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In Silico Screening and Molecular Docking Studies of Unique Phytoconstituents Present in Different Unripe Fruits as Potential Antidiabetic and Anti-hyperlipidemic Agents

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Abstract: Lifestyle disorders like hyperlipidemia and Diabetes mellitus have become a threat to survival in the modern technology-based sedentary life generation. These chronic diseases need to be managed and cannot be completely cured even with medication. For lifestyle management, the consumption of natural products is a focus nowadays. Unripe fruits are rich in different phytocomponents, which show different biological activities. This study predicts the efficacy of different phytoconstituents of unripe fruits as anti-diabetic and anti-hyperlipidemic agents using in-silico approaches. Several components of unripe fruits were screened from the existing literature. Drug-like molecules were docked against proteins: α-amylase (1B2Y), DPP-IV (4A5S), HMG-CoA reductase (1DQ9), and PPAR-γ (4YT1) to quantify their binding affinities, RMSD values, and binding interaction, comparing against standard drugs. ADMET properties of ligands with satisfactory docking parameters were observed for further analysis. Multiple ligands showed a good molecular docking profile against different proteins. Based on *in silico* parameters, Limonin, artocarpin, reticuline, and phyllanthin were found to effectively interact with either of the receptors with acceptable ADMET properties. Further research can be extended to design the pharmacophore of these moieties and QSAR modelling, followed by synthesizing these molecules chemically to check their *in vitro* and *in vivo* properties.

Keywords: Unripe fruits; Molecular docking; Lipinski rule; RMSD; ADMET; Toxicity.

1. Introduction

The modern lifestyle is mainly characterized by the availability of high convenience, a fast-paced environment, and technology. Unfortunately, this advancement of technology has marked the increase of different chronic and metabolic disorders like Cardiovascular diseases (CVD) [1]. CVD is hallmarked by hyperlipidemia or increased accumulation of low-density lipoproteins and their oxidation on the walls of the artery, narrowing the arterial lumen and reducing blood flow. The morbidity and mortality rates are greatly increased in the case of the presence of other metabolic diseases, such as Diabetes mellitus (DM). It is diagnosed mainly due to impaired or insufficient release of insulin in the body [2]. The inability to produce insulin

leads to DM type 1, an insulin-dependent DM. It is termed an autoimmune disorder, which is characterized by destruction of the β-cells mediated by the immunogenic T-cells, leading to insulin-deficient hyperglycemia [3]. While DM type-2 (T2DM) is a non-insulin-dependent DM, it occurs when the peripheral cells of the body offer a high resistance towards the action of insulin, and finally, the impaired functioning of the β-cells. These two events are co-related as when insulin resistance occurs due to some disruption of cellular pathways in the body, the peripheral cells of skeletal muscles, liver, and the adipose tissues become less sensitive towards insulin [4]. The pathophysiology of Diabetes Mellitus is closely related to increased concentrations of Triglycerides (TG) and Low-density lipoproteins (LDL) in the body. The detailed pathophysiology of the diseases is represented in Figure 1.

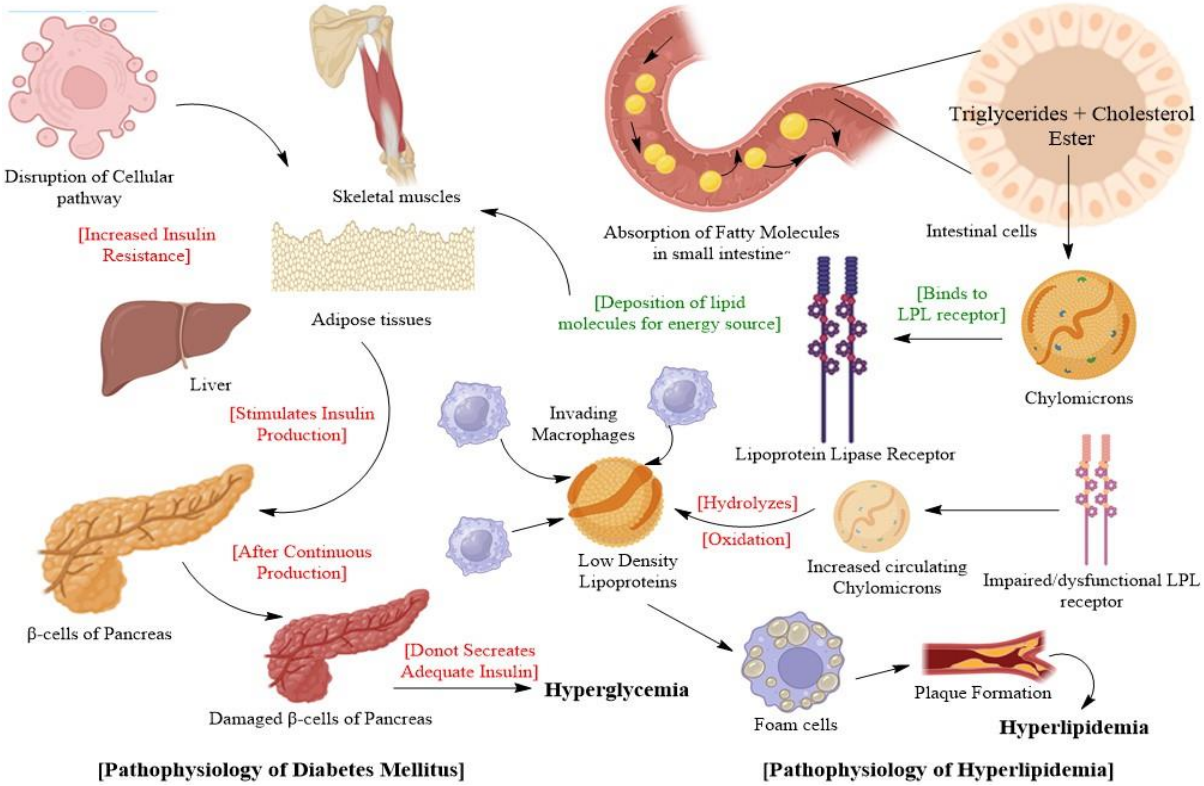


Figure 1. The basic pathogenesis of Diabetes mellitus and hyperlipidemia.

Multiple enzymes are involved in the progression of T2DM. Alpha-amylase (EC 3.2.1.1) is a hydrolase enzyme primarily present in pancreatic juices and also in saliva. It promotes the hydrolysis of the α-1,4-glycosidic linkages present in different carbohydrate molecules like glucose, sucrose, maltose, starch, cellulose, and amylopectin, which induces the postprandial hyperglycemia in the body [5]. Dipeptidyl peptidase-IV or DPP-IV (EC 3.4.14.5) is an aminopeptidase protein distributed in numerous tissues, such as the intestine, endothelial cells of the liver, lungs, and kidneys. It causes the degradation of incretins like Glucagon-like peptide-1 (GLP-1) and Glucose-dependent Insulinotropic peptide (GIP), thus leading to insulin resistance and hyperglycemic conditions [6]. Overexpression or improper functioning of these two enzymes can cause prolonged high blood glucose in the body, which eventually leads to insulin resistance and chronic hyperglycemia. Therefore, inhibiting these two enzymes can be used as an inevitable therapeutic target for regulating the symptoms and complications of T2DM.

Hyperlipidemia, or an increase in lipid content, is characterized by increased levels of Triglycerides and cholesterol. The synthetic pathway of cholesterol begins with the conversion of acetyl-CoA to 3-hydroxy-3-methyl-glutaryl-coA (HMG-CoA), a key intermediate in the

synthesis. The HMG-CoA then converts to Mevalonate by the action of the enzyme HMG-CoA reductase (EC 1.1.1.34), which is considered to be the rate-limiting step. Cholesterol is required for maintaining the structural integrity of the cell membranes and production of hormones; however, synthesis of excess cholesterol (especially LDL) can lead to Atherosclerosis and other cardiovascular complications. Consequently, by inhibiting the action of HMG-CoA reductase, the cholesterol production is decreased. In such a situation, the liver compensates by expressing more LDL receptors on the hepatocyte surface. As a result, higher concentrations of bad LDL are being cleared out by the liver and balancing out the cholesterol levels in the blood plasma [7].

On the other hand, the pathophysiology of hyperlipidemia has a direct link with etiology and the extent of T2DM. Peroxisome proliferator-activated receptor-γ (PPAR-γ) is a master regulator of fatty acid metabolism in the body. It converts preadipocytes to mature adipocytes, thereby enhancing the storage of excess fats in adipocytes, leading to decreased ectopic fat deposition. Furthermore, their activation also leads to the upregulation of proteins involved in fatty acid reuptake, like CD36 and Lipoprotein Lipase, resulting in suppressed plasma triglyceride levels and higher production of HDL in the body [8]. PPAR-γ also aids in the anti-hyperglycemic activity in the body. In fact, PPAR-γ agonists have been shown to increase the transcription of several genes responsible for glucose uptake, metabolism, and insulin-dependent glucose distribution in the muscles. Being a major modulator of circulating free fatty acids in the body, it helps to lower the lipotoxicity in the body, which is considered to be a major risk factor of T2DM [9].

