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Quassia amara bioactive compounds as a Novel DPP-IV inhibitor: an *in-silico* study

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Abstract

Background: Diabetes, a cardiometabolic condition with social and health ramifications, is already a global epidemic. Diabetes affects 422 million people worldwide, with the majority living in middle- and low-income countries, resulting in 1.5 million deaths each year. Inhibiting DPP-IV, an enzyme whose main biological function in diabetes is the breakdown of metabolic hormones like GLP-1, *Quassia amara*, a plant that contains numerous phytochemicals, has been claimed to be used as a traditional treatment for a variety of metabolic illnesses, as well as having anti-malaria, anti-biotic, anti-diabetes, and anti-anemic characteristics. This work investigated the in-silico inhibitory ability of phytochemicals obtained from *Quassia amara* against a diabetes-related enzyme, DPP-IV, with the aim of confirming the drug-like potential of ligands from the plant (*Quassia amara)* in comparison with the standard drug, Alogliptin.

Result: As a result of the investigation, five compounds (Vitexin, Quassimarin, Simalikalactone D, Brucein D, and Quassinol) obtained docking scores ranging from − 7.47 to − 6.49 kcal/mol.

Conclusion: Many medications have been offered, but the typical side effects have prompted researchers to look for new herbal plants which can be used as permanent treatment with minute side effects. Thus, utilizing computational studies such as molecular docking, molecular mechanics generalized born surface area (MM-GBSA) and the lead compounds' ADMETox characteristics were computed.

Keywords: Diabetes, Dipeptidyl peptidase-4 (DPP-IV), Glucagon like peptide (GLP-1), *Quassia amara*, In-silico, Molecular docking

Background

Diabetes mellitus is a significant upstream event in terms of molecular pathophysiology, with a slew of sequelae including immunological, metabolic, and genetic malformations, as well as a common symptom of interest, persistently high blood glucose levels (Egan and Dinnen 2019; Yaribeygi et al. 2020).

The consequences of untreated diabetic cases, according to the World Health Organization (2019), include retinopathy, nephropathy, and neuropathy, among other issues. Patients with diabetes, on the other hand, are at risk for heart, peripheral artery, and cerebrovascular disease, obesity, cataracts, erectile dysfunction, and nonalcoholic fatty liver disease, to name a few.

Type 1 diabetes mellitus (T1DM) is a chronic condition characterized by persistently high blood glucose and insulin insufficiency or deficit. This happens when the cells that produce insulin in the beta cells of the pancreatic islet of Langerhans have been disturbed. This could be thought of as a link between hereditary and environmental influences (Chetan et al. 2019).

Over the years, there has been a large amount of knowledge about type 1 diabetes, prompting many researchers to go deeper into the subject in order to gain

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a better grasp of the disease's numerous features. Genetics, epidemiology, immunological and cell morphologies, and disease load are all factors to consider.

However, therapies to maintain the cells alive have been tested, as well as a number of strategies to improve clinical illness management. Despite this, there are still significant gaps in our knowledge of type 1 diabetes and our capacity to standardize clinical care and so reduce the likelihood of complications (DiMeglio et al. 2018).

Type 2 diabetes mellitus, which is directly linked to the obesity epidemic, is one of the main worldwide health problems wreaking havocs. As a result of hyperglycemia and individual components of the insulin resistance (metabolic) syndrome, many people with T2DM are at risk for microvascular problems (such as retinopathy, nephropathy, and neuropathy) as well as macrovascular issues (such as cardiovascular comorbidities). However, some environmental variables (such as obesity, a poor diet, and physical inactivity), in combination with genetic factors, contribute to the exponential pathophysiological disturbances that cause glucose regulation failure in type 2 diabetes mellitus. Despite advances in our understanding of insulin resistance, decreased insulin secretion remains the most serious flaw in type 2 diabetes mellitus (DeFronzo et al. 2015).

Epidemiology

According to the International Diabetes Federation, there are currently 463 million adults living with diabetes worldwide, with this number expected to double by 2030 (International Diabetes Federation 2019). Over 90% of this prevalence is due to type 2 diabetes (Melmed et al. 2011; Australian Indigenous Health info net 2016). There are two recognized variables that cause type 2 diabetes: environmental influences and genetic factors. Each continent has a different prevalence of type II diabetes, with Europe having the lowest (0.7–11.6)% and the Middle East having the highest (4.6–40)% (Adeghate et al. 2006). Individuals going to areas such as South Asia, Africa, and the Caribbean find that type 2 diabetes is more common in areas with a high population prevalence compared to areas with a low prevalence (Forouhi et al. 2006). Diabetes is not evenly distributed throughout Iran's communities; however, it is believed to be present in 5% of rural areas (Larejani and Zahedi 2001). The prevalence of diabetes type 2 differs insignificantly between men and women, but it rises dramatically with age (International Diabetes Federation, 6th edition 2013). According to WHO, diabetes is the eighth largest cause of mortality worldwide, although complications and metabolic syndrome diseases (kidney disease, cardiometabolic disease, and so on) connected with diabetes have resulted in more

deaths (WHO 2016; Public Health Agency of Canada 2011).

Etiology

Diabetes, often known as or referred to as diabetes mellitus, is a group of disorders that result in extremely high blood sugar, also known as high blood glucose. It is a disorder of carbohydrate metabolism marked by a decrease in the body's ability to produce or respond to insulin, resulting in an inability to maintain predicted blood sugar levels. Hyperglycemia and diabetes mellitus are caused by a lack of insulin, the creation of faulty insulin, or the inability of body cells to properly and effectively use insulin. Recurrent urination was originally reported as a sign of a weird ailment in the year 1552 B.C., when Hesy-Ra, an Egyptian doctor, recorded it as a sign of a strange illness that also made patients emaciated and scrawny. Early physicians also noticed that ants were drawn to the urine of people who had this ailment around this time. A Greek physician named Arateus described what is now known as diabetes as the "melting down of flesh and limbs into urine" in the year 150 AD. From that point forward (McCoy 2009), physicians began to obtain a better understanding of diabetic mellitus. Arateus of Cappadocia was the first to invent the term "diabetes" (81–133 AD). After discovering the sweetness of patients' urine and blood, Thomas Willis (Britain) added the name "mellitus" (meaning "honey sweet") in 1675. (First noticed by the ancient Indians). In 1776, Dobson (Britain) was the first to confirm the existence of extra sugar in urine and blood as a reason for their sweetness. The emergence of experimental medicine coincides with the history of diabetes in contemporary times. The discovery of the involvement of the liver in glycogenesis and the hypothesis that diabetes is caused by excessive glucose synthesis (Claude Bernard (France) in 1857) are significant milestones in the history of diabetes. In 1889, Mering and Minkowski (Austria) established the involvement of the pancreas in the etiology of diabetes. In 1921, Banting and Best (Canada) isolated it and used it in therapeutic trials as a result of this discovery. Trials to develop an orally administered hypoglycemic drug were successful, and tolbutamide and carbutamide were first marketed in 1955 (Ahmed 2002).

