Avocado Fruit Peel as a Source of Antidiabetic drugs: Evidence from Molecular Docking Studies and ADMET Profiling

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Abstract
Diabetes mellitus is a long-term metabolic disorder characterized by persistent hyperglycemia, which can lead to various health problem if left untreated. The quest for new, more effective, and safer anti-diabetic therapies continues, with a growing interest in natural compounds derived from medicinal plants. Among the promising natural sources, the avocado fruit has garnered attention for its potential antidiabetic properties. Avocado peel was earlier reported to have higher alpha-amylase inhibitory activities compared to other part of the fruit, thus suggested to possess antidiabetic properties. Reported phytochemicals isolated from Avocado peel were subjected to screening via molecular docking simulation using PyRx docking tool for visualization against alpha-amylase and human glucosidase enzyme and ADMET profiling. The docking scores with ADMET profiling reported three of the screened ligands: rutin (-9.4 kcal/mol), epigallocatechin gallate (-9.3 kcal/mol), and delphinidin-3-O-glucoside (-9.0 kcal/mol) as very effective potential drug candidates as compared to the conventional medications of diabetes, glipizide (-8.1 kcal/mol) and biguanide (-5.0 kcal/mol) against human glucosidase (2QMJ). Rutin (-7.9 kcal/mol) also exhibited excellent ADMET properties and was found to be more potent against alpha-amylase (3IJ7) compared to glipizide (-7.8 kcal/mol) and biguanide (-4.3 kcal/mol). These studies reveal the anti-diabetic activities of avocado peel to be linked to the presence of rutin, epigallocatechin gallate and delphinidin-3-O-glucoside and therefore recommends these compounds for additional in vivo animal studies and clinical trials to aid in the development and formulation of new anti-diabetic drugs.
Keywords: *Diabetes mellitus, Alpha-amylase, Human glucosidase*

1.0 INTRODUCTION

Diabetes mellitus is a chronic metabolic condition categorized by elevated blood glucose levels due to inadequate insulin production or inability of the body to utilize insulin [1]. The word "diabetes" originates from the Greek word meaning "to pass through," while "mellitus" comes from the Latin word for "honey-sweet," referring to the sweet taste of urine in those affected. [2]. The two most common forms are Type 1 and Type 2 diabetes. Type 1 diabetes is caused by the autoimmune destruction of insulin-producing beta cells in the pancreas, resulting in a complete lack of insulin. It is typically diagnosed in younger individuals. Conversely, Type 2 diabetes,

which accounts for about 90% of cases, is mainly characterized by insulin resistance and is Frequently linked to obesity and inactive lifestyles [3].

Diabetes has emerged as a global pandemic, affecting over 463 million individuals and posing substantial public health concerns. This chronic condition is accompanied by serious complications, such as cardiovascular disease, kidney failure, and neuropathy, underscoring the critical need for effective management strategies. As diabetes continues to present a major health challenge, a thorough understanding of its pathophysiology, risk factors, and management approaches is essential for alleviating the strain on healthcare systems and improving the lives of millions affected by this disease [4].

As of 2021, around 537 million adults were living with diabetes, a number expected to increase to 783 million by 2045 if current trends persist. This chronic condition is not only a major cause of morbidity and mortality ranking among the top ten causes of death worldwide but it also significantly contributes to the burden of non-communicable diseases (NCDs), which are accountable for over 80% of premature deaths globally [5]. The economic impact of diabetes is staggering. The overall healthcare expenditure related to diabetes is expected to reach one trillion USD by 2030, exerting significant pressure on healthcare systems, especially in low- and middle-income countries (LMICs) where resources are already limited. [6]. Furthermore, nearly half of those with diabetes remain undiagnosed, complicating management efforts and increasing the risk of serious complications such as cardiovascular disease, kidney failure, and neuropathy. The World Health Organization has identified diabetes as a critical public health issue, highlighting the need for comprehensive strategies to improve prevention, early diagnosis, and management of the disease [7].

Glucosidase and amylase are enzymes exert significant roles in the digestion and metabolism of carbohydrates in the human body. Understanding their functions is crucial for understanding their effects on diabetes [8]. Glucosidases are a class of enzymes that catalyze the hydrolysis (breakdown) of complex carbohydrates, specifically disaccharides and oligosaccharides, into simpler sugars, such as glucose. They are primarily located in the small intestine and on the surface of intestinal cells [9]. In the context of diabetes, glucosidase inhibitors are medications used to manage blood sugar levels. These inhibitors retard the action of glucosidase enzymes in the small intestine. By doing so, they delay the digestion and absorption of carbohydrates, particularly complex carbohydrates, leading to a slower and more regular increase in blood glucose levels after eating [10].

Amylase is another enzyme involved in carbohydrate digestion. Salivary amylase, produced in the salivary glands, and pancreatic amylase, produced in the pancreas, are the two primary forms of amylase. These enzymes convert starches and glycogen, which are complex carbohydrates, into simpler sugars, chiefly maltose. Amylase itself does not directly impact diabetes, but it is an important part of the digestive process that converts carbohydrates into glucose, which can affect blood sugar levels [11]. For individuals with diabetes, it's crucial to monitor carbohydrate intake and its impact on blood sugar. Some people with diabetes may use insulin or other medications to help regulate their blood sugar levels after meals that contain carbohydrates, which are broken down by amylase. In summary, α-glucosidase inhibitors can be used to slow down carbohydrate digestion and help control blood sugar levels in people with diabetes by slowing down the absorption of glucose. α-amylase, on the other hand, is tasked with

breaking down carbohydrates into simpler sugars, which can affect blood sugar levels in individuals with diabetes depending on their carbohydrate intake and the management strategies they employ. Inhibition of α-glucosidase and α-amylase enzymes is therefore very important [12].

The rising prevalence of diabetes, particularly type 2, underscores the urgency for targeted interventions that address lifestyle factors and enhance healthcare access, especially in vulnerable populations [13], Given that the use of certain synthetic drugs and therapies has led to severe side effects, and remains both expensive and inaccessible to the low- and middle-income classes [14].

In pursuit of a healthy lifestyle, synthetic drugs are being replaced by traditional plants. Herbal medicine is a traditional form of healthcare, and it has been practiced for thousands of years by millions of people in Africa as well many other parts of the world [15]. People have used herbs as the main system of healthcare with astounding great success for many, many years. In this era of modernization and the fast spread of so good old conventional health care system, there are a few people who would still have prefer what is homemade or proven in terms national knowledge as an ancient healing process called herbal medicine [16]. Phytochemicals obtained from different plant parts have great antioxidant activity and are of great interest due to their valuable effect on health of human beings, and they give tremendously great health benefits to the consumers, Epidemiological and animal trials suggest that the regular intake of fruits, vegetables and whole grains decreases the risk and effect of various ailments [17].

For centuries, these tropical tree fruits have been prized for their sweet flavor. Recently, research has revealed additional benefits, including nutrients that help combat disease, maintain a healthy weight, and even reduce signs of aging. Herbal drugs are derived from plants and botanical sources, which are perceived as natural and less processed compared to synthetic medications. Many people prefer natural remedies because they are mostly gentler on the body and have fewer side effects. Among the promising natural sources, the avocado peel has garnered attention for its potential antidiabetic properties. Avocado, a fruit widely consumed worldwide, is identified to possess a variety of bioactive compounds, including phenolic compounds, carotenoids, and vitamins, which have been linked with various health benefits. While the pulp and seed of the avocado have been extensively studied, the peel, which is often discarded as waste, has been relatively unexplored. Meanwhile, studies have also shown that avocado leaves contain phytochemicals with potent antioxidant properties that combat DPPH [18]. Meanwhile, [19], reported that Avocado peel has the highest significance of alpha amylase inhibitory activities.

Avocado peel, often discarded, holds promising potential as a complementary element in diabetic treatment due to its rich array of bioactive compounds [20]. Recent research suggest that the peel contains beneficial phytochemicals such as polyphenols, flavonoids, and dietary fibers, which may contribute to improved glycemic control, enhanced insulin sensitivity, and mitigated complications associated with diabetes [21]. Thus, the reported therapeutic effects of avocado peel have aroused our interest in studying its isolated secondary metabolites as potential treatments for managing diabetes.