Modern synthetic drugs are usually used to treat these lifestyle-related chronic diseases. Still, they only play a sustaining role in regulating the blood glucose and triglyceride levels in the body. These synthetic drugs, therefore, show a wide array of side effects and toxicity. So, in modern days, the focus of treatment has now shifted from synthetic sources to natural resources like vegetables, fruits, and other medicinal plants. Fresh fruits are quite a good option for the daily intake of different bioactive components helpful for the prevention of many diseases. Fruits do not need to be cooked, thus most of the phytochemical content remains intact [10]. However, as fruits have different stages of ripening, like Unripe, Ripe, and Overripe stages, the phytochemical contents also differ based on the morphological changes of the fruit. The different bioactive components present have been seen to be in higher concentrations in unripe fruits than their ripened counterparts. The presence of these phytoconstituents makes unripe fruits a great potential to be added to the daily diet for the prevention and control of complications of CVD and Diabetes [11].

Thus, in order to scientifically methodize and channelize our biological investigations, we aimed to perform *in silico* screening to evaluate the antidiabetic and anti-hyperlipidemic potential of the unique phytocomponents present in commonly consumed unripe fruits—medicine using bioinformatics tools. As potential therapeutic targets, we considered alpha-amylase, DPP-IV, HMG-CoA reductase, and PPAR-γ due to their pivotal role in the etiology and progression of the diseases. Different computational techniques like Drug likeliness analysis, Molecular docking simulations, calculation of binding free energies, assessment of binding interactions, pharmacokinetic assessment, and ADMET profiling have been performed on different bioactive phytoconstituents against individual proteins. The outcome of the study suggests that various phytochemicals obtained can act as agonists/antagonists to these proteins and effectively ameliorate the complications of chronic diseases like hyperlipidemia and T2DM. To the best of our knowledge, this is the first report to establish the efficacy of different

bioactive components present in unripe fruits as potential anti-hyperglycemic and anti-hyperlipidemic agents.

2. Materials and Methods

2.1. Protein selection, validation, and modification.

The crystal structures of the respective proteins α-amylase (1B2Y), Dipeptidyl Peptidase IV (4A5S), HMG-coA reductase (1DQ9), and Peroxisome Proliferator-Associated Receptor-gamma (4YT1) were obtained from the Protein Data Bank (www.rcsb.org). The 3D structures of the proteins were validated by visualizing the Ramachandran plot using Biovia Discovery Studio Visualizer 2025 software. The protein modification was done using USF Chimera 1.9. The pre-existing ligands, water, and other heteroatoms were selected and deleted. Based on the presence of active sites on the proteins, one of the identical chains of the protein was selected for further investigation. Chain A of 1B2Y and 1DQ9 was selected, while Chain B of 4A5S and 4YT1 was selected. To the modified protein side chains, Kollman united atom charges and Gasteiger charge was added, followed by the addition of polar hydrogen to the protein to make it ideal for further docking.

2.2. Ligand selection.

Based on a literature review of different unique phytoconstituents present in unripe fruits, which are generally grown in Bengal, 50 different ligands, as mentioned in Table 1, were selected. Their 3D conformers in .sdf format were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) for further analysis.

Table 1. Unique phytoconstituents are present in different commonly consumed fruits.

Sl. No.	Common name	Scientific name	Family	Chemical Constituents	PMID	Ref
1	Green Banana	*Musa acuminata*	Musaceae	Campesterol (Phytosterols) Cyanidin-3-rut (Anthocyanins) Kaempferol (Flavonoids) Pectin (Polysaccharides) Stigmasterol (Phytosterols) Violaxanthin (Carotenoids)	173183 441674 5280863 3722617 5280794 448438	[12–14]
2	Fig	*Ficus carica*	Moraceae	Angelicin (Coumarin) Kaempferol (Flavonoids) Naringenin (Flavonoids) Psoralen (Coumarin) Zeaxanthin (Carotenoids)	10658 5280863 439246 6199 5280899	[15–17]
3	Guava	*Psidium guajava*	Myrtaceae	Asiatic acid (Terpenoid) Campesterol (Phytosterols) Guaijaverin (Glycosides) Limonene (Terpenoids) Naringenin (Flavonoids) Stigmasterol (Phytosterols)	119034 173183 5481224 22311 431246 5280794	[18–20]
4	Cucumber	*Cucumis sativus*	Cucurbitaceae	Indole-3-aldehyde (Indole alkaloid) Kaempferol (Flavonoid) Cucurbitacin A (Terpenoids) Cucurbitacin B (Terpenoids) Cucurbitacin C (Terpenoids)	10256 5280863 5281315 5281316 5281317	[21–23]
5	Limes, Bengal lime	*Citrus aurantiifolia*	Rutaceae	Octopamine (Alkaloids) Synephrine (Alkaloids) Naringenin (Flavonoids) Citral (Terpenoids) Limonin (Terpenoids)	4581 7172 439246 638011 179651	[24–26]

Sl. No.	Common name	Scientific name	Family	Chemical Constituents	PMID	Ref
6	Ceylon olive/Jolpai	*Elaeocarpus serratus*	Elaeocarpaceae	Esculetin (Coumarin) Elaeocarpine (Alkaloid) Elaeocarpidine (Alkaloid) Zeaxanthin (Carotenoids) Kaempferol (Flavonoid) α -amyrin (Terpenoids)	5281416 280286 355436 5280899 5280863 73170	[27–29]
7	Indian Gooseberry/Amla	*Phyllanthus emblica*	Phyllanthaceae	Phyllanthin (Lignan) Harmalol (Alkaloid) Kaempferol (Flavonoid) Chebulagic acid (Polyphenolic) Chlorogenic acid (Polyphenolic) Chebulanin (Polyphenolic)	358901 3565 5280863 72285 1794427 75034370	[30–32]
8	Green Jackfruit	*Artocarpus heterophyllus*	Moraceae	Artocarpin (Flavonoid) Moracin A (Benzofuran) Jacquilenin (Alkaloid) Zeaxanthin (Carotenoids) Naringenin (Flavonoids) Kaempferol (Flavonoids) Punicalagin (Tannins)	5458461 441839 14163574 5280899 439246 5280863 16129719	[33–35]
9	Green peas	*Pisum sativum*	Fabaceae	Diosmin (Glycosides) Psidinin C (Peptides) Sparteine (Alkaloid) Zeaxanthin (Carotenoids) Violaxanthin (Carotenoids) Naringenin (Flavonoids) Kaempferol (Flavonoids)	5281613 131752695 644020 5280899 448438 439246 5280863	[36–38]
10	Green Tomatoes	*Solanum lycopersicum*	Solanaceae	Solanine (Alkaloids) α-Tomatine (Alkaloids) Naringenin (Flavonoids) Kaempferol (Flavonoids) Ascorbic acid (Vitamins)	9549171 28523 439246 5280863 54670067	[39–41]
11	Capsicum	*Capsicum annuum*	Solanaceae	Capsaicin (Alkaloids) Homocapsaicin (Alkaloids) Nonivamide (Methoxy phenols) Zeaxanthin (Carotenoids) Violaxanthin (Carotenoids) Kaempferol (Flavonoids) Limonene (Terpenoids)	1548943 6442566 2998 5280899 448438 5280863 22311	[42–44]
12	Custard Apple/Ata	*Annona squamosa*	Annonaceae	Anonaine (Alkaloid) Bullatacin (Lactone) Corydine (Alkaloid) Reticuline (Alkaloid)	160597 11124994 10153 439653	[45–47]
13	Mango	*Mangifera indica*	Anacardiaceae	Theobromine (Alkaloid) Mangiferin (Alkaloid)	5429 5281647	[48,49]

These molecules were analyzed in SwissADME [50], to determine their drug likeliness based on their adherence to Lipinski's rule. Molecules that showed more than two violations of the Lipinski rule were removed in the initial screening.

Based on the Literature review, the compounds that act as standard agonists or antagonists against the particular protein to ameliorate the progression of diabetes or hyperlipidemia were selected as standard or reference compounds.

2.3. Molecular docking simulation.

Molecular docking of the ligand that passed the initial screening was conducted against the modified proteins using AutoDock software (v4.2.6). The docking model used was semi-flexible, keeping the protein as a rigid molecule and docking various poses of the same ligand in a minimized energy conformer. The results were analyzed to determine the binding affinity of the ligands to the proteins (kcal/mol), keeping in consideration that the Root Mean Square

Deviation (RMSD) value is within the standard limit of 1-3Å. The 3D image of the docked ligand-protein complex was taken for further analysis. The interaction of amino acid residues in the ligand-protein complex at different ligand poses was observed, followed by estimation of their individual binding bond lengths. The ligands showing unfavorable molecular interaction with the protein were discarded at this stage.