Pathophysiology of diabetes mellitus

Diabetes is a disease in which the body's ability to process blood glucose, often known as blood sugar, is impaired. There are different forms of diabetes, each with their own set of treatment options (From 2004 through 2022, Medical News Today). Type 1, type 2, and gestational diabetes are the most prevalent types of diabetes, which we go over in more detail below. Monogenic diabetes and cystic fibrosis-related diabetes

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are two less prevalent kinds of diabetes (From 2004 through 2022, Medical News Today).

Symptoms of diabetes

The following are the most prevalent indications and symptoms of high blood sugar:

- Increased thirst
- Frequent urination
- Excessive exhaustion
- Increased hunger
- Unexplained weight loss despite increased food consumption.
- Lack of energy

Hyperglycemia is caused by both decreased insulin action due to insulin resistance and impaired insulin production due to pancreatic cell failure in type 2 diabetes. Insulin resistance.

Insulin resistance is a key aspect of type 2 diabetes and is described as the inability of insulin to produce its usual biological actions at physiological doses. Insulin's ability to

- inhibit hepatic glucose output, resulting in increased fasting glucose levels
- stimulate skeletal muscle glucose uptake, resulting in higher post meal glucose levels; and
- suppresses lipolysis in adipose tissue, resulting in higher plasma non-esterified fatty acids.

The mechanisms that lead to insulin resistance aren't completely understood. Although insulin resistance can develop at a variety of signaling levels in type 2 diabetes, the fundamental flaw appears to be a significantly reduced ability to phosphorylate insulin receptor substrate 1, the post receptor insulin receptor substrate. Reduced glucose absorption and various abnormalities in glucose and lipid metabolism result from this abnormality. The mitogen activated protein kinase pathway, which activates a number of intracellular pathways implicated in inflammation, cellular proliferation, and atherosclerosis, is still responsive to insulin, which is surprising. Nutrient overload is a major cause of insulin resistance. An adipocyte is a cell that is made up of fat cells. Uncontrolled lipolysis raises circulating free fatty acids, which drive gluconeogenesis and cause insulin resistance in the liver and muscles by accumulating particular lipid intermediates like diacylglycerol in these organs (7th Edition of Essential Endocrinology and Diabetes).

Beta cell dysfunction

Changes in cell function are the most important predictors of type 2 diabetes progression. The loss of early-phase insulin production and the cells' ability to recognize and respond to changes in blood glucose content are the first anomalies. Many years before the onset of hyperglycemia and overt type 2 diabetes, these changes can be noticed in predisposed individuals. Individuals have lost 40–60% of their cell function by the time they are diagnosed, and this continues to deteriorate. The loss of cell function appears to happen in two stages: first, there is a steady reduction of 2% per year that starts many years before diagnosis, but then it increases to 18% per year around the time diabetes develops. The steady loss of cell activity explains why people with diabetes find it increasingly difficult to control their hyperglycemia over time, necessitating an increase in the quantity and doses of oral antidiabetic medicines and why oral therapies eventually fail and insulin is required. The mechanisms that underpin cell dysfunction appear to be complex. The changing metabolic environment, however, appears to be the most essential contributor. High blood glucose and fatty acid levels both harm cell function, a condition known as "glucolipotoxicity." The increased metabolic demand imposed on the cell by nutritional excess causes oxidative and endoplasmic reticulum stress, as well as the production of islet amyloid, all of which have a negative impact on cell function and may lead to apoptosis (programmed cell death). In order to maintain normal glucose concentrations, cell insulin production must rise as insulin resistance develops. The cell's maximum insulin secretory capacity is attained over time, and continuous stimulation causes cell damage. Insulin production begins to drop and plasma glucose concentrations begin to rise after this stage, generally in the postprandial period, as the individual develops impaired glucose tolerance prior to the start of frank diabetes. (From the 7th edition of Essential Endocrinology and Diabetes.)

Diabetes medication alternatives

Thiazolidinediones

One of the adverse effects of stimulating the PPARγ is the increased proliferation of peripheral adipocytes to expand free fatty acid absorption. This could lead to weight gain and increased peripheral fat accumulation (Greenfield and Chisholm 2004). Thiazolidinedione is also used to engineer fluid retention. The sodium-coupled bicarbonate absorption from the renal proximal tubule may be activated, resulting in edema development in the kidney. As a result, the volume of the kidneys increases. It can also cause bone fractures, heart failure, bladder cancer in women, and an increase in bad cholesterol (Liao 2020).

Metformin

Metformin lowers the activity of pyruvate dehydrogenase, which leads to lactic acidosis (Fowler 2007). Nausea, gas, bloating, diarrhea, vitamin B12 deficiency, and stomach discomfort are some of the other metformin adverse effects (Liao 2020).

Sulfonylureas

It's linked to a higher risk of cardiovascular disease. According to studies, sulfonylureas may cause an arrest of the cardiac kATP channels while stimulating the closure of the pancreatic beta cells' kATP channels to accelerate insulin secretion, resulting in a higher cardiovascular incidence in those people (Aquilante 2010). Weight gain, dizziness, dark urine, and skin rashes are some of the other negative effects (Liao 2020).

Meglitinides

It can result in hypoglycemia (low blood glucose) and weight gain (Liao 2020).

