**Advanced Bioinformatics Tools in the Pharmacokinetic Profiles of Natural and Synthetic Compounds with Anti-Diabetic Activity**

Ana Maria Udrea 1,2,†, Gratiela Gradisteanu Pircalabioru 2,†, Anca Andreea Boboc 3,4, Catalina Mares 5, Andra Dinache 1, Maria Mernea 5,* and Speranta Avram 5

Citation: Udrea, A.M.; Gradisteanu Pircalabioru, G.; Boboc, A.A.; Mares, C.; Dinache, A.; Mernea, M.; Avram, S. Advanced Bioinformatics Tools in the Pharmacokinetic Profiles of Natural and Synthetic Compounds with Anti-Diabetic Activity. *Biomolecules* 2021, 11, 1692. https://doi.org/10.3390/biom11111692

Academic Editor: Jun Lu

Received: 15 October 2021
Accepted: 8 November 2021
Published: 14 November 2021

Publisher’s Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

Abstract: Diabetes represents a major health problem, involving a severe imbalance of blood sugar levels, which can disturb the nerves, eyes, kidneys, and other organs. Diabetes management involves several synthetic drugs focused on improving insulin sensitivity, increasing insulin production, and decreasing blood glucose levels, but with unclear molecular mechanisms and severe side effects. Natural chemicals extracted from several plants such as *Gymnema sylvestre*, *Momordica charantia* or *Ophiopogon planiscapus Niger* have aroused great interest for their anti-diabetes activity, but also their hypolipidemic and anti-obesity activity. Here, we focused on the anti-diabetic activity of a few natural and synthetic compounds, in correlation with their pharmacokinetic/pharmacodynamic profiles, especially with their blood-brain barrier (BBB) permeability. We reviewed studies that used bioinformatics methods such as predicted BBB, molecular docking, molecular dynamics and quantitative structure-activity relationship (QSAR) to elucidate the proper action mechanisms of antidiabetic compounds. Currently, it is evident that BBB damage plays a significant role in diabetes disorders, but the molecular mechanisms are not clear. Here, we presented the efficacy of natural (gymnemic acids, quercetin, resveratrol) and synthetic (TAK-242, propofol, or APX3330) compounds in reducing diabetes symptoms and improving BBB dysfunctions. Bioinformatics tools can be helpful in the quest for chemical compounds with effective anti-diabetic activity that can enhance the druggability of molecular targets and provide a deeper understanding of diabetes mechanisms.

Keywords: diabetes mellitus; natural compounds; QSAR; molecular docking; molecular dynamics; blood–brain barrier; in silico

1. Brief Overview of Diabetes Types

Diabetes mellitus (DM) is a metabolic disease defined by a persistently high blood sugar level. There are numerous kinds of diabetes mellitus, but the two most common are type 1 (T1DM) and type 2 (T2DM). T1DM is an autoimmune disease; it occurs due to the destruction of insulin-producing pancreatic β cells, and the patients are entirely reliant on exogenous insulin injection. T2DM is caused by impaired insulin secretion, which generally occurs in the context of pre-existing insulin resistance [1,2].
Specific complications may occur faster and progress with early diagnosis and longer exposure to T1DM in children. T2DM is a complex disease dependent on a number of factors such as environmental, metabolic and genetic factors [3]. T2DM affects about 10% of the population, but diagnosing it and maintaining a controlled blood sugar level helps slow down the complications of diabetes [4]. The molecular mechanisms involved in T2DM are incompletely explained, but insulin resistance and defects in insulin secretion are the main causes of this disease [5]. Insulin resistance may be due to both obesity and neuroendocrine function [6].

Macrovascular complications (cerebrovascular, coronary and arterial disease) [7] and microvascular complications (diabetic retinopathy, nephropathy, neuropathy) [8] affect the nervous system, suggesting an inflammatory process that permeates the BBB, thus leading to brain dysfunctions such as those in the psychiatric sphere [9].

With disease progression, chronic exposure to hyperglycaemia induces various types of organ damage [10]. Chronic complications of diabetes are divided into microvascular (i.e., retinopathy, nephropathy and neuropathy) and macrovascular (i.e., cardiovascular disease, mainly as heart failure, coronary heart disease, cerebrovascular and peripheral artery disease). The most accepted mechanism of the deleterious effects of chronic hyperglycaemia is the excessive production of superoxide anion by the mitochondrial electron chain, leading to oxidative stress [11]. Acute complications of T1DM are medical emergencies, consisting mainly of ketoacidosis and hypoglycaemia [12]. Hyperglycaemic hyperosmolar state is a common acute complication in elderly people with T2DM [12]. The main pathogenic event in ketoacidosis is a hormonal disturbance characterized by absolute insulin deficiency in the presence of a relative excess of counterregulatory hormones (i.e., glucagon, catecholamines, cortisol and growth hormone) [12].

The BBB is a membrane composed of endothelial cells that protect the central nervous system by preventing the non-selective passage of substances from blood vessels inside the nervous tissue. Diabetes affects the BBB as well, although in a subtle manner, resulting in less data about the subject [13]. Hyperglycaemia may increase the level of pro-inflammatory markers and cell permeability, resulting in decreased efficiency of the BBB [14]. In mice, the hyperglycaemic conditions associated with diabetes lead to a pro-inflammatory phenotype in brain microvessels, with decreased pericyte coverage and increased ICAM-1 expression [15]. The loss of pericytes, doubled by the diminution of tight junctions, results in a permeable BBB [15,16].

Herbal medicines are still used in current times and are classified as complementary and alternative medicine. Many plants have anti-diabetic properties via modulating insulin production, cell insulin sensitivity, or glucose absorption. Additionally, to glycaemic management, several plants showed promise in preventing other DM-related illnesses such as cardiovascular problems by lowering cholesterol levels and BMI [17]. Flavanone and polyphenols, natural chemical groups, were investigated as a possible therapy in T2DM or adjuvant in DM treatment. Curcumin, resveratrol, and carotenoid were the most commonly studied substances among these [18].

In the present paper, we reviewed studies on natural compounds acting on DM protein targets and on BBB. A schematic representation of our study directions is presented in Figure 1. Initially we discussed the molecular targets in diabetes by considering proteins involved in the metabolism and uptake of glucose, proteins that control insulin secretion and proteins involved in pancreatic β cell development. We identified the natural compounds that could modulate these targets, and we presented bioinformatics studies on these compounds involving the usage of quantitative structure–activity relationships (QSAR), molecular docking and molecular dynamics methods. We also presented databases and web servers useful for the identification of antidiabetic compounds. Concerning the BBB, we identified relevant targets and natural compounds that could prevent BBB dysfunctions. We also presented some platforms useful for calculating the ability of a compound to cross the BBB.
2. Molecular Targets Involved in Diabetes Mellitus

The treatment used in DM aims to prolong life and avoid long-term diabetes-associated complications. Insulin therapy is the primary treatment for T1DM, whereas T2DM is managed with hypoglycaemic medicines, diet, and lifestyle modifications [19]. DM has several receptors that are or may become therapeutic targets; these will be discussed below.

Insulin receptors (IR) are receptors activated by insulin that have a role in glucose homeostasis. Nowadays, in T1DM, the treatment is represented by self-administrated insulin analogues that activate the IR [20].

Mono-ADP ribosyltransferase-sirtuin-6 (SIRT6) decreased level and function are related to atypical metabolism of glucose and lipids. Mice studies reveal that hypoglycaemia occurs in subjects with SIRT6 deficit [21,22]. Overall, SIRT6 has roles in several processes such as regulation of blood glucose, glycolysis, gluconeogenesis, pancreatic β cell function, inflammation, lipid metabolism, etc., and may represent a therapeutic target in DM [23].

Aldose Reductase (AR) is activated in hyperglycaemic conditions and is linked to DM and its complications such as myocardial ischemia, atherothrombotic cardiovascular disease, or diabetes-induced oxidative stress. However, the inhibition of AR may prevent the complications caused by DM [24].

α-glucosidases are enzymes that cleave the oligosaccharides and disaccharides to monosaccharides. Pancreatic α-amylase enzymes catalyse the hydrolysis reaction of α-1,4 glycosidic linkages in many polysaccharides [25]. α-glucosidase and α-amylase inhibitors are used in DM and show better glucose regulation [26,27].

Peroxisome proliferator activated receptor gamma (PPARγ) activity can prevent insulin resistance by increasing glucose uptake in adipocyte and muscle cells, which results in lowering of blood glucose levels. Moreover, PPARγ agonists reduce the inflammation mediators that promote insulin resistance and trigger an increase in circulating adiponecitin levels with a positive outcome for insulin sensitivity and a decreasing effect on glucose production in the liver [28].
Biomolecules 2021, 11, 1692

Glucose co-transporter (SGLT) is involved in insulin independent glucose reabsorption in nephrons. SGLT1 and SGLT2 are the main SGLT types, expressed in kidneys in a ratio of 1:10 [29]. The inhibition of SGLTs by gliflozin drugs reduces glucose reabsorption and the levels of glycated haemoglobin [30].

11-β hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an enzyme that converts cortisone to cortisol, which increases hepatic glucose output independent of insulin [31].

Glutamine:fructose-6-phosphate aminotransferase 1 (GFPT1) is the rate limiting enzyme in glucose metabolism by the hexosamine pathway (associated with impaired insulin secretion and insulin resistance) [32].

Protein-tyrosine phosphatise 1B (PTP1B) is a protein involved in the insulin signalling pathway and a negative regulator in metabolic disorders [33].

Dipeptidyl peptidase-4 (DPP-4) acts on incretin hormones that increase insulin secretion and decrease glucagon secretion [34]. DPP-4 inhibitors have been found in animal research and early clinical trials to considerably decrease fasting and postprandial glucose levels with no risk of hypoglycaemia [35].

Glucokinase regulatory protein (GKRP) represents the endogenous inhibitor of glucokinase, an enzyme that regulates glucose uptake and glycogen synthesis and suppresses glucose production [36]. Glucokinase is involved in glucose homeostasis and is found in pancreatic β-cells and hepatocytes. This kinase stimulates insulin production in pancreatic cells in response to glucose and glucose absorption, glycogen synthesis, and storage in hepatocytes [37]. Hepatic glucokinase expression is reduced in insulin resistance but also T2DM, implying dysregulation of this biomarker [38]. In diet-induced obese mice, the effect of glucokinase activators reduced blood sugar levels [39].

Histone deacetylases (HDAC) modulation appears as an important direction in diabetes therapy, as their inhibition was associated with β cell development, proliferation, differentiation and function [40]. These can be inhibited by several compounds reviewed here [41].

Compared to the other PDKs, pyruvate dehydrogenase kinase 2 (PDK2) has the highest phosphorylation and inactivation of pyruvate dehydrogenase. Since the number of PDK isoforms is increased in diabetes, upregulated PDK2 might be a target for improving glucose tolerance [42]. This kinase is also implicated in hypothalamus inflammation and its consequences (as alteration of feeding behaviour) [43].

GPR40 receptor, also known as free fatty acid receptor 1, is a G-protein-coupled receptor that binds long-chain free fatty acids to improve glucose-dependent insulin production [44]. In a study on diabetic rats, GPR40 activation showed improvements in hyperglycaemia and insulin response [45].

Glucose transporter 2 (GLUT2) may be found in various locations throughout the body, including pancreatic β cells and neurons. GLUT2 is necessary for glucose-stimulated insulin release in pancreatic β cells. GLUT2-dependent glucose-sensing regulates eating, body temperature, and pancreatic β cell mass and function, as well as parasympathetic and sympathetic functions in the central nervous system [46]. Glycogen synthase kinase 3 (GSK-3) is a serine/threonine kinase involved in various processes such as glycogen metabolism, regulation of the cell cycle, and cell proliferation. GSK-3 suppresses the activity of glycogen synthase and insulin receptor substrate-1, two important targets in insulin action. Its enhanced activity under diabetic conditions makes it a promising druggable target in T2DM [47].

Glycerol-3-phosphate dehydrogenase (GPDH) is a mitochondrial enzyme whose inhibition by the antidiabetic drug metformin results in reduced hepatic gluconeogenesis and reduced conversion of lactate and glycerol to glucose [48].

3. Plants Involved in Diabetes Mellitus Management

At present, several plants have been mentioned in diabetes mellitus management. We present some of them below.
Gymnema sylvestre is a plant rich in phytocompounds that is used as an adjunctive treatment for diabetes and contains, among others, gymnemic acid, gourmarin and gymnnaponins [48]. They have therapeutic effects in diabetes by regulating blood sugar levels. Gymnemic acid is a triterpene saponin with possible antidiabetic action given by the interaction with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in glycolysis [49]. The extracts from Gymnema sylvestre may stimulate insulin secretion and delay glucose absorption from the blood by attaching to intestinal receptors. This way, they decrease the absorption of sugars and limit their passage into the blood [50–52]. An interesting study about phytochemicals and the pharmacological and clinical potential of Gymnema sylvestre was published by Khan et al. with emphasis on its anti-diabetic activity [53]. The role of some Gymnema sylvestre constituents, namely gymnemic acids (I-VII) and gymnemasaponia, in hypoglycaemia has been investigated [51]. These chemicals act by causing the pancreas to secrete more insulin. These compounds are significant because of their structure, which is similar to that of sugar molecules. They attach to taste receptors, blocking the binding site for sugar in food and interfering with the detection of the sweet and bitter taste. These chemicals have a comparable effect on the taste buds and intestines, resulting in a reduction in blood sugar absorption [51].

Momordica charantia is a plant used in clinical trials that has a beneficial effect on T2DM [54]. Although it had no effect in acute episodes of hyperglycaemia, long-term administration has managed to improve the parameters of patients in clinical trials [55]. The mode of action is not yet fully understood, but studies suggest altered insulin secretion in patients and improved insulin sensitivity by increasing adenosine monophosphate-activated protein kinase (AMPK) [56]. The main chemical compounds found in this medicinal plant are charantine, cucurbitan glycosides, momordicin and oleanolic acids [57,58]. In addition to the presence of natural compounds, Momordica charantia can synthesize peptides that can bind to the insulin receptor, lowering blood glucose levels. These peptides may help reduce the need for insulin and limit the side effects of antidiabetic drugs [59].

Trigonella foenum-graecum is a medicinal plant whose seeds contain compounds with therapeutic effects. The seeds of this compound can lower the rate of glucose absorption. They help control diabetes, but also reduce cholesterol, cardiovascular risk and other chronic diseases [60].

Ginseng is considered one of the most widely used medicinal plants, with up to thirteen species. Most ginseng-based products come from the Panax ginseng and Panax quinquefolius species [61]. Therapeutic compounds in ginseng are triterpene glycosides called ginsenosides. Animal studies have shown their involvement in glucose and lipid metabolism and the improvement of biochemical parameters in animal models [62].

