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Computational Screening of *Persea americana* Peel and Seed Phytochemicals as Potential Multi-Target Antidiabetic Agents

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Abstract

Diabetes mellitus (DM) is a global health burden, and current oral antidiabetic drugs are associated with undesirable side effects. Avocado (*Persea americana*) peel and seed are underutilized by-products rich in bioactive phytochemicals. This study aimed to evaluate the antidiabetic potential of ten gas chromatography-mass spectrometry (GC-MS)-derived compounds (five from peel and five from seed) against five protein targets, α-glucosidase, α-amylase, dipeptidyl peptidase-4 (DPP-4), protein tyrosine phosphatase 1B (PTP1B), and AMP-activated protein kinase (AMPK) using PASS Online bioactivity prediction and molecular docking. PASS Online predicted high antidiabetic probabilities (probability active > 0.7) for epicatechin and chrysoeriol-4′-O-pentoside-7-O-rutinoside. Molecular docking with AutoDock Vina 1.2.0 showed that epicatechin bound strongest to α-glucosidase (−9.2 kcal/mol) and α-amylase (−8.7 kcal/mol), comparable to acarbose. Chrysoeriol-4′-O-pentoside-7-O-rutinoside exhibited high affinity for α-glucosidase (−8.8 kcal/mol), DPP-4 (−8.4 kcal/mol), PTP1B (−8.1 kcal/mol), and AMPK (−8.0 kcal/mol). ADMET predictions indicated that epicatechin has favorable drug-likeness properties (no Lipinski violations, high GI absorption). At the same time, chrysoeriol-4′-O-pentoside-7-O-rutinoside may face bioavailability challenges due to its large, glycosylated structure (molecular weight 742.68 g/mol). These results suggest that avocado seed flavonoids, particularly epicatechin, are promising multi-target antidiabetic candidates for nutraceutical development, though experimental validation is required to confirm these computational predictions.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. According to the International Diabetes Federation, approximately 589 million adults aged 20–79 years were living with diabetes in 2024, and this number is projected to reach 783 million by 2045 [1]. Type 2 diabetes mellitus (T2DM) accounts for 90–95% of all cases and involves multiple interconnected pathophysiological defects, including peripheral insulin resistance, progressive pancreatic β-cell dysfunction, excessive hepatic glucose production, and dysregulated incretin hormone secretion [2]. The chronic hyperglycemia of T2DM leads to severe microvascular and macrovascular complications such as retinopathy, nephropathy, neuropathy, and cardiovascular disease, imposing a burden on healthcare systems worldwide [3, 4].

Current oral antidiabetic drugs target various aspects of T2DM pathophysiology. α-Glucosidase and α-amylase inhibitors (e.g., acarbose) delay carbohydrate digestion and reduce postprandial hyperglycemia [5]. Dipeptidyl

peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin) increase incretin levels, enhancing glucose-dependent insulin secretion [6]. Metformin, the most widely prescribed first-line drug, activates AMP-activated protein kinase (AMPK), thereby improving insulin sensitivity and reducing hepatic glucose output [7]. Protein tyrosine phosphatase 1B (PTP1B) inhibitors are an emerging class that enhances insulin signaling by prolonging receptor phosphorylation [8, 9]. However, each drug class has limitations. Acarbose frequently causes flatulence, diarrhea, and abdominal discomfort due to undigested carbohydrates [5]. Sitagliptin has been associated with rare but serious adverse events, including acute pancreatitis and severe arthralgia [6]. Long-term metformin use may lead to vitamin B12 deficiency and, rarely, lactic acidosis [7]. Moreover, the high cost of some oral antidiabetics limits access in low- and middle-income countries. These shortcomings underscore the urgent need for safer, more affordable, and more effective antidiabetic agents.

Natural products have historically been a rich source of drug leads, and many currently used antidiabetic drugs originated from plant-derived compounds [10–12]. Bioactive phytochemicals such as flavonoids, phenolic acids, terpenoids, and fatty acids exhibit multiple biological activities, including antioxidant, anti-inflammatory, and enzyme-inhibitory effects that can ameliorate hyperglycemia [13]. Among the numerous plants studied for antidiabetic potential, avocado (*Persea americana* Mill.) has gained attention not only for its nutritious pulp but also for its underutilized peel and seed, which are often discarded as agricultural waste. These by-products contain high levels of bioactive compounds. Avocado peel has been shown to possess a higher total phenolic content and greater antioxidant capacity than the pulp [14]. In contrast, avocado seeds are rich in flavonoids (e.g., epicatechin), fatty acids, and phytosterols [15]. Gas chromatography-mass spectrometry (GC-MS) analyses of avocado peel from the Bener Meriah region in Indonesia and of seeds from secondary data have identified numerous compounds with documented bioactivity, including caryophyllene, oleic acid, epicatechin, and chrysoeriol glycosides [16, 17].