Several researchers have written on the advantage of insilico methods off drug discovery over in vitro and in vivo studies [22] [23]. Computational chemistry is recently used in drug discovery, which decreases cost, time and resources compared to traditional experimental approaches [24] [25]. Molecular docking is a widely used computational method in drug discovery and development to predict the binding mode and affinity of small molecules (ligands) to a target

protein (receptor). Molecular docking involves the prediction of the preferred orientation of one molecule to a second when bound to each other to form a stable complex [24][25]. The docking process typically involves a search algorithm that systematically explores various binding poses of the ligand within the receptor's binding site, aiming to identify the most favorable orientation.

The ADMET analysis will also be carried out on the ligands and standards using pkcsm software, the admet properties that will be analyzed include absorption, distribution, metabolism, excretion and toxicity etc. In conclusion, the computational study of the binding affinity and interactions of the isolated phytochemicals from Persea americana peel and the two standard drug compounds against the target receptor will provide valuable insights into their potential as anti-diabetic agents. The ADME/pharmacokinetic properties of these compounds will also be evaluated to assess their drug-like characteristics.

2.0 MATERIALS AND METHODS

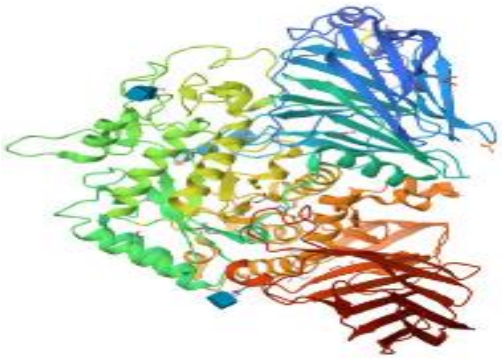
2.1 Ligands Preparation

Previously isolated phytochemical compounds from the peel of *Persea americana* (avocado) and two standard drug compounds with reported completed randomized clinical trials against the target receptor were utilized as comparisons in this research. The two-dimensional (2D) structures of all ligands and standard compounds were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) [26] and subsequently converted to three-dimensional (3D) structures using Spartan 14 software. To determine the most stable conformations of the ligands and standard compounds for docking simulations, a conformer search was performed using the Conformer Distribution feature in Spartan 14. The most stable conformers were then optimized using the density functional theory (DFT) method at the B3LYP level with the 6-31G* basis set to achieve the optimal equilibrium geometry.

2.2 Preparation of Target Receptor

The crystal structures of Human maltase-glucoamylase (MGAM) (PDB ID: 2QMJ) and Human pancreatic alpha-amylase (PDB ID: 3IJ7) were retrieved from the Protein Data Bank (RCSB) (http://www.rcsb.org/pdb). The proteins were prepared by removing impurities, including water molecules, using Discovery Studio software to avoid interference. The binding pockets of the initial inhibitors in 2QMJ and 3IJ7 were analyzed to determine the binding parameters and preferences.

A



B

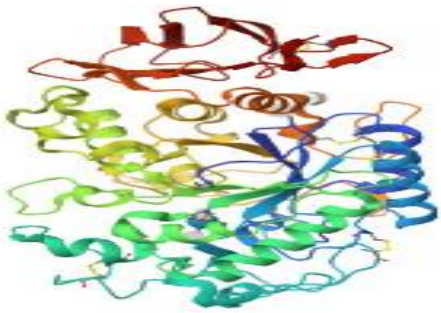


Figure 1. The Crystal Structure of (A) Human Intestinal Maltase-Glucoamylase Receptor (PDB ID:2QMJ) and (B) Alpha amylase receptor (PDB ID:3ij7)

2.3 Molecular Docking Protocol

The molecular docking of the ligands and standard compounds against the target receptor will be carried out using Pyrex Software. The receptor structure was obtained from the Protein Data Bank and prepared for docking by removing water molecules, adding hydrogen atoms, and assigning Kollman charges. The grid box parameters for the docking were set to encompass the entire binding site of the receptor. The docking results were analyzed based on binding affinity and inhibition constant. The inhibition constants (Ki) in µM for the ligands and the standard were calculated using their binding affinities (ΔG) in kcal/mol, as shown in the equation below, thereby reflecting their potency against the target receptor.

$K_I = \exp(\Delta G/RT)$

Where R=Gas constant (1.987×10^{-3} kcal/mol); T=298.15K (absolute temperature);

K_I=Inhibition Constant and ΔG=Binding energy

2.4 ADMET Profiling

The Absorption, Distribution, Metabolism, Excretion, and Toxicity properties of the docked ligands and standard compounds were evaluated using the pkCSM web server (https://biosig.lab.uq.edu.au/pkcsm/prediction), which is a free web tool for assessing ADMET characteristics [27].

3.0 RESULTS AND DISCUSSIONS

Through Molecular Docking simulation of the phytochemicals already named above and the standard drug glipizide and biguanide against the target receptor (2QMJ and 3IJ7), it was shown that the binding energies of the docked ligands against the 2QMJ target receptor range from -9.4 kcal/ mol and -4.4 kcal/mol. A reasonable number of ligands among the docked phytochemicals such as Rutin (-9.4 kcal/mol), Epigallocatechin gallate (-9.3 kcal/mol), Delphinidin-3-O-glucoside (-9.0 kcal/mol), Quercetin (-8.9 kcal/mol), Multinoside (-8.6 kcal/mol), Ceceline (-8.4 kcal/mol), and Cassythicine (-8.3 kcal/mol), Catechin (-8.2 kcal/mol), Epicatechin (-8.2 kcal/mol), Myricetin (-8.2 kcal/mol), have better binding affinities than the standard drug, Glipizide (-8.1 kcal/mol) and Biguanide (-5.0 kcal/mol). It was also shown that the binding energies of the docked ligands against the target receptor 3IJ7 range from -8.9 kcal/mol and -3.3 kcal/mol. A reasonable number of ligands among the docked phytochemicals such as Beta-sitosterol (-8.9 kcal/mol), Ceceline (-8.6 kcal/mol),Naringenin (-8.3 kcal/mol), Apigenin (-8.0 kcal/mol), Flavonol (-8.0 kcal/mol),Catechin (-7.9 kcal/mol), and Rutin (-7.9 kcal/mol), have better binding affinities than the standard drug, Glipizide (-7.8 kcal/mol) and Biguanide (-4.3kcal/mol) and were subjected to further Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) (pharmacokinetics) profiling. Furthermore, the ADME/pharmacokinetic analysis suggests that these phytochemical compounds possess favorable drug-like properties, making them promising candidates for further development as anti-diabetic agents**.**

3.1 Structural Elucidation and Active Site Analysis of Target Receptor

3.1.1 Human Intestinal Maltase-Glucoamylase Receptor (PDB ID: 2QMJ)

Human maltase-glucoamylase (MGAM) is one of the two enzymes responsible for catalyzing the final glucose-releasing step in starch digestion. MGAM is located on the small-

intestinal brush-border epithelial cells and consists of two homologous catalytic subunits from glycosyl hydrolase family 31: an N-terminal subunit (NtMGAM) near the membrane-bound end and a C-terminal luminal subunit (CtMGAM).

The amino acids in the active site residue of 2QMJ include Asn 209, Asn 393, Asn 741, Asp327, Asp542, His600, Arg526, Asp 443, Tyr299, Ile328, Ile 364, Trp 441and Met 444, Cys 307, Trp 345, Lys 414, Asp 306 [28].

3.1.2 Alpha Amylase Receptor (PDB ID: 3IJ7)

Human pancreatic α-amylase is a crucial endoglycosidase involved in the digestion of dietary starch in the gut, breaking it down into a mixture of oligosaccharides, including maltose, as well as R-(1-4)- and R-(1-6)-branched oligoglucans, which are further hydrolyzed to glucose by other glucosidases. The activity of human pancreatic α-amylase in the small intestine has been shown to correlate closely with postprandial blood sugar levels【29】. Therefore, regulating the activity of HPA presents a promising therapeutic strategy for managing diseases such as diabetes and obesity.

The amino acids in the active site residue of 3IJ7 include Arg210, Asn257, Tyr552, Lys699, Tyr700, Phe209, Leu428, Glu424, Gly518, His553, Arg463, Arg534, Arg536, Asn519, Ser517, Trp541, Glu542, Thr543, Asn544, Lys545, Phe546, Ser547, Gly548, Arg511 [30].