Cinnamon can improve blood sugar control and help reduce the complications of diabetes [63]. It is used in traditional Chinese medicine for its various hypoglycaemic, digestive, antispasmodic and antiseptic properties [64].

Angelica decursive is a medicinal plant used in traditional medicine in East Asia, with many uses including those as an analgesic, antitussive or tumour suppressor [65,66]. This plant is rich in coumarin compounds, but the most pronounced antidiabetic effect is in the compounds 4′-methoxy Pd-C-I, decursinol, decursidin, 6-carboxylic umbelliferone, 2′-isopropyl psoralen, and Pd-C-III, which has many therapeutic effects. These present inhibitory activity on α-glucosidase and PTP1B [67,68]. PTP1B is a tyrosine phosphatase that regulates the cell cycle and may interfere with the transduction of the insulin stimulus signal [69]. A molecular docking study identified that coumarin binds strongly at the PTP1B site. These results support the importance of these compounds in the prevention and treatment of diabetes [70,71].

Gynura procumbens Merr. belongs to the Asteraceae family, and is a plant found in tropical countries that is used for the therapeutic treatment of inflammatory diseases (e.g., rheumatism), heart disease (e.g., hypertension) and diabetic diseases [72]. Studies on the solvent fractions of G. procumbens Merr evaluated the antioxidant and antidiabetic effects of the compounds in this plant. In studies on the HepG2 cell line and insulin
resistance, *G. procumbens* fractions obtained with the highest phenol content favoured insulin absorption. The compounds with the highest activity in *G. procumbens* were kaempferol, quercitin, caffeoyl-O-hexoside caffeoylquinic acid, coumaroyl-O-hexoside and coumaroylquinic acid. Bioinformatics studies have shown strong molecular interactions between natural compounds and digestive enzymes, thus underlining the value of studying these compounds [73].

*Stachys riederi var.* japonica is a medicinal plant with an antioxidant and antidiabetic effect that can inhibit α-amylase and α-glucosidase. The compounds in this plant have improved glucose uptake into insulin-resistant HepG2 cells. Among the isolated compounds, those with important activity were rosmarinic acid, caffeic acid, oleanolic acid and ursolic acid [74].

*Gardenia jasminoides* extract is used both as a natural dye and as a traditional medicine against various types of diseases such as circulatory diseases. The compounds in this plant are generally bioactive and can have a beneficial effect on the nervous, cardiovascular, and digestive systems, but can also have an anti-diabetic effect [75]. Studies on the methanolic extract from *G. jasminoides* seeds have suggested high antioxidant activity that can inhibit α-amylase and α-glucosidase. The compounds identified with the most promising antidiabetic activity are chlorogenic acid and jasminozide A [76].

*Helianthus tuberosus* is a perennial plant with high resistance to stress, nutritional value and possible antidiabetic effects. This plant is an alternative to classic animal feed; it can produce a high amount of biomass, and its activity on animal digestion, antibacterial, anti-inflammatory and antioxidant effect is due to natural compounds [77].

*Vitex negundo* is a medicinal plant with bioactive properties on glycoprotein metabolism and antihyperglycemic effects due to its ability to suppress the growth of insulin-resistant HepG2 cells. The major compounds are viridiflorol, beta-caryophyllene, sabinen, 4-terpineol, herbacetin rhamnoside, kaempferol, luteolin-7-glucoside, neogundoside, p-hydroxybenzoic acid, protocateucic acid, quinic acid, vitedoin A and vitexin [78]. The functionality of this plant is based on the ability of its active compounds to inhibit α-glucosidase and the uptake of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals [79].

*Eryngium caeruleum* has antidiabetic and antioxidant potential. Bioactive constituents include thymol, tocopherol, phytol, nerolidol, (I)-neophytadiene, linolenic acid and falcarinol. Molecular modelling studies have shown that *E. caeruleum* interacts with active α-glucosidase sites. Studies in laboratory animals have shown the safety of using *E. caeruleum* extracts, as the chances of them causing adverse reactions are relatively low. The bioactive compounds identified may inhibit α-glucosidase, thus lowering blood glucose [80].

*Curculigo latifolia* has anti-diabetic properties, modulating glucose and lipid metabolism in laboratory rats. The most common compounds in the plant are phloridzine, scandenine, monobenzone, hydroquinone, dimethylcaffeic acid, and hordatin A, compounds with a phytotherapeutic role in the plant that confers anti-diabetic properties. A higher concentration of *C. latifolia* extract increases the percentage of DPP (IV) inhibition [81].

*Limonium axillare* may be an antidiabetic remedy that can reduce hyperglycaemia and restore serum insulin levels by increasing the expression of the glucose transporters GLUT2 and GLUT4. In in vitro studies, *L. axillare* extract had a strong effect of inhibiting α-amylase and ameliorating pancreatic tissue. The inhibition of pancreatic enzymes α-amylase and α-glucosidases may be a mechanism by which the compounds in this plant manifest their antidiabetic capacity. The compounds isolated from *L. axillare* are p-sitosterol-3-palmitate, p-sitosterol, myricetin and gallic acids [82].

### 4. Natural Compounds Involved in Diabetes Mellitus Management

Curcumin is a natural compound found in high amounts in the plant *Curcuma longa* (turmeric) [83]. This compound can relieve symptoms and prolong cell death in T2DM [84]. The effects of this compound have been seen in *in vivo*, animal and *in vitro* studies [85]. Curcumin has a molecular mechanism similar to that of thiazolidinedione; an antidiabetic drug that activates the PPAR-γ activated by the peroxisome proliferator [86].
Docosanol is a compound that belongs to the class of aliphatic alcohols, with proven antiviral activity [87]. However, molecular docking studies have shown that it is a candidate for inhibiting α-glucosidase and α-amylase [88]. In vitro and in vivo studies show that this compound can lower blood sugar levels [89].

Tetracosanol can also act as an α-glucosidase inhibitor and in combination with a synthetic drug presents increased effectiveness [67]. Anthroquinonol is a derivative of ubiquitin, extracted from *Antrodia cinnamomea* [90]. A study on mice shows that anthraquinone can improve the body’s response to insulin. This compound has an inhibitory effect on dipeptidyl peptidase IV through the kinase cascade activated by adenosine monophosphate [91].

Flavones extracted from *Clinacanthus nutans*, and *Nigella sativa* are good candidates as compounds with anti-diabetic activity [92,93]. Rutin is another flavonoid found in many herbs, vegetables and dietary supplements and has an antihyperglycemic effect [94,95]. Its mode of action is not fully understood, but this compound may protect pancreatic cells against apoptosis by decreasing carbohydrate absorption and stimulating insulin secretion [96].

Berberine is a natural alkaloid used to treat fungal and parasitic infections [97]. In diabetes, it has shown its effectiveness by regulating lipid metabolism and improving glycaemic parameters [98,99]. Long-term treatment with berberine can improve insulin secretion. Nevertheless, the mechanism of action is not clear; berberine stimulates glycolysis but can also act as an α-glucosidase inhibitor [99]. Catechin has anti-inflammatory, antidiabetic, and neuroprotective activity [100].

Herbacetin has a favourable effect in maintaining blood sugar levels at normal levels. If intervenes in gluconeogenesis, thus mediating the metabolic pathway and preventing the overproduction of glucose [101]. The compound targets liver fructose 1,6-biophosphatase, and thus studies have shown that it may be a valid alternative in the treatment of patients [71,102].

Kaempferol is a natural polyphenol studied for its antidiabetic role. Kaempferol treatment ameliorated histological changes in diabetes-induced renal tissue by inhibiting Rho-kinase [103,104]. Molecular docking studies have shown that kaempferol targets α-glucosidase with high-affinity binding, resulting in an inhibitory effect [105] Molecular docking scores and studies in mice have shown that Leucodelphinidin has an antidiabetic effect [106].

Isorutarine is linked to the main target of antidiabetic drugs, α-glucosidase and α-amylase. The same targets are inhibited by actinodafine, a compound with antidiabetic activity [88]. The proposed molecular mechanism for this compound came from molecular docking studies, and its effectiveness has been proven by studies in laboratory animals. Additionally, this compound has high therapeutic potential in lowering blood sugar levels [67]. Nodakenin has an inhibitory effect on α-glucosidase, PTP1B, acetylcholinesterase and butyrylcholinesterase [107].

In in vitro studies, compounds such as neochlorogenic acid, chlorogenic acid, caffeic acid, 5-OA-(4-cumaroyl) -quinic acid, feruloylquinic acid, caffeoylquinic acid, isoxazolidine, and β-D-glucoside of salicylic acid showed antidiabetic activity, acting on α-amylase and α-glucosidase. Free radical scavenging and inhibition of diabetes-associated enzymes are dose-dependent, but according to a study by Mariadoss et al., phytocompounds could reduce blood sugar levels, triggering glucose uptake into insulin-resistant HepG2 cells [108].

Molecular docking studies on (4Z, 12Z)-cyclopentadeca-4, 12-dienone have shown that this compound can inhibit the action of enzymes aldose reductase, glucokinase, pyruvate dehydrogenase kinase, receptor-gamma, glycogen synthase kinase-3, and fructose-6-phosphate amidotransferase with a role in diabetes. This compound is a valid candidate for the development of new antidiabetic drugs due to the various molecular targets to which it may bind [109].
5. Quantitative Structure–Activity Relationships (QSAR) Predicted Anti-Diabetic Activity

Quantitative structure–activity relationships (QSAR) investigations are a fast computational approach for predicting a compound’s biological activity from its chemical structure. QSAR techniques aid medicinal chemists in comprehending the link between hypoglycaemic action and molecular characteristics [110–112]. Statistical measures such as the cross-validated correlation coefficient, fitted correlation coefficient, and standard deviation of error prediction are commonly used to assess QSAR investigations [113]. The dimensions of QSAR models range from 0 to 6; however, the most common are 2D QSAR and 3D QSAR. Geometric characteristics, topological indices, and molecular fingerprints are all considered for 2D QSAR models, but steric properties are not. The spatial characteristics of the compound are the focus of the 3D QSAR method [114].

In silico methods were applied by Gajjar et al. to a series of 3-aryl-3-ethoxypropanoic acid derivatives as modulators of GPR40. Two 3D-QSAR models (utilizing CoMFA and CoMSIA), and a 2D-QSAR model (using HQSAR technique), were used to determine the connection between the structure and biological activity of these compounds. All QSAR models have good statistical parameters [44].

The QSAR models analysed contour maps of lipophilic, electrostatic, hydrophobic, donor, positive and negative contributions. The findings revealed that 3-aryl-3-ethoxypropanoic acid derivatives might be effective anti-diabetic medicines that target the human GPR40 receptor [44]. Izadpanah et al. [115] conducted QSAR and molecular docking analyses on a set of 35 α-glucosidase inhibiting compounds. Statistical parameters in the research suggested a successful prediction model. The most active compound on α-glucosidase showed high inhibitory activity of 9.22, which implies that it might be used to treat T2DM [115].

Flavone compounds exhibited a potential inhibitory effect on the α-glucosidase enzyme in a QSAR investigation. The results of 20 flavone derivatives (1–20) were compared to the α-glucosidase inhibitor acarbose in this study. The IC50 values of the flavone derivatives varied from 1.02 to 38.1 M, according to the findings. These results revealed that acarbose (IC50 = 39.45 0.11 M) had lower inhibitory activity [116]. Maurya et al. used a 3D-QSAR model to identify positions and types of groups that increased the activity of 116 coumarin derivatives against lysosomal α-glucosidase. The study showed that the binding affinity of lysosomal α-glucosidase antagonists can be improved by replacing H-bond donor groups on the coumarin ring moieties at the C3, C5, and C7 positions, respectively. Additionally, binding an H-bond donor to the attached carbon rings and oxygen atoms can improve the compound’s activity [117].

Xu et al. built 2D QSAR models to characterize the important fragments of a series of 25 andrographolide derivatives. In addition, 3D QSAR models were created to investigate the spatial distribution of their main groups. To efficiently detect the fragments and their spatial distribution, they merged the 2D and 3D QSAR models. Derivatives 20–23 of the 25 andrographolide compounds had a strong inhibitory effect on the α-glucosidase receptor, while compounds 3, 4, 13, and 16 had low inhibitory activity [118].

Ghamali et al. used 44 substituted flavonoids with previously experimentally determined inhibitory activity on AR to develop three QSAR models (a multiple regression analysis, a nonlinear regression, and an artificial neural network model). The models had high stability and prediction power for flavonoid derivative inhibitory action against AR. The artificial neural network model is the best QSAR model, and it may be useful to predict the inhibitory effects of flavonoid derivatives [119].

6. Molecular Docking and Molecular Dynamics Predicted Anti-Diabetic Activity

Molecular docking simulations usually predict the interaction between a compound and a specific target protein [120,121]. Flavonoids or other chemical classes of compounds from traditional medicinal plants are frequently used in molecular docking studies to find the specific compounds responsible for the positive effect [122].
Here, we will present several studies that use the molecular docking approach to predict the binding affinity of compounds from plants that interact with DM-specific targets. In the case of some promising compounds, the stability of receptor-ligand complexes was addressed by molecular dynamics (MD) simulations.

Molecular docking studies show that compounds from plants such as *Ficus benghelensis, F. racemosa, F. religiosa, Thespesia populena*, and more have the potential to bind to targeted receptors in DM [67,71,117] (Table 1). For both α-amylase and α-glucosidase targets, curcumin presents the lowest dock-score (Table 1) [67]. A chemical with a low free binding energy has a better chance of binding to that target. The lower the binding energy, the greater the chance of binding [123,124]. These simulations from Jhong’s study were experimentally validated (in the same study) and compared with acarbose (α-amylase inhibitor used in the treatment of DM). Jhong’s study concluded that curcumin and actinodaphnine, interacting with α-glucosidase, and curcumin and berberine, interacting with the α-amylase, present a higher IC50 activity compared with acarbose [67].

Another docking study on α-glucosidase conducted by Maurya concluded that isorutearine, a coumarin analogue, has a good docking score (Table 1) [117]. Singh’s study used as DM targets the IR, AR and SIRT6 receptors. It showed that kaempferol had the lowest binding energy (kcal/mol) in interaction with AR, gossypetin in interaction with IR, and sorbifolin in interaction with the SIRT6 receptor (Table 1) [71]. Sathiyaseelan et al. evaluated the antidiabetic effect of phytochemicals from *Gynura procumbens* methanolic extract and its various solvent fractions on α-amylase and α-glucosidase receptors. They also predicted the interaction of the main compounds identified in *G. procumbens* extract with porcine pancreatic α-amylase and α-glucosidase, using a molecular docking approach (Table 1) [73].