2.4. Pharmacokinetic analysis.

The pharmacokinetic parameters (ADME) were analyzed. The absorption (GI absorption), distribution (bioavailability score and blood-brain barrier penetration), and metabolism profile (inhibition of liver CYP enzymes) were determined using SwissADME software [50]. Molecules with low GI absorption were removed from the screening process in this stage of analysis. The elimination profile of the ligands (biological half-life in hours and clearance mL/min/kg) was tested using ADMETlab 3.0 [51].

2.6. Toxicity analysis.

The toxicity of the ligands based on their Lethal Dose (LD_{50}) values was analyzed using ProTox-3.0 [52], where toxicity like hepatotoxicity, nephrotoxicity, and neurotoxicity was analyzed, followed by analysis of long-term toxicity like carcinogenicity and mutagenicity. The toxicity scale value was also observed. Ligands with a toxicity score above 3, with higher LD_{50} values, and no long-term toxicity were selected as best ligands for further analysis.

3. Results and Discussion

Chronic diseases like T2DM, CVD, and hyperlipidemia have spread at an alarming rate by the end of the 21st century. Due to the severe mortality and morbidity rates of these diseases, there is an urgent need to regulate the blood glucose and lipid profiles in our bodies. Existing synthetic drug molecules for the treatment of T2DM and HL, like Atorvastatin and Sitagliptin, show severe hepatotoxicity, neurotoxicity, and respiratory toxicities. On the other hand, rosiglitazone shows high neurotoxicity and respiratory toxicity. Thus, the need to develop semi-synthetic drug molecules derived from natural sources has emerged. Unripe fruits, which are consumed in our daily diet, due to their lower carbohydrate content and extremely high content of phytoconstituents, show a plethora of biological activities. Compared to the ripened counterparts, unripe fruits show a lesser glucose spike when consumed with a greater enrichment of bioactive compounds.

3.1. Protein selection and modification

Multiple proteins and enzymes are associated with the progression of T2DM and HL. α-amylase (EC 3.2.1.1) is an important carbohydrate-digesting enzyme secreted by the pancreas and salivary glands. The core active site consists of Asp 197, Glu 233, and Asp 300 at domains A and B of the protein [53]. DPP-4 (EC 3.4.14.5) is another important enzyme that breaks down complex carbohydrates into simpler forms. The active site amino acid residues include Ser 630, Asp 708, and His 740 in domains A and B of the protein structure [54]. HMG coA reductase (EC 1.1.1.34), which is a key enzyme in cholesterol synthesis, has Lys691, Glu559, Asp767, and His866 amino acid residues in its active site [55]. PPAR-γ, a nuclear factor receptor, is associated with the etiology of both T2DM and HL, has Cys285, Ser289, His323, Tyr327, Lys367, His449, and Tyr473 amino acid residues in its active site [56]. The

four selected proteins with PDB IDs 1B2Y, 4A5S, 1DQ9, and 4YT1 are shown in Figure 2 with their 3D structure and Ramachandran plot. Each protein shows 60-90% amino acid in favorable zones (shown as green dots), confirming that the proteins are biologically feasible for ligand binding.

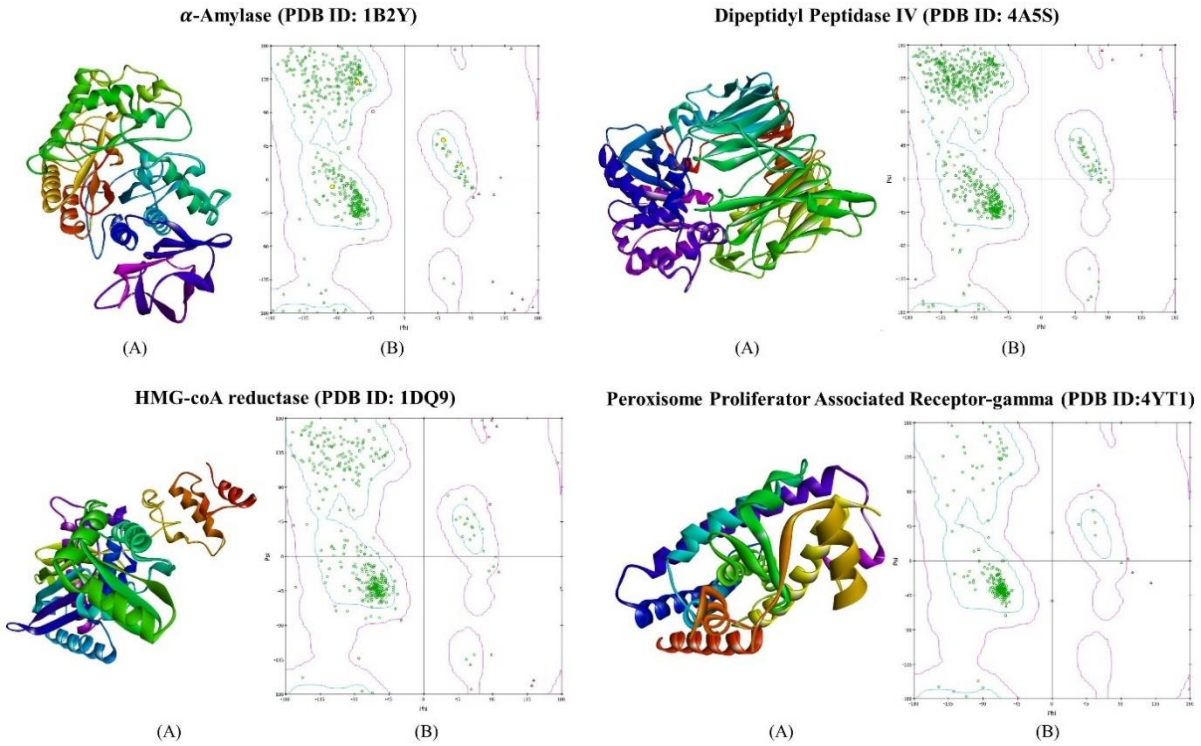


Figure 2. Visualization and validation of protein structure **(A)** 3D-structure of selected chains of four different proteins; **(B)** Protein validation by Ramachandran plot

3.2. Drug-likeness analysis.

This study includes 50 different unique phytocompounds, which are found in several commonly consumed unripe fruits and are screened based on their effective interactions with the respective proteins. The phytocompounds were further compared with the standard drugs based on their binding interactions, docking score with the protein, and their toxicity. The standard compounds were found from the initial structure downloaded from the Protein Data Bank. Since the phytocompounds showed binding interaction in the same active site as the standard compound, this indicates their similar activity (agonism/antagonism). Screening of ligands from Table 1 based on their drug likeliness as per Lipinski rule shows 35 out of 50 ligands can be processed for further study since they show less than 2 violations from the Lipinski rule. The omitted ligands include Cyanidin-3-rutinoside, Chebulagic acid, Chebulanin, Diosmin, Guaijaverin, Mangiferin, Pectin, Psidinin A, Punicalagin, Solanine, Violaxanthin, and Zeaxanthin. Hence, these ligands were not further studied.

Initial screening of the molecules based on their Lipinski rule led to the elimination of 15 compounds since they violated the criteria of drug likeliness. The criteria include molecular weight less than 500 Dalton for effective binding to active site without electrostatic repulsion; log P less than 5 for effective penetration through plasma membrane; Hydrogen bond donor and acceptor less than 5 and 10 respectively for effective bonded and non-bonded interactions with amino acid residues; rotatable bonds less than 5 ensuring a smaller number of pose conformers for binding to protein, hence increasing ligand specificity for the protein.

3.3. Molecular docking analysis.

The docking score of the ligands showing the best binding affinity to the selected proteins was determined. Some of the ligands were suitable for further analysis. The remaining ligands were discarded based on the following parameters exhibited by them: Ligand showing higher RMSD values (>3Å) as they are not energetically favourable; The ligands that did not satisfy Easson-Stedman hypothetical three-point binding interaction; Presence of unfavorable binding interactions (bumps) in ligand-protein binding complex.

An example of unfavourable binding of a ligand in the receptor cavity is illustrated in Figure 3.