While several preclinical studies have reported antidiabetic effects of avocado by-product extracts [14, 15], computational methods have not systematically explored the specific molecular interactions between individual avocado compounds and multiple diabetes-related targets. In particular, three critical knowledge gaps remain: (1) the relative binding affinities of individual avocado peel versus seed compounds against major antidiabetic targets have not been compared; (2) whether specific compounds exhibit multi-target potential that could inform polypharmacological strategies remains unknown; and (3) the structure-activity relationships underlying any differential target selectivity have not been elucidated. Addressing these gaps is scientifically important because identifying which compounds from which avocado part (peel versus seed) show the most promising multi-target profiles can guide the rational design of enriched extracts or nutraceutical formulations, rather than relying on empirical screening of crude mixtures. We hypothesized that specific flavonoid compounds from avocado seed would exhibit stronger and more selective binding affinities against multiple diabetes-related targets compared to fatty acid and terpene compounds from avocado peel, reflecting their known bioactive phenolic structures. Therefore, this study aimed to systematically evaluate the antidiabetic potential of ten GC-MS-derived compounds from avocado peel and seed against five target proteins (α-glucosidase, α-amylase, DPP-4, PTP1B, and AMPK) using PASS Online bioactivity prediction and molecular docking. The results will provide a rational basis for selecting the most promising avocado compounds for subsequent experimental validation. They will support the valorization of avocado by-products as functional food ingredients.

2. Materials and Methods

2.1. Compound Dataset

Ten compounds were selected from previously published GC-MS analyses of avocado peel (Bener Meriah region, Indonesia) and seed [16, 17]. The selection criteria were: (1) compounds with relative abundance > 3.0% in the respective GC-MS chromatograms to ensure they represent meaningful constituents; (2) compounds previously reported to possess antidiabetic, antioxidant, or anti-inflammatory activities based on literature review, ensuring biological relevance; (3) compounds representing diverse chemical classes (fatty acids, terpenes, flavonoids, and phytosterols) to enable structure-activity relationship analysis; and (4) compounds with available three-dimensional structures in the PubChem database for docking. This approach deliberately included compounds with varying structural features, from simple fatty acids (n-hexadecanoic acid) to complex glycosylated flavonoids (chrysoeriol-4′-O-pentoside-7-O-rutinoside) to assess whether antidiabetic activity correlates with specific structural motifs. From the peel, five compounds were selected: *n*-hexadecanoic acid, oleic acid, caryophyllene, bis(2-ethylhexyl)phthalate, and caryophyllene oxide. From the seed, five compounds were selected: epicatechin, tetradecanoic acid, 9,12-

Table 1. Molecular docking parameters.

Target	PDB ID	Grid Box Dimensions (Å)	Grid Box Center Coordinates (x, y, z)	Exhaustiveness	Validation RMSD (Å)
α-Glucosidase	5NN8	22 × 22 × 22	12.5, -8.3, 21.7	16	1.52
α-Amylase	4GQR	24 × 24 × 24	15.8, 42.5, 18.3	16	1.38
DPP-4	2QOE	20 × 20 × 20	-25.6, 34.2, 42.8	16	1.67
PTP1B	7KLX	18 × 18 × 18	10.2, -15.7, 8.4	16	1.45
AMPK	4CFF	20 × 20 × 20	8.6, -5.3, 12.9	16	1.71

octadecadienoic acid methyl ester, phytol, and chrysoeriol-4′-O-pentoside-7-O-rutinoside. Three-dimensional structures were downloaded from PubChem in SDF format.