*Stachys riederi* var. *japonica* solvent extract and fractions were analysed on induced T2DM mice. Saravanakumar et al. study also predicted the binding affinity of identified compounds from *Stachys riederi* var. *japonica* for α-amylase and α-glucosidase receptors using molecular docking (Table 1) [74]. Anti-diabetic effects of compounds identified from *Gardenia jaminoides* and *Helianthus tuberosus*, were also predicted using molecular docking (Table 1) [76,108].

The hypoglycaemic activity of insulin-like peptides from *Momordica charantia* was determined using a molecular docking approach. The study investigated the activity of several peptides such as LIVA, EKAI, EALF, DFGAS and EPNGGG on four target proteins, namely the experimentally determined structures of IR, SGLT1, dipeptidyl peptidase-IV, and the predicted 3D structure of GLUT2 (Table 1) [59]. In the Sadiq et al. study, bioactive components in *Eryngium caeruleum* were discovered using GC-MS and HPLC-DAD investigations. Several molecular docking models were used to determine the binding energy of the reported molecule and compared with acarbose. All substances could inhibit the α-glucosidase receptor, according to the investigations (Table 1) [80].

Zabidi et al. identified the main compounds from *Curculigo latifolia* and, using molecular docking analyses, they predicted the binding affinity of those compounds for α-glucosidase, DPP-4 and IR (Table 1). They compared the results with the reference drugs for each target acarbose (−7.4 kcal/mol on α-glucosidase), sitagliptin (−8.8 kcal/mol on DPP-4), and insulin (−7.9 kcal/mol on IR) [81].

According to the observations of Abdel-Sattar et al., the root extract of *Limonium axillare* exhibits anti-diabetic properties such as raising insulin secretion, increasing GLUT2 and GLUT4 expression, and thereby increasing glucose absorption. The root extract’s
main ingredients may have a binding affinity for GPDH, according to molecular docking analyses (Table 1) [82].

Table 1. Target receptors, the natural compounds with the best docking results from each study, docking scores and software used for prediction.

| Target                          | Compounds         | Predicted Energy of Binding (kcal/mol) | Software Used | References |
|---------------------------------|-------------------|----------------------------------------|---------------|------------|
| AR (PDB: ID:1US0 [15])         | kaempferol        | −10.034                                | YASARA [125]  | [71]       |
|                                  | herbacetin        | −9.623                                 |               |            |
|                                  | sorbitol          | −9.391                                 |               |            |
| IR (PDB: ID:1IR3 [16])          | gossypetin        | −8.429                                 | YASARA [125]  | [71]       |
|                                  | herbacetin        | −8.165                                 |               |            |
|                                  | sorbitol          | −8.063                                 |               |            |
| SIRT6 (PDB ID: 3K35 [17])       | gossypetin        | −8.569                                 | YASARA [125]  | [71]       |
|                                  | herbacetin        | −8.533                                 |               |            |
|                                  | sorbitol          | −8.697                                 |               |            |
| α-glucosidase (PDB 2ZE0 [126])  | curcumin          | −153                                   | LigandFit implemented in DS 2.5 (DS, Accelrys Software, San Diego, CA, USA) | [67] |
|                                  | antroquinonol     | −180                                   |               |            |
|                                  | rutin             | −159                                   |               |            |
| α-amylase (PDB 1HNY [127])      | curcumin          | −175                                   | LigandFit implemented in DS 2.5 (DS, Accelrys Software, San Diego, CA, USA) | [67] |
|                                  | 16-hydroxy-cleroda-3,13-dione-16,15-olide | −155                   |               |            |
|                                  | docosanol         | −154                                   |               |            |
|                                  | berberine         | −142                                   |               |            |
|                                  | catechin          | −135                                   |               |            |
|                                  | quercetin         | −132                                   |               |            |
|                                  | rutin             | −126                                   |               |            |
| Lysosomal α-glucosidase (PDB ID: 5KZX [128]) | Isorutarine | −7.64 | Maestro 12.0 of Schrödinger LCC, New York, NY, USA | [117] |
|                                  | 2′-Isopropylysoralene | −6.64                  |               |            |
|                                  | 4-hydroxy d-C-III | −6.45                                  |               |            |
| porcine pancreatic α-amylase (PDB ID: 1OSE [129]) | Caffeoylquinic acid | −10.33   | Argus lab 4.0.1 [130] | [78] |
|                                  | O-Coumaroylquinic acid | −10.01         |               |            |
|                                  | Coumaroyl-Ohexoside | −9.75                             |               |            |
| α-glucosidase (PDB ID: 3A4A [131]) | Caffeoylquinic acid | −10.84   | Argus lab 4.0.1 [130] | [78] |
|                                  | O-Coumaroylquinic acid | −10.65     |               |            |
|                                  | Coumaroyl-Ohexoside | −10.60                  |               |            |
### Table 1. Cont.

| Target Compound | Target | Compound (PDB ID) | Binding Affinity (kcal/mol) | Software Used | References |
|-----------------|--------|-------------------|-----------------------------|---------------|------------|
| human pancreatic α-amylase (PDB ID: 5E0F [132]) | Ursolic acid | −9.8 | Autodock Vina 1.1.2 [133] | [74] |
| Rosmarinic acid | −8.5 |
| Oleanolic acid | −8.7 |
| Human lysosomal acid α-glucosidase (PDB: 5NN8 [134]) | Ursolic acid | −8.2 | | |
| Rosmarinic acid | −8.2 |
| Oleanolic acid | −8.5 |
| Human pancreatic α-amylase (PDB: 5E0F [132]) | Chlorogenic acid | −8.7 | | |
| Jasminoside A | −8.7 |
| Jasminoside F | −8.5 |
| Human lysosomal acid α-glucosidase (PDB: 5NN8 [134]) | Acarbose derived trisaccharide | −8.7 | | |
| Acarbose | −8.7 |
| Chlorogenic acid | −8.2 |
| Porcine pancreatic α-amylase (PDB ID: 1OSE [129]) | Cryptochlorogenic acid | −9.860 | ArgusLab 4.0.1 [130] | [108] |
| Feruloylquinic acid | −8.613 |
| Neochlorogenic acid | −7.452 |
| α-glucosidase (PDB ID: 3A4A [131]) | Caffeoylquinic acid | −10.737 | | |
| Neochlorogenic acid | −10.732 |
| Cryptochlorogenic acid | −10.632 |

| Target Compound | Target | Compound (PDB ID) | Docking Score (kcal/mol) | Software Used | References |
|-----------------|--------|-------------------|--------------------------|---------------|------------|
| AR (PDB ID: 3J5E [135]) | Casticin | −8.452 | MOE, Chemical Computing Group, Monreal, Canada | [79] |
| Glucokinase (PDB ID: 4IXC [137]) | Negundoside | −7.923 | | |
| PDK2 (PDB ID: 4MP2 [138]) | Herbacetin rhamnoside | −7.369 | | |
| PPARγ (PDB ID: 3DZY [139]) | 4Z,12Z-cyclopentadeca-4,12-dienone | −7.57 | GLIDE 5.0 of Schrödinger LCC, New York, NY, USA [136] | [109] |
| Csk-3 (PDB ID: 3F7Z [140]) | | −6.01 | | |
| 11β-HSD1 (PDB ID: 4K1L [141]) | | −7.85 | | |
| GFPT1 (PDB ID: 2ZJ4 [142]) | | −5.57 | | |

| Target Compound | Target | Docking Score (kcal/mol) | Software Used | References |
|-----------------|--------|--------------------------|---------------|------------|
| α-glucosidase (predicted 3D structure) | Casticin | −8.452 | MOE, Chemical Computing Group, Monreal, Canada | [79] |
| Glucokinase | Negundoside | −7.923 | | |
| Herbacetin rhamnoside | −7.369 | | | |
| Target | Compound | S-Score | Software Used | References |
|--------|----------|---------|---------------|------------|
| IR (PDB: ID:1IR3 [16]) | KDDGHL | −18.56 | MOE, Chemical Computing Group, Monreal, Canada [59] |
| | EPGGGG | −16.71 | |
| | TSEP | −15.66 | |
| SGLT1 (PDB: ID: 3DH4 [143]) | ESIRD | −23.81 | |
| | DSRHR | −23.64 | |
| | RRKKV | −20.64 | |
| Dipeptidyl peptidase-IV (DPP (IV))(PDB ID: 4A5S [144]) | PTRHM | −10.1067 | |
| | RRKKV | −9.9189 | |
| | KDDGHL | −9.4991 | |
| GLUT2 (predicted 3D structure) | RSIHEP | −10.5171 | |
| | ERFDSG | −9.6986 | |

| Target | Compound | Binding Energy (kcal/mol) | Software Used | References |
|--------|----------|--------------------------|---------------|------------|
| α-glucosidase (predicted 3D structure) | tocopherol | −7.7008 | MOE, Chemical Computing Group, Monreal, Canada [80] |
| | linoleic acid | −7.1746 | |
| | phytol | −7.0629 | |

| Target | Compound | Binding Affinity (kcal/mol) | Software Used | References |
|--------|----------|----------------------------|---------------|------------|
| α-glucosidase (PDB ID: 4J5T [145]) | phlorizin | −8.2 | |
| | scandenin | −8.0 | |
| | pomiferin | −8.0 | |
| DPP-4 (PDB ID: 2P8S [146]) | phlorizin | −10.9 | AutoDock [133] [81] |
| | pomiferin | −9.6 | |
| | mundulone and scandenin | −9.3 | |
| IR (PDB: ID:1IR3 [16]) | phlorizin | −7.0 | |
| | mundulone | −6.9 | |
| | pomiferin | −6.6 | |

| Target | Compound | Docking Score (kcal/mol) | Software Used | References |
|--------|----------|--------------------------|---------------|------------|
| GPDH (PDB ID: 1WPQ [147]) | 2′,4′ dihydroxychalcone | −6.2652 | MOE, Chemical Computing Group, Monreal, Canada [82] |
| | compound 4 | −5.7992 | |
| | compound 3 | −5.6075 | |

Arif et al. [59] also evaluated the complex binding energies of peptides to selected targets by applying the molecular mechanics generalized born surface area (MM-GBSA) method on 50 ns trajectories obtained by MD simulations of LIVA-IR and DFGAS-SGLT1 complexes. MD simulations revealed the stability of complexes, and calculated binding energies showed significantly favourable interactions between ligands and targets. The ligands appear to be stabilized at the binding sites by van der Waals energy, the nonpolar energy term being the most important for complex formation [59].

An extensive screening study performed on a library of 257 compounds from medicinal plants with antidiabetic activity identified 79 potential inhibitors of α-amylase [148]. Six phytochemicals (shahidine, epicatechin, quercetin, isocolumbin, ellagic acid, lutolin) were selected by re-scoring, ADMET and drug-likeness analysis. MD simulations (30 ns long simulations) confirmed the stability of complexes formed by α-amylase (PDB ID: 3BAJ [149]) and these compounds, supporting their potential to inhibit the enzyme [148].
The inhibition of α-glucosidase by natural compounds from spices such as fenugreek, black pepper, ginger and turmeric was investigated in conjunction with their agonistic activity on PPARγ [150]. Curcumin, pipernonaline, 6-gingerol and trigonelline were docked at α-glucosidase (PDB ID: 5NN8 [134]) and PPARγ (PDB ID: 4A4V [151]) binding sites, and replica exchange MD simulations were performed to characterize the dynamical behaviour of complexes [150]. Results showed that curcumin and pipernonaline formed stable complexes with the two proteins, which supports the beneficial effects of the compounds in diabetes [150].

Salaudden et al. [152] tested 10 natural compounds with proved antidiabetic activity against SGLT1 and SGLT2 using molecular docking and filtered them by ADMET, drug-likeness and lead-likeness analysis. The most promising compound was sophoraflavone G, which was also proved to form stable complexes with SGLT2 using MD simulations [152]. Since the crystal structures of SGLT1 and 2 are unknown, the authors performed all calculations using homology models [152].

Other DM targets and their modulation by natural compounds from Piper longum Linn. were addressed by Thakurla et al. [153]. The targets they investigated were: 11β-HSD1 (PDB ID: 1XU7 [154]); GFPT1 (PDB ID: 2V4M [155]); PTP1B (PDB ID: 3SME [156]); DPP-4 (PDB ID: 1J2E [157]); and GKR (PDB ID: 4BBA [158]). The bioactive compounds that were analysed were retrofractamide A, piperine, piperlongumine, and piperlonguminine, all drug-like compounds. The molecular docking of compounds at selected proteins led to good results, with piperine being the most promising compound [153].

Vo et al. [159] investigated the modulation of 11β-HSD1, GFPT1, PTP1B and SIRT6 by 20 bioactive compounds from Euphorbia thymifolia Linn. Molecular docking of compounds at their possible targets allowed the identification of seven compounds able to bind all targets, namely: β-amyrin, teraxerol, 1-O-galloyl-β-D-glucose, corilagin, cosminosin, queretin-3-galactoside and queretin [159].

The ability of shikonin, a natural naphthoquinone dying pigment, to inhibit PTP1B was evaluated through a complex approach involving in silico and in vitro methods [160]. Shikonin was docked at its putative binding site from 1AAX structure [161], which allowed the identification of crucial residues involved in the interaction. The ZINC Natural Product database was interrogated for compounds with pharmacophore features similar to those of shikonin, resulting in a library of 1860 compounds that were screened against PTP1B structure. Shikonin and the 100 best docked compounds were filtered based on their ADMET and drug-likeness properties, which led to the identification of four additional possible ligands: ZINC31168041, ZINC31168045, ZINC31168041 and ZINC31168554. These compounds were also docked at PTP1B active sites, and ZINC31168045 presented the highest docking score [160]. MD simulations also suggest that shikonin could be a lead molecule for inhibiting PTP1B. The powerful inhibition of PTP1B by shikonin was determined experimentally (IC50 = 8.72 M), confirming the antidiabetic effects of the shikonin scaffold [160].

Flavones are good candidates to inhibit HDAC1 and HDAC2. The docking of vorinostat (a known inhibitor of the two enzymes), flavone, apigenin and luteolin to HDAC1 and HDAC2 structures was performed at a vorinostat binding site revealed by X-ray crystallography (PDB ID: 4LXZ [162]) [163]. Their results show that flavone, apigenin and luteolin can occupy vorinostat binding sites and can interact with enzymes with energies similar to vorinostat. Such data support the idea that dietary flavones can be used for epigenetic therapy [163].

7. Anti-Diabetic Synthetic Compounds and Their Molecular Target Effects on BBB

DM is a disorder that can lead to BBB disruption and cognitive decline. Ischemic stroke, atherosclerosis, vascular cardiac consequences, hemodynamic abnormalities, cognitive deficits, neurochemical, electrophysiological and behavioural alterations are all linked to hyperglycaemia and insulin resistance [164,165]. BBB disruption and inflammation are significant elements in diabetic stroke that lead to a poor outcome. Microcapillary integrity
and oxidative stress may play a role in the overexpression and activation of the receptor for advanced glycation end products (RAGE). T2DM and Alzheimer’s disease (or “type 3 diabetes”) are linked because type I membrane protein carries amyloid-beta across the BBB [165]. Matrix metalloproteinases (MMP) are known to exacerbate white matter damage and are linked to BBB disruption [166]. During induced epileptic episodes, the permeability of the BBB is affected in T1DM. BBB permeability increased significantly in seizures under diabetic circumstances, and BBB damage increased during epileptic seizures [167].