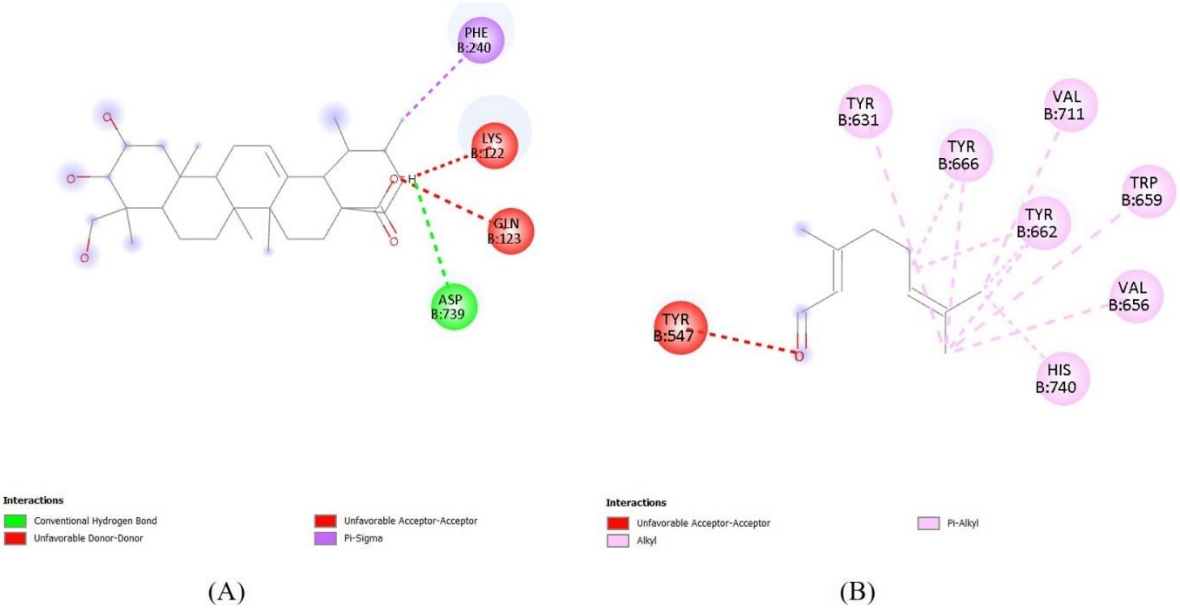


Figure 3. Unfavourable amino acid binding of the ligands **(A)** Asiatic acid; **(B)** Citral to the protein DPP-IV at RMSD values 1-3Å, which leads to rejection of these molecules in the final molecule list, as in the human body, due to unfavourable donor-donor and acceptor-acceptor interaction, causing electrostatic repulsion, leading to failure in successful protein-ligand binding

Table 2 shows the ligands that were found suitable for further analysis by molecular docking studies.

Table 2. Molecular docking analysis of different ligands.

Sl. No.	Ligand	Minimized energy (kcal/mol)	Binding affinity (kcal/mol)	RMSD (Å)	Interacted with amico acid residues
Protein: α-amylase (1B2Y); Chain A			**Grid dimension: 81.6146Å (X-axis); 89.3511Å (Y-axis); 71.5813Å (Z-axis)**		
0.	Acarbose	852.13	-7.9	1.73	LYS278; GLU282; PRO332; SER289; ASP402; HIS331
1.	α-Amyrin	681.31	-9.8	1.34	LEU165; LEU162; ALA198; GLU233; ARG195; HIS299; ASP300; TRP58; TYR62; TRP59
2.	Limonin	2490.2	-9.3	1.66	TRP59; TRP58; HIS299; TYR62; HIS101; LEU165
3.	Stigmasterol	546.19	-9.1	1.82	TYR62; HIS101; LEU165; ILE51; PRO54; TRP59; TRP58
4.	Anonaine	424.87	-8.6	1.89	ASP300; TRP58; TYR62; LEU165; GLN63; TRP59;
5.	Cucurbitacin A	887.49	-8.5	2.06	ARG10; THR6; GLY334; ARG252; PHE335; TYR333; SER289; PRO4
6.	Cucurbitacin C	883.66	-8.3	2.34	LEU165; GLY104; THR163; VAL107; VAL49; ALA198; HIS101; LEU162; TYR62

Sl. No.	Ligand	Minimized energy (kcal/mol)	Binding affinity (kcal/mol)	RMSD (Å)	Interacted with amico acid residues
7.	Chlorogenic Acid	863.05	-8.2	1.56	PRO332; ARG421; ASP402; GLY403; ARG398; THR11; PHE335; GLY334; ARG252; ALA292; SER289; TYR333; GLU282 TRP280
8.	Cucurbitacin B	863.05	-8.2	1.52	LEU165; TYR162; ALA198; GLU233; ARG195; ASP197; TRP56; TRP59
9.	Elaeocarpidine	634.8	-8.1	2.01	GLN63; LEU165; LEU162; ASP197; HIS299; TYR62; ASP300; TRP58; TRP59
10.	Kaempferol	362.5	-8.1	1.96	GLU233; ASP197; ALA198; LEU162; TRP59; GLN63; LEU165; HIS101; TYR62; TRP58; ASP300; HIS299; ARG195
11.	Naringenin	195.81	-8.1	2.33	ASP197; HIS299; TRP58; TYR62; ASP300; LEU165; GLN63; TRP59; ASN298; ILE235; GLU233ARG195
Protein: DPP-4 (4A5S); Chain B			**Grid Dimension: 87.9162Å (X-axis); 68.0964Å (Y-axis) and 61.2561 (Z-axis)**		
0.	Sitagliptin	526.94	-9	2.1	ARG125; ASP545; VAL546; TYR547; LYS554; TRP627; TRP629; GLY639; TRP659; TYR662; TYR666; ASN710; HIS740
1.	Artocarpin	617.78	-9.8	1.53	ARG125; GLU205; GLU206; TYR547; TRP629; SER630; TYR631; GLY632; VAL656; TRP659; TYR662; TYR666; ASN710; VAL711
2.	Limonin	2490.2	-9.7	1.94	TYR381; THR401; TRP402; ASN420; GLY424; PRO426; GLN586
3.	Cucurbitacin A	887.49	-9.4	2.27	ARG125; GLU205; GLU206; ARG358; ARG669; TYR662; TYR666; TRP659; SER630; ASN710; VAL711; HIS740
4.	α-Amyrin	681.31	-9.3	1.12	TYR238; PHE240; LYS250; ALA707; ASP737
5.	Anonaine	424.87	-8.9	1.64	GLU205; GLU206; PHE357; TYR666; ARG669
6.	Kaempferol	362.5	-8.3	1.03	PRO475; PRO510; LYS512; ILE529; VAL558; PHE559; ARG560; ASN562; ALA564; THR565
7.	Naringenin	195.81	-8.3	1.58	ARG125; GLU205; VAL656; TRP659; TYR662; TYR666; SER630; TYR631; ASN710; VAL711; HIS740
8.	Elaeocarpidine	634.8	-8.1	1.24	ARG125; ASP545; VAL656; LYS554; TRP563; ASN562; SER630; ASN710; HIS740
9.	Moracin A	449.11	-8.1	2.23	TYR547; ARG358; TYR662; TYR666; ARG669
10.	Elaeocarpine	399.47	-8	1.27	LYS122; TRP124; TRP201; PHE240; LYS250; VAL254
Protein: HMG-coA reductase (1DQ9); Chain A			**Grid Dimension: 81.3693Å (X-axis); 65.7755Å (Y-axis); 75.684Å (Z-axis)**		
0.	Atorvastatin	1011.8	-7.8	1.93	ALA556; ALA763; ALA768; GLN766; GLN814; ILE536; ILE762; MET534; PRO535; TYR517; TYR533; VAL538
1.	Limonin	2490.2	-9.8	1.29	ALA556; ALA763; ALA768; GLN814; ILE536; ILE762; MET534; VAL538
2.	Elaeocarpidine	634.8	-9.8	1.91	ALA556; ALA763; CYS527; GLN814ILE536; ILE762; TYR517; VAL522; VAL530; VAL538
3.	Phyllanthin	394.58	-9.6	0.24	ALA816; GLN814; ILE536; ILE762; PRO535; PRO813; TYR517; TYR533; VAL538
4.	Moracin A	449.11	-9.1	2.1	ALA525; ASP767; ASN658; GLN766; GLY803; GLY806; ILE802; MET655; MET657; THR809; TYR761
5.	Stigmasterol	546.19	-8.8	1.73	CYS527; GLY532; LEU811; TYR517; TYR519; VAL522; VAL530
6.	Anonaine	424.87	-8.7	2.07	ALA556; ALA763; ILE536; ILE762; PRO535; TYR517; TYR533; VAL538
7.	Artocarpin	617.78	-8.7	1.83	ALA768; ASP767; GLN766; GLN814; GLY765; ILE536; ILE762; LEU811; PRO535; PRO813; TYR517; TYR533; VAL538
8.	Kaempferol	362.5	-8.7	2.31	ALA556; CYS526; CYS527; GLN814; GLY532; ILE536; ILE762; LEU814; TYR517; TYR519; TYR533; VAL522; VAL530; VAL538