2.2. Protein Target Selection

Five protein targets were selected based on their central roles in type 2 diabetes pathophysiology and their established relevance as drug targets [2, 3, 5–7, 9]. α-Glucosidase and α-amylase were selected because they are critical enzymes in carbohydrate digestion, and their inhibition is a proven strategy for reducing postprandial hyperglycemia [5]. Dipeptidyl peptidase-4 (DPP-4) was selected because its inhibition prolongs incretin hormone activity, enhancing glucose-dependent insulin secretion [6]. Protein tyrosine phosphatase 1B (PTP1B) was selected because it is a negative regulator of insulin signaling, and its inhibition represents an emerging therapeutic strategy for improving insulin sensitivity [9]. AMP-activated protein kinase (AMPK) was selected because it is a master regulator of cellular energy homeostasis and a key target for metformin, the most widely prescribed first-line antidiabetic drug [7]. These five targets collectively represent complementary mechanisms: two affect carbohydrate absorption (α-glucosidase, α-amylase), one enhances incretin-mediated insulin secretion (DPP-4), one improves insulin signaling (PTP1B), and one regulates energy metabolism (AMPK). This multi-target selection enables a comprehensive evaluation of the antidiabetic potential of avocado compounds across the major pathophysiological pathways of T2DM. Five protein structures were retrieved from the Protein Data Bank (PDB): α-glucosidase (5NN8), α-amylase (4GQR), DPP-4 (2QOE), PTP1B (7KLX), and AMPK (4CFF). Water molecules and heteroatoms were removed using PyMOL and Biovia Discovery Studio. Hydrogen atoms were added, and structures were minimized using the CHARMM force field [16].

2.3. PASS Online Bioactivity Prediction

The PASS Online web service (https://way2drug.com/PassOnline/) was used to predict the probability of being active (Pa) for antidiabetic activities. PASS Online predicts bioactivity based on the compound's structural formula (in SMILES format) against a comprehensive database of known structure-activity relationships [17]. For this study, antidiabetic activity was queried using the specific PASS activity terms: "Antidiabetic" and "Hypoglycemic", which are pre-defined activity classes within the PASS database. The "Antidiabetic" term encompasses compounds with general glucose-lowering activity across multiple mechanisms, while "Hypoglycemic" specifically refers to agents that lower blood glucose levels. For each compound-target combination, we used the Pa value from the "Antidiabetic" prediction, as it represents the most comprehensive antidiabetic activity class. We considered compounds with Pa > 0.7 as high-confidence candidates, following the standard interpretation where Pa > 0.7 indicates high probability of activity, 0.5 < Pa < 0.7 indicates moderate probability, and Pa < 0.5 indicates low probability [17]. We uploaded the SMILES strings for all ten compounds to the PASS Online server and retrieved the Pa values for antidiabetic activity. To assess the pharmacological potential of the lead compounds, we evaluated their physicochemical properties, drug-likeness, and ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) profiles using the SwissADME and pkCSM web servers [18, 19].

2.4. Molecular Docking

Molecular docking was performed using AutoDock Vina 1.2.0 [20, 21]. Ligand structures were energy-minimized using the MMFF94 force field in Open Babel 3.1.1. Gasteiger partial charges were assigned, and non-polar hydrogens were merged. Protein structures were prepared by removing water molecules and heteroatoms, adding polar hydrogens, and assigning Kollman charges using AutoDock Tools. Grid boxes were centered on the active sites based on co-crystallized ligands. Docking exhaustiveness was set to 16 (Table 1). For validation, we re-docked each co-crystallized ligand into its respective binding site using the same parameters. The RMSD values were calculated by superimposing the re-docked ligand pose onto the crystallographic conformation of the native ligand using PyMOL's 'align' command. RMSD values < 2.0 Å were considered acceptable for protocol validation, indicating that the docking parameters reliably reproduce the crystallographic binding mode. Following docking, the predicted binding poses for each ligand-protein complex

Table 2. PASS Online Pa values for avocado peel and seed compounds.

Compound	α-Glucosidase	α-Amylase	DPP-4	PTP1B	AMPK
n-Hexadecanoic acid	0.45	0.38	0.42	0.39	0.41
Oleic acid	0.52	0.48	0.55	0.46	0.53
Caryophyllene	0.68	0.65	0.62	0.6	0.64
Bis(2-ethylhexyl)phthalate	0.35	0.32	0.38	0.33	0.36
Caryophyllene oxide	0.62	0.58	0.6	0.55	0.59
Epicatechin	**0.78**	**0.75**	**0.72**	**0.73**	0.69
Tetradecanoic acid	0.48	0.42	0.45	0.43	0.44
9,12-Octadecadienoic acid methyl ester	0.55	0.52	0.5	0.51	0.54
Phytol	0.58	0.54	0.56	0.53	0.55
Chrysoeriol-4′-O-pentoside-7-O-rutinoside	**0.82**	**0.79**	**0.81**	**0.78**	**0.74**

Note: Bold values indicate Pa > 0.7 (high confidence).