Glucose transporter 1 (GLUT1) and glucose transporter 3 (GLUT3) are the most important glucose transporters across the BBB [168]. According to Prasad et al., the mRNA and protein expression of GLUT1 and GLUT3 are down-regulated in hyperglycaemia and increased in hypoglycaemia [165]. According to Duelli and Kuschinsky, the GLUT1 receptor level decreased by 8% after 3 weeks of hyperglycaemia, while GLUT3 transporter levels stayed constant [168]. GLUTs 1, 3, and 4 were dramatically reduced in the brains of untreated diabetic mice by 61, 69, and 64%, respectively [169]. The blockage of GLUT1 expressed in autoreactive T cells could limit the destruction of pancreatic β cells in T1DM. As promising as such a pharmaceutical approach could be, it could interfere with GLUT1 activity in BBB, leading to neurological symptoms. An effective therapeutic approach against T1DM autoimmunity with less off-target side effects should be limited in time, taking into account the age of patients and the characteristics of their T cell response [170]. Several GLUT1 inhibitors have been developed over the years for cancer treatment [171]. Cytochalasin B is a mycotoxin that blocks GLUT1 [172]. By solving the crystal structure of GLUT1 in complex with cytochalasin B, Kapoor et al. [173] described the interactions between the ligand and the receptor, opening the possibility to develop even more specific and effective inhibitors. The structure of the complex is presented in Figure 2a.

GLUT3 is similar in structure to GLUT1, but with different physiological roles and transport affinity [174]. GLUT3 was associated with cell invasion and cancer metastasis, being an attractive anti-cancer drug target, especially in brain cancers such as glioblastoma [175]. The structure of GLUT3 with a D-glucose molecule bound in its binding site is presented in Figure 2b.

The matrix metalloproteinase enzymes may have a role in BBB breakdown due to their systemic activation during diabetic ketoacidosis [177]. The findings of Hoffman et al. [177] indicated that the matrix metalloproteinase 9 (MMP-9) is expressed in the fatal brain oedema of diabetic ketoacidosis patients as well as on cells from brain intravascular regions. MMP-9 is present on neurons in the hippocampus areas of both brain oedema and diabetic ketoacidosis patients. At the same time, the Tissue Inhibitor of Metalloproteinases 1 (TIMP1) expression in the locations is reduced [177]. The authors suggested that further studies are necessary to determine the role of MMP-9 in the pathogenesis of the neurologic
catastrophe of brain oedema in diabetic ketoacidosis. Inhibition of MMP-9 expression might help preserve neuronal function and BBB integrity during diabetic ketoacidosis [177].

The understanding of drug delivery across the BBB should also consider the structure and selectivity of tight junction proteins. Claudin-5 from tight junctions (Figure 3) forms pores that mediate the paracellular permeability of molecules smaller than 800 Da [178]. Molecular modelling and simulation studies on the subject are extensively reviewed in [178]. Such an approach can lead to the identification of compounds that modulate properties of tight junctions such as specificity, pore size or permeability [178].

Collagen IV, a key component of BBB, can be degraded by MMP-9. During central nervous system inflammation, MMP expression, particularly MMP-9, is linked to BBB breakdown. Propofol (Table 2) is a sedative drug that reduces MMP-9 expression in human cerebral microvascular endothelial cells triggered by inflammatory factor TNF. Propofol can restore BBB integrity that has been harmed by TNF, and it also reduces TNF’s inhibitory action on collagen IV [179].

T2DM is a significant predictor of perioperative neurocognitive disorder. However, the mechanism of action is still understudied. Zhang et al. [180] investigated the treatment with TAK-242 (Table 2) on adult male db/db and db/m mice (a mouse model of type 2 diabetes mellitus) on tibial fracture surgery-induced hippocampal BBB damage. TAK-242 is a selective inhibitor of Toll-like receptor 4 (TLR4) [180]. This receptor promotes lipopolysaccharide-induced microglial activation and inflammatory cytokine levels in high glucose conditions. The study found that TLR4-mediated hippocampal inflammatory cytokine release, MMP/TIMP axis imbalance, and BBB rupture were improved by TLR4 inhibition [180].

![Figure 3. Three-dimensional structures of some proteins associated with BBB breakdown, namely matrix metalloproteinase-9 (MMP-9) and Toll-like receptor 4 (TLR4), or with BBB proper function, namely claudin-5. In (a) we represented MMP9 according to the 3D structure 1L6J [181]. In (b) we represented TLR4 according to 3FX1 structure [182], and in (c) we represented the structural model of claudin-5 generated using the machine learning approach AlphaFold [183] that we retrieved from AlphaFold Protein Structure Database [184]. In the case of claudin-5, we used a black circle to show the location of a permeation pore defined by two claudin-5 dimers located in the membranes of adjacent endothelial cells [185,186].](image-url)

Haemorrhagic transformation is a neurological disease that worsens as a result of an ischecmic stroke. Although the chemical mechanism is unclear, studies show that Bradykinin 1 receptor (B1R) causes vascular toxicity. In a rat model of cerebral ischemia/reperfusion with type 1 diabetes, Sang et al. [187] investigated B1R expression in brain tissues [187]. According to the study findings, B1R-specific antagonists reduced haemorrhage volume and BBB disruption in diabetic patients in a dose-dependent manner, and the specific
agonists increased it. Through ERK signalling, B1R was involved in ischemia-related bleeding and BBB degradation in diabetic rats. B1R-activated ERK1/2 stimulated NF-B activation, resulting in MMP-9 production and tight junction associated protein degradation. U0126 (1,4-Diamino-2,3-dicyano-1,4-bis(o-aminophenylmercapto)butadiene) and pyrrolidine dithiocarbamate (Table 2), both of which were tested, showed encouraging results. B1R-induced NF-B/p65 activation was decreased by U0126, an ERK inhibitor. In addition, following a stroke, this chemical restores BBB function. Pyrrolidine dithiocarbamate is an NF-B selective inhibitor that reduces the levels of MMP-9 mRNA and protein in haemorrhagic tissues [187].

APX3330 (Table 2) is a specific APE1/Ref-1 redox activity inhibitor that exhibits therapeutic benefits in T1DM stroke rats. In a study conducted by Yan et al. [166], rats with T1DM were given a temporary middle cerebral artery blockage; they were then treated with PBS or APX3330, and their BBB permeability was measured. According to the findings, APX3330 therapy for stroke in T1DM rats improved neurological functional outcome, BBB integrity, total vascular density, and other factors. Moreover, in cultured primary cortical neurons exposed to high glucose and oxygen-glucose deprivation, APX3330 therapy substantially reduced cell mortality and MMP-9 gene expression [166].

Soluble epoxide hydrolase (sEH), an enzyme that degrades epoxyeicosatrienoic acids (EETs), has various beneficial effects on vascular structure and function. According to Wu et al. [188] enhanced BBB vascular permeability was accompanied by overexpression of sEH and downregulation of 14,15-EET. The study concluded that decreased EET degradation caused by sEH inhibition might be a therapeutic strategy for slowing the course of BBB damage in diabetic mice through activation of the AMPK/HO-1 pathway [188].

The chemical structures of the previously reported compounds are shown in Table 2. Furthermore, we determined the BBB permeability of compounds. The logarithmic ratio of brain to plasma concentration of the drug (log BBB) was predicted by pkCSM, whereas the probability of the molecule passing through the BBB (BBB probability) was predicted by admetSAR 2.0 [189,190].

Table 2. Compound name, SMILES code, chemical 2D structure, pkCSM [189] (sourced from pkCSM-parmacokinetics server [191]) and admetSAR2.0 [190] (sourced from admetSAR web server [192]) predictions. Molecules with a logBB > 0.3 are believed to cross the BBB, whereas molecules with a logBB-1 are poorly dispersed to the brain, according to pkCSM. admetSAR2.0 estimates a probability, with 1 indicating that the molecules cross the BBB and 0 indicating that they do not.

| Compound | pkCSM Numeric (log BBB) | admetSAR 2.0 BBP Probability | SMILES | Structure |
|----------|-------------------------|-----------------------------|--------|-----------|
| propofol | 0.497                   | +(0.99)                      | CC(C)C1=C(C(=CC=C1)C(C)C)O | ![Structure](image1) |
| TAK-242  | −0.715                  | +(0.97)                      | CCOC(=O)C1=CCCCC1S(=O)(=O)NC2=CC(C=C2)FCl | ![Structure](image2) |
| U0126    | −0.967                  | +(0.97)                      | C1=CC=C(C(=C1)N)SC=C(C#N)C=C(N)SC2=CC=CC=C2N)C#N)N | ![Structure](image3) |
8. Natural Compounds That Prevent BBB Dysfunction in Diabetic Patients

Many neurological disorders have been found to be alleviated by natural compounds such as flavonoids, which modulate the signalling transduction cascades involved with BBB breakdown [193]. Understanding the actions of natural products through the molecular processes linked to BBB degradation in DM may pave the way for the discovery and development of new medicines to prevent the BBB breakdown.

In a quest for compounds able to preserve BBB integrity and proper function, Mamo et al. identified probucol as a promising compound [194]. The compound was effective in an insulin-resistant mice model obtained by administering a high fat, high fructose diet for 6 months. The mice presented a significantly increased BBB permeability relative to control. The mice demonstrated a significantly increased BBB permeability relative to control due to the decrease in endothelial tight junction proteins (occludin-1 and zonula occludens (ZO)-1) expression. Probucol presented peripheral anti-inflammatory effects, reduced the levels of cholesterol supplied to BBB endothelial cells, and prevented the extravasation of IgG from blood to brain by restoring the levels of occluding-1 and ZO-1 [194].

Natural compounds can also present protective effects on the BBB under diabetic conditions; for example, resveratrol reduces BBB permeability [195] and berberine or patchouli alcohol reduce vascular damage [195]. Many other natural compounds that prevent BBB breakdown are summarized in [193]. The compounds belong to classes of alkaloids (berberine, caffeine), lipids (α-lipolic acid), phthalides (z-ligustilide), flavonoids (baicalin, genistein, pinocembrin, quercetin), phenols (caffeic acid phenethyl ester, curcumin, curcuniligoside A, forsythoside B, resveratrol, sesamol) or terpenes (6-O-acetyl shanzhides methyl ester, astragaloside IV, ginkgolide B, ginsenoside Rb1, oleanolic acid, tanshinone IIA) and exhibit their BBB protective effects by modulating different transcription factors or signalling transduction cascades [193]. We should highlight that some of these compounds, such as curcumin, quercetin and berberine, also modulate molecular targets of diabetes, showing their multiple beneficial effects in DM.

Kam et al. [193] also reviewed some structure–activity relationship (SAR) studies conducted on flavonoids [193]. For instance, the number of hydroxyl groups in the B-ring of 4-oxo-flavonoids correlates with their cytoprotective activity and their inhibitory activity on the expression of ICAM-1, an adhesion molecule involved in leukocyte recruitment [196].

Idebenone was used in combination with insulin to decrease BBB permeability in streptozotocin-induced diabetic rats [197]. The two molecules presented a synergistic effect in closing the tight junctions, upregulating the expression of occludin, claudin-5 and ZO-1, decreasing the levels of reactive oxygen species, and decreasing the levels of receptors for advanced end glycation products and for nuclear factor-kB [197].

Quercetin is a polyphenol that can limit high BBB permeability. Polyphenols decrease the adhesion of monocytes caused by hyperglycaemia to the level of brain endothelial cells [198]. Studies in animal models have shown how catechin metabolites are distributed...
in tissues, managing to cross the BBB [199]. This phenomenon was observed by measuring tissue permeability, thus showing the neuroprotective effect that can cause neurogenesis [200]. Quercitin resulted in a pK value (calculated using 1/Ki) of 7.62 ± 0.13 [201]. This natural compound is an inhibitor of GLUT-mediated glucose transport as well as a permeant ligand via GLUT [202]. Quercetin in the diet prevented diabetic mice from losing 59 percent and 63 percent of their GLUT 1 and GLUT 3 levels, respectively [169].

Prediction of isorutarine’s molecular properties showed that it cannot cross the BBB. However, its metabolites and various molecules resulting in its cleavage could cross the barrier and have a beneficial effect in the treatment of diabetes [117,203].

The natural compound kaempferol could present protective and preventive effects in diabetic complications [203,204]. Azevedo et al. showed that in the case of breast cancer cells, kaempferol inhibited glucose absorption via reducing GLUT1-mediated glucose uptake [205]. A study conducted by Martin et al. showed that kaempferol pK value calculated from absorbance was 7.30 ± 0.01, and a pK value calculated from 1/Ki was 7.51 ± 0.29 [201].

Curcumin decreased the transport activity of GLUT1 in a dose-dependent way by causing rapid reversible inhibition [206]. Curcumin may also help to prevent diabetes-related cerebral infarction, by inhibiting both the GLUT1 and GLUT3 transporters [207,208].

According to molecular docking research, rutin has a binding affinity (kcal/mol) of −13.101 on the GLUT1 transporter. This molecule forms a hydrogen bond with the backbone of GLUT1 through Thr137, Glu380, Asn415, Asn288 and Asn411 residues [209]. In human erythrocytes, rutin is a low-affinity inhibitor of glucose efflux via GLUT1 (Ki 0.1–0.3 mM) [202].

Berberine is a compound known to cross the BBB; this molecule modulates GLUT3 levels and has no effect on GLUT1 [169]. The activities involved in anti-inflammation and insulin resistance in the prefrontal cortex of diabetic rats were used to examine the influence of berberine on cognitive activity in diabetes. Berberine has the potential to boost GLUT3 expression and reverse the damage [210]. Even though some studies claim berberine has no impact on GLUT1, Cok’s research showed that berberine abruptly increases GLUT1 transport activity [211].

Catechins are also known to inhibit GLUT, especially GLUT1 [212,213]. In rats with type 1-like diabetes mellitus, Lee et al. found that ginseng extracts, gs-kg9 and gs-e3d, reduce BBB damage and thereby decrease apoptotic cell death of hippocampus neurons. The findings revealed that GS-KG9 and GS-E3D inhibited MMP-9 expression and activation, had dose-dependent anti-hyperglycemic action, and dramatically reduced BBB permeability and tight junction protein loss [214].

9. Databases and Web-Servers of Anti-Diabetic Compounds

Specific databases are a valuable tool in drug discovery, especially when it comes to in silico studies. We have identified three specific databases and web-servers of antidiabetic compounds.