Sl. No.	Ligand	Minimized energy (kcal/mol)	Binding affinity (kcal/mol)	RMSD (Å)	Interacted with amico acid residues
9.	Esculetin	104.17	-8.6	1.09	ARG496; GLN497; GLN510; LEU509; PRO506; SER493; SER500; TYR514;
10.	Naringenin	195.81	-8.2	2.13	ALA654; ASN658; ASP767; GLN766; GLN770; GLY656; GLY765; GLY803; GLY806; GLY807; MET655; MET; 657; MET659; THR809
Protein name: PPAR-γ (4YT1); Chain B			**Grid Dimension: 30.8375Å (X-axis); 38.8050Å (Y-axis); 32.8412 (Z-axis)**		
0.	Rosiglitazone	222.36	-7.6	2.04	LEU228; CYS285; ARG288; GLU295; MET329; LEU333
1.	Reticuline	417.03	-8.1	1.52	PRO227; LEU228; ILE281; CYS285; ARG288; ALA292; ILE341; SER342; GLU343; MET348
2.	Stigmasterol	546.19	-10	2.22	HIS266; CYS285; ARG288; ALA 292; ILE326; MET 329; ILE 341
3.	Limonin	490.24	-8.1	1.69	GLN286; LEU 469; TYR473
4.	Jacquilenin	398.43	-8.4	1.23	ARG288; GLU291; ALA292; SER342; GLU343
5.	Kaempferol	362.5	-8.2	2.38	PRO227; LEU228; ARG288; SER289; ALA292; GLU295; LEU330
6.	Elaeocarpidine	634.8	-9.1	1.74	CYS285; ARG288; ALA292; ILE326; MET329
7.	Elaeocarpine	399.47	-8.4	1.78	CYS285; ARG288; ALA292; ILE326; MET329
8.	Anonaine	424.87	-9.3	2.06	ARG288; ALA292; GLU295; ILE326; MET329; LEU330; LEU333; SER342
9.	Chlorogenic acid	254.42	-8.4	1.64	LEU228; CYS285; ARG288; SER289; LEU330
10.	Corydine	596.79	-8.6	1.81	PRO227; ARG288; ALA292; ILE296; ILE325; ILE326; MET329; LEU340

The 0-serial number of the ligand against each protein represents the docking result of the standard ligand. This standard ligand was pre-present in the protein binding site when downloaded from the Protein Data Bank.

Molecular docking interaction of these 35 ligands individually to four different proteins, ensuring RMSD value 1-3Å and no unfavourable bumps in amino acid interaction, satisfying three-point interaction, resulted in 10-11 ligands that perfectly bound to individual proteins, satisfying all criteria. All the bound phytocompound ligands showed better binding affinity and binding score to the protein when compared with the standard ligand.

3.4. ADMET profiling of selected ligands.

Based on the ligands that qualified molecular docking analysis in Table 2, the ligands selected based on their satisfactory ADMET profile are Artocarpin, Limonin, Phyllanthin, and Reticuline. Tables 3 and 4 show the drug likeliness based on Lipinski's rule and the detailed ADMET profiling of these ligands.

Table 3. Lipinski rule of 5 and physicochemical properties of ligands passing ADMET profile.

Physicochemical Parameters	Ligands			
	Artocarpin	Limonin	Phyllanthin	Reticuline
Molecular Weight	436.5	470.51	418.52	329.39
No. of Rotatable bonds	6	1	13	4
Hydrogen Bond Acceptor	6	8	6	5
Hydrogen Bond Donor	3	0	0	2
Lipophilicity (iLogp)	4.14	2.82	4.24	3.32

Table 4. ADMET profiling of different ligands.

ADMET profile		Artocarpin	Limonin	Phyllanthin	Reticuline
Suitable protein against which the ligand acts as an agonist/ antagonist		4A5S, 1DQ9	1B2Y, 4A5S, 1DQ9, 4YT1	1DQ9	4YT1
Absorption	GI Absorption	High	High	High	High

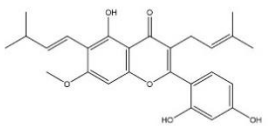
Distribution	BBB penetration	No	No	Yes	Yes
	Bioavailability score	0.55	0.55	0.55	0.55
Metabolism (Enzyme inhibition)	CYP1A2	No	No	No	Yes
	CYP2C19	Yes	No	No	No
	CYP2C9	No	No	No	No
	CYP2D6	No	No	Yes	Yes
	CYP3A4	No	No	Yes	No
Excretion	Biological Half-life (hr)	1.574	1.581	1.301	2.451
	Clearance (ml/min/kg)	2.28	6.674	8.733	5.274
Toxicity	Toxicity scale (Based on ProTox 3.0)	5	3	4	4
	LD_{50} (mg/kg)	4000	244	1300	700
	Hepatotoxicity	Inactive (p=0.65)	Inactive (p=0.84)	Inactive (p=0.78)	Inactive 0.94
	Neurotoxicity	Inactive (p=0.71)	Inactive (p=0.86)	Inactive (p=0.66)	Inactive 0.52
	Nephrotoxicity	Active (p=0.60)	Inactive (p=0.57)	Inactive (p=0.56)	Inactive 0.52
	Carcinogenicity	Inactive (p=0.66)	Inactive (p=0.52)	Inactive (p=0.51)	Inactive 0.63
	Mutagenicity	Inactive (p=0.72)	Inactive (p=0.78)	Inactive (p=0.75)	Inactive 0.50

Molecules that showed less GI penetration/ absorption were eliminated at the initial stage of screening because they lead to poor bioavailability when consumed orally. Secondly, molecules that were shown to inhibit more than two liver metabolizing CYP enzymes were eliminated from the list since they showed more hepatotoxicity. Ligands with biological half-lives of more than 2.5 hours and a lower clearance rate were also discarded since long-term use causes bioaccumulation of these ligands in the body. After the initial pharmacokinetic screening, toxicity profiling was analyzed. Ligands with active hepatotoxicity, neurotoxicity, and nephrotoxicity with a probability >60% were discarded. Any ligand that showed traces of carcinogenicity and mutagenicity was expelled from the study.

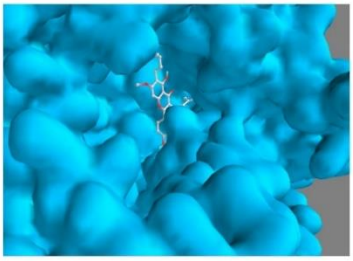
Figures 4A to 4D represent the 2D structure, binding interaction, 3D binding image, and toxicity radar profile of Artocarpin, Limonin, Phyllanthin, and Reticuline against their respective binding protein, as mentioned in Table 4. The bond length in Armstrong for each individual amino acid interaction is represented in Figures 4A to 4D.

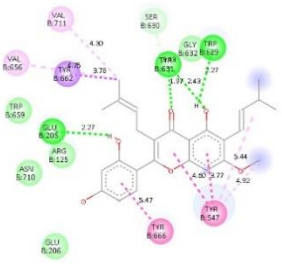
Pharmacokinetic studies and toxicity profile of the ligands individually showed Artocarpin (present in Jackfruit), Limonin (present in Bengal lemon), Reticuline (present in Custard apple), and Phyllanthin (present in Indian Gooseberry) to be the most appropriate ligands with the least toxicity. This, in turn, ensures that different active secondary metabolites have the potential to treat Hyperlipidemia and Diabetes Mellitus.

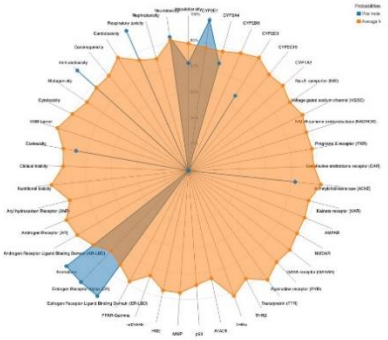
Nevertheless, these excluded compounds can be proved to be effective with further extensive QSAR modelling and appropriate drug designing to suit our biological systems better. More software can be used to predict the biological efficacy of the predicted compounds by QSAR before actual synthesis to maximize cost efficiency and minimize loss.



