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Screening and druggability analysis of *Zingiber officinale* bioactive compounds against diabetes mellitus using a computational approach

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The prevalence of diabetes mellitus is increasing globally at an alarming rate. It is a metabolic disorder characterized by elevated blood glucose levels due to either inadequate insulin production or ineffective use of insulin, which eventually leads to micro and macrovascular complications. The present study is aimed to screen antidiabetic compounds of ginger using an *in silico* approach. Total 132 ginger phytocompounds are screened based on Druglikeness properties using DruLito software. The key targets such as GCK, PPAR-γ, and DPP4 are selected from 18 diabetes targets using Network analysis. The molecular docking is performed between the selected key targets and bioactive compounds of ginger using PyRx. A total of four bioactives such as compound-I (curcumin), compound-II (7-(3′,4′-Dihydroxy-5′-methoxyphenyl)-5-hydroxy-1-(4″-hydroxy-3″-methoxyphenyl)heptan-3-one), compound-III (1,7-bis(3′,4′-Dihydroxyphenyl)-3,5-diacetate heptane), compound-IV (1,7-bis(4′- Hydroxy -3′-methoxyphenyl)-3,5-diacetate heptane) are selected based on their docking score. Among these bioactives, compound I showed the highest binding affinity with GCK, DPP4, and PPAR-γ, with scores of -8.0, -7.8, and -7.5 kcal/mol, respectively, followed by compound II -7.4, -7.6 and -7.8 kcal/mol, compound III -7.2,-7.4, and -7.5 kcal/mol, and compound IV -7.1,-7.1,and -7.7 kcal/mol respectively, though slightly lower than compound I. All four compounds (Compound-I, II, III, IV) are found to exhibit high absorption rates (60-80%), within the acceptable range for Caco-2 permeability and skin permeability. However, they show poor distribution across the blood-brain barrier and acted as substrates for CYP3A4 in drug metabolism. Therefore, our findings suggest that these four bioactive compounds could be potential drug candidates for managing diabetes by regulating insulin synthesis, glucose, and lipid metabolism.

Keywords: Curcumin, Diabetes mellitus, Drug-likeness Molecular docking, *Zingiber officinale*

Introduction

Diabetes mellitus is a life-threatening metabolic disorder characterized by elevated blood glucose levels, leading to complications like diabetic retinopathy, nephropathy, neuropathy, renal failure, foot ulcers, and cardiopathy[1]. It is expected that by the year 2045, nearly 700 million people will have diabetes[2] . Therefore, great emphasis must be paid to successful detection and treatment at an early stage before it leads to unfavourable outcomes[2-4]. The shift in dietary patterns and lifestyle has led to increased cardiovascular risk factors like insulin resistance, obesity, and high blood pressure[5]. Although synthetic drugs (biguanides, sulphonylureas, acarbose, alogliptin, and thiazolidinediones) are therapeutically beneficial, long-term use can have numerous kinds of adverse side effects, emphasizing the significance of employing natural medicine[6–8]. Researchers and professional organizations emphasize the importance of proper diet in managing diabetes mellitus (DM). Plant-based dietary supplements offer health benefits like nutritional and medicinal values, which support diabetic patients regulate their blood glucose level[9]. Nutritional supplements like Alpha lipoic acid, Bitter melon, Chromium, Curcumin extract, Fenugreek, Magnesium, Nicotinamide (B3), Omega-3 polyunsaturated fatty acid, and Vitamin D are proven to have preventive roles in managing DM and its complications[10].

Ginger, a member of the *Zingiberaceae* family, is extensively used as a spice, flavouring agent, and nutritional supplement[11]. Their phytochemicals are broadly classified as volatile oils, gingerols, and diarylheptanoids. Major bioactive compounds such as gingerol, shagaol, and zingerone have been shown to regulate several metabolic disorders[12]. Ginger rhizome, rich in phenolic, flavonoids, terpenes, fiber, and polysaccharides compounds, offers numerous pharmacological benefits, including antioxidant, anti-inflammatory, antimicrobial, neuroprotective, and antiemetic properties, which aid in treating various ailments such as obesity, NAFLD, diabetes, cancer, cardiovascular diseases, stomach ache, arthritis[12–14].