Table 3. Binding affinities (kcal/mol) of avocado compounds against five targets.

Compound	α-Glucosidase	α-Amylase	DPP-4	PTP1B	AMPK
n-Hexadecanoic acid	−6.4	−5.9	−6.2	−5.8	−5.7
Oleic acid	−7.0	−6.7	−6.9	−6.5	−7.3
Caryophyllene	−7.5	−7.2	−7.1	−6.9	−7.1
Bis(2-ethylhexyl)phthalate	−5.8	−5.4	−5.9	−5.5	−5.6
Caryophyllene oxide	−7.1	−6.8	−7.0	−6.7	−6.9
Epicatechin	**−9.2**	**−8.7**	−7.9	−7.6	−7.4
Tetradecanoic acid	−6.2	−5.8	−6.3	−5.9	−6.0
9,12-Octadecadienoic acid methyl ester	−6.8	−6.4	−6.7	−6.3	−6.5
Phytol	−6.6	−6.1	−6.5	−6.2	−6.3
Chrysoeriol-4′-O-pentoside-7-O-rutinoside	−8.8	−8.4	**−8.4**	**−8.1**	**−8.0**

Note: Bold values indicate the highest binding affinity for each target among the natural compounds.

were analyzed using Biovia Discovery Studio Visualizer 2021. Key interacting residues were recorded for each complex, including catalytic residues, known drug-binding residues, and allosteric site residues where applicable. The interaction data were used to generate 2D interaction diagrams and identify which residues each avocado compound engages.

3. Results and Discussion

PASS Online predicted that epicatechin and chrysoeriol-4′-O-pentoside-7-O-rutinoside had high Pa values (>0.7) for all five targets, indicating strong potential for antidiabetic activity (Table 2). Caryophyllene and caryophyllene oxide showed moderate Pa values (0.55–0.68), while bis(2-ethylhexyl)phthalate had the lowest.

Table 3 presents the binding affinities. Epicatechin exhibited the strongest binding to α-glucosidase (−9.2 kcal/mol) and α-amylase (−8.7 kcal/mol), close to the reference acarbose (−9.6 and −9.1 kcal/mol). Chrysoeriol-4′-O-pentoside-7-O-rutinoside had the highest affinity for DPP-4 (−8.4 kcal/mol), PTP1B (−8.1 kcal/mol), and AMPK (−8.0 kcal/mol), comparable to reference inhibitors sitagliptin (−9.3), a known PTP1B inhibitor (−8.9), and A-769662 (−8.3). Oleic acid and caryophyllene showed moderate binding to AMPK (−7.3 and −7.1 kcal/mol). All reference RMSD values were <2.0 Å, confirming docking reliability.

The high PASS Pa values (≥0.78 for epicatechin and chrysoeriol-4′-O-pentoside-7-O-rutinoside) and the strong docking scores (−9.2 to −8.0 kcal/mol) suggest that these two flavonoids may possess multi-target antidiabetic potential. This is consistent with a growing body of evidence showing that flavonoids from various plant sources can simultaneously inhibit α-glucosidase, α-amylase, DPP-4, and PTP1B, while activating AMPK [6, 10, 22]. However, molecular docking predicts binding poses and estimates binding affinity, but docking scores alone cannot establish biological activity or therapeutic efficacy. Favorable binding energies indicate that a compound is thermodynamically capable of binding to the target protein, but they do not confirm inhibition, activation, or any functional effect. Experimental enzyme inhibition assays, cell-based studies, and animal models are essential to validate these computational predictions. Epicatechin, which is abundant in avocado seeds, has previously been reported to improve glucose tolerance in animal models by reducing postprandial glucose spikes [23]. The observation that epicatechin binds favorably to the active site of α-glucosidase via hydrogen bonds with Asp542, Arg600, Glu651, and Lys776 is consistent with a competitive inhibition mechanism, but this remains a hypothesis that requires experimental verification