The plant, *Quassia amara*

Amargo, Tropical Plant Database (2013) *Quassia amara* (*Q. amara*) (Spanish for "large man") Quassia species (Tree of the Month: Hombre Grande 2017) is a Quassia species that some botanists see as the genus' sole species. Graman Quassi, a Surinamese freedman, is a character in the film Graman Quassi. *Q. amara* is employed as an insecticide, as well as in traditional medicine and as a food ingredient. *Quassia amara* (species) is a small evergreen shrub or tree native to the tropics that belongs to the Simaroubaceae family (Morton 1912–1981; Barwick 2004; Paulo and Villalobos 2019). Quassi, an enslaved healer and botanist who demonstrated the plant's fever-curing properties to Europeans, was given the name *Q. amara* (Barwick 2004). The name "amara" comes from the Latin word "bitter," which indicates the bitterness of the fruit. In its tissues, *Q. amara* includes around thirty phytochemicals with biological activity, including the very bitter Quassin compound. As a result, it's employed as an insecticide, in traditional medicine to treat a variety of diseases, and as a bitter-tasting food additive (Barwick 2004). All parts of the plant have therapeutic effects, and the bark extracts are primarily utilized as a flavoring in drinks, but they can also be employed as insecticides. (Morton 1912–1981; Paulo and Villalobos 2019; Barwick 2004).

Health benefits

Quassia amara has traditionally been used for antimalarial, stomachic, anti-anaemic, antibiotic, cytotoxic, and anti-amoebic purposes. The literature also mentions its reproductive, insecticidal, larvicidal, and vermifuge activities. Quassinoids are the principal bitter components of *Quassia amara* and are important phytoconstituents of this plant. Quassin is a white crystalline compound with a bitter flavor that is frequently utilized in Chinese herbal medicine (Patel and Patel 2018). Quassia is a plant, and the wood and occasionally the leaves are used for medicinal purposes. Quassia is used to treat stomach and intestinal disorders, diabetes, lice, skin conditions, and a variety of other ailments. Other circumstances may exist, although most of them are not supported by scientific evidence. Quassia is used to flavor foods, beverages, lozenges, and laxatives in the production process. Insecticides have been employed on the bark and wood.

Quassia contains compounds that may inhibit the growth of the malaria parasite and kill mosquito larvae. These compounds may also cause an increase in stomach acid and bile secretions, which could account for the appetite stimulant and digestive effects (WebMD. Therapeutic Research Faculty 2020).

Dipeptidyl-peptidase (DPP-IV)

Drucker (2007) describes how DPP-IV, also known as Dipeptidyl peptidase-4, is a peptidase located on the cell membrane that aids in the activation of intracellular signal transduction pathways and the regulation of cell-enzyme interactions. These biological tasks are carried out by DPP-IV through pleiotropic effects (Mulvihill and Drucker 2014). The human gene that houses DPP-IV has been identified as 2q24.3 on chromosome 2 (Abbott et al. 1994). DPP-IV inhibition or inactivation raises the concentration. Glucose-dependent protein level: The two active incretin hormones and physiological substrates for DPP-IV are insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) (Vella 2012; Drucker 2007). This boosts the pancreatic beta cells' responsiveness to high glucose levels while lowering the risk of diabetes. Glucagon manufacturing is a process in which the hormone glucagon is produced. When DPP-IV is inhibited or inactivated for a long time, blood glucose is lowered via insulin stimulation while glucagon production is suppressed (Vella 2012; Drucker 2007) Other glycopeptides, such as vasoactive intestinal peptide, Pituitary Adenylate Cyclase Activating Peptide (PACAP), oxyntomodulin, and Gastrin Releasing Peptide (GRP), have been discovered to be reactive to DPP-IV inactivation (Lambeir et al. 2001; Zhu et al. 2003; Drucker 2007). As a result, it's safe to assume that one of the peptides, along with GLP-1 and GIP, is responsible for the drop in glycaemia observed following DPP-IV inactivation or inhibition (Drucker 2007).

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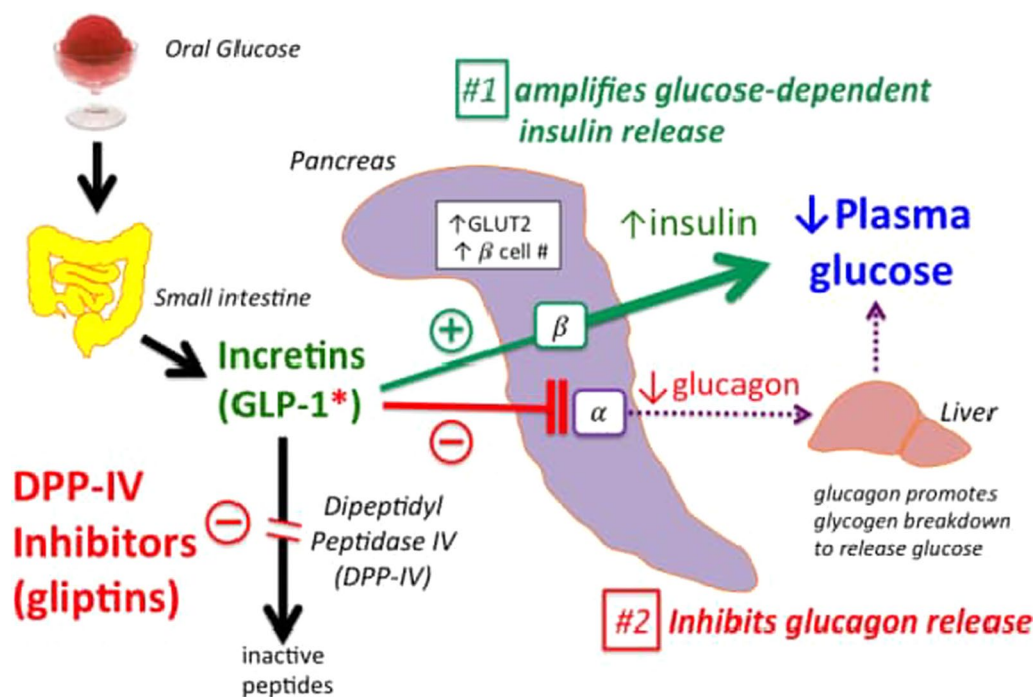
* Physiological t ½ ≈2 mins due to rapid inactivation by DPP-IV