2D Structure

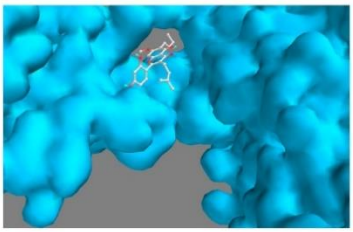


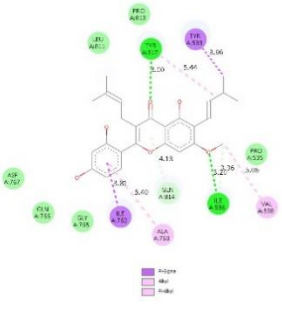




Toxicity Radar Chart

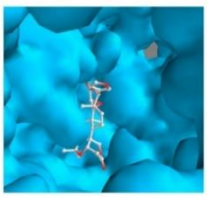
3D Image and Amino acid residue interaction of Ligand-Protein binding complex with DPP-IV

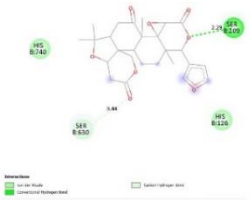




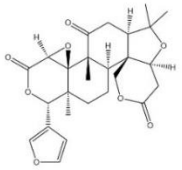
3D Image and Amino acid residue interaction of Ligand-Protein binding complex with HMG coA reductase

(A)

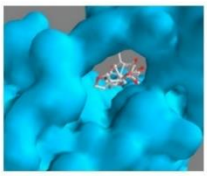


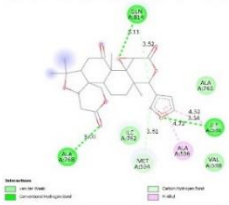


3D Image and Amino acid residue interaction of Ligand-Protein binding complex with DPP-IV

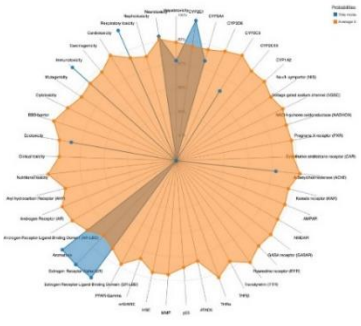


2D Structure

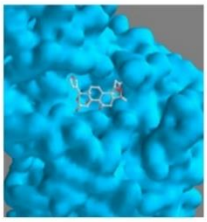


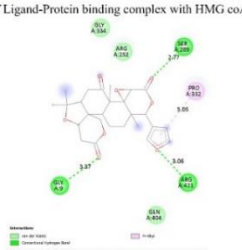


3D Image and Amino acid residue interaction of Ligand-Protein binding complex with HMG coA reductase

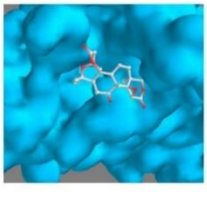


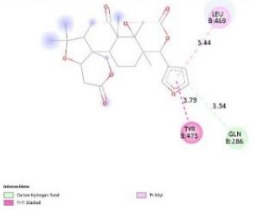
Toxicity Radar Chart





3D Image and Amino acid residue interaction of Ligand-Protein binding complex with α-amylase





3D Image and Amino acid residue interaction of Ligand-Protein binding complex with PPAR-γ

(B)

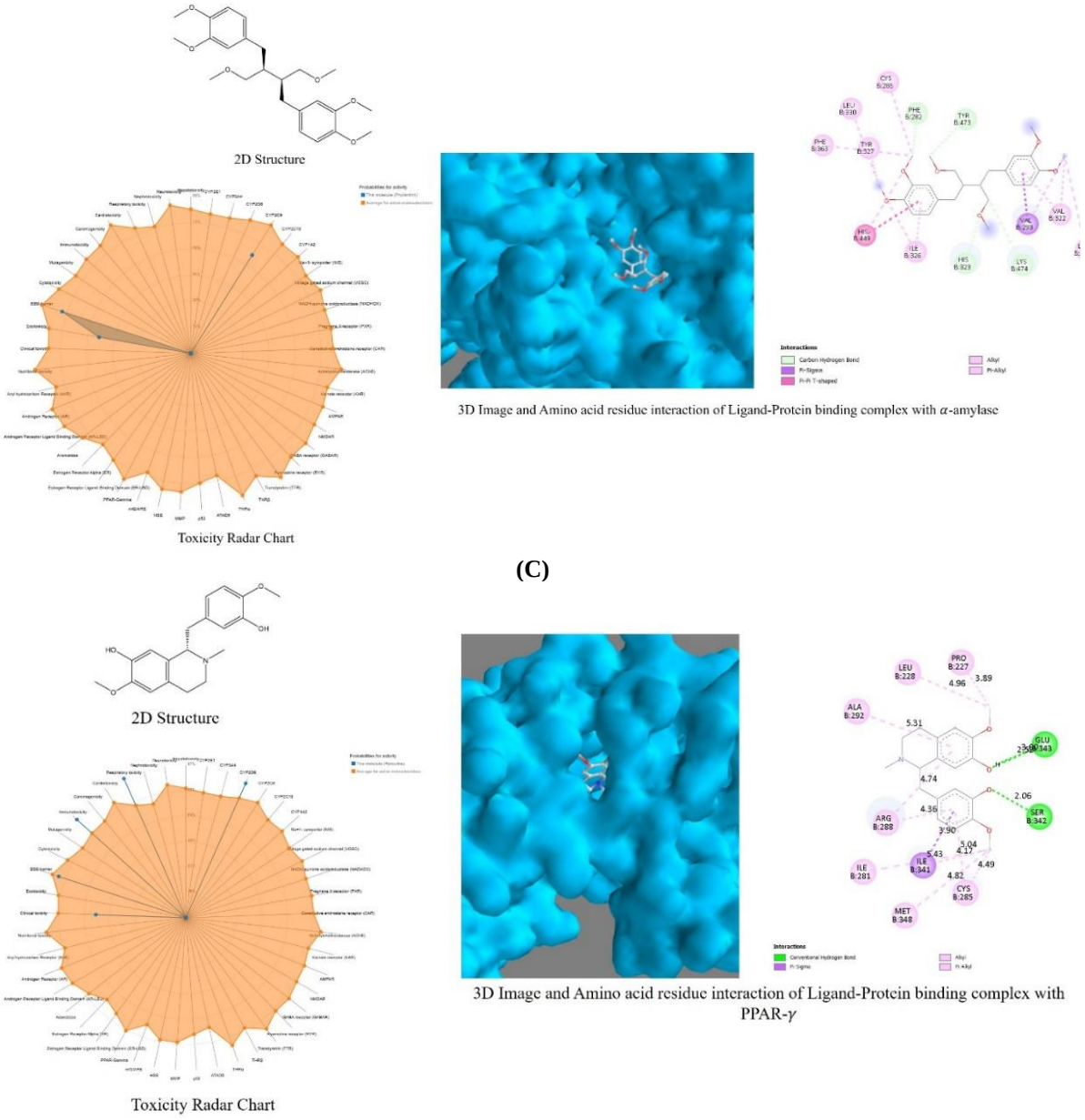


Figure 4. (A) 2D structure, binding interaction of Artocarpin to DPP-IV and HMG coA reductase; **(B)** 2D structure, binding interaction of Limonin to DPP-IV, HMG coA reductase, α-amylase, and PPAR-γ; **(C)** 2D structure, binding interaction of Phyllanthin to α-amylase; **(D)** 2D structure, binding interaction of Reticuline to PPAR-γ.

4. Conclusions

This study explores the effect of different unique phytoconstituents found in commonly consumed unripe fruits, which are effective in binding with other proteins associated with the progression of Diabetes Mellitus and hyperlipidemia. Out of the 50 compounds screened, two unique phytocompounds, Limonin and Artocarpin, showed effective interaction with a safe toxicity profile against HMG coA reductase and Dipeptidyl Peptidase-IV. Limonin was proven to be a less selective compound effective against all four proteins. Phyllanthin and reticuline had higher binding affinity with α-amylase and PPAR-γ, respectively. Therefore, from these outcomes, we conclude that Limonin, Artocarpin, Reticuline, and Phyllanthin could become potential molecules in ameliorating the symptoms and complications of Diabetes Mellitus and hyperlipidemia. Future research can be extended to design a pharmacophore suitable for the

inhibition of the progression of these chronic diseases and QSAR modelling to make these molecules more specific and potent. Synthetically designing these molecules for *in vitro* and *in vivo* studies can establish the foundation for formulating modern medicine.