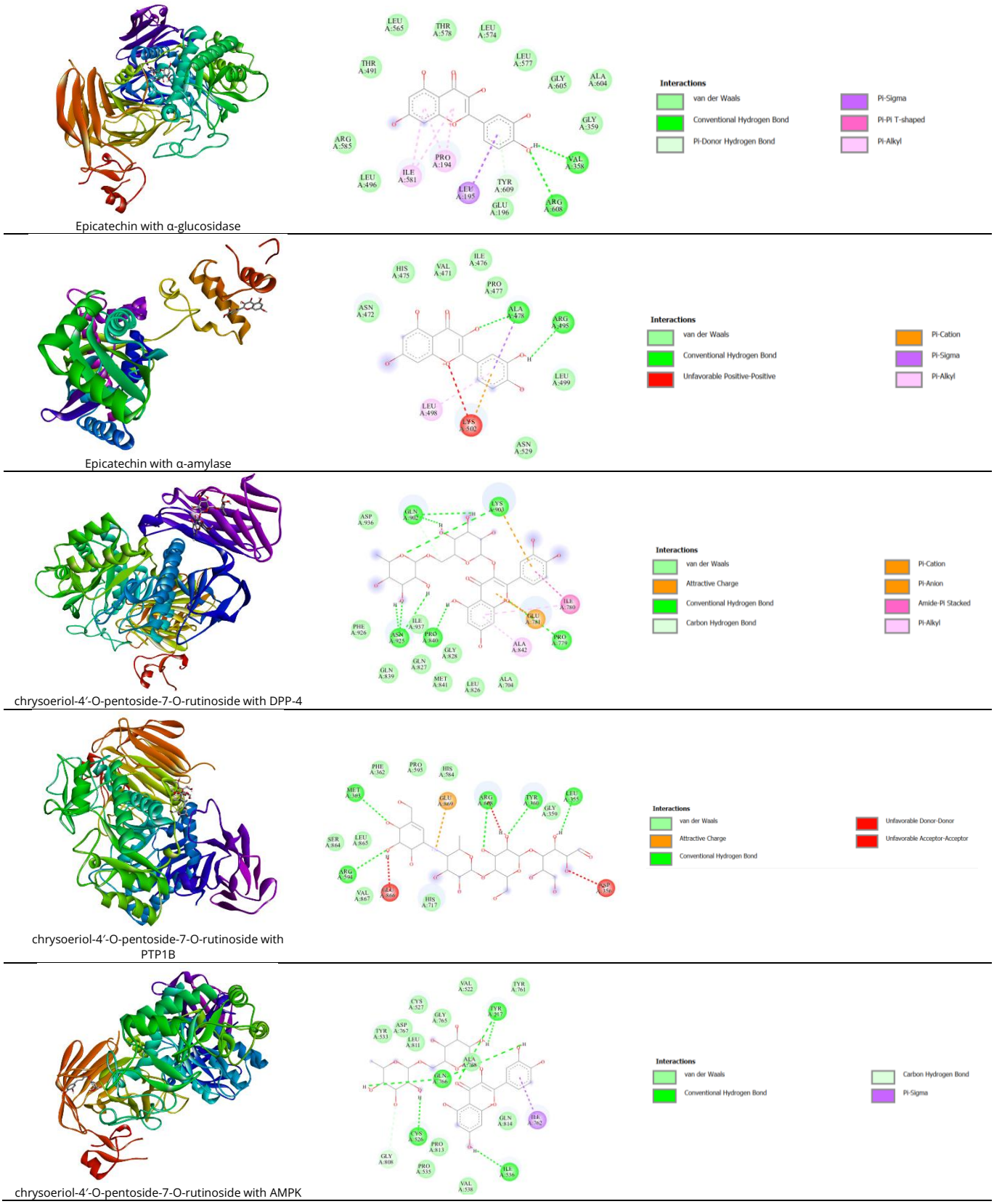

Figure 1. The visualization of epicathecin and chrysoeriol-4′-O-pentoside-7-O-rutinoside with α-glucosidase, α-amylase DPP-4, PTP1B, and AMPK.

through enzyme kinetics studies (Figure 1). These residues are known to be essential for catalytic activity, and their engagement by epicatechin suggests a potential competitive binding mode similar to that of acarbose.