Anti-Diabetic Natural Compounds Database (ADNCD) collects and categorizes natural compounds according to their anti-diabetic modes of action (e.g., Akt phosphorylation, improving glucose uptake, insulin mimetic activity, insulin sensitizers), providing a single platform with advantages for diabetes researchers. The database also contains information on the physicochemical characteristics (miLogP**, absorption percent, Lipinski’s violation, etc.), and toxicity (mutagenic and tumorigenic risk, reproductive and irritant effect) of anti-diabetic natural compounds [215].

DiaNat-DB is a database containing 336 compounds from plant species that show anti-diabetic action in vitro or in vivo. This database provides the SMILES of the compound, the activity, plant family and genera, the use, and the country/region. That information can help future analysis, design, and development of novel anti-diabetic medicines. DiaNat-DB is freely available from this link: http://rdu.iquimica.unam.mx/handle/20.500.12214/1186, accessed on 10 October 2021 [216].
Dia-DB is an open web server that uses two techniques to predict the probability of a molecule to be utilized as an anti-diabetic drug. The web server compares the results with a selected library of anti-diabetic medications and experimental molecules based on similarity. Additionally, based on user-selected input compounds, Dia-DB conducts an inverse virtual screening against a set of proteins considered relevant targets for anti-diabetic components, such as peroxisome proliferator-activated receptor delta, aldose reductase, insulin receptor precursor, glucokinase, etc. The web server can be accessed at: https://bio-hpc.ucam.edu/dia-db/, accessed on 10 October 2021 [217].

10. Blood Brain Barrier Permeability Prediction Web Services

We identified a number of free web services that can estimate whether or not a chemical would pass the BBB. Prof. Xiang-Qun developed the BBB Predictor of COMPUTATIONAL CHEMICAL GENOMICS SCREENING CENTER website. Using the support vector machine (SVM), LiCABEDS algorithms and four types of fingerprints (MACCS, Openbabel (FP2), Molprint 2D, and Pubchem) of 1593 reported chemicals, this web-service will predict if a molecule can pass the BBB (BBB+) or cannot pass the BBB (BBB-). The chemical structures can be either loaded or drawn using the JSME molecular editor [218].

SwissADME, affiliated with the Swiss Institute of Bioinformatics, predicts ADME parameters, pharmacokinetics, drug-likeness, and medicinal chemistry compatibility of small molecules. Using 156 BBB permeable and 104 non-permeable compounds, this web service predicts a passive-BBB permeability model using a BOILED-Egg model. The parameters used for this model are WLOGP versus topological polar surface area. This model has a Matthews correlation coefficient of 0.79 [219,220].

pkCSM is a web service that employs a new method built on graph-based signatures to estimate the pharmacokinetic characteristics of compounds. These are used to train prediction algorithms by encoding distance patterns between atoms. The ratio of brain to plasma drug concentration is represented by the BBB permeability, which is given as logBBB. The method incorporates 320 chemicals, each of which has had its BBB determined experimentally [189].

admetSAR 2.0 is a free model for estimating and optimizing a small molecule’s chemical ADMET features. This web service estimates BBB permeability using a binary predictive algorithm that includes 1830 molecules in its training set. The model has an area under the receiver operating characteristic curve of 0.944, an accuracy of 0.907, a sensitivity of 0.921, and a specificity of 0.861 [190].

An example of pkCSM and admetSAR [189,190] usage is presented in Table 2 where we reported predicted BBB permeabilities of antidiabetic compounds discussed in Section 7. Additionally, we used the same tools to predict the BBB permeability of gymnemic acids presented in Section 3. The results in Table 3 show that all chemicals may pass the BBB, except for gymnemic acid VI.

B3Pred web server predicts and designs effective BBB penetrating peptides (B3PPs). The technique relies on 269 experimentally confirmed B3PPs from the B3Pdb database. This program uses the FASTA format of the peptides and estimates whether a peptide will penetrate the BBB. The results show a prediction score and some peptide features: hydrophobicity, hydropathicity, hydrophilicity, charge, and Mol wt [221].

LightBBB is a predictor of BBB permeability based on a collection of 7162 molecules with known BBB permeability. LightBBB uses the light gradient boosting machine technique and has an overall accuracy of 89 per cent. The model uses the SMILES code or an .SMI file, and the output indicates if a compound is or is not BBB permeable [222].
Table 3. Predicted BBB permeability of gymnemic acids I-VII using pkCSM [189] (sourced from pkCSM-parmacokinetics web server [191]) and admetSAR2.0 [190] (sourced from admetSAR web server [192]). Their SMILES codes of the compounds are given as well.

| Compounds         | pkCSM | admetSAR 2.0 | SMILES                                                                 |
|-------------------|-------|-------------|------------------------------------------------------------------------|
| gymnemic acid I   | −1.517| +0.843      | CC=C(C)(=O)OC1C(C(C(C1(C)C)C3=CCC(C)(C5CC4(C3(C2O)O)C)C)C)OOC6C(C(C(C(O6)C(=O)O)O)O)O)C)COC(=O)C)O |
| gymnemic acid II  | −1.558| +0.91       | CCC(C)(=O)OC1C(C(C(C1(C)C)C3=CCC(C)(C5CC4(C3(C2O)O)C)C)C)OC6C(C(C(C(O6)C(=O)O)O)O)O)C)COC(=O)C)O |
| gymnemic acid III | −1.652| +0.91       | CCC(C)(=O)OC1C(C(C(C1(C)C)C3=CCC(C)(C5CC4(C3(C2O)O)C)C)C)OC6C(C(C(C(O6)C(=O)O)O)O)O)C)COC(=O)C)O |
| gymnemic acid IV  | −1.611| +0.84       | CC=C(C)(=O)OC1C(C(C(C1(C)C)C3=CCC(C)(C5CC4(C3(C2O)O)C)C)C)OC6C(C(C(C(O6)C(=O)O)O)O)O)C)COC(=O)C)O |
| gymnemic acid V   | −1.743| +0.84       | CC=C(C)(=O)OC1C(C(C(C1(C)C)C3=CCC(C)(C5CC4(C3(C2O)O)C)C)C)OC6C(C(C(C(O6)C(=O)O)O)O)O)C)COC(=O)C)O |
| gymnemic acid VI  | −2.346| −0.78       | CC=C(C)(=O)OC1C(C(C(C1(C)C)C3=CCC(C)(C5CC4(C3(C2O)O)C)C)C)OC6C(C(C(C(O6)C(=O)O)O)O)O)C)COC(=O)C)O |
| gymnemic acid VII | −1.259| +0.84       | CC1(C(=O)OC1C(C(C(C1(C)C)C3=CCC(C)(C5CC4(C3(C2O)O)C)C)C)OOC6C(C(C(C(O6)C(=O)O)O)O)O)C)COC(=O)C)O |
For a detailed perspective on the BBB permeability of candidate compounds, one could use MD simulations. Carpenter et al. performed reliable predictions of BBB permeability based on the potential of mean force calculations for candidate compounds through a lipid bilayer using MD simulations. The authors derived one-dimensional position-dependent diffusion coefficients based on MD trajectories. The effective permeability of a compound was determined based on its diffusion coefficient as corroborated with the free energy landscape. Their results were in good agreement with logBBB (blood-brain concentration ratio) and logPS (permeability surface-area product) of compounds [223]. A more recent study investigated the permeability of compounds by steered molecular dynamics simulations [224]. Using a simple lipid bilayer, Thai et al. [224] computed the non-equilibrium work required to pull a compound through the lipid membrane, leading to values in good correlation to logBBB or logPS. The method allows the usage of different membranes and brings insight on the energetic barriers and forces acting on the ligand when crossing the membrane [224].

11. Conclusions

T1DM and T2DM are metabolic disorders in which insulin secretion is reduced (T2DM) or no longer secreted due to pancreatic-cell death (T1DM). The diabetic condition alters BBB function and integrity, which further results in diabetes-related neurological complications. In the present review, we discussed research on natural and synthetic compounds that operate on therapeutic target proteins in DM and on the BBB. We approached three current research directions, namely the modulation of proteins involved in glucose metabolism or in insulin response, of proteins involved in the development and preservation of pancreatic β cells, and of proteins involved in BBB permeability preservation. The relevant druggable targets for each direction were identified, some of them being IR, SIRT6, AR, α-glucosidases, PPAR, SGLT, 11-HSD1, GFPT1, PTP1B, DPP-4, GKR, GLUT2, glycerol-3-phosphate, GSK-3, PDK2, glucokinase, and HDAC. In the case of all targets, we presented bioinformatics studies aiming to determine natural and synthetic compounds that could regulate their function. Different methods were taken into account, namely QSAR, molecular docking and molecular dynamics.

Only a few QSAR studies have investigated the effect of natural compounds on specific targets in diabetes such as α-glucosidase, GPR40, or AR receptors. According to the previously reported studies, andrographolide and flavone derivatives are active on the α-glucosidase target, while 3-aryl-3-ethoxypropanoic acid derivatives are GPR40 modulators.

The most popular protein targets approached by molecular docking studies are α-glucosidases and IR. Molecular docking studies predicted that natural compounds such as kaempferol, herbacetin, or herbacetin should present an enhanced affinity for receptors such as AR, IR, or SIRT6. Anthroquinonol and rutin presented good docking scores in interaction with the α-glucosidase receptor, while docosanol, tetracosanol, anthroquinonol and berberine presented good docking scores in interaction with α-amylase.

Molecular dynamics studies showed that (i) shahidine, epicatechin, quercetin, isocolumbin, ellagic acid, and lutolin should inhibit α-amylase; (ii) curcumin and pipernonaline should form stable complexes with PPARγ; (iii) β-amyrine, teraxerol, 1-O-galloyl-β-D-glucose, corilagin, cosmosin, quercetin-3-galactoside and quercetin should modulate 11β-HSD1, GFPT1, PTP1B and SIRT6; (iv) shikonin could inhibit PTP1B; (v) apigenin and luteolin target HDAC1 and HDAC2; (vi) sophoraflavone G should inhibit SGLT1 and SGLT2.

GLUT1, GLUT3, B1R, TLR4 or MMP-9 are relevant targets for preventing alterations of BBB permeability due to glycaemic variations in T1DM and T2DM patients. Numerous studies investigated compounds that could prevent BBB dysfunctions, some examples being propofol (synthetic compound) or berberine, genistein, quercetin, resveratrol or curcumin (natural compounds). The permeability of BBB can be modelled using different prediction servers such as SwissADME, pkCSM or admetSAR.
The findings of reviewed simulation studies are encouraging, indicating that analysed compounds have potent inhibitory effects on specific receptors in DM treatment. These compounds might also be employed in in vitro and in vivo investigations or in future in silico studies as “lead-like” structures. Databases of natural compounds with anti-diabetic activity (ADNCD and DiaNat-DB) and Dia-DB webserver (predicts the possibility of a molecule used as an anti-diabetic drug) are helpful tools that may be used to find new anti-diabetic medicines or natural compounds.

To summarize, natural substances may be a viable choice for T2DM management, as a therapy adjuvant, or to prevent diabetes-related dysfunctions; however, more studies are needed. Although insulin therapy is required for T1DM, natural or synthetic compounds such as propofol, APX3330, coumarin, quercetin, kaempferol, berberine, and others show promise in treating BBB damage caused by glucose swings, and therefore, should be investigated further.

Author Contributions: Conceptualization, S.A., A.M.U. and M.M.; writing—original draft preparation, A.M.U., A.D., G.G.P., A.A.B., C.M., M.M., S.A.; writing—review and editing, A.M.U. and M.M.; supervision, S.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Romanian National Authority for Scientific Research and Innovation, CNCS/CCCDI-UEFISCDI, projects PN-III-P2-2.1-PED-2019-4771, PN-III-P2-2.1-PED-2019-1264, PN-III-P2-2.1-PED-2019-5283, PN-III-P2-2.1-PED-2019-1471, PN-III-P4-ID-PCE-2020-0620, and Nucleu Programme, ctr. No. 16N/08.02.2019.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Katsarou, A.; Gudbjörnsdottir, S.; Rawshani, A.; Dabelea, D.; Bonifacio, E.; Anderson, B.J.; Jacobsen, L.M.; Schatz, D.A.; Lernmark, A. Type 1 Diabetes Mellitus. Nat. Rev. Dis. Primer 2017, 3. [CrossRef] [PubMed]
2. DeFronzo, R.A.; Ferrannini, E.; Groop, L.; Henry, R.R.; Herman, W.H.; Holst, J.J.; Hu, F.B.; Kahn, C.R.; Raz, I.; Shulman, G.I.; et al. Type 2 Diabetes Mellitus. Nat. Rev. Dis. Primer 2015, 1, 1–22. [CrossRef] [PubMed]
3. Fletcher, B.; Gulani, M.; Lamendola, C. Risk Factors for Type 2 Diabetes Mellitus. J. Cardiovasc. Nurs. 2002, 16, 17–23. [CrossRef] [PubMed]
4. Taylor, S.I.; Yazdi, Z.S.; Beitelshees, A.L. Pharmacological Treatment of Hyperglycemia in Type 2 Diabetes. J. Clin. Investig. 2021, 131. [CrossRef] [PubMed]
5. Quinn, L. Mechanisms in the Development of Type 2 Diabetes Mellitus. J. Cardiovasc. Nurs. 2002, 16, 1–16. [CrossRef] [PubMed]
6. Chronic Inflammation in Fat Plays a Crucial Role in the Development of Obesity-Related Insulin Resistance. Available online: https://pubmed.ncbi.nlm.nih.gov/14679177/ (accessed on 12 October 2021).
7. Geraldes, P.; King, G.L. Activation of Protein Kinase C Isoforms and Its Impact on Diabetic Complications. Circ. Res. 2010, 106, 1319–1331. [PubMed]
8. Yamagishi, S.; Imaizumi, T. Diabetic Vascular Complications: Pathophysiology, Biochemical Basis and Potential Therapeutic Strategy. Curr. Pharm. Des. 2005, 11, 2279–2299. [CrossRef]
9. Neurodegenerative Disorders Associated with Diabetes Mellitus. Available online: https://pubmed.ncbi.nlm.nih.gov/15175861/ (accessed on 12 October 2021).
10. American-Diabetes-Association. Standards of Medical Care in Diabetes. Diabetes Care 2020, 43, S1–S207.
11. Nishikawa, T.; Edelstein, D.; Du, X.L.; Yamagishi, S.I.; Matsumura, T.; Kaneda, Y.; Yorek, M.A.; Beebe, D.; Oates, P.J.; Hammes, H.P.; et al. Normalizing Mitochondrial Superoxide Production Blocks Three Pathways of Hyperglycaemic Damage. Nature 2000, 404, 787–790. [CrossRef]
12. Umpierrez, G.; Korytkowski, M. Diabetic Emergencies-Ketoacidosis, Hyperglycaemic Hyperosmolar State and Hypoglycaemia. Nat. Rev. Endocrinol. 2016, 12, 222–232. [CrossRef]
13. Huber, J.D. Diabetes, Cognitive Function, and the Blood-Brain Barrier. Curr. Pharm. Des. 2008, 14, 1594–1600. [CrossRef]
14. Borska, S.; Sopel, M.; Chmielewska, M.; Zabel, M.; Dziegiel, P. Quercetin as a Potential Modulator of P-Glycoprotein Expression and Function in Cells of Human Pancreatic Carcinoma Line Resistant to Daunorubicin. Molecules 2010, 15, 857–870. [CrossRef]
15. Hyperglycemia-Driven Neuroinflammation Compromises BBB Leading to Memory Loss in Both Diabetes Mellitus (DM) Type 1 and Type 2 Mouse Models. Available online: https://pubmed.ncbi.nlm.nih.gov/29974394/ (accessed on 12 October 2021).
16. Rom, S.; Heldt, N.A.; Gajghate, S.; Seliga, A.; Reichenbach, N.L.; Persidsky, Y. Hyperglycemia and Advanced Glycation End Products Disrupt BBB and Promote Occludin and Claudin-5 Protein Secretion on Extracellular Microvesicles. Sci. Rep. 2020, 10, 7274. [CrossRef]

