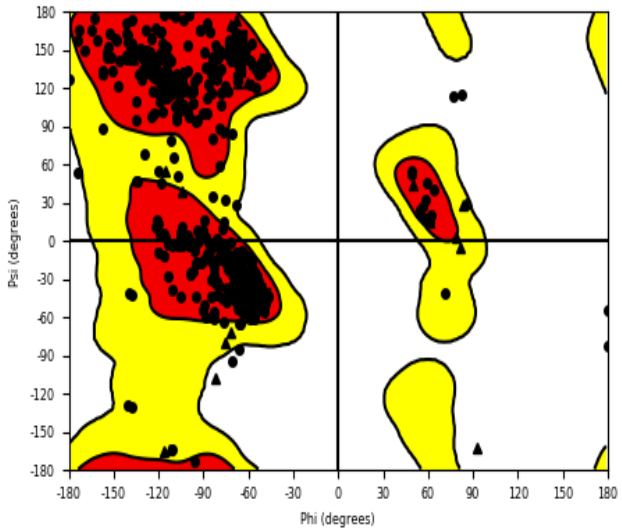

Figure 3: Ramachandran Plot of the target protein

Docking/MMGBSA

The graphical representation of docking scores and MM/GBSA results for compounds with the highest binding affinity can be found in Figure 6 and Table 1, respectively. Figure 4 displays the two-dimensional (2D) structures of these high-affinity compounds. Additionally, the post-docking analysis, which includes the examination of binding poses and interactions between these compounds and amino acid residues within the active site of 2FJN, is presented in both 2D and 3D formats in Figures 4 and 5.

Table 1 reveals the docking scores for the top five ligands, each showcasing distinct binding energies. Isoorientin leads with the highest binding energy at -8.60 kcal/mol and an MM-GBSA score of -56.46, followed by Chlorogenic acid with a docking score of -7.95 and an MM-GBSA score of -51.13, Isovitexin with a docking score of -7.81 kcal/mol and an MM-GBSA value of -51.63, Caffeic acid with a binding affinity of -6.54 kcal/mol and an MM-GBSA value of -53.06, and Ferulic acid with a binding energy of -6.44 kcal/mol and an MM-GBSA score of -52.65. In comparison, the standard drug, Trodusquemine, has a lower docking score of -4.79 kcal/mol, with an MM-GBSA value of -18.92.

Notably, Isoorientin's notably high binding affinity can be attributed to a substantial number of hydrophobic interactions involving amino acids like LEU 619, TYR 546, VAL 549, PHE 682, CYS 715, ALA 717, and ILE 719, along with hydrogen bonds at ARG 547, GLU 526, ASP 522, and a Pi–Pi interaction. As displayed in Table 4, chlorogenic acid and Isovitexin exhibit varying hydrogen binding affinities within the binding pocket but share common amino acids (PHE 682, LEU 619, CYS 715, ALA 717, ILE 719, TRY 546, VAL 549) in their hydrophobic interactions. Caffeic acid forms hydrogen bond interactions with amino acids (ARG 721, GLY 720, CYS 715, GLN 762) and engages in hydrophobic interactions with amino acids (PHE 682, ILE 719, ALA 717, CYS 715, LEU 619, TYR 546, VAL 519). Ferulic acid, on the other hand, establishes hydrogen bonds with amino acids (ARG 721, CYS 715) and engages in hydrophobic interactions with amino acids (TYR 585, CYS 551, PRO 550, TYR 631, TYR 666, TYR 547, PHE 357) around the PTP1B binding site (Figure 4). These results from MM/GBSA indicate that the bioactive compounds possess higher binding energies than the reference molecule, highlighting their strong binding potential.