http://tmedweb.tulane.edu/pharmwiki/doku.php/dpp-4_inhibitors

Glucagon-like peptides (GLP1) are peptide hormones produced in the bloodstream by the intestinal epithelium of the endocrine or intestinal L cells in response to meal consumption (wikipedia.org). GLP is an incretin hormone that increases protein secretion, inhibiting glucagon production and stimulating insulin production (Drucker et al. 2017). Studies have revealed that GLP-1 inhibits glucagon secretion, the rate at which foods are ingested, and stomach emptying is vividly and efficiently helped by GLP-1 receptor agonists in the treatment of diabetes, according to Drucker et al. (2017). Type 2, which has also aided in the reduction of obesity, the activity of GLP-1 in the islet cells causes a drop in blood glucose, known as hypoglycemia, which has led to the creation of a number of GLP-1 receptor agonists for the treatment of diabetes, particularly type 2 diabetes (Drucker et al. 2017; Drucker and Nauck 2006; Ussher and Drucker 2014). At least 10–15 min after GLP-1 is released from the intestinal L cells that predominate largely in the distal colon in response to carbohydrate and fat consumption into the hepatic portal system (Baggio and Drucker 2007). The release of GLP-1 causes the GLP-1 receptor in the pancreas to become activated. The GLP receptor then works on the ATP present in the pancreatic cells, converting it to cyclic Adenosine Mono Phosphate (cAMP), which stimulates insulin synthesis (Pharmacology Update Website 2017).

Previous studies on the phytochemicals of the plant, *Quassia amara*, that indicated it had anti-diabetic qualities were revised, and in this research, an *in-silico* study into the ligands of *Quassia amara* with the highest potential to be a medication based on its inhibitory ability was thoroughly explored and compared with the standard drug, Alogliptin.

Molecular docking

Molecular docking, a crucial method in structural molecular biology and computer-assisted drug creation, was used in this study. It also investigates how tiny compounds such as phytochemicals interact or behave in a target protein's active region (Pagadala et al. 2017). Among the techniques employed are ligand library development and preparation from an online database, target retrieval from a PDB database, receptor grid generation, molecular docking, and ADME-Tox Screening.

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Methods

Virtual screening and docking platform

Schrödinger Suite software and Maestro 11.1 were used to conduct computer-based drug screening (Schrödinger 2017). A total of 21 compounds that have been described with *Quassia amara* were collected from an online database and docked to the active site of DPP-IV to predict compounds with the best inhibitory potential to block DPP- IV action in the treatment of diabetes.

The normal molecular docking principles were followed. Ligand library generation and preparation. Kim et al. (2016) mined two-dimensional (2D) structures of secondary metabolites from the *Quassia amara* plant in SDF format from the PubChem online database and found that they had anti-diabetic activities (WebMD. Therapeutic Research Faculty 2020). The ligands were gotten from research reviews of the plant (Alves et al. 2014), and some of the ligands not found on the database, were drawn using ChemDraw (RRID:SCR_016768). The mined structures were transformed into three-dimensional structures using the ligprep tool (Schrödinger 2017) by adding hydrogen atoms, ionizing at pH (7.2 0.2), and removing salt using Ep2i/UNEP/-Zk (Shelley et al. 2007; Schrodinger 2021). The OPLS3e force field (Harder et al. 2016) was utilized for ionization and tautomeric state formation. The number of stereoisomers generated per ligand was set to 32, resulting in 169 structures from 21 compounds.

Target preparation

The Protein Data Bank (PDB ID: 3VJM) was used to get the X-ray crystallographic structure of the DPP-IV complexed with an inhibitor (Asthana et al. 2014; Berman et al. 2000). According to Tomohiro, 3VJM has been used as a target receptor in diabetic condition in prior studies and this was repeated in this work (Yoshida et al. 2012). To visualize the structure, PyMol (DeLano 2002), a molecular graphics tool for protein structural visualization, was used. The protein preparation wizard tool in Maestro's Schrodinger Suite was used to prepare the protein. Bond orders were assigned, hydrogens were added, zero-order metal bonds were made, disulfide bonds were created, water molecules were removed, and het states were generated using Epik at pH 7.0 0.2 during the protein production. The protein was refined by optimizing the H-bond assignment, and then the OPLS3e (Optimized potentials for liquid simulation) force field was used to reduce the protein.

Receptor grid generation

The receptor grid panel was used to set up the grid creation job and specify a receptor structure. The receptor grid depicts the area where the ligand and protein interact. The Receptor Grid Generation tool was used to create the prepared protein grid on the binding site (Glide Grid). Selecting the co-crystallized ligand at the active site of 3VJM revealed the binding location. A cubic grid box including all of the amino acid residues at the active site was automatically produced. The produced grid's three-dimensional coordinates X, Y, and Z were 51.67 Ao, 63.91 Ao, and 35.05 Ao, respectively.

Molecular docking

Docking was done on Maestro 11.1 (Schrödinger 2017) with the Glide tool (Friesner et al. 2004). Using Extra Precision (XP) docking techniques, the obtained crystal structure of DPP-IV (3VJM) was utilized to digitally screen the 21 synthesized compounds to find molecules with the lowest docking score. The docking experiment was carried out with the protein treated as a rigid body and the ligand's rotatable bonds set to be free.

ADME/Tox screening

The pharmacokinetic profile, drug-likeness, and toxicity of the hit compounds were determined using the SwissADME (http://www.swissadme.ch) and Pro-Tox II online servers (https://tox-new.charite.de/protox II) online servers.