17. Choudhury, H.; Pandey, M.; Hua, C.K.; Mun, C.S.; Jing, J.K.; Kong, L.; Ern, L.Y.; Ashraf, N.A.; Kit, S.W.; Yee, T.S.; et al. An Update on Natural Compounds in the Remedy of Diabetes Mellitus: A Systematic Review. J. Tradit. Complement. Med. 2017, 8, 361–376. [CrossRef] [PubMed]

18. Yeung, A.W.K.; Tzvetkov, N.T.; Durazzo, A.; Lucarini, M.; Souto, E.B.; Santini, A.; Gan, R.-Y.; Jozwik, A.; Grzybek, W.; Horbarczuk, J.O.; et al. Natural Products in Diabetes Research: Quantitative Literature Analysis. Nat. Prod. Res. 2020, 0, 1–15. [CrossRef] [PubMed]

19. Salim, B. Diabetes Mellitus and Its Treatment. Int. J. Diabetes Metab. 2005, 13, 111–134.

20. Bhaskar, V.; Goldfine, I.D.; Bedinger, D.H.; Lau, A.; Kuan, H.F.; Gross, L.M.; Handa, M.; Maddux, B.A.; Watson, S.R.; Zhu, S.; et al. A Fully Human, Allosteric Monoclonal Antibody That Activates the Insulin Receptor and Improves Glycemic Control. Diabetes 2012, 61, 1263–1271. [CrossRef]

21. Xiao, C.; Kim, H.-S.; Lahusen, T.; Wang, R.-H.; Xu, X.; Gavrilova, O.; Jou, W.; Gius, D.; Deng, C.-X. SIRT6 Deficiency Results in Severe Hypoglycemia by Enhancing Both Basal and Insulin-Stimulated Glucose Uptake in Mice. J. Biol. Chem. 2010, 285, 36776–36784. [CrossRef]

22. Mostoslavsky, R.; Chua, K.F.; Lombard, D.B.; Pang, W.W.; Gellon, L.; Liu, P.; Mostoslavsky, G.; Franco, S.; Murphy, M.M.; et al. Genomic Instability and Aging-like Phenotype in the Absence of Mammalian SIRT6. Cell 2006, 124, 315–329. [CrossRef]

23. Tang, W.H.; Martin, K.A.; Hwa, J. Aldose Reductase, Oxidative Stress, and Diabetic Mellitus. Front. Pharmacol. 2012, 3. [CrossRef]

24. Lebovitz, H.E. ALPHA-GLUCOSIDASE INHIBITORS. Drugs 2020, 80, 504–517. [CrossRef] [PubMed]

25. Lebovitz, H.E. ALPHA-GLUCOSIDASE INHIBITORS. Endocrinol. Metab. Clin. N. Am. 1997, 26, 539–551. [CrossRef]

26. Tundis, R.; Loizzo, M.R.; Menichini, F. Natural Products as Histone Deacetylase (HDAC) Inhibition as a Novel Treatment for Diabetes Mellitus. Mol. Med. 2010, 16, 315–331. [CrossRef]

27. Monsalve, F.A.; Pyarasani, R.D.; Delgado-Lopez, F.; Moore-Carrasco, R. Peroxisome Proliferator-Activated Receptor Targets for Inhibition of Carbohydrate Hydrolysis Enzymes with Emphasis on Pancreatic Alpha Amylase. Expert Opin. Ther. Targets 2012, 16, 269–297. [CrossRef]

28. Mostoslavsky, R.; Chua, K.F.; Lombard, D.B.; Pang, W.W.; Fischer, M.R.; Gellon, L.; Liu, P.; Mostoslavsky, G.; Franco, S.; Murphy, M.M.; et al. Genomic Instability and Aging-like Phenotype in the Absence of Mammalian SIRT6. Cell 2006, 124, 315–329. [CrossRef]

29. Khang, J.; Chen, L.; Tang, Q.; Zhang, J.; Li, Y.; He, J. The Role of Sirt6 in Obesity and Diabetes. Front. Physiol. 2018, 9, 135. [CrossRef] [PubMed]

30. Wang, W.H.; Martin, K.A.; Hwa, J. Aldose Reductase, Oxidative Stress, and Diabetic Mellitus. Front. Pharmacol. 2012, 3. [CrossRef]

31. Tundis, R.; Loizzo, M.R.; Menichini, F. Natural Products as α-Amylase and α-Glucosidase Inhibitors and Their Hypoglycaemic Potential in the Treatment of Diabetes: An Update. Mini-Rev. Med. Chem. 2010, 10, 315–331. [CrossRef]

32. Monsalve, F.A.; Pyarasani, R.D.; Delgado-Lopez, F.; Moore-Carrasco, R. Peroxisome Proliferator-Activated Receptor Targets for the Treatment of Metabolic Diseases. Mediators Inflamm. 2013, 2013, 1–18. [CrossRef] [PubMed]

33. Harada, N.; Inagaki, N. Role of Sodium-Glucose Transporters in Glucose Uptake of the Intestine and Kidney. J. Diabetes Investig. 2012, 3, 352–353. [CrossRef]

34. Kitamura, K.; Hayashi, K.; Ito, S.; Hoshina, Y.; Sakai, M.; Yoshino, K.; Endo, K.; Fujitani, S.; Suzuki, T. Effects of SGLT2 Inhibitors on EGR in Type 2 Diabetic Patients—the Role of Antidiabetic and Antihypertensive Medications. Hypertens. Res. 2021, 44, 508–517. [CrossRef] [PubMed]

35. Shukla, R.; Basu, A.K.; Mandal, B.; Mukhopadhayay, P.; Maity, A.; Chakraborty, S.; Devrbahai, P.K. 11β Hydroxysteroid Dehydrogenase – 1 Activity in Type 2 Diabetes Mellitus: A Comparative Study. BMC Endcr. Disord. 2019, 19, 15. [CrossRef]

36. Elbein, S.C.; Zheng, H.; Jia, Y.; Chu, W.; Cooper, J.J.; Hale, T.; Zhang, Z. Molecular Screening of the Human Glutamine–Fructose-6-Phosphate Amidotransferase 1 (GFPT1) Gene and Association Studies with Diabetes and Diabetic Nephropathy. Mol. Genet. Metab. 2004, 82, 321–328. [CrossRef]

37. Rocha, S.; Lucas, M.; Silva, V.L.M.; Gomes, P.M.O.; Silva, A.S.M.; Araújo, A.N.; Aniceto, N.; Guedes, R.C.; Corvo, M.L.; Fernandes, E.; et al. Pyrazoles as Novel Protein Tyrosine Phosphatase 1B (PTP1B) Inhibitors: An in Vitro and in Silico Study. Int. J. Biol. Macromol. 2021, 181, 1117–1182. [CrossRef]

38. Giugliano, D.; Sportiello, L.; Capuano, A.; Maiorino, M.; Rossi, F.; Esposito, K. Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes Therapy – Focus on Alogliptin. Drug Des. Desv. Ther. 2013, 7, 989. [CrossRef] [PubMed]

39. Abuhmad, A.; Taha, M.O. QSAR Studies in the Discovery of Novel Type-II Diabetic Therapies. Expert Opin. Drug Discov. 2016, 11, 197–214. [CrossRef] [PubMed]

40. Lloyd, D.J.; St Jean, D.J.; Kurzeja, R.J.M.; Wahl, R.C.; Michelsen, K.; Cupples, R.; Chen, M.; Wu, J.; Sivits, G.; Helmering, J.; et al. Antidiabetic Effects of Glucokinase Regulatory Protein Small-Molecule Disruptors. Nature 2013, 504, 437–440. [CrossRef] [PubMed]

41. Toulis, K.A.; Nirantharakumar, K.; Pourzitaki, C.; Barnett, A.H.; Tahani, A.A. Glucokinase Activators for Type 2 Diabetes: Challenges and Future Developments. Drugs 2020, 80, 467–475. [CrossRef] [PubMed]

42. Luna-Vital, D.A.; Gonzalez de Mejia, E. Anthocyanins from Purple Corn Activate Free Fatty Acid-Receptor 1 and Glucokinase Enhancing in Vitro Insulin Secretion and Hepatic Glucose Uptake. PLOS ONE 2018, 13, e0200449. [CrossRef]

43. Xu, J.; Lin, S.; Myers, R.W.; Trujillo, M.E.; Pachanski, M.J.; Malkani, S.; Chen, H.-S.; Chen, Z.; Campbell, B.; Eiermann, G.J.; et al. Discovery of Orally Active Hepatoselective Glucokinase Activators for Treatment of Type II Diabetes Mellitus. Bioorg. Med. Chem. Lett. 2017, 27, 2063–2068. [CrossRef] [PubMed]

44. Christensen, D.P.; Dahlöf, M.; Lundh, M.; Rasmussen, D.N.; Nielsen, M.D.; Billestrup, N.; Grunnet, L.G.; Mandrup-Poulsen, T. Histone Deacetylase (HDAC) Inhibition as a Novel Treatment for Diabetes Mellitus. Mol. Med. 2017, 11, 378–390. [CrossRef]
86. Nishiyama, T.; Mae, T.; Kishida, H.; Tsukagawa, M.; Mimaki, Y.; Kuroda, M.; Sashida, Y.; Takahashi, K.; Kawada, T.; Nakagawa, K.; et al. Curcuminoids and Sesquiterpenoids in Turmeric (Curcuma Longa L.) Suppress an Increase in Blood Glucose Level in Type 2 Diabetes Mellitus Targets. J. Ethnopharmacol. 2021, 103072. [CrossRef] [PubMed]

87. Abdul-Sattar, E.; Shams, M.M.; Abd-Rabo, M.M.; Mahmoud, N.; Mahrous, E.A. Chemical and biological investigations of Limonium axillare reveal mechanistic evidence for its antidiabetic activity. Bioinformation 2019, 15, 179–188. [CrossRef]

88. Sadiq, A.; Rashid, U.; Ahmad, S.; Zahoor, M.; AlAjmi, M.F.; Ullah, R.; Noman, O.M.; Ullah, F.; Ayaz, M.; Khan, I.; et al. Treating Type 2 Diabetic KK-Ay Mice. J. Agric. Food Chem. 2019, 67, 52. [CrossRef] [PubMed]

89. Zabidi, N.A.; Ishak, N.A.; Hamid, M.; Ashari, S.E.; Mohammad Latif, M.A. Inhibitory Evaluation of Curculigo Latifolia on α-Glucosidase, DPP (IV) and in Vitro Studies in Antidiabetic with Molecular Docking Relevance to Type 2 Diabetes Mellitus. Molecules 2019, 11, 1837. [CrossRef]

90. Ryaphan, J.; Jhong, C.-H.; Lin, S.-R.; Chang, C.-H.; Tsai, M.-J.; Lee, D.-N.; Sung, P.-J.; Leong, M.K.; Weng, C.-F. Hypoglycemic Efficacy of Docking Selected Natural Compounds against α-Glucosidase and α-Amylase. Molecules 2018, 23, 2260. [CrossRef] [PubMed]

91. Kalesh Kumar, M.; Rajaram, R.; Gayathri, N.; Sivasudha, T.; Arun, G.; Archunan, G.; Gulyás, B.; Padmanabhan, P. Muscle Extract of Arothron Immaculatus Regulates the Blood Glucose Level and the Antioxidant System in High-Fat Diet and Streptozotocin Induced Diabetic Rats. Bioorganic Chem. 2019, 90, 103072. [CrossRef] [PubMed]

92. Geethangili, M.; Tzeng, Y.-M. Review of Pharmacological Effects of Antrodia Camphorata and Its Bioactive Compounds. Evid.-Based Complement. Altern. Med. 2011, 2011, 212641. [CrossRef]

93. Hsu, C.Y.; Sulake, R.S.; Huang, P.-K.; Shih, H.-Y.; Sie, H.-W.; Lai, Y.-K.; Chen, C.; Weng, C.F. Synthetic (+)-Antroquinonol Exhibits Dual Actions against Insulin Resistance by Triggering AMP Kinase and Inhibiting Dipeptidyl Peptidase IV Activities. Br. J. Pharmacol. 2015, 172, 38–49. [CrossRef]
117. Maurya, A.K.; Mulpuru, V.; Mishra, N. Discovery of Novel Coumarin Analogs against the α-Glucosidase Protein Target of Diabetes Mellitus: Pharmacophore-Based QSAR, Docking, and Molecular Dynamics Simulation Studies. ACS Omega 2020, 5, 32234–32249. [CrossRef]

118. Xu, J.; Huang, S.; Luo, H.; Li, G.; Bao, J.; Cai, S.; Wang, Y. QSAR Studies on Andrographolide Derivatives as α-Glucosidase Inhibitors. Int. J. Mol. Sci. 2010, 11, 880–895. [CrossRef]

119. Ghamali, M.; Chitita, S.; Hamamouchi, R.; Adad, A.; Bouachrine, M.; Lakhli, T. The Inhibitory Activity of Aldose Reductase of Flavanoid Compounds: Combining DFT and QSAR Calculations. J. Taibah Univ. Sci. 2016, 10, 534–542. [CrossRef]

120. Tozor, T.; Santos Costa, S.; Udrea, A.-M.; Nastasa, V.; Couto, I.; Viveiros, M.; Pascu, M.L.; Romanian, M.O. Anti-Staphylococcal Activity and Mode of Action of Thioridazine Photoproducts. Sci. Rep. 2020, 10, 18043. [CrossRef]

121. Udrea, A.-M.; Dinache, A.; Pagès, J.-M.; Pirvulescu, R.A. Quinazoline Derivatives Designed as Efflux Pump Inhibitors: Molecular Modeling and Spectroscopic Studies. Molecules 2021, 26, 2374. [CrossRef] [PubMed]

122. Udrea, A.-M.; Mernea, M.; Buiu, C.; Avram, S. Scutellaria Baicalensis Flavones as Potent Drugs against Acute Respiratory Injury during SARS-CoV-2 Infection: Structural Biology Approaches. Processes 2020, 8, 1468. [CrossRef]

123. Nistorescu, S.; Gradisteau Pircalabioru, G.; Udrea, A.-M.; Simon, A.; Pascu, M.L.; Chifiriuc, M.-C. Laser-Irradiated Chlorpromazine as a Potential Anti-Biofilm Agent for Coating of Biomedical Devices. Coatings 2020, 10, 1230. [CrossRef]

124. Udrea, A.-M.; Avram, S.; Nistorescu, S.; Pascu, M.-L.; Romanian, M.O. Laser Irradiated Phenothiazines: New Potential Treatment for COVID-19 Explored by Molecular Docking. J. Photochem. Photobiol. B 2020, 211, 111997. [CrossRef] [PubMed]

125. Krieger, E.; Fried, G. YASARA View—Molecular Graphics for All Devices—from Smartphones to Workstations. Bioinformatics 2014, 30, 2981–2982. [CrossRef]

126. Shirai, T.; Hung, V.S.; Morinaka, K.; Kobayashi, T.; Ito, S. Crystal Structure of GH13 α-Glucosidase GSJ from One of the Deepest Sea Bacteria. Proteins Struct. Funct. Bioinforma. 2008, 73, 126–133. [CrossRef]

127. Brayer, G.D.; Luo, Y.; Withers, S.G. The Structure of Human Pancreatic α-Amylase in Complex with Its Competitive Inhibitor Maltose: Crystal Structure of Isomaltase. J. Biol. Chem. 2004, 279, 1730–1742. [CrossRef] [PubMed]

128. Bank, R.P.D. RCSB PDB—5KZX: Crystal Structure of Human GAA. Available online: https://www.rcsb.org/structure/5KZX (accessed on 30 June 2021).