3.2 Molecular Docking Analysis

Molecular docking is a key technique in Computer-Aided Drug Design (CADD) used for the virtual screening of small molecules during the early stages of drug discovery. It helps to understand the interactions between a hit compound and the receptor macromolecule, enabling the precise positioning of a ligand within the target receptor's binding site and assessing the effectiveness of the ligand's binding to the receptor. The crystal structure of the alpha amylase and human glucosidase which are key enzyme in the digestive system (PDB ID: 2QMJ) and (PDB ID: 3IJ7) respectively was used as the target receptor in the virtual screening exercise. Sixty-four (64) phytochemicals from *Persea americana* peel (ligands) and two (2) standard drug (Biguanide and Glipizide) were docked with the target receptor (2QMJ and 3IJ7).

The binding affinity of a ligand is used to estimate its inhibition constant (Ki). A lower Ki value (typically in the micromolar range for a hit or lead compound, and no more than 10 nM for a drug) indicates greater effectiveness and higher inhibition efficiency. As shown in Table 1, the Ki value of the docked ligands ranges from 0.13 µM to 597.12 µM. However, only 13 of the docked ligands have inhibition constant values that fall within the recommended range of 0.1 µM and 1.0 µM and are considered as Hit compounds

$K_I = \exp(\Delta G/RT)$

Where R=Gas constant (1.987×10^{-3} kcal/mol); T=298.15K (absolute temperature);

K_I=Inhibition Constant and ΔG=Binding energy

Table 1. The docking scoring, binding affinities and inhibition constant (K_i) values of the interactions of ligands and the standard with human glucosidase receptor (PDB ID:2QMJ)

LIGANDS	**BINDING AFFINITIES (ΔG), kcal/mol**	**INHIBITION CONSTANT (K_I), µM**
	Flavonoids	
Rutin	-9.4	0.13
Anthocyanin	-7.7	2.28
Apigenin	-8.1	1.16
Catechin	-8.2	0.98
Delphinidin- 3- O Glucoside	-9.0	0.25
Dihydrochalcone	-6.8	10.41
di-hydroflavonol	-7.8	1.93
Flavone	-8.1	1.16
Flavonol	-7.4	3.78
Flavanol	-7.2	5.3
Gardenin_B	-7.0	7.43
Kaempferol	-8.0	1.37
Myricetin	-8.2	0.98
Quercetin	-8.9	0.30
	Alkaloids	
Anibamine	-7.5	3.20
Anibine	-6.7	12.33
Ceceline	-8.4	0.70
Cassythicine	-8.3	0.83
Isoboldine	-7.6	2.70
Nantenine	-8.1	1.16
N-methylcoclaurine	-8.2	0.98
Reticuline	-6.9	8.80
Riparin_III	-7.1	6.28
	Phenolics	
Epigallocatechin Gallate	-9.3	0.15
Mutinoside	-8.6	0.50
Epicatechin	-8.2	0.98
Pro-anthocyanidin	-8.2	0.98
Procyanidin	-8.2	0.98
3-Caffeoylquinic-acid	-8.0	1.37
Naringenin	-7.9	1.63
Resveratrol	-7.8	1.93
5_Hydroxyferulic_acid	-6.8	10.41
4-Hydrobenzoic_acid	-6.7	12.33
Chlorogenic_acid	-7.2	5.30

Caffeic_acid	-7.1	6.28
Ferulic_acid	-6.2	28.65
Gentisic_acid	-6.1	33.92
Sakuranetin	-7.8	1.93
Hydroxycinnamic_acid	-7.0	7.43
Hydroxycoumarin	-6.7	12.33
Pyrocatechol	-5.7	66.61
Quinic_acid	-5.7	66.61
Scopoletin	-6.4	20.45
Sinapic_acid	-6.2	28.65
Syringic_acid	-6.0	40.15
Vanillic_acid	-5.4	110.5
Vanillin	-5.2	154.84
Tyrosol	-6.0	40.15
Hydroxytyrosol	-6.2	28.65
	Terpenoids	
Beta-pinene	-5.2	154.84
Alpha-pinene	-4.9	256.86
Beta-Sitosterol	-7.2	5.30
Limonene	-5.3	130.8
Phytol	-4.7	359.95
Squalene	-4.9	256.86
	Vitamin	
Vitamin_c	-5.3	130.8
	Lignan	
Matairesinol	-6.7	12.33
	Fatty Acids	
Palmitoleic_acid	-5.2	154.84
Linolenic_acid	-5.1	183.3
Stearic_acid	-4.9	256.86
Oleic_acid	-4.7	359.95
Linoleic_acid	-4.6	426.11
Myristic_acid	-4.6	426.11
Palmitic_acid	-4.4	597.12
	Carotenoids	
Lutein	-7.1	6.28
Zeaxanthin	-7.0	7.43
	Standards	
Biguanide	-5.0	216.99
Glipizide	-8.1	1.16

Table 2. The docking scoring, binding affinities and inhibition constant (K_i) values of the interactions of ligands and the standard with alpha amylase receptor (PDB ID:3IJ7)

LIGANDS	**BINDING AFFINITIES (ΔG), kcal/mol**	**INHIBITION CONSTANT (K_I),µM**
	Flavonoids	
Rutin	-7.9	1.63
Anthocyanin	-7.4	3.78
Apigenin	-8.0	3.87
Catechin	-7.9	1.63
Delphinidin- 3- O Glucoside	-7.4	3.78
Dihydrochalcone	-6.4	20.45
di-hydroflavonol	-7.7	2.28
Flavone	-7.4	2.28
Flavonol	-8.0	1.37
Flavanol	-7.8	1.93
Gardenin_B	-6.5	17.27
Kaempferol	-7.6	2.70
Myricetin	-7.3	4.48
Quercetin	-7.8	1.93
	Alkaloids	
Anibamine	-4.4	597.12
Anibine	-6.5	17.27
Ceceline	-8.6	0.50
Cassythicine	-7.4	3.78
Isoboldine	-7.4	3.78
Nantenine	-7.4	3.78
N-methylcoclaurine	-7.2	5.30
Reticuline	-7.2	5.30
Riparin_III	-7.5	3.20
	Phenolics	
Epigallocatechin Gallate	-7.0	7.43
Mutinoside	-7.9	1.63
Epicatechin	-7.5	3.20
Pro-anthocyanidin	-7.5	3.20
Procyanidin	-7.5	3.20
3-Caffeoylquinic-acid	-7.6	2.70
Naringenin	-8.3	0.83
Resveratrol	-6.6	14.59
5_Hydroxyferulic_acid	-7.0	7.43
4-Hydrobenzoic_acid	-5.5	93.34
Chlorogenic_acid	-7.5	3.20

Caffecic_acid	-6.6	14.59
Ferulic_acid	-6.3	24.20
Gentisic_acid	-5.7	66.61
Sakuranetin	-7.1	6.28
Hydroxycinnamic_acid	-6.3	24.20
Hydroxycoumarin	-6.3	24.20
Pyrocatechol	-4.9	256.86
Quinic_acid	-6.1	33,92
Scopoletin	-6.4	20.45
Sinapic_acid	-5.6	78.85
Syringic_acid	-5.4	110.50
Vanillic_acid	-5.7	66.61
Vanillin	-5.2	154.84
Tyrosol	-5.7	66.61
Hydroxytyrosol	-5.9	47.53
	Terpenoids	
Beta-pinene	-5.7	66.61
Alpha-pinene	-5.7	66.61
Beta-Sitosterol	-8.9	0.30
Limonene	-5.7	66.61
Phytol	-5.3	130.80
Squalene	-5.0	216.99
	Vitamin	
Vitamin_c	-5.4	110.50
	Lignan	
Matairesinol	-7.7	2.28
	Fatty Acids	
Palmitoleic_acid	-5.2	154.84
Linolenic_acid	-5.4	110.50
Stearic_acid	-4.5	504.42
Oleic_acid	-4.7	359.95
Linoleic_acid	-5.5	93.32
Myristic_acid	-5.1	183.30
Palmitic_acid	-4.6	426.11
	Carotenoids	
Lutein	-7.7	2.28
Zeaxanthin	-7.2	5.30
	Standards	
Biguanide	-4.3	706.86
Glipizide	-7.8	1.93

3.3 ADMET (pharmacokinatics) of the ligands

Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) evaluation is important in the early stages of drug discovery. A high-quality therapeutic agent must not only demonstrate excellent efficacy against the target receptor but also possess favorable ADMET properties at a therapeutic dose. Evaluating the pharmacokinetic profile of compounds is essential to prevent drug failure in later stages. It has been reported that 50% of drug candidates fail due to poor ADMET profiles. The PKCSM web tool (https://biosig.lab.uq.edu.au/pkcsm/prediction) was used to assess the ADMET properties of the ligands.