MM/GBSA

The Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) continuum solvent model was used to determine the docked protein–ligand complex binding free energy.
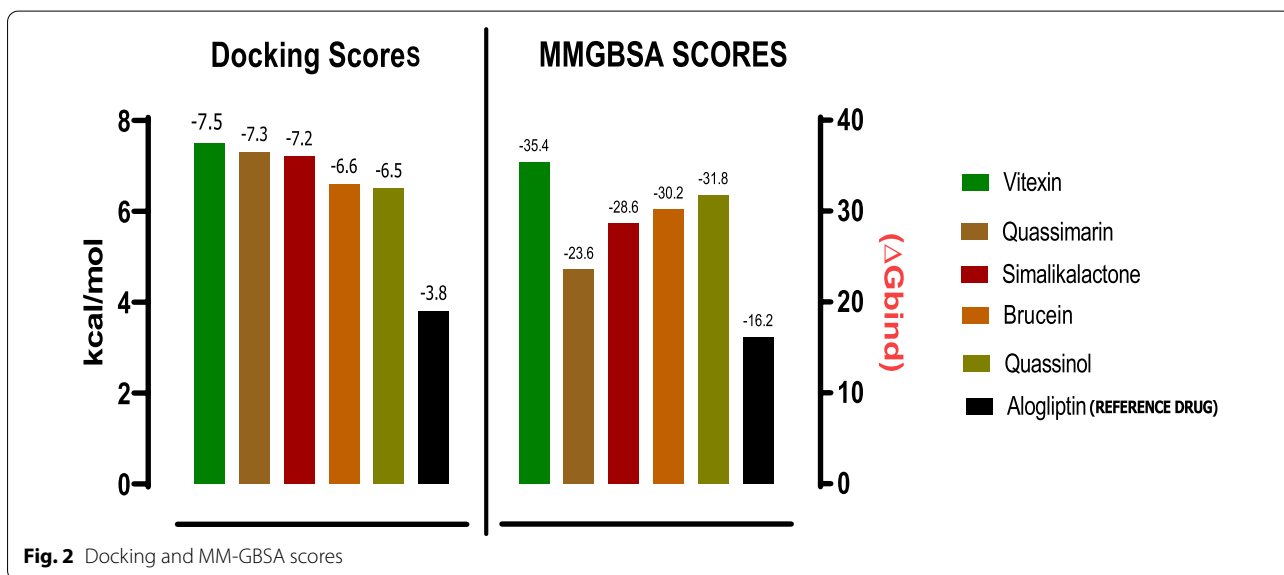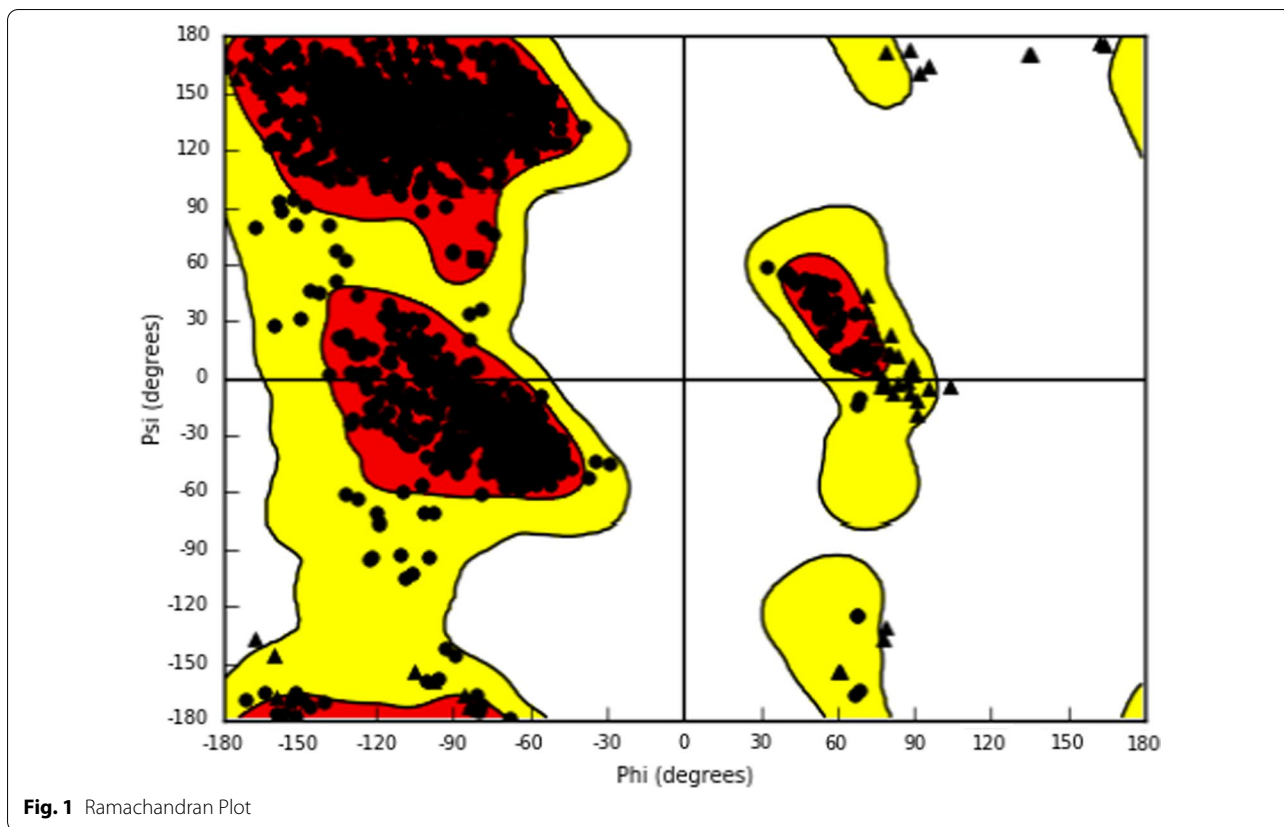
To complete this project, rotamer search techniques from Prime were used in conjunction with the OPLS3 force field and the VSGB solvent model.

Results

See Figs. 1, 2, 3, 4, Tables 1, 2, 3 and 4.

Discussion

Increase in blood glucose causes diabetes, which is a metabolic disorder. Previous research has linked some proteins to diabetes, alpha-amylase, alpha-glucosidase, DPP-IV, and GLP-1 are among them (Chaudhury et al. 2017). Without the costly, time-consuming, and inefficient laboratory screening procedure, *in-silico* screening of natural compounds for drug creation has proven to be effective. Overall, computational analyses have lowered the likelihood of a drug's late-stage failure (Rifaioglu et al. 2019). It has been stated that *Quassia amara* is utilized as a male contraceptive and anti-malaria medication. However, this study shows the *in-silico* effect of phytochemicals found in *Quassia amara* on DPP-IV, which,