Author Contributions

Conceptualization, S.G. and A.C.; methodology, S.G., A.C., A.S., and S.H.; Software, S.G., T.A., S.K.D. and N.G.; validation, S.K.D. and N.G.; formal analysis, S.G., A.C., A.S., and S.H.; investigation, S.G. and A.C.; resources, S.G.; data curation, S.G., A.C., A.S., and S.H.; writing—original draft preparation, S.G. and A.C.; writing—review and editing, T.A.; visualization, T.A.; supervision, T.A.; project administration, T.A.; All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

Not Applicable.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
ADMET	Absorption, Distribution, Metabolism, Excretion, and Toxicity
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DPP-IV	Dipeptidyl Peptidase-IV
EC	Enzyme Commission
GIP	Glucose-dependent Insulinotropic Peptide
GLP-1	Glucagon-like Peptide-1
HDL	High-Density Lipoprotein
HMG-coA	3-hydroxy-3-methyl-glutaryl-coenzyme A

Abbreviation	Definition
HMG-coA reductase	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
LDL	Low-Density Lipoprotein
LD50	Lethal Dose 50 (dose required to kill 50% of a test population)
PPAR-γ	Peroxisome Proliferator-Activated Receptor-gamma
TG	Triglycerides
T2DM	Type-2 Diabetes Mellitus

References

1. Nelson, R.H. Hyperlipidemia as a Risk Factor for Cardiovascular Disease. *Prim. Care - Clin. Off. Pract.* **2013**, *40*, 195-211, https://doi.org/10.1016/j.pop.2012.11.003.
2. Leon, B.M.; Maddox, T.M. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World J. Diabetes* **2015**, *6*, 1246-1258, https://doi.org/10.4239/wjd.v6.i13.1246.
3. Knip, M.; Siljander, H. Autoimmune mechanisms in type 1 diabetes. *Autoimmun. Rev.* **2008**, *7*, 550-557, https://doi.org/10.1016/j.autrev.2008.04.008.
4. Muoio, D.M.; Newgard, C.B. Molecular and metabolic mechanisms of insulin resistance and β-cell failure in type 2 diabetes. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 193–205, https://doi.org/10.1038/nrm2327.
5. Kashtoh, H.; Baek, K.-H. New Insights into the Latest Advancement in α-Amylase Inhibitors of Plant Origin with Anti-Diabetic Effects. *Plants* **2023**, *12*, 2944, https://doi.org/10.3390/plants12162944.
6. Sun, A.-l.; Deng, J.-t.; Guan, G.-j.; Chen, S.-h.; Liu, Y.-t.; Cheng, J.; Li, Z.-w.; Zhuang, X.-h.; Sun, F.-d.; Deng, H.-p. Dipeptidyl peptidase-IV is a potential molecular biomarker in diabetic kidney disease. *Diabetes Vasc. Dis. Res.* **2012**, *9*, 301-308, https://doi.org/10.1177/1479164111434318.
7. Kou, S.; Han, B.; Wang, Y.; Huang, T.; He, K.; Han, Y.; Zhou, X.; Ye, X.; Li, X. Synergetic cholesterol-lowering effects of main alkaloids from *Rhizoma Coptidis* in HepG2 cells and hypercholesterolemia hamsters. *Life Sci.* **2016**, *151*, 50-60, https://doi.org/10.1016/j.lfs.2016.02.046.
8. Rouhi-Boroujeni, H.; Rouhi-Boroujeni, H.; Heidarian, E.; Mohammadizadeh, F.; Rafieian-Kopaei, M. Herbs with anti-lipid effects and their interactions with statins as a chemical anti- hyperlipidemia group drugs: A systematic review. *ARYA Atheroscler.* **2015**, *11*, 244-251.
9. Mirza, A.Z.; Althagafi, I.I.; Shamshad, H. Role of PPAR receptor in different diseases and their ligands: Physiological importance and clinical implications. *Eur. J. Med. Chem.* **2019**, *166*, 502-513, https://doi.org/10.1016/j.ejmech.2019.01.067.
10. Asgary, S.; RafieianKopaei, M.; Sahebkar, A.; Shamsi, F.; Goli-malekabadi, N. Anti-hyperglycemic and anti-hyperlipidemic effects of Vaccinium myrtillus fruit in experimentally induced diabetes (antidiabetic effect of Vaccinium myrtillus fruit). *J. Sci. Food Agric.* **2016**, *96*, 764-768, https://doi.org/10.1002/jsfa.7144.
11. Rop, O.; Sochor, J.; Jurikova, T.; Zitka, O.; Skutkova, H.; Mlcek, J.; Salas, P.; Krska, B.; Babula, P.; Adam, V.; Kramarova, D.; Beklova, M.; Provaznik, I.; Kizek, R Effect of Five Different Stages of Ripening on Chemical Compounds in Medlar (*Mespilus germanica* L.). *Molecules* **2011**, *16*, 74-91, https://doi.org/10.3390/molecules16010074.
12. Alexandra Pazmiño-Durán, E.; Giusti, M.M.; Wrolstad, R.E.; Glória, M.B.A. Anthocyanins from banana bracts (*Musa X paradisiaca*) as potential food colorants. *Food Chem.* **2001**, *73*, 327-332, https://doi.org/10.1016/S0308-8146(00)00305-8.
13. Subagio, A.; Morita, N.; Sawada, S. Carotenoids and Their Fatty-Acid Esters in Banana Peel. *J. Nutr. Sci. Vitaminol.* **1996**, *42*, 553-566, https://doi.org/10.3177/jnsv.42.553.
14. Marangoni, F.; Poli, A. Phytosterols and cardiovascular health. *Pharmacol. Res.* **2010**, *61*, 193-199, https://doi.org/10.1016/j.phrs.2010.01.001.
15. Hassan, H.A; Attia, E.Z.; Desoukey, S.Y.; Mohamed, K.M.; Kamel, M.S. Quantitative Analysis of Total Phenolic and Total Flavonoid Constituents of some Ficus species. *J. Adv. Biomed. Pharm. Sci.* **2019**, *2*, 38-40, https://doi.org/10.21608/jabps.2018.5945.1027.
16. Yemiş, O.; Bakkalbaşı, E.; Artık, N. Changes in pigment profile and surface colour of fig (*Ficus carica* L.) during drying. *Int. J. Food Sci. Technol.* **2012**, *47*, 1710-1719, https://doi.org/10.1111/j.1365-2621.2012.03025.x.
17. Al-matani, S.K.; Al-Wahaibi, R.N.S.; Hossain, M.A. *In vitro* evaluation of the total phenolic and flavonoid contents and the antimicrobial and cytotoxicity activities of crude fruit extracts with different polarities from

Ficus sycomorus. *Pac. Sci. Rev. A Nat. Sci. Eng.* **2015**, *17*, 103-108, https://doi.org/10.1016/j.psra.2016.02.002.
18. Alquezar, B.; Rodrigo, M.J.; Zacarías, L. Regulation of carotenoid biosynthesis during fruit maturation in the red-fleshed orange mutant Cara Cara. *Phytochemistry* **2008**, *69*, 1997-2007, https://doi.org/10.1016/j.phytochem.2008.04.020.
19. Jain, N.; Dhawan, K.; Malhotra, S.; Singh, R. Biochemistry of Fruit Ripening of Guava (*Psidium guajava* L.): Compositional and Enzymatic Changes. *Plant Foods Hum. Nutr.* **2003**, *58*, 309-315, https://doi.org/10.1023/B:QUAL.0000040285.50062.4b.
20. Prabu, G.R.; Gnanamani, A.; Sadulla, S. Guaijaverin – a plant flavonoid as potential antiplaque agent against *Streptococcus mutans*. *J. Appl. Microbiol.* **2006**, *101*, 487-495, https://doi.org/10.1111/j.1365-2672.2006.02912.x.
21. Horie, H.; Ito, H.; Ippoushi, K.; Azuma, K.; Sakata, Y.; Igarashi, I. Cucurbitacin C—Bitter Principle in Cucumber Plants. *Jpn. Agric. Res. Q.: JARQ* **2007**, *41*, 65-68, https://doi.org/10.6090/jarq.41.65.
22. Kai, H.; Baba, M.; Okuyama, T. Two New Megastigmanes from the Leaves of *Cucumis sativus*. *Chem. Pharm. Bull.* **2007**, *55*, 133-136, https://doi.org/10.1248/cpb.55.133.
23. Krauze-Baranowska, M.; Cisowski, W. Flavonoids from some species of the genus *Cucumis*. *Biochem. Syst. Ecol.* **2001**, *29*, 321-324, https://doi.org/10.1016/S0305-1978(00)00053-3.
24. Cruz-Valenzuela, M.R.; Tapia-Rodríguez, M.R.; Vazquez-Armenta, F.J.; Silva-Espinoza, B.A.; Ayala-Zavala, J.F. Chapter 61 - Lime (*Citrus aurantifolia*) Oils. In Essential Oils in Food Preservation, Flavor and Safety, Preedy, V.R., Ed.; Academic Press: San Diego, **2016**; pp. 531-537, https://doi.org/10.1016/B978-0-12-416641-7.00061-4.
25. He, D.; Shan, Y.; Wu, Y.; Liu, G.; Chen, B.; Yao, S. Simultaneous determination of flavanones, hydroxycinnamic acids and alkaloids in citrus fruits by HPLC-DAD–ESI/MS. *Food Chem.* **2011**, *127*, 880-885, https://doi.org/10.1016/j.foodchem.2010.12.109.
26. Ghasemzadeh, A.; Azarifar, M.; Soroodi, O.; Jaafar, H.Z.E. Flavonoid compounds and their antioxidant activity in extract of some tropical plants. *J. Med. Plants Res.* **2012**, *6*, 2639-2643, https://doi.org/10.5897/JMPR11.1531.
27. Hettiarachchi, H.; Gunathilake, K. Bioactives and bioactivity of selected underutilized fruits, vegetables and legumes grown in Sri Lanka: a review. *J. Med. Plants. Stud.* **2020**, *8*, 34-44, https://doi.org/10.22271/plants.2020.v8.i6a.1227.
28. Bergonzi, M.C.; Heard, C.M.; Garcia-Pardo, J. Bioactive Molecules from Plants: Discovery and Pharmaceutical Applications. *Pharmaceutics* **2022**, *14*, 2116, https://doi.org/10.3390/pharmaceutics14102116.
29. de Lima, F.F.; Breda, C.A.; Cardoso, C.A.L.; Duarte, M.C.T.; Sanjinez-ArgandoÃ±a, E.J. Evaluation of nutritional composition, bioactive compounds and antimicrobial activity of Elaeocarpus serratus fruit extract. *Afr. J. Food Sci.* **2019**, *13*, 30-37, https://doi.org/10.5897/AJFS2018.1760.
30. Pareek, S.; Shikov, A.N.; Pozharitskaya, O.N.; Makarov, V.G.; González-Aguilar, G.A.; Ramalho, S.A.; Narain, N. Indian Gooseberry (*Emblica officinalis* Gaertn.). In Fruit and Vegetable Phytochemicals; Yahia, E.M., Ed.; John Wiley & Sons: **2017**; pp. 1077-1106, https://doi.org/10.1002/9781119158042.ch54.
31. Kaur, A.; Gupta, M.; Kaur, G.; Gill, P.P.S.; Singh, H.; Suneja, Y. Evaluation of Cape Gooseberry Varieties for Growth and Bioactive Compounds Under Subtropical Conditions of Northwestern India. *Appl. Fruit Sci.* **2024**, *66*, 1387-1395, https://doi.org/10.1007/s10341-024-01105-9.
32. Srinivasan, K. Chapter 30 - Indian gooseberry. In Nutritional Composition and Antioxidant Properties of Fruits and Vegetables, Jaiswal, A.K., Ed.; Academic Press: **2020**; pp. 483-496, https://doi.org/10.1016/B978-0-12-812780-3.00030-1.
33. Tripathi, K.; Kumar, P.; Kumar, R.; Saxena, R.; Kumar, A.; Badoni, H.; Goyal, B.; Mirza, A.A. Efficacy of jackfruit components in prevention and control of human disease: A scoping review. *J. Educ. Health Promot.* **2023**, *12*, 361, https://doi.org/10.4103/jehp.jehp_1683_22.
34. Sayago-Ayerdi, S.; García-Martínez, D.L.; Ramírez-Castillo, A.C.; Ramírez-Concepción, H.R.; Viuda-Martos, M. Tropical Fruits and Their Co-Products as Bioactive Compounds and Their Health Effects: A Review. *Foods* **2021**, *10*, 1952, https://doi.org/10.3390/foods10081952.
35. Cheng, M.; He, J.; Gu, Y.; Wu, G.; Tan, L.; Li, C.; Xu, F.; Zhu, K. Changes in Phenolic Compounds and Antioxidant Capacity of *Artocarpus heterophyllus* Lam. (Jackfruit) Pulp during In Vitro Gastrointestinal Digestion. *Antioxidants* **2024**, *13*, 37, https://doi.org/10.3390/antiox13010037.