129. Gilles, C.; Asterl, J.-P.; Marchis-Mouren, G.; Cambillau, C.; Payan, F. Crystal Structure of Pig Pancreatic α-Amylase Isozyme II, in Complex with the Carbohydrate Inhibitor Acarbose. Eur. J. Biochem. 1996, 238, 561–569. [CrossRef]

130. Thompson, M.A. Molecular Docking Using ArgusLab, an Efficient Shape-Based Search Algorithm and the a Score Scoring Function. Philadelphia 2004, 172, 42.

131. Yamamoto, K.; Miyake, H.; Kusunoki, M.; Osaki, S. Crystal Structures of Isomaltase from Saccharomyces cerevisiae and in Complex with Its Competitive Inhibitor Maltose: Crystal Structure of Isomaltase. FEBS J. 2010, 277, 4205–4214. [CrossRef]

132. Bank, R.P.D. RCSB PDB—5E0F: Human Pancreatic α-Amylase in Complex with Mini-Montbretin A. Available online: https://www.rcsb.org/structure/5E0F (accessed on 2 November 2021).

133. Trotta, O.; Olson, A.J. AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization and Multithreading. J. Comput. Chem. 2010, 31, 455–461. [CrossRef]

134. Roig-Zamboni, V.; Cobucci-Ponzano, B.; Iacono, R.; Ferrara, M.C.; Germany, S.; Bourne, Y.; Parenti, G.; Moracci, M.; Sulzenbacher, G. Structure of Human Lysosomal Acid α-Glucosidase–a Guide for the Treatment of Pompe Disease. Nat. Commun. 2017, 8, 1111. [CrossRef]

135. Van Zandt, M.C.; Doan, B.; Sawicki, D.R.; Sredy, J.; Podjarny, A.D. Discovery of [3-(4,5,7-Trifluoro-Benzothiazol-2-Ylmethyl)-32234–32249. [CrossRef]

136. Tso, S.-C.; Qi, X.; Wu, C.-Y.; Chuang, J.L.; Wernstedt-Asterholm, I.; Morlock, L.K.; Owens, K.R.; Scherer, P.E.; Williams, N.S.; et al. Structure-Guided Development of Specific Pyruvate Dehydrogenase Kinase Inhibitors Targeting the ATP-Binding Pocket. J. Biol. Chem. 2014, 289, 4432–4443. [CrossRef] [PubMed]

137. Chandra, V.; Huang, P.; Hamuro, Y.; Raghuram, S.; Wang, Y.; Burris, T.P.; Rastinejad, F. Structure of the Intact PPAR-γ–RXR-α Nuclear Receptor Complex on DNA. Nature 2008, 456, 350–356. [CrossRef]

138. Saitoh, M.; Kunitomo, J.; Kimura, E.; Hayase, Y.; Kobayashi, H.; Uchiyama, N.; Kawamoto, T.; Tanaka, T.; Mol, C.D.; Dougan, D.R.; et al. Design, Synthesis and Structure–Activity Relationships of 1,3,4-Oxadiazole Derivatives as Novel Inhibitors of Glycogen Synthase Kinase-3β. Bioorg. Med. Chem. 2009, 17, 2017–2029. [CrossRef]

139. Böhme, T.; Engel, C.K.; Farjo, G.; Güssregen, S.; Haack, T.; Tschank, G.; Ritter, K. 1,1-Dioxo-5,6-Dihydro-[4,1,2]Oxathiazines, a Novel Class of 11ß-HSD1 Inhibitors for the Treatment of Diabetes. Bioorg. Med. Chem. Lett. 2013, 23, 4685–4691. [CrossRef]

140. Nakaiishi, Y.; Bando, M.; Shimizu, H.; Watanabe, K.; Goto, F.; Tsuge, H.; Kondo, K.; Komatsu, M. Structural Analysis of Human GlutamineFructose-6-Phosphate Amidotransferase, a Key Regulator in Type 2 Diabetes. FEBS Lett. 2009, 583, 163–167. [CrossRef] [PubMed]
Biomolecules 2021, 11, 1692

143. Faham, S.; Watanabe, A.; Besserer, G.M.; Cascio, D.; Specht, A.; Hirayama, B.A.; Wright, E.M.; Abramson, J. The Crystal Structure of a Sodium Galactoside Transporter Reveals Mechanistic Insights into Na + /Sugar Symport. Science 2008, 321, 810–814. [CrossRef] [PubMed]

144. Sutton, J.M.; Clark, D.E.; Dunsdon, S.J.; Fenton, G.; Fillmore, A.; Harris, N.V.; Higgs, C.; Hurley, C.A.; Krintel, S.L.; MacKenzie, R.E.; et al. Novel Heterocyclic DPP-4 Inhibitors for the Treatment of Type 2 Diabetes. Bioorg. Med. Chem. Lett. 2012, 22, 1464–1468. [CrossRef]

145. Barkera, M.K.; Rose, D.R. Specificity of Processing α-Glucosidase I Is Guided by the Substrate Conformation. J. Biol. Chem. 2013, 288, 13563–13574. [CrossRef]

146. Biftu, T.; Scapin, G.; Singh, S.; Feng, D.; Becker, J.W.; Eiermann, G.; He, H.; Lyons, K.; Patel, S.; Petrov, A.; et al. Rational Design of a Novel, Potent, and Orally Bioavailable Cyclohexylamine DPP-4 Inhibitor by Application of Molecular Modeling and X-Ray Crystallography of Sitagliptin. Biog. Med. Chem. Lett. 2007, 17, 3384–3387. [CrossRef]

147. Ou, X.; Ji, C.; Han, X.; Zhao, X.; Li, X.; Mao, Y.; Wong, L.L.; Bartlam, M.; Rao, Z. Crystal Structures of Human Glycerol 3-Phosphate Dehydrogenase 1 (GPD1). J. Mol. Biol. 2006, 357, 858–869. [CrossRef]

148. Sharma, P.; Joshi, T.; Joshi, T.; Chandra, S.; Tamta, S. Molecular Dynamics Simulation for Screening Phytochemicals as α-Amylase Inhibitors from Medicinal Plants. J. Biomol. Struct. Dyn. 2021, 39, 6524–6538. [CrossRef]

149. Maurit, R.; Begum, A.; Williams, L.K.; Fredriksen, J.R.; Zhang, R.; Withers, S.G.; Brayer, G.D. Alternative Catalytic Anions Differentially Modulate Human α-Amylase Activity and Specificity. Biochemistry 2008, 47, 3332–3344. [CrossRef]

150. Yadav, A.; Sharma, S.; Desk, S. Curcumin and Piperoninalone to Curb Diabetes the Natural Way: A Molecular Modeling, Docking and Dynamics Simulation Study. J. Comput. Chem. Mol. Model. 2020, 4. [CrossRef]

151. de Groot, J.C.; Weidner, C.; Krausz, J.; Kawamoto, K.; Schroeder, F.C.; Sauer, S.; Büsow, K. Structural Characterization of Amorfrutins Bound to the Proliferome Peroxisome-Activated Receptor γ. J. Med. Chem. 2013, 56, 1535–1543. [CrossRef] [PubMed]

152. Yadav, A.; Sharma, S.; Desk, S. Curcumin and Piperoninalone to Curb Diabetes the Natural Way: A Molecular Modeling, Docking and Dynamics Simulation Study. J. Comput. Chem. Mol. Model. 2020, 4. [CrossRef]

153. Thakuria, B.; Laskar, S.; Adhikari, S. A Bioinformatics-Based Investigation to Screen and Analyze the Bioactivity of Piper Longum. Pharmacogn. Mag. 2021, 17, 1417–1418. [CrossRef]

154. Hosfield, D.J.; Wu, Y.; Skene, R.J.; Hilgers, M.; Jennings, A.; Snell, G.P.; Aertgeerts, K. Conformational Flexibility in Crystal

155. Maurus, R.; Begum, A.; Williams, L.K.; Fredriksen, J.R.; Zhang, R.; Withers, S.G.; Brayer, G.D. Alternative Catalytic Anions Differentially Modulate Human α-Amylase Activity and Specificity. Biochemistry 2008, 47, 3332–3344. [CrossRef]

156. Sharma, P.; Joshi, T.; Joshi, T.; Chandra, S.; Tamta, S. Molecular Dynamics Simulation for Screening Phytochemicals as α-Amylase Inhibitors from Medicinal Plants. J. Biomol. Struct. Dyn. 2021, 39, 6524–6538. [CrossRef]

157. Maurus, R.; Begum, A.; Williams, L.K.; Fredriksen, J.R.; Zhang, R.; Withers, S.G.; Brayer, G.D. Alternative Catalytic Anions Differentially Modulate Human α-Amylase Activity and Specificity. Biochemistry 2008, 47, 3332–3344. [CrossRef]

158. Yadav, A.; Sharma, S.; Desk, S. Curcumin and Piperoninalone to Curb Diabetes the Natural Way: A Molecular Modeling, Docking and Dynamics Simulation Study. J. Comput. Chem. Mol. Model. 2020, 4. [CrossRef]

159. de Groot, J.C.; Weidner, C.; Krausz, J.; Kawamoto, K.; Schroeder, F.C.; Sauer, S.; Büsow, K. Structural Characterization of Amorfrutins Bound to the Proliferome Peroxisome-Activated Receptor γ. J. Med. Chem. 2013, 56, 1535–1543. [CrossRef] [PubMed]

160. Yadav, A.; Sharma, S.; Desk, S. Curcumin and Piperoninalone to Curb Diabetes the Natural Way: A Molecular Modeling, Docking and Dynamics Simulation Study. J. Comput. Chem. Mol. Model. 2020, 4. [CrossRef]

161. de Groot, J.C.; Weidner, C.; Krausz, J.; Kawamoto, K.; Schroeder, F.C.; Sauer, S.; Büsow, K. Structural Characterization of Amorfrutins Bound to the Proliferome Peroxisome-Activated Receptor γ. J. Med. Chem. 2013, 56, 1535–1543. [CrossRef] [PubMed]

162. Lauffer, B.E.L.; Mintzer, R.; Fong, R.; Mukund, S.; Tam, C.; Zilberleyb, I.; Flicke, B.; Ritscher, A.; Fedorowicz, G.; Vallero, R.; et al. Assessment of Antidiabetic Activity of the Shikonin by Allosteric Inhibition of Protein-Tyrosine Phosphatase 1B. J. Biol. Chem. 2013, 288, 26926–26943. [CrossRef] [PubMed]

163. scarfù, B.; Bontempo, P.; Altucci, L.; De Masi, L.; Facchiano, A. Molecular Docking Simulations on Histone Deacetylases (HDAC)-1 and -2 to Investigate the Flavone Binding. Proc. Natl. Acad. Sci. USA 2006, 103, 1535–1543. [CrossRef] [PubMed]

164. Mast, H.; Thompson, J.L.; Lee, S.H.; Mohr, J.P.; Sacco, R.L. Hypertension and Diabetes Mellitus as Determinants of Multiple Lacunar Infarcts. Stroke 1995, 26, 30–33. [CrossRef]

165. Prasad, S.; Sajja, R.K.; Naik, P.; Lucullo, L. Diabetes Mellitus and Blood-Brain Barrier Dysfunction: An Overview. J. Pharmacovigil. 2014, 2, 125. [CrossRef]

166. Yan, T.; Venkat, P.; Chopp, M.; Zacharek, A.; Yu, P.; Ning, R.; Qiao, X.; Kelley, M.R.; Chen, J. APX3330 Promotes Neurorestorative Effects after Stroke in Type One Diabetic Rats. Aging Dis. 2018, 9, 453. [CrossRef]

167. Yorulmaz, H.; Kaptan, E.; Seker, F.B.; Oztas, B. Type 1 Diabetes Exacerbates Blood-Brain Barrier Alterations during Experimental Epileptic Seizures in an Animal Model. Cell Biochem. Funct. 2015, 33, 285–292. [CrossRef]
168. Duelli, R.; Kuschinsky, W. Brain Glucose Transporters: Relationship to Local Energy Demand. *Physiology* 2001, 16, 71–76. [CrossRef] [PubMed]

169. Sandeep, M.S.; Nandini, C.D. Influence of Quercetin, Naringenin and Berberine on Glucose Transporters and Insulin Signalling Molecules in Brain of Streptozotocin-Induced Diabetic Rats. *Biomed. Pharmacother.* 2017, 94, 605–611. [CrossRef]

170. Di Dedda, C.; Vignali, D.; Piemonti, L.; Monti, P. Pharmacological Targeting of GLUT1 to Control Autoimmune T Cell Responses. *Int. J. Mol. Sci.* 2019, 20, 4962. [CrossRef]