ADMETox

The top five ligands derived from Cucumis sativus exhibited no inhibitory effects on oxidase enzymes, including CYP2C19, CYP2C9, CYP1A2, CYP2D6, and CYP3A4, as indicated in Table 3. However, with the exception of Ferulic acid, none of these ligands could penetrate the blood-brain barrier due to their high molecular weights. The gastrointestinal absorption rates for each ligand varied, with Isoorientin, Chlorogenic acid, and Isovitexin displaying low absorption, while Caffeine and Ferulic acid showed high absorption. Bioavailability, which represents the fraction of unaltered medication that enters the systemic circulation after administration by any route, was assessed (Kim et al., 2016). Ligands with a bioavailability score below 0.5 are considered to have low oral bioavailability, whereas those with a score exceeding 0.5 are expected to have high oral bioavailability. Isovitexin and Caffeic acid scored 0.5 in terms of bioavailability, while Ferullic acid scored 0.8. In contrast, Isoorientin and Chlorogenic acid exhibited low bioavailability with a score of 0.1, according to SWISS ADME analysis. This suggests that, with the exception of Isoorientin and Chlorogenic acid, all other compounds hold promise as potential drug candidates. Hepatotoxicity assessments were conducted, and it was determined that none of the compounds exhibited hepatotoxic effects, except for Isoorientin and Isovitexin.

Druglikeness

Furthermore, the Ilog P values for the ligands ranged from 0.87 to 1.62, indicating that they are not very soluble in water and may have difficulty passing through the gut lining. However, they did exhibit some degree of penetration into the target cell membrane, which is a desirable trait for orally administered drugs. Except for Isoorientin, Chlorogenic acid, and Isovitexin, all of the top bioactive compounds met Lipinski's Rule of Five for orally administered drugs, with none of the rule's criteria being violated (Table 2). Lipinski's Rule of Five states that orally administered drugs should have a molecular weight below 500 g/mol, no more than ten hydrogen bond

acceptors, no more than five hydrogen bond donors, and a log P value below five.

Furthermore, any pharmaceutical molecule that violates two or more of these rules is likely to be ineffective when administered orally (Walters, 2012). The bioavailability scores of these compounds also support this observation. Topological Polar Surface Area (TPSA) is a measure of a drug's ability to penetrate cell membranes and is related to the presence of polar molecules such as oxygen, hydrogen, and nitrogen. The TPSA scores in this study revealed that three out of the five ligands had values exceeding 140 Å², indicating that the absorption potential for Isoorientin, Chlorogenic acid, and Isovitexin is low. In contrast, the TPSA scores for the other two compounds, Caffeic and Ferulic acid, were lower, suggesting better absorption potential (Figure 5).

Table 1: Docking (kcal/mol) and MM/GBSA (ΔG_{bind}) scores of the top 5 lead compounds and the standard drug.

PubChem ID	Entry Name	Docking score	MMGBSA dG Bind
114776	Isoorientin	-8.607	-56.46
1794427	Chlorogenic acid	-7.952	-51.13
162350	Isovitexin	-7.813	-51.63
689043	Caffeic acid	-6.544	-53.06
445858	Ferulic acid	-6.447	-52.65
9917968	Trodusquemine	-4.792	-18.92

Table 2: In silico drug likeness prediction of the compounds.

Entry Name	mol MW	donorHB	accptHB	Tpsa	ILOGP	LOGKP	ROV
Isoorientin	448.382	7	13	201.28	1.60	-9.14 cm/s	2
Chlorogenic acid	354.313	6	9.65	164.75	0.87	-8.76 cm/s	1
Isovitexin	432.383	6	12.25	181.05	1.60	-8.79 cm/s	1
Caffeic acid	180.16	3	3.5	77.76	0.97	-6.58 cm/s	0
Ferulic acid	194.187	2	3.5	66.76	1.62	-6.41 cm/s	0

Table 3: The bio-availability, pharmacokinetic properties and Cytochrome P450 metabolizing enzymes inhibitory potentials of selected Cucumis sativus phytochemical constituent

	Isoorientin	Chlorogenic acid	Isovitexin	Caffeic acid	Ferulic acid
Blood Brain Barrier	-	-	-	-	+
Bioavailability Score	0.17	0.11	0.55	0.56	0.85
CYP1A2 inhibition	-	-	-	-	-
CYP2C19 inhibition	-	-	-	-	-
CYP2C9 inhibition	-	-	-	-	-
CYP2C9 substrate	-	+	-	-	-
CYP2D6 inhibition	-	-	-	-	-
CYP2D6 substrate	-	-	-	-	-
CYP3A4 inhibition	-	-	-	-	-
CYP3A4 substrate	+	+	+	-	-
GI Absorption	Low	Low	Low	High	High
Hepatotoxicity	**+**	**-**	**+**	**-**	**-**