36. Rungruangmaitree, R.; Jiraungkoorskul, W. Pea, Pisum sativum and its Anticancer Activity. *Pharmacogn. Rev.* **2017**, *11*, 39-42, https://doi.org/10.4103/phrev.phrev_57_16.
37. Singh, B.; Singh, J.P.; Shevkani, K.; Singh, N.; Kaur, A. Bioactive constituents in pulses and their health benefits. *J. Food Sci. Technol.* **2017**, *54*, 858-870, https://doi.org/10.1007/s13197-016-2391-9.
38. Roy, F.; Boye, J.I.; Simpson, B.K. Bioactive proteins and peptides in pulse crops: Pea, chickpea and lentil. *Food Res. Int.* **2010**, *43*, 432-442, https://doi.org/10.1016/j.foodres.2009.09.002.
39. Fais, A.; Era, B. Phytochemical Composition and Biological Activity. *Plants* **2024**, *13*, 331, https://doi.org/10.3390/plants13030331.
40. Del Giudice, R.; Raiola, A.; Tenore, G.C.; Frusciante, L.; Barone, A.; Monti, D.M.; Rigano, M.M. Antioxidant bioactive compounds in tomato fruits at different ripening stages and their effects on normal and cancer cells. *J. Funct. Foods* **2015**, *18*, 83-94, https://doi.org/10.1016/j.jff.2015.06.060.
41. Szabo, K.; Cătoi, A.-F.; Vodnar, D.C. Bioactive Compounds Extracted from Tomato Processing by-Products as a Source of Valuable Nutrients. *Plant Foods Hum. Nutr.* **2018**, *73*, 268-277, https://doi.org/10.1007/s11130-018-0691-0.
42. Antonio, A.S.; Wiedemann, L.S.M.; Veiga Junior, V.F. The genus *Capsicum*: a phytochemical review of bioactive secondary metabolites. *RSC Adv.* **2018**, *8*, 25767-25784, https://doi.org/10.1039/C8RA02067A.
43. de Sá Mendes, N.; Branco de Andrade Gonçalves, É.C. The role of bioactive components found in peppers. *Trends Food Sci. Technol.* **2020**, *99*, 229-243, https://doi.org/10.1016/j.tifs.2020.02.032.
44. Asnin, L.; Park, S.W. Isolation and Analysis of Bioactive Compounds in *Capsicum* Peppers. *Crit. Rev. Food Sci. Nutr.* **2015**, *55*, 254-289, https://doi.org/10.1080/10408398.2011.652316.
45. Kazman, B.S.M.A.; Harnett, J.E.; Hanrahan, J.R. The Phytochemical Constituents and Pharmacological Activities of *Annona atemoya*: A Systematic Review. *Pharmaceuticals* **2020**, *13*, 269, https://doi.org/10.3390/ph13100269.
46. Moussa, A.Y.; Siddiqui, S.A.; Elhawary, E.A.; Guo, K.; Anwar, S.; Xu, B. Phytochemical constituents, bioactivities, and applications of custard apple (*Annona squamosa* L.): A narrative review. *Food Chem.* **2024**, *459*, 140363, https://doi.org/10.1016/j.foodchem.2024.140363.
47. Shehata, M.G.; Abu-Serie, M.M.; Abd El-Aziz, N.M.; El-Sohaimy, S.A. Nutritional, phytochemical, and in vitro anticancer potential of sugar apple (*Annona squamosa*) fruits. *Sci. Rep.* **2021**, *11*, 6224, https://doi.org/10.1038/s41598-021-85772-8.
48. Fitmawati, F.; Resida, E.; Kholifah, S.N.; Roza, R.M.; Almurdani, M.; Emrizal, E. Phytochemical screening and antioxidant profiling of Sumatran wild mangoes (*Mangifera* spp.): a potential source for medicine antidegenerative effects. *F1000Research* **2020**, *9*, 220, https://doi.org/10.12688/f1000research.22380.3.
49. Quintana, S.E.; Salas, S.; García-Zapateiro, L.A. Bioactive compounds of mango (*Mangifera indica*): a review of extraction technologies and chemical constituents. *J. Sci. Food Agric.* **2021**, *101*, 6186-6192, https://doi.org/10.1002/jsfa.11455.
50. SwissADME, Swiss Drug Design. Available online: http://www.swissadme.ch/ (accessed on 01 April **2025**).
51. ADMETlab 3.0. Available online: https://admetlab3.scbdd.com/ (accessed on 02 April **2025**).
52. Protox 3.0, Tox-Prediction. Available online: https://tox.charite.de/protox3/index.php?site=compound_input (accessed on 03 April **2025**).
53. Brayer, G.D.; Luo, Y.; Withers, S.G. The structure of human pancreatic α-amylase at 1.8 Å resolution and comparisons with related enzymes. *Protein Sci.* **1995**, *4*, 1730-1742, https://doi.org/10.1002/pro.5560040908.
54. Mathur, V.; Alam, O.; Siddiqui, N.; Jha, M.; Manaithiya, A.; Bawa, S.; Sharma, N.; Alshehri, S.; Alam, P.; Shakeel, F. Insight into Structure Activity Relationship of DPP-4 Inhibitors for Development of Antidiabetic Agents. *Molecules* **2023**, *28*, 5860, https://doi.org/10.3390/molecules28155860.
55. Gesto, D.S.; Pereira, C.M.S.; Cerqueira, N.M.F.S.; Sousa, S.F. An Atomic-Level Perspective of HMG-CoA-Reductase: The Target Enzyme to Treat Hypercholesterolemia. *Molecules* **2020**, *25*, 3891, https://doi.org/10.3390/molecules25173891.
56. Kroker, A.J.; Bruning, J.B. Review of the Structural and Dynamic Mechanisms of PPARγ Partial Agonism. *PPAR Res.* **2015**, *2015*, 816856, https://doi.org/10.1155/2015/816856.

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