The findings of the ADMET predictor, which has a numerical value with specific constraints, are used in virtual screening. Absorption Water solubility (-), Caco-2 permeability (> 0.9), Intestinal absorption (human) (> 30%) , Skin permeability (≥ -2.5), P-glycoprotein substrate(Yes/No), P-glycoprotein I inhibitor (Yes/No), P-glycoprotein II inhibitor (Yes/No), Distribution VDss (human) (≥ -0.15), Fraction unbound (human)(-), BBB permeability(≥ -1) CNS permeability (≥ -3), Metabolism CYP2D6 substrate (Yes/No), CYP3A4 substrate (Yes/No), CYP1A2 inhibitor (Yes/No), CYP2C19 inhibitor (Yes/No), CYP2C9 inhibitor (Yes/No), CYP2D6 inhibitor (Yes/No), CYP3A4 inhibitor (Yes/No), Excretion Total clearance (Higher is better), Renal OCT2 substrate (Yes/No), Ames mutagenesis AM (No), hERG I inhibitor (No), Hepatotoxicity (No), Skin sensitization (No), T.Pyriformis toxicity (≤0.5) and Minnow toxicity (> −0.3) were used as qualifiers.

The analysis of absorption properties revealed that 39 compounds exhibited excellent absorption characteristics, meeting the stated requirements. Additionally, 13 compounds were found to satisfy the criteria for distribution and excretion properties. Consequently, the phytochemicals delphinidin 3-O-glucoside, rutin, and epigallocatechin gallate can be considered as promising anti-diabetic drug candidates, as they possess favorable ADME profiles, with the three compounds meeting the requirements for absorption, distribution, and excretion predictors. The evaluation of the metabolism properties of the 66 compounds provided insights into their potential for hepatic metabolism. Furthermore, the toxicity assessment showed that 41 out of the 64 screened compounds had excellent results concerning the specified predictors. In contrast, the standard drug compounds used for comparison did not meet the toxicity test requirements.

Table 3: The prediction results of absorption properties of compounds previously isolated from avocado peel and 2 standards using pkCSM

Compound	**MW**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**
Phenolics								
3-Caffeoylquinic acid	354.31	-2.45	-0.84	36.38	-2.74	Yes	No	No
4-Hydrobenzoic acid	183.12	-2.27	0.02	66.03	-2.73	No	No	No
5-Hydroxyferulic acid	210.19	-2.77	0.10	81.86	-2.74	Yes	No	No
Caffeic acid	180.16	-2.33	0.63	69.41	-2.72	No	No	No
Chlorogenic acid	354.31	-2.45	-0.84	36.38	-2.74	Yes	No	No
Epicathechin	290.27	-3.12	-0.28	68.83	-2.74	Yes	No	No
Epigallocatechin gallate	**458.38**	**-2.89**	**-1.52**	**47.40**	**-2.74**	**Yes**	**No**	**Yes**

Ferulic acid	194.19	-2.82	0.18	93.69	-2.72	No	No	No
Gentisic acid	154.12	-2.01	0.54	80.08	-2.74	No	No	No
Hydroxycinnamic acid	**164.16**	**-2.38**	**1.21**	**93.50**	**-2.72**	**No**	**No**	**No**
Hydroxycoumarin	**162.14**	**-2.13**	**1.21**	**94.55**	**-2.60**	**No**	**No**	**No**
Hydroxytyrosol	**154.17**	**-1.14**	**1.10**	**72.81**	**-2.89**	**No**	**No**	**No**
Multinoside	610.52	-2.89	-0.97	15.59	-2.74	Yes	No	No
Naringenin	**270.24**	**-3.33**	**1.01**	**93.25**	**-2.74**	**Yes**	**No**	**No**
Procyanidins	594.53	-2.89	0.13	55.53	-2.74	Yes	Yes	Yes
Pyrocatechol	**110.11**	**-0.76**	**1.68**	**86.86**	**-2.62**	**No**	**No**	**No**
Proanthocyanidin	**592.55**	**-2.89**	**0.19**	**71.72**	**-2.74**	**Yes**	**Yes**	**Yes**
Sakuranetin	**286.28**	**-3.14**	**1.36**	**92.60**	**-2.76**	**Yes**	**No**	**No**
Scopoletin	**192.17**	**-2.50**	**1.18**	**95.28**	**-2.94**	**No**	**No**	**No**
Sinapic acid	224.21	-2.87	0.27	93.06	-2.73	Yes	No	No
Quinic acid	192.17	-1.12	-0.26	32.27	-2.74	No	No	No
Vanillic acid	168.15	-1.84	0.33	78.15	-2.73	No	No	No
Vanillin	**152.15**	**-1.31**	**1.22**	**84.97**	**-2.83**	**No**	**No**	**No**
Syringic acid	198.17	-2.22	0.49	73.08	-2.74	Yes	No	No
Resveratrol	**228.25**	**-3.18**	**1.17**	**90.94**	**-2.74**	**Yes**	**No**	**No**
Tyrosol	**138.17**	**-1.15**	**1.69**	**85.26**	**-2.80**	**No**	**No**	**No**
Flavonoids								
Anthocyanin	207.25	-4.85	1.63	96.18	-2.13	No	No	No
Apigenin	**270.24**	**-3.33**	**1.01**	**93.25**	**-2.74**	**Yes**	**No**	**No**
Catechin	290.27	-3.12	-0.28	68.83	-2.74	Yes	No	No
Delphinidin 3-O glucoside	**465.39**	**-2.87**	**-1.12**	**32.50**	**-2.74**	**Yes**	**No**	**No**
Dihydrochalcone	274.27	-3.08	-0.34	60.5	-2.74	Yes	No	No
Dihydroflavonol	**240.26**	**-3.27**	**1.23**	**94.82**	**-2.92**	**Yes**	**No**	**No**
Flavanol	**226.28**	**-3.29**	**1.31**	**93.95**	**-2.78**	**Yes**	**No**	**No**
Flavone	222.24	-3.84	1.26	97.39	-2.22	Yes	No	No
Flavonol	**238.24**	**-3.68**	**1.26**	**94.78**	**-2.78**	**Yes**	**No**	**No**
Gardenin B	**358.35**	**-4.10**	**1.15**	**96.15**	**-2.74**	**Yes**	**Yes**	**Yes**
Kaempferol	286.24	-3.04	0.03	74.29	-2.74	Yes	No	No
Myricetin	318.24	-2.92	0.10	65.93	-2.74	Yes	No	No
Quercetin	302.24	-2.92	-0.23	77.21	-2.74	Yes	No	No
Rutin	**610.52**	**-2.89**	**-0.95**	**23.45**	**-2.74**	**Yes**	**No**	**No**
Alkaloids								
Isoboldine	**327.38**	**-3.89**	**0.95**	**92.62**	**-2.83**	**Yes**	**No**	**Yes**
Nantenine	**339.39**	**-3.76**	**1.96**	**96.45**	**-2.81**	**Yes**	**Yes**	**Yes**
N-methylcoclaurine	**299.37**	**-3.71**	**1.22**	**92.94**	**-2.79**	**Yes**	**No**	**No**
Reticuline	**329.40**	**-3.86**	**0.92**	**91.28**	**-2.89**	**Yes**	**No**	**Yes**