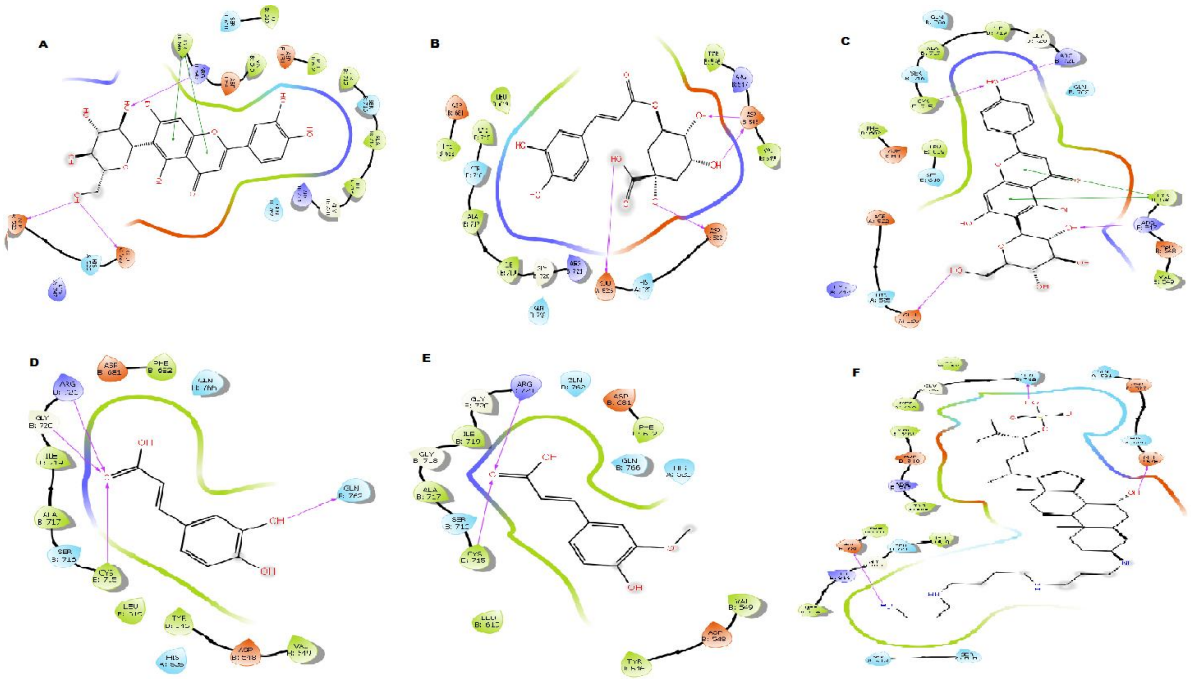

Figure 4: 2D-Molecular Interactions of amino-acid residues of protein tyrosine phosphatase 1B with Cucumis sativus phytochemical constituents. **A** Isoorientin, **B** Chlorogenic acid, **C** Isovitexin, **D** Caffeic acid, **E** Ferullic acid and **F** Trodusquemine