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Fig. 1 Ramachandran Plot
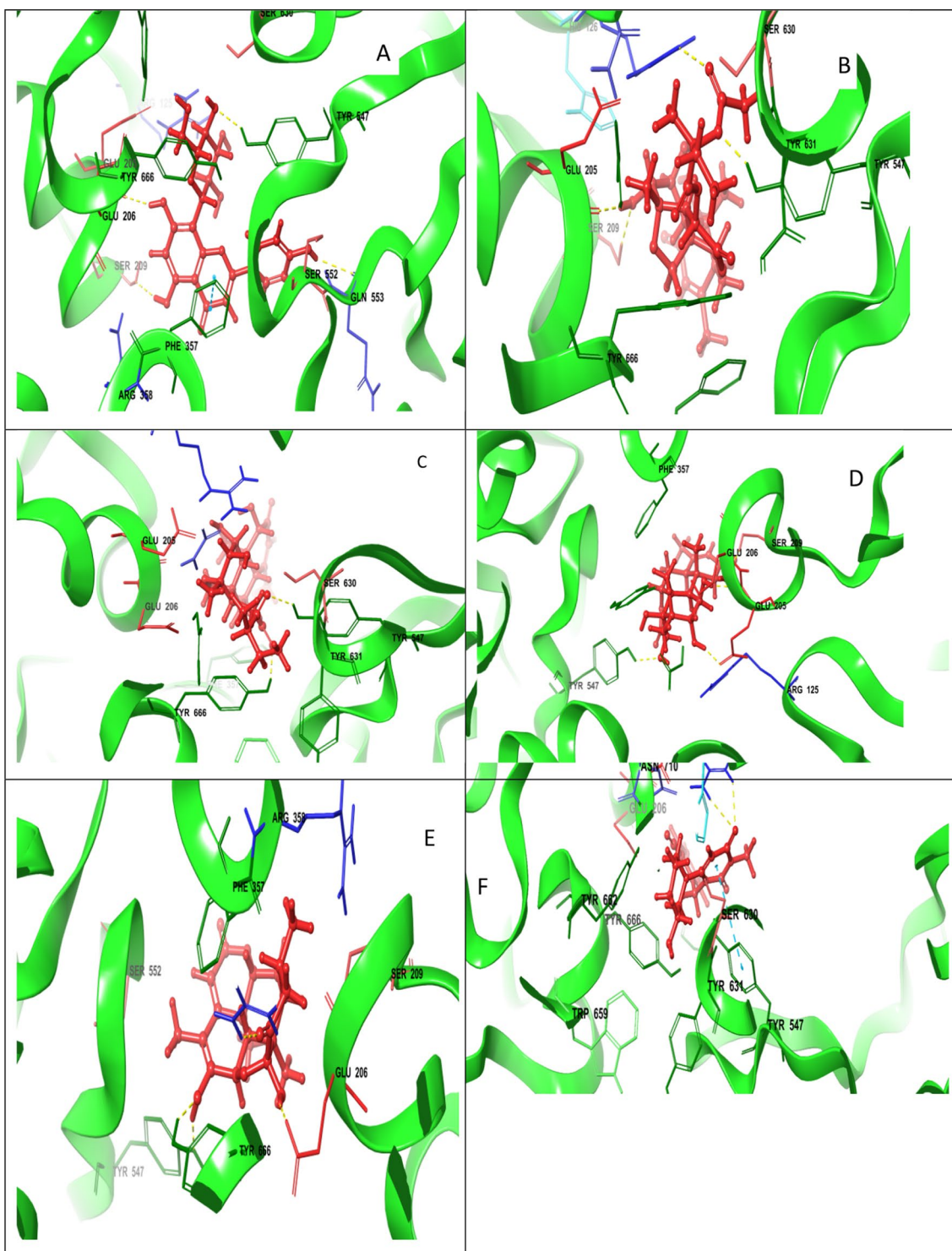

Fig. 2 Docking and MM-GBSA scores

when inhibited, increases the activities of GLP-1 (Glucagon Like Peptide-1) and GIP (Gastric Inhibitory Peptide), resulting in increased glucose-mediated insulin secretion and suppression of glucagon secretion (Nathan et al. 2007). The protein, DPP-IV was docked to the generated library of compounds in this study to reveal the molecular interaction, inhibitory potential, and binding pose of compounds from the *Quassia amara* plant against DPP-IV. The findings indicate that five compounds, Vitexin,

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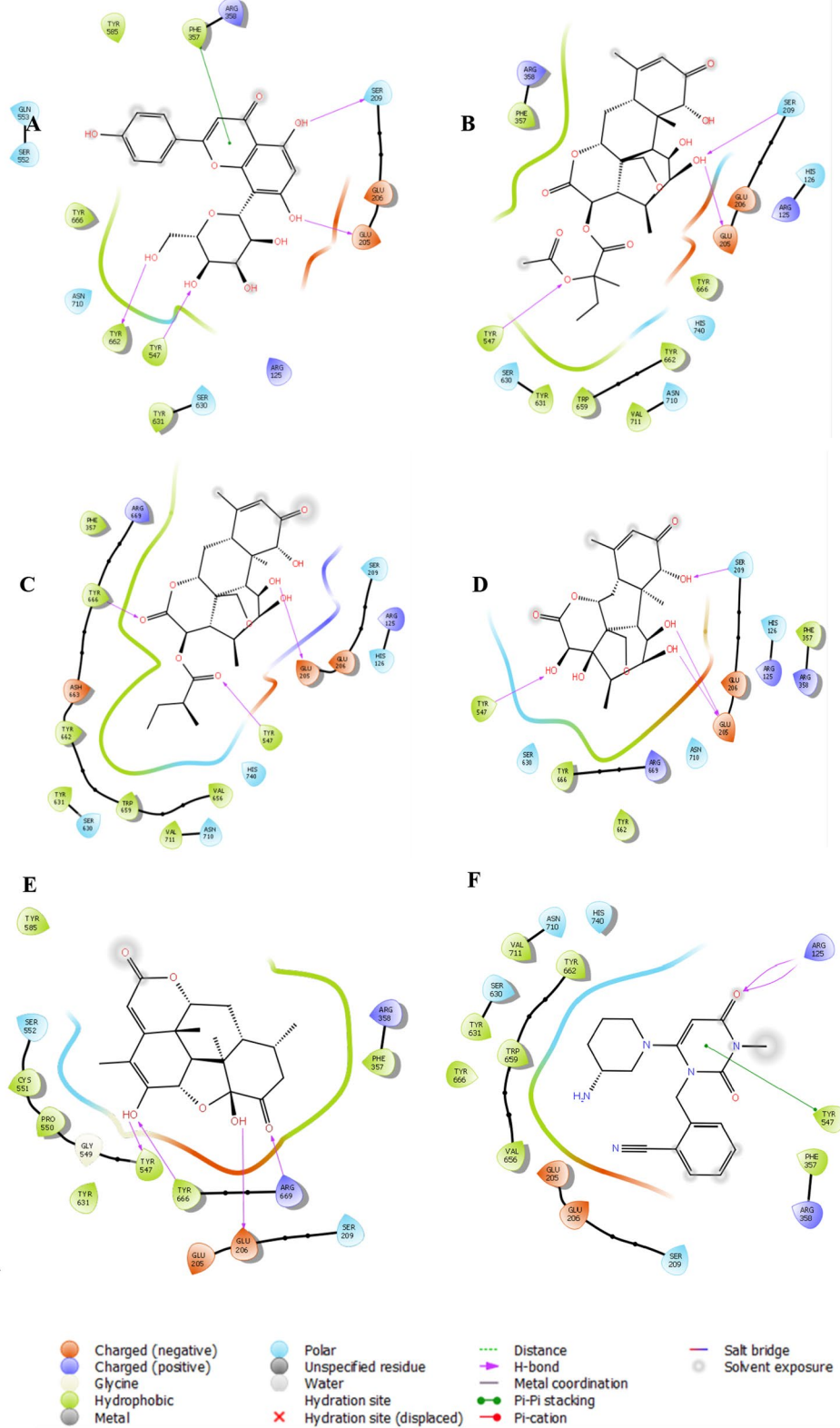
Fig. 3 2D-Molecular interactions of amino-acid residues of alpha-amylase with *Quassia amara* phytochemical constituents. **A** Vitexin, **B** Quassimarin, **C** Simalikalactone D, **D** Brucein D, **E** Quassinol and **F** Alogliptin