Riparin III	**287.32**	**-2.96**	**1.15**	**91.60**	**-2.80**	**Yes**	**No**	**No**
Anibamine	**424.74**	**-7.42**	**1.07**	**90.26**	**-2.77**	**Yes**	**No**	**Yes**
Anibine	203.20	-1.88	1.27	100	-2.33	No	No	No
Cassythicine	**325.36**	**-3.75**	**1.27**	**93.88**	**-2.91**	**Yes**	**Yes**	**Yes**
Ceceline	**304.35**	**-4.08**	**1.24**	**93.63**	**-2.74**	**Yes**	**No**	**Yes**
Lignan								
Matairesinol	**358.39**	**-3.69**	**1.12**	**93.53**	**-2.77**	**Yes**	**Yes**	**Yes**
Fatty Acids								
Linoleic acid	**280.45**	**-5.86**	**1.57**	**92.33**	**-2.72**	**No**	**No**	**No**
Linolenic acid	**278.44**	**-5.79**	**1.58**	**92.84**	**-2.72**	**No**	**No**	**No**
Myristic acid	**228.38**	**-4.95**	**1.56**	**92.69**	**-2.71**	**No**	**No**	**No**
Oleic acid	**282.47**	**-5.92**	**1.56**	**91.82**	**-2.73**	**No**	**No**	**No**
Palmitic acid	**256.43**	**-5.56**	**1.56**	**92.00**	**-2.72**	**No**	**No**	**No**
Palmitoleic acid	**254.41**	**-5.48**	**1.57**	**92.51**	**-2.72**	**No**	**No**	**No**
Stearic acid	**284.48**	**-5.97**	**1.56**	**91.32**	**-2.73**	**No**	**No**	**No**
Terpenoids								
Alpha-pinene	136.24	-3.73	1.38	96.04	-1.83	No	No	No
Phytol	**296.54**	**-7.55**	**1.52**	**90.71**	**-2.58**	**No**	**No**	**Yes**
Beta- pinene	**136.24**	**-4.19**	**1.39**	**95.53**	**-1.65**	**No**	**No**	**No**
Limonene	136.24	-3.57	1.40	95.90	-1.72	Yes	No	No
Beta-sitosterol	**414.72**	**-6.77**	**1.20**	**94.46**	**-2.78**	**No**	**Yes**	**Yes**
Squalene	**410.73**	**-8.52**	**1.22**	**90.34**	**-2.77**	**No**	**No**	**Yes**
Vitamins								
Vitamin C	176.12	-1.56	-0.26	39.15	-2.96	No	No	No
Carotenoids								
Zeaxanthin	**568.89**	**-6.84**	**1.25**	**89.45**	**-2.74**	**Yes**	**No**	**Yes**
Lutein	**568.89**	**-6.82**	**1.25**	**89.78**	**-2.74**	**Yes**	**No**	**Yes**
Standards								
Glipizide	445.55	-3.41	0.58	63.10	-2.78	Yes	No	No
Biguanide	101.11	-2.63	-0.44	58.24	-2.74	Yes	No	No

Note: = The compounds that satisfy the requirement values were bolded, MW = Molecular Weight (g/mol), A1 = Water solubility, A2 = Caco2 permeability, A3 = Intestinal absorption (human), A4 = Skin Permeability, A5 = P-glycoprotein substrate, A6 = P-glycoprotein I inhibitor, A7 = P-glycoprotein II inhibitor

Table 4: The prediction results of distribution and excretion properties of compounds isolated from avocado peel and 2 standards using pkCSM

Compounds	MW	D1	D2	D3	D4	E1	E2
Alkaloids							
Anibamine	424.74	1.58	0.00	1.40	-1.44	1.83	No
Anibine	203.20	-0.42	0.37	-0.10	-2.93	0.91	No
Cassythicine	325.36	1.01	0.16	-0.39	-2.01	1.05	No
Ceceline	304.35	-0.08	0.05	0.05	-1.92	0.42	No
Isoboldine	327.38	0.99	0.16	-0.44	-2.12	1.02	No
Nantenine	339.39	1.08	0.14	-0.05	-1.36	1.07	Yes
N-methylcoclaurine	299.37	0.97	0.20	0.14	-2.10	1.01	No
Reticuline	329.40	0.78	0.13	-0.50	-2.24	1.04	Yes
Riparin III	287.32	-0.04	0.07	-0.70	-2.61	0.24	No
Flavonoids							
Anthocyanin	207.25	0.24	0.15	0.45	-1.27	0.72	No
Apigenin	270.24	0.82	0.15	-0.73	-2.06	0.57	No
Catechin	**290.27**	**1.03**	**0.24**	**-1.05**	**-3.30**	**0.18**	**No**
Delphinidin 3-O glucoside	**465.39**	**1.11**	**0.31**	**-2.16**	**-4.45**	**0.57**	**No**
Dihydrochalcone	274.27	0.41	0.00	0.61	-1.29	0.32	No
Dihydroflavonol	240.26	0.70	0.34	0.33	-2.51	0.17	No
Flavanol	226.28	0.19	0.05	0.61	-1.67	0.24	No
Flavone	222.24	0.10	0.08	0.22	-1.47	0.09	No
Flavonol	238.24	0.24	0.15	0.46	1.73	0.23	No
Gardenin B	358.35	0.22	0.13	-0.91	-3.17	0.69	Yes
Kaempferol	286.24	1.27	0.18	-0.94	-2.22	0.48	No
Myricetin	**318.24**	**1.32**	**0.24**	**-1.49**	**-3.71**	**0.42**	**No**
Quercetin	**302.24**	**1.56**	**0.21**	**-1.10**	**-3.07**	**0.41**	**No**
Rutin	**610.52**	**1.66**	**0.19**	**-1.90**	**-5.18**	**-0.37**	**No**
Carotenoids							
Lutein	568.89	-0.23	0.00	-0.22	-1.44	0.92	No
Zeaxanthin	568.89	-0.23	0.00	-0.21	-1.14	1.04	No
Terpenoids							
Beta-sitosterol	414.72	0.19	0.00	0.78	-1.71	0.63	No
Beta-pinene	136.24	0.69	0.35	0.82	-1.86	0.03	No
Alpha-pinene	136.24	0.67	0.43	0.79	-2.20	0.04	No
Limonene	136.24	0.40	0.48	0.73	-2.37	0.21	No
Phytol	296.54	0.47	0.00	0.81	-1.56	1.69	No
Squalene	410.73	0.41	0.00	0.98	-0.96	1.79	No
Vitamin							
Vitamin C	**176.12**	**0.22**	**0.83**	**-1.00**	**-3.22**	**0.63**	**No**
Lignan							

Matairesinol	358.39	-0.27	0.00	-0.49	-3.07	0.15	No
Phenolics							
Caffeic acid	180.16	-1.10	0.53	-0.65	-2.61	0.51	No
Chlorogenic acid	**354.31**	**0.58**	**0.66**	**-1.41**	**-3.86**	**0.31**	**No**
Epicathechin	**290.27**	**1.03**	**0.24**	**-1.05**	**-3.30**	**0.18**	**No**
Epigallocatechin gallate	**458.38**	**0.81**	**0.22**	**-2.18**	**-3.96**	**0.29**	**No**
Ferulic acid	194.19	1.37	0.34	-0.24	-2.61	0.62	No
Gentisic acid	154.12	-1.52	0.69	-0.70	-3.28	0.59	No
Hydroxycinnamic acid	164.16	-1.02	0.39	0.42	-1.89	0.34	No
Hydroxycoumarin	162.14	0.03	0.43	-0.28	-2.74	0.77	No
Hydroxytyrosol	154.17	-0.08	0.59	-0.39	-2.67	0.23	No
Multinoside	**610.52**	**1.56**	**0.20**	**-2.07**	**-5.15**	**-0.36**	**No**
Naringenin	270.24	-0.02	0.06	-0.58	-2.23	0.06	No
3-Caffeoylquinic acid	**354.31**	**0.58**	**0.66**	**-1.41**	**-3.86**	**0.31**	**No**
4-Hydrobenzoic acid	183.12	-1.79	0.43	-0.35	-2.55	0.63	No
5-Hydroxyferulic acid	210.19	-1.06	0.50	-0.90	-2.75	0.66	No
Procyanidins	**594.53**	**0.19**	**0.28**	**-1.78**	**-4.11**	**-0.06**	**No**
Proanthocyanidin	**592.55**	**-0.31**	**0.27**	**-1.68**	**-3.99**	**0.05**	**No**
Pyrocatechol	110.11	-0.02	0.62	-0.32	-2.08	0.15	No
Quinic acid	192.17	-0.22	0.82	-0.89	-3.67	0.64	No
Resveratrol	228.25	0.30	0.17	-0.05	-2.07	0.08	No
Sakuranetin	286.28	-0.05	0.03	-0.22	-2.25	0.17	No
Scopoletin	192.17	0.03	0.36	-0.30	-2.32	0.73	No
Sinapic acid	224.21	-1.11	0.45	-0.25	-2.66	0.72	No
Syringic acid	198.17	-1.44	0.60	-0.19	-2.70	0.65	No
Tyrosol	138.17	-0.11	0.49	-0.22	-2.11	0.28	No
Vanillic acid	168.15	-1.74	0.52	-0,38	-2.63	0.63	No
Vanillin	152.15	-0.15	0.43	-0.24	-2.24	0.60	No
Fatty Acids							
Linoleic acid	280.45	-0.58	0.05	-0.15	-1.60	1.94	No
Linolenic acid	278.44	-0.62	0.05	-0.12	-1.55	1.99	No
Myristic acid	228.38	-0.58	0.17	-0.02	-1.93	1.69	No
Oleic acid	282.47	-0.56	0.05	-0.17	-1.65	1.88	No
Palmitic acid	256.43	-0.54	0.10	-0.11	-1.82	1.76	No
Palmitoleic acid	254.41	-0.57	0.10	-0.08	-1.76	1.82	No
Stearic acid	284.48	-0.53	0.05	-0.20	-1.71	1.83	No
Standards							
Glipizide	**445.55**	**-0.25**	**0.25**	**-1.04**	**-3.37**	**1.13**	**No**
Biguanide	101.11	-0.51	0.83	-0.96	-4.29	0.22	No