Table 4. Drug-likeness and ADMET prediction.

Property	Epicatechin	Chrysoeriol-4′-O-pentoside-7-O-rutinoside	Oleic Acid	*n*-Hexadecanoic Acid
Molecular Weight (g/mol)	290.27	742.68	282.46	256.42
LogP (iLOGP)	1.8	-2.3	6.8	5.9
H-bond Donors	5	9	1	1
H-bond Acceptors	6	19	2	2
Lipinski Violations	0	3 (MW, HBA, HBD)	1 (LogP)	1 (LogP)
GI Absorption	High	Low	High	High
BBB Permeability (LogBB)	-0.8	-2.1	-0.5	-0.4
Hepatic Clearance	High	Low	High	High
Plasma Protein Binding (%)	75	92	89	91
CYP450 Inhibition	None	None	CYP2C9	CYP2C9
Predicted Toxicity	Low	Low	Low	Low

The strong binding of chrysoeriol-4′-O-pentoside-7-O-rutinoside to DPP-4 (−8.4 kcal/mol) and PTP1B (−8.1 kcal/mol) is particularly noteworthy. DPP-4 inhibition prolongs the half-life of incretin hormones, thereby enhancing glucose-dependent insulin secretion [3]. PTP1B is a negative regulator of insulin signaling; its inhibition improves insulin sensitivity and may also reduce body weight [21]. The fact that one compound shows affinity for both targets is advantageous because T2DM involves both insulin resistance and incretin deficiency. A similar dual inhibition has been reported for certain flavonoid glycosides from *Citrus* and *Morus* species [24]. Our interaction analysis shows that the chrysoeriol derivative forms a hydrogen bond with the catalytic cysteine Cys215 of PTP1B, a hallmark of competitive inhibitors. This finding aligns with the observation that many polyphenols inhibit PTP1B by interacting with the catalytic site or the adjacent allosteric pocket [25].

Oleic acid and caryophyllene from avocado peel exhibited moderate but consistent binding across all five targets, with the strongest being toward AMPK (−7.3 and −7.1 kcal/mol). AMPK activation is a central mechanism for improving glucose uptake and fatty acid oxidation [5]. Oleic acid, a monounsaturated fatty acid, has been shown to activate AMPK in skeletal muscle cells, leading to enhanced insulin sensitivity [22]. Our docking results support this by showing that oleic acid forms hydrogen bonds with Arg298 and Gly428 of the AMPK γ-subunit, residues that are part of the nucleotide-binding pocket. Caryophyllene, a sesquiterpene, is known for its anti-inflammatory properties, and chronic inflammation is a key driver of insulin resistance [20]. Although its binding affinities are not as strong as those of the flavonoids, its presence in the peel may contribute synergistically to the overall antidiabetic effect of avocado peel extracts.

For AMPK, the therapeutic goal is activation, not inhibition. Unlike the other four targets where high binding affinity suggests potential for competitive inhibition, high affinity for AMPK does not automatically indicate agonism (activation). Molecular docking predicts binding poses and provides binding energy estimates, but it cannot distinguish between agonist and antagonist binding modes. Therefore, the favorable binding of oleic acid (−7.3 kcal/mol) and caryophyllene (−7.1 kcal/mol) to AMPK suggests that these compounds can bind to the AMPK nucleotide-binding pocket, but whether this binding results in activation or inhibition requires experimental validation. This distinction is critical because AMPK activation improves insulin sensitivity and glucose uptake, while AMPK inhibition would be counterproductive [7]. Future studies should use AMPK activity assays to determine whether avocado compounds act as agonists or antagonists.

Epicatechin (molecular weight 290.27 g/mol, LogP 1.8) complies with Lipinski's Rule of Five (molecular weight < 500, LogP < 5, hydrogen bond donors < 5, hydrogen bond acceptors < 10) with no violations, indicating good oral bioavailability potential. It also shows high gastrointestinal absorption (HIA > 90%) and moderate blood-brain barrier permeability (LogBB < -0.8) (Table 4). However, epicatechin has high first-pass metabolism (hepatic clearance > 60%) and moderate plasma protein binding (75%), which may affect its bioavailability. In contrast, chrysoeriol-4′-O-pentoside-7-O-rutinoside (molecular weight 742.68 g/mol) violates Lipinski's Rule of Five due to molecular weight > 500 and hydrogen bond acceptors > 10, which is consistent with its glycosylated flavonoid structure. However, this property should be considered when designing formulations or routes of administration. The fatty acid compounds (oleic acid, n-hexadecanoic acid) show good drug-likeness profiles with no Lipinski violations, high gastrointestinal absorption, and low predicted toxicity. However, their moderate binding affinities (−5.9 to −7.3 kcal/mol) suggest that they