Earlier, AL-Syaad *et al*., found that the ginger ethanoic extract (200 mg/kg) improves blood glucose levels, HbA1c, insulin resistance, liver function, and antioxidant activity, while also diminishing the inflammatory cytokines TNF-α and NF-κB in STZ-induced diabetic rats[3]. Treatment with 500 mg/kg ginger extract for six weeks in diabetic rats enhanced overall antioxidant capacity, reducing blood glucose levels and pro-inflammatory cytokines (TNF-α, IL-6, IL1β)[1]. In STZ-induced diabetic rats, 500 mg/kg ginger extract treatment reduced the blood glucose level and increased liver and muscle glycogen. Additionally, it significantly increased hepatic glycolytic enzymes including glucokinase, phosphofructokinase, and pyruvate kinase[11]. The enhanced insulin secretion and glucose utilization in skeletal muscles with the supplementation of 6-Gingerdiol was assessed by Samad *et al*., and they found that it was mainly attributed to increasing glycogen synthase 1 activity and enhancing GLUT4 transporter[14]. Thorough several scientific analyses have been carried out on ginger, with most focusing on crude extracts. However, very few studies have reported on the bioactive compounds that contribute to ginger's multi-therapeutic potential, and many remain unknown. Therefore, the present study aims to screen potential drug molecules from ginger against key therapeutic targets for diabetes

Screening and selection of lead compounds from crude is the crucial step, a costly and time-consuming conventional approach in drug discovery and development. Therefore, *in silico* approaches using computer-aided algorithms to screen the potential compound based on their interactions and affinities between the target protein and ligands seem to be cost-effective and time-saving. The availability of biological databases in the public domain and advancement in computational methods have made the *in-silico* approach an integral part of the field of drug discovery[15]. *In silico* analysis, like molecular docking and network analysis, is an ideal method for the early evaluation of herbal remedies[16]. It predicts binding affinities, interactions, and molecular mechanisms of action between the bioactive molecules and targets, aiding in screening potential targets and elucidating molecular mechanisms. There are several anti-diabetic, anti-cancer, and anti-microbial drugs that have been developed successfully through computational analysis[5,15]. Ginger compounds such as 7-methylcoumarine, supinine, and 12-hydroxyl-corynoline showed higher binding affinity (-6.3, -7.6, -10.5 kcal/mol) with α-glucosidase inhibitor[4]. Based on the network pharmacology and molecular docking study investigated by Fitra *et al*., the astragalin from ginger leaves has potential antioxidant and anti-inflammatory activity[16]. *In vitro* and *in silico* studies conducted by Bahman *et al*., found that α-terpineol from ginger oil interacts strongly with the active sites of α-amylase[17]. As a result, the current work primarily focuses on *in silico* screening of ginger-derived bio actives against target proteins of diabetes.

Experimental Section

Materials and methods

The databases and software used for the present study include PubChem, STRING, Cytoscape v.3.7.2, DruLiTo, RCSB PDB, Discovery Studio, PyRx Autodock vina, pkCSM, and Molinspiration Cheminformatics.

Construction of PPI network

The proteins associated with diabetes were obtained from literature studies and DIA-DB web server that mainly involved in regulating insulin secretion, glucose, and lipid metabolism, such as Dipeptidyl-peptidase 4 (DPP4), Free Fatty Acid Receptor 1 (FFAR1), Amylase Alpha 2A (AMY2A), Maltase-Glucoamylase (MGAM), Insulin Receptor (INSR), Protein Tyrosine Phosphatase Non-Receptor Type 9 (PTPN9), Retinol binding protein 4(RBP4), Aldo-Keto Reductase Family 1 Member B (AKR1B1), Fructose-Bisphosphatase 1(FBP1), Glucokinase (GCK), Hydroxysteroid 11-Beta Dehydrogenase 1 (HSD11B1), Pyruvate Dehydrogenase Kinase 2(PDK2), Glycogen Phosphorylase L (PYGL), Liver receptor Homolog-1 (NR5A2), Peroxisome Proliferator-Activated Receptor alpha (PPAR-α), Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ), Peroxisome Proliferator-Activated Receptor-delta(PPAR-δ), Retinoid X Receptor Alpha (RXRA) were added to STRING database (https://string-db.org/)[2,16,18,19]. The confidence level was set to highest percentage (>90). Disconnected nodes from the network were excluded from the network construction. The molecular interaction of the network was analyzed in Cytoscape v.3.7.2 to study the properties of interactive nodes and edges. Properties such as closeness, betweenness, degree of centrality, and the nodes with the shortest path length were analyzed using the Network analyzer plugin in Cytoscape[6].