Note: = The compounds that satisfy the requirement values were bolded, D1 = VDss (human),

D2 = Fraction unbound (human), D3 = BBB permeability, D4 = CNS permeability, E1 = Total Clearance, E2 = Renal OCT2 substrate

Table 5: The prediction results of metabolism properties of compounds isolated from avocado peel and 2 standards using pkCSM

Compounds	**MW**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**
			Alkaloids					
Anibamine	424.74	Yes	Yes	No	No	No	Yes	No
Anibine	203.20	No	No	Yes	No	No	No	No
Cassythicine	325.36	No	Yes	Yes	No	No	No	No
Ceceline	304.35	No	Yes	Yes	Yes	Yes	Yes	Yes
Isoboldine	327.38	No	Yes	Yes	No	No	No	No
Nantenine	339.39	No	Yes	No	No	No	No	No
N-methylcoclaurine	299.37	Yes	Yes	Yes	No	No	Yes	No
Reticuline	329.40	Yes	Yes	Yes	No	No	No	No
Riparin III	287.32	No	Yes	Yes	No	No	No	No
			Flavonoids					
Anthocyanin	207.25	No	Yes	Yes	Yes	No	No	No
Apigenin	270.24	No	No	Yes	Yes	No	No	No
Catechin	290.27	No	No	No	No	No	No	No
Delphinidin 3-O glucoside	**465.39**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Dihydrochalcone	274.27	No	Yes	Yes	Yes	Yes	No	No
Dihydroflavonol	240.26	No	Yes	Yes	No	No	No	No
Flavanol	226.28	No	Yes	Yes	Yes	No	No	No
Flavone	222.24	No	Yes	Yes	Yes	No	No	No
Flavonol	238.24	No	Yes	Yes	Yes	No	No	No
Gardenin B	358.35	No	Yes	Yes	Yes	No	No	No
Kaempferol	286.24	No	No	Yes	No	No	No	No
Myricetin	**318.24**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Quercetin	302.24	No	No	Yes	No	No	No	No
Rutin	**610.52**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
			Terpenoids					
Beta-sitosterol	414.72	No	Yes	No	No	No	No	No
Beta-pinene	**136.24**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Limonene	**136.24**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Phytol	296.54	No	Yes	Yes	No	No	No	No
Squalene	410.73	No	Yes	No	No	No	No	No
Alpha-pinene	**136.24**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
			Vitamins					
Vitamin C	**176.12**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
			Lignan					

Matairesinol	358.39	No	Yes	Yes	Yes	Yes	No	Yes
Carotenoids								
Lutein	568.89	No	Yes	No	No	No	No	No
Zeaxanthin	568.89	No	Yes	No	No	No	No	No
Phenolics								
Caffeic acid	**180.16**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Chlorogenic acid	**354.31**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Epicathechin	**290.27**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Epigallocatechin gallate	**458.38**	**No**	**No**	**No**	**No**	**No**	**No**	**Yes**
Ferulic acid	**194.19**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Gentisic acid	**154.12**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Hydroxycinnamic acid	**164.16**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Hydroxycoumarin	162.14	No	No	Yes	No	No	No	No
Hydroxytyrosol	154.17	No	No	No	No	No	No	No
Multinoside	**610.52**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Naringenin	270.24	No	No	Yes	No	No	No	No
Procyanidin	**594.53**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Proanthocyanidin	**592.55**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Pyrocatechol	**110.11**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Quinic acid	**192.17**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Resveratrol	228.25	No	Yes	Yes	Yes	No	No	No
Sakuranetin	286.28	No	No	Yes	Yes	No	No	No
Scopoletin	192.17	No	No	Yes	No	No	No	No
Sinapic acid	**224.21**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Syringic acid	**198.17**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Tyrosol	**138.17**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Vanillic acid	**168.15**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Vanillin	**152.15**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
3-Caffeoylquinic acid	**354.31**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
4-Hydrobenzoic acid	**183.12**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
5-Hydroxyferulic acid	**210.19**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Fatty Acid								
Linoleic acid	280.45	No	Yes	Yes	No	No	No	No
Linolenic acid	278.44	No	Yes	Yes	No	No	No	Yes
Myristic acid	**228.38**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Palmitic acid	256.43	No	Yes	No	No	No	No	No
Palmitoleic acid	254.41	No	Yes	No	No	No	No	No
Stearic acid	284.48	No	Yes	Yes	No	No	No	No
Oleic acid	282.47	No	Yes	Yes	No	No	No	No
Standard drugs								

Glipizide	445.55	No	No	No	No	Yes	No	No
Biguanide	**101.11**	**No**	**No**	**No**	**No**	**No**	**No**	**No**

Note: = The compounds that satisfy the requirement values were bolded, M1 = CYP2D6 substrate, M2 = CYP3A4 substrate, M3 = CYP1A2 inhibitor, M4 = CYP2C19 inhibitor, M5 = CYP2C9 inhibitor, M6 = CYP2D6 inhibitor, M7= CYP3A4 inhibitor

Table 6: The prediction results of toxicity properties of compounds isolated from avocado peel and 2 standards using pkCSM

Compounds	**MW**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**
					Alkaloids					
Anibamine	424.74	No	0.48	Yes	1.90	0.36	No	No	0.52	-3.94
Anibine	**203.20**	**No**	**0.28**	**No**	**2.56**	**2.64**	**No**	**No**	**0.27**	**2.01**
Cassythicine	325.36	Yes	-0.32	No	2.70	0.60	Yes	No	0.79	1.27
Ceceline	304.35	No	0.09	No	2.18	0.41	Yes	No	0.33	0.58
Isoboldine	327.38	No	0.12	No	2.41	1.49	No	No	0.69	1.44
Nantenine	339.39	Yes	-0.33	No	2.97	1.82	Yes	No	0.83	0.60
N-methylcoclaurine	**299.37**	**No**	**0.04**	**No**	**2.48**	**1.08**	**No**	**No**	**0.94**	**1.01**
Reticuline	**329.40**	**No**	**0.23**	**No**	**2.30**	**1.54**	**No**	**No**	**0.90**	**1.26**
Riparin III	**287.32**	**No**	**0.34**	**No**	**1.68**	**2.51**	**No**	**No**	**0.78**	**0.86**
					Flavonoids					
Catechin	**290.27**	**No**	**0.44**	**No**	**2.43**	**2.50**	**No**	**No**	**0.35**	**3.59**
Anthocyanin	207.25	No	0.04	No	1.85	1.12	No	No	1.11	0.17
Apigenin	**270.24**	**No**	**0.33**	**No**	**2.45**	**2.30**	**No**	**No**	**0.38**	**2.43**
Delphinidin 3-O glucoside	**465.39**	**No**	**0.51**	**No**	**2.59**	**4.09**	**No**	**No**	**0.29**	**7.65**
Dihydrochalcone	274.27	No	1.09	No	1.82	1.15	No	Yes	1.34	0.78
Dihydroflavonol	240.26	Yes	0.98	No	1.72	2.37	No	No	1.15	1.67
Flavanol	226.28	Yes	0.14	No	2.02	2.15	Yes	No	1.12	1.23
Flavone	222.24	Yes	-0.03	No	1.99	-1.02	No	No	0.77	0.76
Flavonol	**238.24**	**No**	**-0.09**	**No**	**1.99**	**1.58**	**No**	**No**	**0.70**	**1.21**
Gardenin B	**358.35**	**No**	**0.25**	**No**	**2.34**	**1.17**	**No**	**No**	**0.39**	**1.30**
Kaempferol	**286.24**	**No**	**0.53**	**No**	**2.45**	**2.50**	**No**	**No**	**0.31**	**2.88**
Myricetin	**318.24**	**No**	**0.51**	**No**	**2.50**	**2.72**	**No**	**No**	**0.29**	**5.02**
Quercetin	**302.24**	**No**	**0.59**	**No**	**2.47**	**2.61**	**No**	**No**	**0.29**	**3.72**
Rutin	**610.52**	**No**	**0.45**	**No**	**2.49**	**3.67**	**No**	**No**	**0.29**	**7.68**
					Carotenoid					
Lutein	568.89	No	-1.07	No	3.49	2.57	No	No	0.32	-2.21