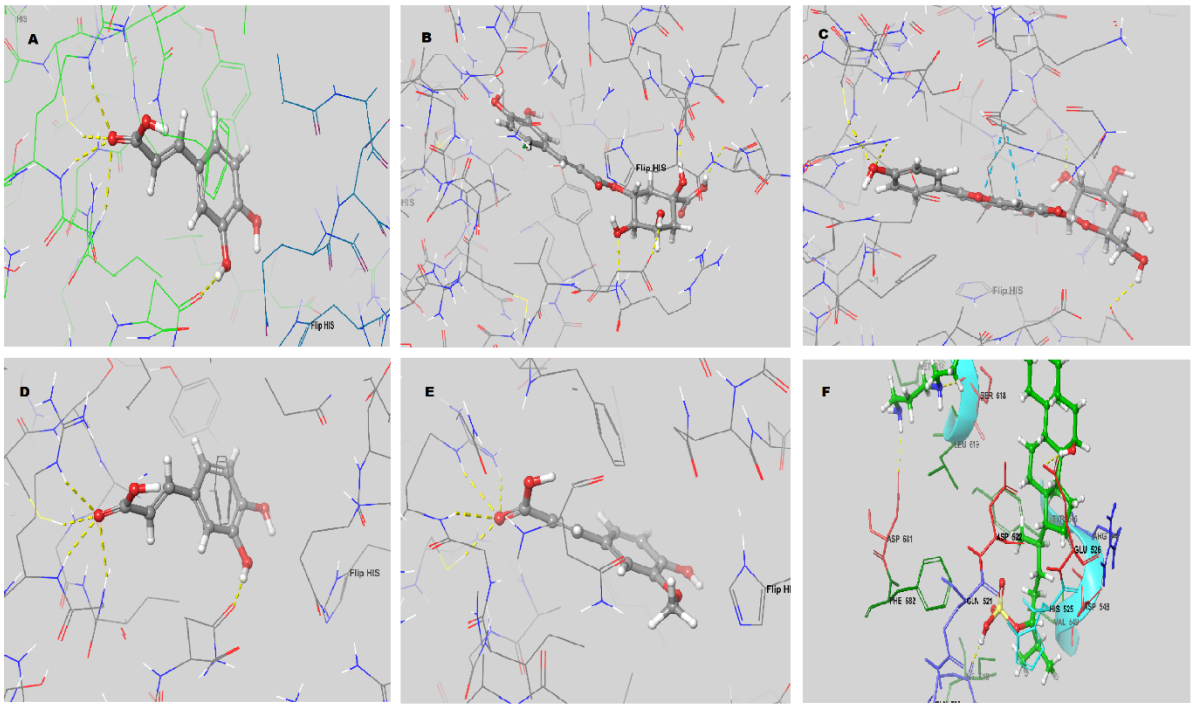

Figure 5: 3D Molecular Interactions of amino-acid residues of protein tyrosine phosphatase 1B with Cucumis sativus phytochemical constituents. **A** Isoorientin, **B** Chlorogenic acid, **C** Isovitexin, **D** Caffeic acid, **E** Ferullic acid and **F** Trodusquemine

Table 4: Hydrogen Bonds and Hydrophobic Interactions of the hit phytoconstituents of Cucumis sativus phytochemicals.

Entry name	Hydrophobic Amino Acid Interacting	H-bond	Other Interaction
Isoorientin	LEU 619, TYR 546, VAL 549, PHE 682, CYS 715, ALA 717, ILE 719	ARG 547, GLU 526, ASP 522	PI-PI INTERACTION: TYR 546
Chlorogenic acid	PHE 682, LEU 619, CYS 715, ALA 717, ILE 719, TYR 546, VAL 549	GLU 526, ASP 548, ASP 522	NONE
Isovitexin	PHE 682, LEU 619, CYS 715, ALA 717, ILE 719, TRY 546, VAL 549	CYS 715, ARG 721, ARG 547, GLU 526	PI-PI INTERACTION: TYR 546
Caffeic acid	PHE 682, ILE 719, ALA 717, CYS 715, LEU 619, TYR 546, VAL 519	ARG 721, GLY 720, CYS 715, GLN 762	NONE
Ferulic acid	PHE 682, ILE 719, ALA 717, CYS 715, LEU 619, TYR 546, VAL 549	ARG 721, CYS 715	NONE
Trodusquemine	ILE 719, MET 758, VAL 549, TYR 546, LEU 619, PHE 682, MET 614	GLN 762, GLU 526, ASP 681	NONE