Druglikeness properties

Drug likeness analysis using DruLiTo software reveals the structural properties such as molecular mass, partition coefficient, electronic distribution, and

molecular properties like the number of hydrogen donors, acceptors, and rotatable bonds that were analysed. Totally, 168 bioactive compounds of ginger were obtained from literature study. The 3D structures of the compounds were retrieved from PubChem Database (https://pubchem.ncbi.nlm.nih.gov)[15] in SDF format. Initially, all bioactive compounds were analysed for Drug-likeness property based on Lipinski's rule of five. Compounds obeying the rule of five were screened and taken for further virtual screening[19].

Preparation of DM target proteins

The 3D structures of selected diabetic target such as DDP4, GCK, PPAR-γ (PDB ID: 1J2E, 6E0I, 3B1M) were retrieved from RCSB PDB site (https://www.rcsb.org/)[6]. The undesired molecules, such as water molecules, ligands, inhibitors and complex molecules, were removed from the target 3D structure using Discovery Studio 2020. Further, these target protein structures were converted into PDBQT format using PyRx v0.8[(Ref. 19)].

Preparation of drug molecules

Initially, the compounds obeying the rule of five (ligands) were subjected to the energy minimization process using Merck Molecular Force Field (mmff94). The protocol was set to 200 steps, with 1 for the update and minimization until the energy difference was < 0.1 kcal/mol through Open Babel 2.3. Further, these ligands were converted into PDBQT format using PyRx 0.8[(Ref.6,19)].

Molecular docking and interaction studies

Molecular docking between the selected targets and ginger bioactive compounds was performed using the open-source software PyRx with AutoDock vina[20]. Initially, the screened targets (macromolecule) DPP4, GCK, and PPAR-γ were loaded, followed by bioactives and the grid box covering the entire area. The docking results were saved in '.csv' format, and the protein & ligand complex file was saved in 'pdb' format. The docked complex with the highest binding affinities was considered for further visualization analysis using Discovery Studio Visualizer to identify the interactions between bioactive and target protein amino acids[16,19]. Additionally, the mode of interactions, including covalent bonds, carbon-hydrogen (C-H) interactions, hydrophobic interactions, and van der Waals forces, were also analyzed.

ADMET properties and Bioactivity score prediction

The conventional methods of drug discovery and development, which demand the demonstration of desired potency and efficacy, can be both time-consuming and expensive. Consequently, ensuring the pharmacokinetic properties with *in silico* approaches is crucial for determining biomolecules as drug candidates while minimizing the rejection risk, time, and manpower. pkCSM is an online web server that predicts the pharmacokinetic properties of drug candidates based on set of criteria that lead molecules must meet[21]. The ligand Canonical SMILES were used to predict the ADMET/Pharmacokinetic properties. The absorption (intestinal absorption, bioavailability, water solubility, Caco-2, and skin permeability), distribution (blood–brain barrier (BBB), central nervous system (CNS) permeability, the volume of distribution (VDss) unbound state, metabolism (Cytochromes P450 (CYP)), excretion (renal clearance) and toxicity (AMES, acute toxicity and hepatotoxicity, Skin Sensitization) properties of the selected small molecules were predicted using pkCSM online server (http://biosig.unimelb.edu.au/pkcsm/)[21–23]. The lead drug molecules were subjected to bioactivity score prediction such as enzyme inhibitors, ion channel modulators, G protein-coupled receptors (GPCR) and nuclear receptor ligands using Molinspiration Cheminformatics server (https://www.molinspiration. com/)[19].

Results and Discussion

Protein- Protein interaction (PPI) network analysis of DM targets

PPI network analysis enhances understanding of human diseases, pathophysiology, and drug discovery by finding novel target genes. Totally, 18 diabetic target protein interactions were analyzed by the STRING PPI networking method. Out of 18 targets, 17 had higher interactions (confidence > 0.9) with other nodes. The supplementary table shows the number of input nodes, edges, clustering coefficient, and node degree (Table S1). Furthermore, the undirected network analysis in Cytoscape revealed six hub nodes with a high degree of centrality and closeness/betweenness among other target nodes: GCK, PPAR-γ, RXRA, MGAM, PYGL, and DPP4 (Fig. 1). Previously based on protein-protein interactions and network analysis, Usman *et al*. reported that AKTI, TCF7L2, KCNJ11, PPAR-γ, GCG, INSR, IAPP, and SOCS3 as key proteins that are closely related with INS in Diabetes[24]. Ge *et al*. reported that the metabolites of *L. chinensis* 5-hydroxymethylfurfural and acacetin are anti-diabetic agents that regulate type 2 diabetes by acting on GSK3B, TNF, MAPK1, INSR, DPP4, and GSK3B[25]. Jian *et al*., highlighted the key