Zeaxanthin	**568.89**	**No**	**-1.84**	**No**	**3.55**	**2.57**	**No**	**No**	**0.33**	**-2.04**
				Fatty Acids						
Linoleic acid	280.45	No	-0.83	No	1.43	3.19	Yes	Yes	0.70	-1.31
Linolenic acid	278.44	No	-0.84	No	1.44	3.12	Yes	Yes	0.72	-1.18
Myristic acid	228.38	No	-0.56	No	1.48	3.03	No	Yes	0.98	-0.60
Oleic acid	282.47	No	-0.81	No	1.42	3.26	No	Yes	0.68	-1.44
Palmitic acid	256.43	No	0.71	No	1.44	3.18	No	Yes	0.84	-1.08
Palmitoleic acid	254.41	No	-0.71	No	1.45	-3.11	No	Yes	0.87	-0.96
Stearic acid	284.48	No	-1.79	No	1.41	3.33	No	Yes	0.65	-1.57
				Lignan						
Matairesinol	**358.39**	**No**	**-0.16**	**No**	**1.94**	**2.15**	**No**	**No**	**0.45**	**0.44**
				Terpenoids						
Alpha-pinene	**136.24**	**No**	**0.48**	**No**	**1.77**	**2.26**	**No**	**No**	**0.45**	**1.16**
Beta-sitosterol	**414.72**	**No**	**-0.62**	**No**	**2.55**	**0.86**	**No**	**No**	**0.43**	**-1.80**
Limonene	136.24	No	0.78	No	1.88	2.34	No	Yes	0.58	1.20
Beta-pinene	**136.24**	**No**	**0.37**	**No**	**1.67**	**2.28**	**No**	**No**	**0.63**	**1.01**
Phytol	296.54	No	0.05	No	1.61	1.04	No	Yes	1.88	-1.50
Squalene	**410.73**	**No**	**-0.39**	**No**	**1.85**	**0.95**	**No**	**No**	**0.46**	**-3.49**
				Vitamin						
Vitamin C	**176.12**	**No**	**1.60**	**No**	**1.06**	**3.19**	**No**	**No**	**0.29**	**4.39**
				Phenolics						
Caffeic acid	**180.16**	**No**	**1.15**	**No**	**2.38**	**2.09**	**No**	**No**	**0.29**	**2.25**
Chlorogenic acid	**354.31**	**No**	**-0.13**	**No**	**1.97**	**2.98**	**No**	**No**	**0.29**	**5.74**
Epicathechin	**290.27**	**No**	**0.44**	**No**	**2.43**	**2.50**	**No**	**No**	**0.35**	**3.59**
Epigallocatechin gallate	**458.38**	**No**	**0.44**	**No**	**2.52**	**3.07**	**No**	**No**	**0.29**	**7.71**
Ferulic acid	**194.19**	**No**	**1.08**	**No**	**2.28**	**2.07**	**No**	**No**	**0.27**	**1.83**
Gentisic acid	**154.12**	**No**	**1.26**	**No**	**2.12**	**2.30**	**No**	**No**	**0.28**	**2.45**
Hydroxycinnamic acid	**164.16**	**No**	**1.11**	**No**	**2.16**	**2.53**	**No**	**No**	**0.32**	**1.61**
Hydroxycoumarin	162.14	No	0.69	No	2.05	1.75	Yes	No	0.55	1.71
Hydroxytyrosol	154.17	Yes	1.15	No	1.85	1.91	No	No	-0.13	2.75
3-Caffeoylquinic acid	**354.31**	**No**	**-0.13**	**No**	**-1.97**	**2.98**	**No**	**No**	**0.28**	**5.74**

4-Hydrobenzoic acid	183.12	Yes	0.82	No	1.73	2.01	No	No	0.26	1.89
5-Hydroxyferulic acid	**210.19**	**No**	**1.11**	**No**	**2.32**	**2.38**	**No**	**No**	**0.28**	**2.50**
5-Hydroxyferulic acid	**210.19**	**No**	**1.11**	**No**	**2.32**	**2.38**	**No**	**No**	**0.28**	**2.50**
Naringenin	**270.24**	**No**	**-0.18**	**No**	**1.79**	**1.94**	**No**	**No**	**0.37**	**2.14**
Multinoside	**610.52**	**No**	**0.46**	**No**	**2.51**	**4.50**	**No**	**No**	**0.29**	**8.83**
Procyanidins	**594.53**	**No**	**0.44**	**No**	**2.48**	**3.86**	**No**	**No**	**0.29**	**10.6**
Proanthocyanidins	**592.55**	**No**	**0.44**	**No**	**2.48**	**3.85**	**No**	**No**	**0.29**	**8.30**
Pyrocatechol	110.11	No	-0.01	No	2.14	2.31	No	Yes	0.11	2.19
Quinic acid	**192.17**	**No**	**1.63**	**No**	**1.13**	**3.53**	**No**	**No**	**0.29**	**4.87**
Resveratrol	228.25	Yes	0.33	No	2.53	1.53	No	No	0.75	1.52
Sakuranetin	**286.28**	**No**	**-0.03**	**No**	**2.17**	**2.07**	**No**	**No**	**0.48**	**1.23**
Scopoletin	**192.17**	**No**	**0.61**	**No**	**1.95**	**1.38**	**No**	**No**	**0.52**	**1.61**
Sinapic acid	**224.21**	**No**	**1.19**	**No**	**2.24**	**2.32**	**No**	**No**	**0.26**	**2.18**
Syringic acid	**198.17**	**No**	**1.37**	**No**	**2.16**	**2.42**	**No**	**No**	**0.29**	**2.55**
Tyrosol	138.17	No	1.40	No	1.86	2.33	No	Yes	-0.24	2.21
Vanillic acid	**168.15**	**No**	**0.72**	**No**	**2.45**	**2.03**	**No**	**No**	**0.27**	**1.93**
Vanillin	**152.15**	**No**	**1.29**	**No**	**1.94**	**2.01**	**No**	**No**	**-0.01**	**1.90**
Standards										
Biguanide	101.11	Yes	0.31	No	2.30	2.38	No	Yes	0.22	4.18
Glipizide	445.55	No	0.04	No	1.78	1.60	Yes	No	0.30	0.94

Note: = The compounds that satisfy the requirement values were bolded,
T1= Ames toxicity, T2=Max. tolerated dose (human), T3 = hERG I inhibitor, T4= Oral Rat Acute Toxicity (LD50) T5= Oral Rat Chronic Toxicity (LOAEL), T6= Hepatotoxicity, T7= Skin Sensitisation, T8= T.Pyriformis toxicity, T9= Minnow toxicity

4.0 Conclusion

This research evaluates phytochemicals isolated from *Persea americana* peel against digestive enzymes alpha-amylase (3IJ7) and human glucosidase (2QMJ) using molecular docking studies. The results obtained show that these ligands include rutin (-9.4 kcal/mol), epigallocatechin gallate (-9.3 kcal/mol), and delphinidin-3-O-glucoside (-9.0 kcal/mol) are potential and better inhibitor of human glucosidase (2QMJ) compared to the standard diabetes drugs glipizide (-8.1 kcal/mol) and biguanide (-5.0 kcal/mol). Additionally, one ligand, rutin (-7.9 kcal/mol), was found to be more potent against alpha-amylase (3IJ7) compared to glipizide (-7.8 kcal/mol) and biguanide (-4.3 kcal/mol) owing to their excellent binding affinities and ADMET properties. However, the importance of conducting additional analyses, such as Hit/Lead optimization,

Molecular Dynamics, MMPBA, and in vivo animal studies, to further validate the findings is highly acknowledged. However, constraints, including time, limited the scope of the current investigation. Hit/Lead optimization involves modifying the structures of identified Hits/Leads to improve their potency, efficacy, reduce their toxicity, and enhance their pharmacokinetics, thereby developing safer and more effective small molecules for the inhibition of alpha amylase and human glucosidase. We hereby recommend that the three Hits be subjected to further optimization and development to design a new therapeutic agent for the treatment and management of diabetes.