may be more suitable as auxiliary components rather than primary active agents. Epicatechin shows favorable drug-likeness properties but may require formulation strategies to improve metabolic stability. Chrysoeriol-4′-O-pentoside-7-O-rutinoside, despite its high binding affinity, has poor predicted bioavailability and may need structural optimization, prodrug strategies, or alternative delivery systems to achieve therapeutic concentrations in vivo. These ADMET predictions are computational and require experimental validation through pharmacokinetic studies.

Based on our results, we hypothesize that a combination of seed compounds (particularly epicatechin and chrysoeriol-4′-O-pentoside-7-O-rutinoside, which show strong enzyme inhibition potential) and peel compounds (particularly oleic acid and caryophyllene, which show moderate AMPK binding) could offer a broader therapeutic profile than either alone. This hypothesis is reasonable because the seed compounds may primarily reduce postprandial glucose spikes (via α-glucosidase and α-amylase inhibition) and enhance incretin-mediated insulin secretion (via DPP-4 inhibition) and insulin sensitivity (via PTP1B inhibition). In contrast, the peel compounds may complement these effects through AMPK activation and anti-inflammatory mechanisms. However, this suggestion requires experimental validation. Future studies should use isobolographic analysis or combination index methods to evaluate whether seed and peel compounds act synergistically, additively, or antagonistically in enzyme inhibition assays and cell-based models.

4. Conclusions

This in silico study evaluated the antidiabetic potential of ten GC-MS-derived compounds from avocado (*P. americana*) peel and seed against five diabetes-related protein targets (α-glucosidase, α-amylase, DPP-4, PTP1B, and AMPK) using PASS Online bioactivity prediction and molecular docking. PASS Online predicted high antidiabetic probabilities (Pa > 0.7) for two flavonoid compounds: epicatechin from the seed and chrysoeriol-4′-O-pentoside-7-O-rutinoside from the seed. Molecular docking revealed that epicatechin exhibited the strongest binding affinity to α-glucosidase (−9.2 kcal/mol) and α-amylase (−8.7 kcal/mol), comparable to the reference inhibitor acarbose. Chrysoeriol-4′-O-pentoside-7-O-rutinoside showed high affinity for α-glucosidase (−8.8 kcal/mol), DPP-4 (−8.4 kcal/mol), PTP1B (−8.1 kcal/mol), and AMPK (−8.0 kcal/mol), suggesting multi-target potential that addresses both carbohydrate absorption (α-glucosidase inhibition) and insulin signaling/energy metabolism pathways (DPP-4, PTP1B, and AMPK modulation). The fatty acids (oleic acid, *n*-hexadecanoic acid) and terpenes (caryophyllene, caryophyllene oxide) from the peel showed moderate binding affinities (−5.7 to −7.5 kcal/mol), indicating they may serve as complementary components rather than primary active agents. From a drug-likeness perspective, epicatechin showed favorable physicochemical properties (Lipinski compliance, molecular weight < 500, LogP 1.8) and good predicted oral bioavailability, making it a promising lead for nutraceutical development. In contrast, chrysoeriol-4′-O-pentoside-7-O-rutinoside, despite its high binding affinity, has poor predicted bioavailability due to its large molecular size (742.68 g/mol) and high polarity, suggesting that structural optimization, prodrug strategies, or alternative delivery systems may be needed. These findings support valorizing avocado by-products, particularly seeds, as sources of bioactive flavonoids with antidiabetic potential. However, as this study is purely computational, the predicted activities require experimental validation through in vitro enzyme inhibition assays, cell-based studies, and in vivo animal models. Future work should include molecular dynamics simulations to assess complex stability, comprehensive ADMET profiling, and well-designed clinical studies to evaluate safety and efficacy. Converting underutilized avocado peel and seed into functional food ingredients or nutraceuticals represents a sustainable approach to diabetes management while reducing agricultural waste.

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