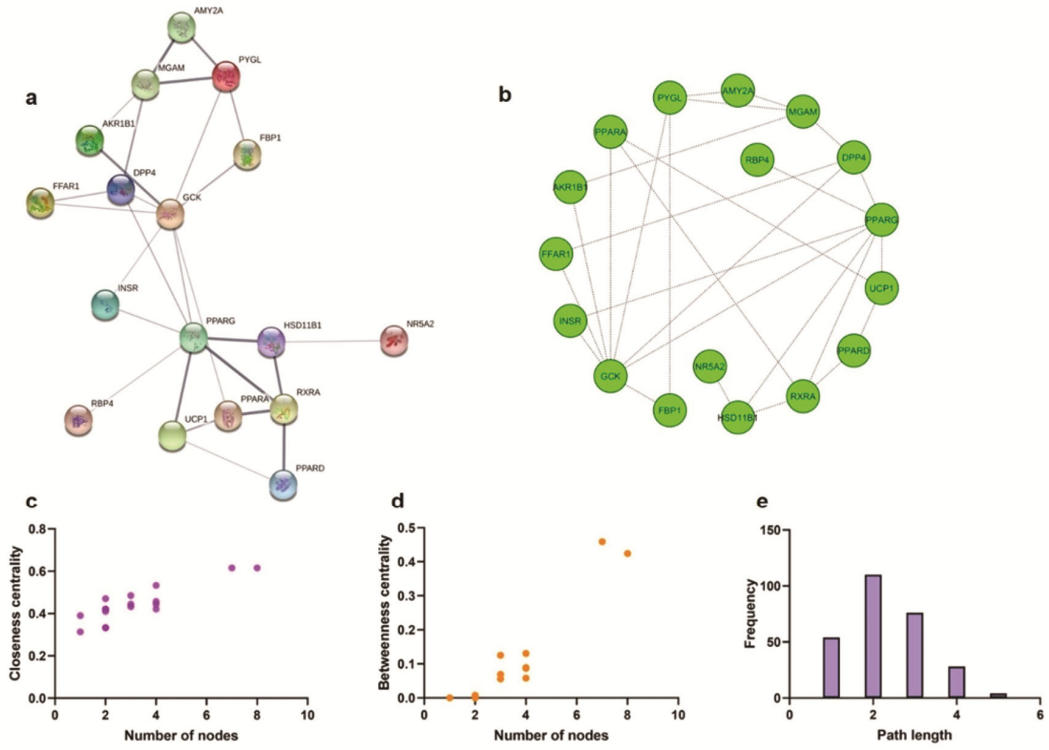

Figure 1 — PPI network analysis of DM associated targets

targets for diabetes management include agonists of GLP-1/GIP, PPAR, and GPCRs, along with GK, AKT, NLK, and TSC22D4 and inhibitors of DPP-4, PTP1B, SGLT-2, α-glucosidase, and α-amylase[2]. Glucokinase, a glucose sensor, is primarily found in pancreatic beta cells and the liver. PPARγ is essential for lipid and glucose homeostasis. DPP4 inhibitors regulate blood glucose levels and stimulate insulin secretion[2,5,23]. Based on the PPI scores, centrality and closeness/ betweenness, literature reports, and structure availability, three target diabeticproteins (GCK, PPAR-γ, DPP4) were finally selected for docking analysis since they can improve insulin secretion/sensitivity, regulate lipid and glucose metabolism, alleviate free radical generation and chronic inflammation, which are all the key factors underlying the pathogenesis and progression of diabetes.

Drug-likeness analysis

Initially, 168 ginger bioactives were subjected to Druglikeness analysis. Out of these, 132 drug candidates were filtered and considered within the acceptable range of Lipinski's rule (Table S2). In addition, TPSA (< 140) and AMR (40–130) properties of bioactive drug candidates were also evaluated by DruLiTo. TPSA is mainly involved in drug transport mechanisms such as BBB, Caco-2 permeability, etc., and AMR properties help to measure the polarizability of the compounds. Further, the filtered drug candidates were subjected to molecular docking analysis to predict their binding affinities toward diabetic targets.