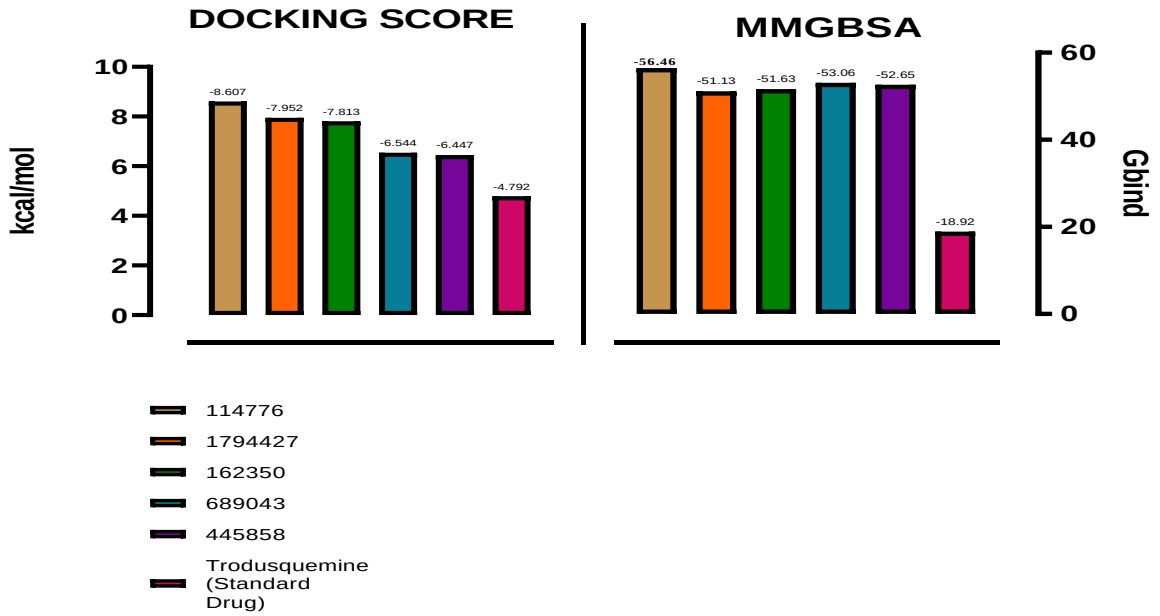

Figure 6: Docking and MM/GBSA scores of the lead compounds

Conclusion

Diabetes, a global metabolic disorder, poses a significant health challenge with a high mortality rate. Scientists worldwide are actively working to address this pressing issue. Protein tyrosine phosphatase 1B (PTP1B) inhibitors are recognized for their potential in treating diabetes mellitus, as they enhance the effects of insulin and leptin in the body. This study focused on utilizing 2D molecules derived from Cucumis sativus and docking them with the PTP1B protein. Among these compounds, including isoorientin, chlorogenic acid, isovitexin, caffeic acid, and ferullic acid, several emerge as promising drug candidates for managing diabetes mellitus due to their favorable binding characteristics. Notably, caffeic and ferullic acid adhere to Lipinski's rules, indicating their suitability for oral administration. Additionally, the remarkably high MMGBSA score of -56.46 further underscores their potential as effective drug candidates for diabetes control. Nonetheless, it is crucial to emphasize that this study relies on computational methods, highlighting the need for validation through *in vivo* research.

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Declaration
None.

Consent for publication
Not Applicable.

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The data underlying this article are available in the article and its online supplementary material.

Competing interest.
The authors declare that there is no conflict of interest regarding the publication of this paper.

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O.O.E, O.B.T, and E.A.O: Conceptualization and Validation of results. O.O.E, O.B.T and E.A.O: Software and Formal analysis. O.O.E, A.O.L, and A.S.O, Data curation. O.B.T and O.O.E: Writing original draft preparation and methodology. O.O.E, O.B.T, A.P.E, and E.A.O: Writing-review and editing. O.J.A : Supervision. All authors read and approved the final manuscript for publication.

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Cucumber fruit developing on plants possessing multiple lateral branching, which is atypical of commercial cucumbers. This type of branching is important because increasing branch number increases yield potential. Date:23 February 2007 (according to Exif data). Source: US-AgriculturalResearchService-Logo.svg. This image was released by the Agricultural Research Service, the research agency of the United States Department of Agriculture, with the ID D730-30.

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