Fig. 4 3D-Molecular interactions of amino-acid residues of alpha-amylase with *Quassia amara* phytochemical constituents. **A** Vitexin, **B** Quassimarin, **C** Simalikalactone D, **D** Brucein D, **E** Quassinol and **F** Alogliptin

Table 1 Docking and MM-GBSA scores of the top 5 lead compounds

S. no.	PUBCHEM ID	Compound name	Docking Score (Kcal/mol)	MM-GBSA
1	5280441	Vitexin	− 7.47	− 35.43
2	429906	Quassimarin	− 7.341	− 23.58
3	6711208	Simalikalactone D	− 7.156	− 28.64
4	122784	Brucein D	− 6.579	− 30.21
5	131752166	Quassinol	− 6.49	− 31.78
6	11450633	Alogliptin	− 3.8	− 16.2

Quassimarin. Silkmalactone D, Brucein D, and Quassinol, have DPP-IV inhibitory potential.

Ramachandran plot

The Ramachandran plot shows the statistical distribution of the combined values of Phi and Psi (Dihedral angles) that are possible for an unidentified amino acid (X) in an Ala-X-Ala tripeptide (Ramachandran et al. 1963).

In Fig. 1, Pictorial evidence of the Ramachandran plot was saved, after protein preparation. Using the Ramachandran plot as shown in Fig. 1 the psi and phi predicted values are used in describing the secondary

structure of the protein DPP-IV. The secondary structure of either an alpha helix or beta sheet conformation depends on the positive or negative values of the torsional values based on the arrangement sequence of amino acids present in the protein.

Docking/MMGBSA

The hit compounds' docking scores and MM/GBSA screening results are depicted graphically in Fig. 2 and Table 2, the two tables, respectively. The hit compounds' 2D structures are shown in Fig. 3. The post-docking analysis of the docking experiment, which includes the analysis of the binding pose and interaction of hit compounds with the amino acid residues at the active site of 3VJM, and the amino acid residues involved in the interaction, is shown in 2D and 3D format in Figs. 3 and 4, respectively. Table 4 also includes the results of the ADME/Tox screening to forecast the hit compounds' drug-likeness features.

The curated ligands from *Quassia amara* were docked with additional precision (XP) in the binding pocket of the target protein, DPP-IV, for their DPP-IV inhibitory capabilities. We looked at the top compounds' structural interactions as well as the critical amino-acid interactions in DPP-binding IV's site.

Table 2 Hydrogen Bonds and Hydrophobic interactions of the hit phytochemicals of *Q. amara* phytochemicals

Compound name	Docking score (Kcal/mol)	H-BOND	Hydrophobic interacting amino acids	Other interactions
Vitexin	− 7.47	TYR 662, TYR 547, GLU 205, SER 209	PHE 357, TYR 585, TYR 666, TYR 662, TYR 547, TYR 631,	Pi–Pi Stack: PHE 357
Quassimarin	− 7.341	SER 209, GLU 205, TYR 547,	PHE 357, TYR 547, TYR 631, TRP 659, VAL 711, TYR 662, TYR 666	None
Simalikalactone D	− 7.156	TYR 666, TYR 547, GLU 205	PHE 357, TYR 666, TYR 662, TYR 631, TRP 659, VAL 711, VAL 656, TYR 547,	None
Brucein D	− 6.579	TYR 547, GLU 205. SER 209	TYR 547, TYR 666, TYR 662, PHE 357	None
Quassinol	− 6.49	TYR 666, TYR 547, GLU 206, ARG 669	TYR 585, CYS 551, PRO 550, TYR 631, TYR 666, TYR 547, PHE 357	None
Alogliptin	− 3.8	ARG 125	VAL 711, TYR 631, TYR 666, TYR 662, TRP 659, VAL 656, TYR 547, PHE 357	Pi–Pi stack; TYR 547

Table 3 In-silico drug likeness prediction of the compounds

COMPOUNDS	MW	HBA	HBD	TPSA	ILOGP	LOGKP	ROV
Vitexin	432.383	10	7	181.05	1.63	− 8.79	1
Quassimarin	536.575	11	3	165.89	2.69	− 9.40	2
Simalikalactone D	478.538	9	3	139.59	2.49	− 8.79	0
Brucein D	410.42	9	5	153.75	0.00	− 10.52	0
Quassinol	360.406	6	2	93.06	1.71	− 7.89	0
Alogliptin	339.39	4	1	97.05	2.38	− 7.93	0

Table 4 The bio-availability, pharmacokinetic properties and Cytochrome P450 metabolizing enzymes inhibitory potentials of selected *Quassia amara* phytochemical constituent

Models	Vitexin	Quassimarin	Simalikalactone D	Brucein D	Quassinol
Blood Brain Barrier	BBB-	BBB-	BBB-	BBB-	BBB-
Bioavaliability Score	0.55	0.17	0.55	0.55	0.55
CYP1A2 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-Inhibitor
CYP2C19 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-Inhibitor
CYP2C9 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-Inhibitor
CYP2D6 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
CYP3A4 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Inhibitor
GI Absorption	Low	Low	High	Low	High
P-glycoprotein substrate	Non-Substrate	Substrate	Substrate	Substrate	Substrate
LD50	832 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg	19 mg/kg
Toxicity class	4	2	2	2	2
Carcinogenicity	Non carcinogenic	Non carcinogenic	Non carcinogenic	Non carcinogenic	Non carcinogenic
Mutagenicity	Active	Inactive	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Active	Active	Active	Inactive