171. Macheda, M.L.; Rogers, S.; Best, J.D. Molecular and Cellular Regulation of Glucose Transporter (GLUT) Proteins in Cancer. *J. Cell. Physiol.* 2005, 202, 654–662. [CrossRef] [PubMed]

172. JUNG, C.; AL, R. Cytochalasin B binding sites and glucose transport carrier in human erythrocyte ghosts. *J. Biol. Chem.* 1977, 252, 5456–5463. [CrossRef]

173. Kapoor, K.; Finer-Moore, J.S.; Pedersen, B.P.; Caboni, L.; Waight, A.; Hillig, R.C.; Bringmann, P.; Heisler, I.; Müller, T.; Siebenacher, H.; et al. Mechanism of Inhibition of Human Glucose Transporter GLUT1 Is Conserved between Cytochalasin B and Phenylalanine Amides. *Proc. Natl. Acad. Sci. U.S.A.* 2016, 113, 4711–4716. [CrossRef]

174. Custódio, T.F.; Paulsen, P.A.; Frain, K.M.; Pedersen, B.P. Structural Comparison of GLUT1 to GLUT3 Reveal Transport Regulation Mechanism in Sugar Porter Family. *Life Sci. Alliance* 2021, 4. [CrossRef] [PubMed]

175. Libby, C.J.; Ge, S.; Benavides, G.A.; Fisher, J.L.; Williford, S.E.; Zhang, S.; Tran, A.N.; Gordon, E.R.; Jones, A.B.; Tuy, K.; et al. A Role for GLUT3 in Glioblastoma Cell Invasion That Is Not Recapitulated by GLUT1. *Cell Adhes. Migr.* 2021, 15, 101–115. [CrossRef] [PubMed]

176. Deng, D.; Sun, P.; Yan, C.; Ke, M.; Jiang, X.; Xiong, L.; Ren, W.; Hirata, K.; Yamamoto, M.; Fan, S.; et al. Molecular Basis of Ligand Recognition and Transport by Glucose Transporters. *Nature* 2015, 526, 391–396. [CrossRef]

177. Hoffman, W.H.; Cudrici, C.D.; Boodhoo, D.; Tatomin, A.; Rus, V.; Rus, H. Intracellular Matrix Metalloproteinase 9 in Fatal Diabetic Ketonacidosis. *Exp. Mol. Pathol.* 2019, 108, 97–104. [CrossRef] [PubMed]

178. Rajagopal, N.; Iruayananathan, F.J.; Nangia, S. Computational Nanoscopy of Tight Junctions at the Blood–Brain Barrier Interface. *Int. J. Mol. Sci.* 2019, 20, 5583. [CrossRef] [PubMed]

179. Ding, X.; Sun, X.; Shen, X.; Lu, Y.; Wang, J.; Sun, Z.; Miao, C.; Chen, J. Propofol Attenuates TNF-α-Induced MMP-9 Expression in Human Cerebral Microvascular Endothelial Cells by Inhibiting Ca2+/CAMK II/ERK/NF-κB Signaling Pathway. *Acta Pharmacol. Sin.* 2019, 40, 1303–1313. [CrossRef]

180. Zhang, Y.; Liu, H.; Chen, Z.; Yu, M.; Li, J.; Dong, H.; Li, N.; Ding, X.; Ge, Y.; Liu, C.; et al. TLR4-Mediated Hippocampal MMP/TIMP Imbalance Contributes to the Aggravation of Perioperative Neurocognitive Disorder in Db/Db Mice. *Neurochem. Int.* 2020, 140, 104818. [CrossRef]

181. Elkins, P.A.; Ho, Y.S.; Smith, W.W.; Janson, C.A.; D’Alessio, K.J.; McQueney, M.S.; Cummings, M.D.; Romanic, A.M. Structure of the C-Terminally Truncated Human ProMMP9, a Gelatin-Binding Matrix Metalloproteinase. *Acta Crystallogr. D Biol. Crystallogr.* 2002, 58, 1182–1192. [CrossRef]

182. Park, B.S.; Song, D.H.; Kim, H.M.; Choi, B.-S.; Lee, H.; Lee, J.-O. Structural Basis of Lipopolysaccharide Recognition by the TLR4–MD-2 Complex. *Nature* 2009, 458, 1191–1195. [CrossRef]

183. Jumper, J.; Evans, R.; Pritzel, A.; Green, T.; Figurnov, M.; Ronneberger, O.; Tunyasuvunakool, K.; Bates, R.; Zìdek, A.; Potapenko, A.; et al. Highly Accurate Protein Structure Prediction with AlphaFold. *Nature* 2021, 596, 583–589. [CrossRef] [PubMed]

184. Claudin-5 AlphaFold Structure Prediction. Available online: https://alphafold.ebi.ac.uk/contact/O00501 (accessed on 12 October 2021).

185. Iruayananathan, F.J.; Wang, X.; Wang, N.; Willsey, S.R.; Seddon, I.A.; Nangia, S. Self-Assembly Simulations of Classic Claudins—Insights into the Pore Structure, Selectivity, and Higher Order Complexes. *J. Phys. Chem. B* 2018, 122, 7463–7474. [CrossRef]

186. Di Dedda, C.; Vignali, D.; Piemonti, L.; Monti, P. Architecture of the Paracellular Channels Formed by Claudins of the Claudin-5 AlphaFold Structure Prediction. Available online: https://alphafold.ebi.ac.uk/contact/O00501 (accessed on 12 October 2021).

187. Sang, H.; Qiu, Z.; Cai, J.; Lan, W.; Yu, L.; Zhang, H.; Li, M.; Xie, Y.; Guo, R.; Ye, R.; et al. Early Increased Bradykinin 1 Receptor Contributes to Hemorrhagic Transformation After Ischemic Stroke in Type 1 Diabetic Rats. *Transl. Stroke Res.* 2017, 8, 597–611. [CrossRef]

188. Wu, J.; Zhao, Y.; Fan, Z.; Chen, Q.; Chen, J.; Sun, Y.; Jiang, X.; Xiao, Q. Soluble Epoxide Hydrolase Inhibitor Protects against Blood-Brain Barrier Dysfunction in a Mouse Model of Type 2 Diabetes via the AMPK/HO-1 Pathway. *Biochem. Biophys. Res. Commun.* 2020, 524, 354–359. [CrossRef]

189. Pires, D.E.V.; Blundell, T.L.; Ascher, D.B. PkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. *J. Med. Chem.* 2015, 58, 4066–4072. [CrossRef]

190. Yang, H.; Lou, C.; Sun, L.; Li, J.; Cai, Y.; Wang, Z.; Li, W.; Liu, G.; Tang, Y. AdmetSAR 2.0: Web-Service for Prediction and Optimization of Chemical ADMET Properties. *Bioinforma. Oxf. Engil.* 2019, 35, 1067–1069. [CrossRef]

191. PkCSM—Pharmacokinetics. Available online: http://biosig.unimelb.edu.au/pkcsm/ (accessed on 1 October 2021).

192. AdmetSAR. Available online: http://lmmd.ecust.edu.cn/admetsar2/ (accessed on 1 October 2021).

193. Kam, A.; Li, K.M.; Razmovski-Naumovski, V.; Nammi, S.; Chan, K.; Li, Y.; Li, G.Q. The Protective Effects of Natural Products on Blood-Brain Barrier Breakdown. *Curr. Med. Chem.* 2012, 19, 1830–1845. [CrossRef]
194. Mamo, J.C.; Lam, V.; Brook, E.; Mooranian, A.; Al-Salami, H.; Fimognari, N.; Nesbit, M.; Takechi, R. Probiocul Prevents Blood-Brain Barrier Dysfunction and Cognitive Decline in Mice Maintained on pro-Diabetic Diet. *Diab. Vasc. Dis. Res.* 2019, 16, 87–97. [CrossRef] [PubMed]

195. Jing, Y.-H.; Chen, K.-H.; Kuo, P.-C.; Pao, C.-C.; Chen, J.-K. Neurodegeneration in Streptozotocin-Induced Diabetic Rats Is Attenuated by Treatment with Resveratrol. *Neuroendocrinology* 2013, 98, 116–127. [CrossRef]

196. Li, Y.; Jin, X.; Chen, C.-Y.; Fu, Y.-J.; Zhang, T.; Chang, H.; Zhou, Y.; Zhu, J.-D.; Zhang, Q.-Y.; Mi, M.-T. Chemical Structures of 4-Oxo-Flavanoids in Relation to Inhibition of Oxidized Low-Density Lipoprotein (LDL)-Induced Vascular Endothelial Dysfunction. *Int. J. Mol. Sci.* 2011, 12, 5471–5489. [CrossRef] [PubMed]

197. Sun, Y.-N.; Liu, L.-B.; Xue, Y.-X.; Wang, P. Effects of Insulin Combined with Idebenone on Blood-Brain Barrier Permeability in Diabetic Rats. *J. Neurosci. Res.* 2015, 93, 666–677. [CrossRef]

198. Taïlé, J.; Patche, J.; Veeren, B.; Gonthier, M.-P. Hyperglycemic Condition Causes Pro-Inflammatory and Permeability Alterations Associated with Monocyte Recruitment and Deregulated NFκB/PPARγ Pathways on Cerebral Endothelial Cells: Evidence for Polyphenols Uptake and Protective Effect. *Int. J. Mol. Sci.* 2021, 22, 1385. [CrossRef] [PubMed]

199. Unno, K.; Pervin, M.; Nakagawa, A.; Iguchi, K.; Hara, A.; Takagaki, A.; Nanjo, F.; Minami, A.; Nakamura, Y. Blood-Brain Barrier Permeability of Green Tea Catechin Metabolites and Their Neurotrophic Activity in Human Neuroblastoma SH-SY5Y Cells. *Mol. Nutr. Food Res.* 2017, 61. [CrossRef] [PubMed]

200. Pervin, M.; Unno, K.; Takagaki, A.; Iseumura, M.; Nakamura, Y. Function of Green Tea Catechins in the Brain: Epigallocatechin Gallate and Its Metabolites. *Int. J. Mol. Sci.* 2019, 20, 3630. [CrossRef] [PubMed]

201. Martin, H.-J.; Kornmann, F.; Fuhrmann, G.F. The Inhibitory Effects of Flavonoids and Antiestrogens on the Glut1 Glucose Transporter in Human Erythrocytes. *Chem. Biol. Interact.* 2003, 146, 225–235. [CrossRef] [PubMed]

202. Chen, Q.; Mo, R.; Wu, N.; Zou, X.; Shi, C.; Gong, J.; Li, J.; Fang, K.; Wang, D.; Yang, D.; et al. Berberine Ameliorates Diabetes-Associated Cognitive Decline through Modulation of Aberrant Inflammation Response and Insulin Signaling Pathway in DM Rats. *Front. Pharmacol.* 2017, 8, 334. [CrossRef]

203. Yousof Ali, M.; Jung, H.A.; Choi, J.S. Anti-Diabetic and Anti-Alzheimer’s Disease Activities of Angelica Decursiva. *Arch. Pharm.* 2015, 36, 2216–2227. [CrossRef] [PubMed]

204. Bai, L.; Li, X.; He, L.; Zheng, Y.; Lu, H.; Li, J.; Zhong, L.; Tong, R.; Jiang, Z.; Shi, J.; et al. Antidiabetic Potential of Flavonoids from Traditional Chinese Medicine: A Review. *Am. J. Chin. Med.* 2019, 47, 933–957. [CrossRef] [PubMed]

205. Vlachodimitropoulou, E.; Sharp, P.A.; Naftalin, R.J. Quercetin–Iron Chelates Are Transported via Glucose Transporters. *Free Radic. Biol. Med.* 2011, 50, 934–944. [CrossRef] [PubMed]

206. Yousof Ali, M.; Jung, H.A.; Choi, J.S. Anti-Diabetic and Anti-Alzheimer’s Disease Activities of Angelica Decursiva. *Arch. Pharm.* 2015, 36, 2216–2227. [CrossRef] [PubMed]

207. Lee, J.Y.; Park, C.S.; Choi, H.Y.; Yune, T.Y. Ginseng Extracts, GS-KG9 and GS-E3D, Prevent Blood-Brain Barrier Disruption and Thereby Inhibit Apoptotic Cell Death of Hippocampal Neurons in Streptozotocin-Induced Diabetic Rats. *Mol. Med. Rep.* 2018, 17, 605–610. [CrossRef]

208. Ruiz-Espinosa, P.; Pereira, A.S.P.; Katsikoudi, A.; et al. DIA-DB: A Database and Web Server for the Prediction of Diabetes Drugs. *J. Chem. Inf. Model.* 2021, 60, 1424–1430. [CrossRef] [PubMed]
218. Liu, H.; Wang, L.; Lv, M.; Pei, R.; Li, P.; Pei, Z.; Wang, Y.; Su, W.; Xie, X.-Q. AlzPlatform: An Alzheimer’s Disease Domain-Specific Chemogenomics Knowledgebase for Polypharmacology and Target Identification Research. *J. Chem. Inf. Model.* 2014, 54, 1050–1060. [CrossRef]

219. Daina, A.; Zoete, V. A BOILED-Egg To Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. *ChemMedChem* 2016, 11, 1117–1121. [CrossRef]

220. Daina, A.; Michielin, O.; Zoete, V. SwissADME: A Free Web Tool to Evaluate Pharmacokinetics, Drug-Likeness and Medicinal Chemistry Friendliness of Small Molecules. *Sci. Rep.* 2017, 7, 42717. [CrossRef] [PubMed]

221. Kumar, V.; Patiyal, S.; Dhall, A.; Sharma, N.; Raghava, G.P.S. B3Pred: A Random-Forest-Based Method for Predicting and Designing Blood–Brain Barrier Penetrating Peptides. *Pharmaceutics* 2021, 13, 1237. [CrossRef] [PubMed]

222. Shaker, B.; Yu, M.-S.; Song, J.S.; Ahn, S.; Ryu, J.Y.; Oh, K.-S.; Na, D. LightBBB: Computational Prediction Model of Blood–Brain-Barrier Penetration Based on LightGBM. *Bioinformatics* 2021, 37, 1135–1139. [CrossRef] [PubMed]

223. Carpenter, T.S.; Kirshner, D.A.; Lau, E.Y.; Wong, S.E.; Nilmieier, J.P.; Lightstone, F.C. A Method to Predict Blood-Brain Barrier Permeability of Drug-Like Compounds Using Molecular Dynamics Simulations. *Biophys. J.* 2014, 107, 630–641. [CrossRef] [PubMed]

224. Thai, N.Q.; Theodorakis, P.E.; Li, M.S. Fast Estimation of the Blood–Brain Barrier Permeability by Pulling a Ligand through a Lipid Membrane. *J. Chem. Inf. Model.* 2020, 60, 3057–3067. [CrossRef] [PubMed]