REFERENCES

[1] Roglic, G. (2016). WHO Global report on diabetes: A summary. *International Journal of Noncommunicable Diseases*, *1*(1), 3-8.
[2] Sapra, A., & Bhandari, P. (2023). Continuing Education Activity. *Diabetes*.
[3] Steyl, T. (2020). Satisfaction with quality of healthcare at primary healthcare settings: Perspectives of patients with type 2 diabetes mellitus. *South African Journal of Physiotherapy*, *76*(1), 1-7.
[4] Ogurtsova, K., da Rocha Fernandes, J. D., Huang, Y., Linnenkamp, U., Guariguata, L., Cho, N. H., ... & Makaroff, L. E. (2017). IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes research and clinical practice*, *128*, 40-50.
[5] Lin, X., Xu, Y., Pan, X., Xu, J., Ding, Y., Sun, X., ... & Shan, P. F. (2020). Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Scientific reports*, *10*(1), 1-11.
[6] Standl, E., Khunti, K., Hansen, T. B., & Schnell, O. (2019). The global epidemics of diabetes in the 21st century: Current situation and perspectives. *European journal of preventive cardiology*, *26*(2_suppl), 7-14.
[7] Ong, K. L., Stafford, L. K., McLaughlin, S. A., Boyko, E. J., Vollset, S. E., Smith, A. E., ... & Brauer, M. (2023). Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet*, *402*(10397), 203-234.
[8] Koye, D. N., Magliano, D. J., Nelson, R. G., & Pavkov, M. E. (2018). The global epidemiology of diabetes and kidney disease. *Advances in chronic kidney disease*, *25*(2), 121-132.
[9] Xiao-Ping, Y. E., Chun-Qing, S. O. N. G., Ping, Y. U. A. N., & Ren-Gang, M. A. O. (2010). α-Glucosidase and α-amylase inhibitory activity of common constituents from traditional Chinese medicine used for diabetes mellitus. *Chinese Journal of Natural Medicines*, *8*(5), 349-352.
[10] Lin, X., Xu, Y., Pan, X., Xu, J., Ding, Y., Sun, X., ... & Shan, P. F. (2020). Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Scientific reports*, *10*(1), 1-11.
[11] Haguet, Q., Le Joubioux, F., Chavanelle, V., Groult, H., Schoonjans, N., Langhi, C., ... & Maugard, T. (2023). Inhibitory potential of α-amylase, α-glucosidase, and pancreatic lipase by a formulation of five plant extracts: TOTUM-63. *International Journal of Molecular Sciences*, *24*(4), 3652.
[12] Jiang, J., Fan, H., Zhou, J., Qin, J., Qin, Z., Chen, M., ... & Liu, X. (2024). In vitro inhibitory effect of five natural sweeteners on α-glucosidase and α-amylase. *Food & Function*, *15*(4), 2234-2248.

[13] Abdul Basith Khan, M., Hashim, M. J., King, J. K., Govender, R. D., Mustafa, H., & Al Kaabi, J. (2020). Epidemiology of type 2 diabetes—global burden of disease and forecasted trends. *Journal of epidemiology and global health*, *10*(1), 107-111.
[14] Arora, K., Tomar, P. C., & Mohan, V. (2021). Diabetic neuropathy: an insight on the transition from synthetic drugs to herbal therapies. *Journal of Diabetes & Metabolic Disorders*, *20*(2), 1773-1784.
[15] Pang, G. M., Li, F. X., Yan, Y., Zhang, Y., Kong, L. L., Zhu, P., ... & Lu, C. (2019). Herbal medicine in the treatment of patients with type 2 diabetes mellitus. *Chinese medical journal*, *132*(1), 78-85.
[16] Builders, P. F., Mohammed, B. B., & Sule, Y. Z. (2020). Preparation and evaluation of the physicochemical and stability properties of three herbal tea blends derived from four native herbs. *Journal of Phytomedicine and Therapeutics*, *19*(2), 448-465.
[17] Golak-Siwulska, I., Kałużewicz, A., Spiżewski, T., Siwulski, M., & Sobieralski, K. (2018). Bioactive compounds and medicinal properties of Oyster mushrooms (sp.). *Folia Horticulturae*, *30*(2), 191-201.
[18] Rahman, N., Tangkas, I. M., Rakhman, A., Sabang, S. M., & Bohari, B. (2022). Effect of avocado (Persea americana Mill.) peel extract on the diabetic male white rats: preclinical study. *Open Access Macedonian Journal of Medical Sciences*, *10*(A), 415-418.
[19] Oboh, G., Isaac, A. T., Akinyemi, A. J., & Ajani, R. A. (2014). Inhibition of key enzymes linked to type 2 diabetes and sodium nitroprusside induced lipid peroxidation in rats' pancreas by phenolic extracts of avocado pear leaves and fruit. *International Journal of Biomedical Science: IJBS*, *10*(3), 208.
[20] Ameer, K. (2016). Avocado as a major dietary source of antioxidants and its preventive role in neurodegenerative diseases. *The benefits of natural products for neurodegenerative diseases*, 337-354.
[21] Jimenez, P., Garcia, P., Quitral, V., Vasquez, K., Parra-Ruiz, C., Reyes-Farias, M., ... & Soto-Covasich, J. (2021). Pulp, leaf, peel and seed of avocado fruit: A review of bioactive compounds and healthy benefits. *Food Reviews International*, *37*(6), 619-655.
[22] Pagadala, N. S., Syed, K., & Tuszynski, J. (2017). Software for molecular docking: a review. *Biophysical reviews*, *9*, 91-102.
[23] Gioia, D., Bertazzo, M., Recanatini, M., Masetti, M., & Cavalli, A. (2017). Dynamic docking: a paradigm shift in computational drug discovery. *Molecules*, *22*(11), 2029.
[24] Sam Paul, D., & Gautham, N. (2018). Protein–small molecule docking with receptor flexibility in iMOLSDOCK. *Journal of Computer-Aided Molecular Design*, *32*, 889-900.
[25] I. A. Guedes, F.S. Pereira & L.E. Dardenne, "Empirical scoring functions for structure-based virtual screening: applications, critical aspects, and challenges", *Frontiers in pharmacology* 9 (2018): 1089.
[26] Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., ... & Bolton, E. E. (2021). PubChem in 2021: new data content and improved web interfaces. *Nucleic acids research*, *49*(D1), D1388-D1395.
[27] Lohohola, P. O., Mbala, B. M., Bambi, S. M. N., Mawete, D. T., Matondo, A., & Mvondo, J. G. M. (2021). In silico ADME/T properties of quinine derivatives using SwissADME and pkCSM webservers. *International Journal of TROPICAL DISEASE & Health*, *42*(11), 1-12.

[28] Sim, L., Quezada-Calvillo, R., Sterchi, E. E., Nichols, B. L., & Rose, D. R. (2008). Human intestinal maltase–glucoamylase: crystal structure of the N-terminal catalytic subunit and basis of inhibition and substrate specificity. *Journal of Molecular Biology*, *375*(3), 782-792.
[29] Krentz, A. J., & Bailey, C. J. (2005). Oral antidiabetic agents: current role in type 2 diabetes mellitus. *Drugs*, *65*, 385-411.
[30] Zhang, R., Li, C., Williams, L. K., Rempel, B. P., Brayer, G. D., & Withers, S. G. (2009). Directed "in situ" inhibitor elongation as a strategy to structurally characterize the covalent glycosyl-enzyme intermediate of human pancreatic α-amylase. *Biochemistry*, *48*(45), 10752-10764.