As indicated in Table 1, the docking scores of the top five ligands varied from the lead chemical, Vitexin, with a binding energy of -7.47 kcal/mol and an MM-GBSA score of -35.43, to Quassinol, with a docking score of -6.49 and an MM-GBSA score of -31.78, while the standard drug, Alogliptin had a docking score of -3.8, with an MM-GBSA value of -16.2, a value that is comparatively low to the values obtained from the compounds gotten from extracts of *Quassia amara.*

Vitexin (-7.47 kcal/mol) has a high binding energy in comparison twiththe standard drug, Alogliptin (-3.8 kcal/mol) which is due to the large number of hydrophobic interactions, which include PHE 357, TYR 585, TYR 666, TYR 662, TYR 547, and TYR 631 (Fig. 2). Hydrogen bonds were also found at TYR 662, TYR 547, GLU 205, SER 209, and PHE 357, as well as a Pi–Pi stack bond. Quassimarin and Simalikalactone D had different binding affinities within the binding pocket (-7.341 kcal/mol and -7.156 kcal/mol, respectively), but shared the amino acids (PHE 357, TYR 666, VAL 711, TYR 662, TRP 659, TYR 547) in their hydrophobic interaction within the DPP-IV binding pocket (Fig. 2). Brucein D has hydrogen bond interactions with the amino acids (TYR 547, GLU 205, SER 209) as well as hydrophobic interactions with the amino acids (TYR 547, TYR 666, TYR 662, PHE 357).

Around the binding site of DPP-IV, Quassinol forms hydrogen bonds with amino acids (TYR 666, TYR 547, GLU 206, ARG) and hydrophobic bonds with amino acids (TYR 585, CYS 551, PRO 550, TYR 631, TYR 666, TYR 547, PHE 357) (Fig. 3).

The methodology of computational thermodynamics to determine the binding affinity of compounds, molecular mechanics generalized born surface area (MM-GBSA) is utilized. MM-GBSA, which is part of the Schrodinger suite's Prime module, has previously been found to provide an accurate statistical post-docking analysis of docked complexes, with the lower the score, the higher the binding. The relative free binding energies of Vitexin, Quassimarin, Simalikalactone D, Brucein D, and Quassinol are -35.43, -23.58, -28.64, -30.2, and -31.78, respectively (Fig. 2). The MM-GBSA results show that the bioactive chemicals in question have a higher binding energy than the reference molecule.

ADMETox

With the exception of Quassinol, which is an inhibitor of CYP3A4, the first five ligands of *Quassia amara* with the highest docking scores were found to be non-inhibitors of the following oxidase enzymes: CYP2C19, CYP2C9, CYP1A2, CYP2D6, and CYP3A4 (Table 4). Because of their high molecular weight, none of the ligands are able to pass the blood–brain barrier. The GI absorption of each ligand varies on average, with Vitexin, Quassimarin, and Brucein D having low absorption and Simalikalactone D and Quassinol having high absorption. Except for Vitexin, all ligands contain a protein glycoprotein substrate.

The fraction of unmodified medicine that enters systemic circulation following administration via any route is referred to as bioavailability (Kim et al. 2016). If a compound's bioavailability score is less than 0.5, it is assumed to have low oral bioavailability. The substance is expected to have a high oral bioavailability if the score is greater than 0.5. Vitexin, Simalikalactone D, Brucein D, and Quassinol all have a bioavailability value of 0.55

using SWISS ADME, however Quassimarin has a low bioavailability score of 0.17. This indicates that, with the exception of Quassimarin, all are potential medication candidates.

Only Vitexin exceeded the recommended LD50 of a medicine, which is less than 500 mm/kg. Other toxicity indicators such as carcinogenicity, mutagenicity and cytotoxicity were evaluated and studied, and none of the ligands were discovered be carcinogenic. Vitexin was shown to least toxic and non-irritant of the five leading ligands.

Druglikeness

Furthermore, the compounds' Ilog *P* values ranged from 0.00 to 2.69, indicating that they are all water-insoluble and hence unable to enter the gut lining, but do penetrate the target's cell membrane to some amount, as required of an orally delivered medicine. With the exception of Vitexin and Quassimarin, all of the top bioactive compounds met the Lipinski rule for orally given drugs, as none of the prerequisites were violated. (Table 3) Orally administered drugs should have a molecular weight of less than 500 g/mol, ten or less hydrogen bond acceptors, five or fewer hydrogen bond donors, and a log P of less than five, according to Lipinski's rule of thumb.

When administered orally, any pharmaceutical molecule that breaks two or more of the rules will be useless (Walters 2012). These ligands' bioavailability scores also support this notion.

Topological Polar Surface Area, or TPSA, is a proportion of absorbance that indicates a drug's capacity to penetrate the cell membrane. This refers to the number of polar molecules such as oxygen, nitrogen, and hydrogen.

This study's TPSA scores revealed that three of the five ligands had values greater than 140 Ao, implying that the absorption ratio for these three compounds, Vitexin, Quassimarin, and Brucein D, is low. The TPSA scores of the other two ligands, simalikalactone D and quassinol, are lower.

Conclusions

Diabetes is a global problem that is being addressed by a number of scientists around the world. However, the number of people who die as a result of this situation is worrying. DPP-IV inhibitors are well-known for their importance in the treatment of diabetes. They improve the body's insulin sensitivity. DPP-IV reduces the half-life of GLP-1; hence, blocking this enzyme would extend the half-life of GLP-1, favoring insulin action. In this investigation, *Quassia amara* recovered 2D molecules that were docked with the protein DPP-IV.

Vitexin, Quasimmarin, Simalikalactone D, Brucein D, and Quassinol are the top five lead compounds. They could be considered as potential medication candidates as a result of their poor docking scores in the treatment of diabetes. Simalikalactone D, Brucein D, and Quassinol did not break any of Lipinski's rules of five, and their lowest MMGBSA scores of −35 indicate that they could be good medication candidates for diabetic mellitus management. However, more research is needed to determine the ligand binding affinity.

Declarations

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