Molecular docking

Molecular docking is an effective *in silico* tool for understanding the interaction between biological targets and drug candidates. High-throughput screening is crucial in modern drug discovery, predicting active drug candidates from large libraries[15]. Total 132 filtered drug candidates were docked with primary diabetic targets (GCK, PPAR-γ, DPP4), and the results were tabulated in Table-S3. Among these compounds listed, Curcumin (compound-I),7-(3′,4′-Dihydroxy-5′-methoxyphenyl)-5-hydroxy-1-(4″-hydroxy-3″methoxy-phenyl) heptane-3-one (compound-II), 1,7-bis(3′,4′-Dihydroxyphenyl)-3,5-diacetate heptane (compound-III), and 1,7-bis (4′-Hydroxy-3′-methoxyphenyl)-3,5-diacetate heptane (compound-IV) were showed the minimized binding energy to the selected targets. Further, the best-docked interactions were taken for visualization analysis to study their bond interactions, such as H-bond, C-H bond, electrostatic, Pi-alkyl interactions, and van der

Waals attractions. Olawale *et al*. 2022 reported that seven phytochemicals, rutin, 1,5-dicaffeoylquinic acid, Vitexin, chlorogenic acid, taxifolin, luteolin, and alstonine from Nigerian medicinal plants had significant binding affinity ranging from -3.3 to -10.6 kcal/mol with multiple diabetes targets like α-amylase, α-glucosidase, adiponectin, GSK-3β, GLUT1, DPP-IV and PPAR-γ[26]. Mahomoodally *et al*. reported that oxo-dihydroxyoctadecenoic acid and trihydroxyoctadecenoic acid in *Anacamptis pyramidalis* Tuber Extracts had a potential binding affinity withα-glucosidase, aldose reductase, PPAR-α, and DPP-IV enzymes, suggesting potential pharmacological benefits against type 2 diabetes[27].

DPP4

Dipeptidyl-peptidase 4 (DPP4) is an enzyme expressed in most tissues, including the pancreas, liver, and adipose cells, involved in cell signaling and immune cell activation. Incretins like GLP 1 play an important role in stimulating insulin secretion upon binding with the G-protein-coupled receptor, thereby regulating the blood glucose level. The degradation of incretins (GIP, GLP1) by DPP4 results in hyperglycemic conditions. DPP4 inhibitors will prevent the degradation of incretins and enhance glucose-stimulated insulin secretion could be effective and safer for managing diabetes[2,28,29]. Studies have shown that oral administration of 6-gingerol from *Z. officinale* improve insulin secretion by diminishing DPP4 levels and increasing incretin levels in diabetes-induced mice[14].

In the present study, the polyphenol of Compound-I was tightly bound to the DPP4 with minimized binding energy (-7.8 kcal/mol) compared to other bioactive candidates, as shown in Table 1. This docked complex formed two hydrogen bonds (SER170; 2.467 Å,

Table 1 — Molecular docking of selected bioactive compounds with DPP4 protein

Compound name	Binding site of amino acids	Distance (Å)	Type of interactions	Category of bonding
Curcumin (Compound-I) (-7.8 kcal/mol)	SER170	2.467	Conventional Hydrogen Bond	Hydrogen Bond
	ARG317	2.342	Conventional Hydrogen Bond	Hydrogen Bond
	ARG317	3.482	Carbon Hydrogen Bond	Hydrogen Bond
	ARG317	3.771	Pi-Sigma	Hydrophobic
	PHE318	4.029	Pi-Pi Stacked	Hydrophobic
7-(3′,4′-Dihydroxy-5′-methoxyphenyl)-5-hydroxy- 1-(4″-hydroxy-3″-methoxyphenyl)heptan-3-one (Compound-II) (-7.6 kcal/mol)	SER170	2.967	Conventional Hydrogen Bond	Hydrogen Bond
	ARG317	2.353	Conventional Hydrogen Bond	Hydrogen Bond
	ARG317	2.200	Conventional Hydrogen Bond	Hydrogen Bond
	ARG319	3.056	Conventional Hydrogen Bond	Hydrogen Bond
	VAL168	2.413	Conventional Hydrogen Bond	Hydrogen Bond
	SER170	3.714	Carbon Hydrogen Bond	Hydrogen Bond
	GLU167	3.953	Pi-Anion	Electrostatic
	ARG317	3.842	Pi-Sigma	Hydrophobic
1,7-bis(3′,4′-Dihydroxyphenyl)-3,5-diacetate heptane (Compound-III) (-7.4 kcal/mol)	ARG86	2.154	Conventional Hydrogen Bond	Hydrogen Bond
	ARG86	2.147	Conventional Hydrogen Bond	Hydrogen Bond
	ARG86	2.572	Conventional Hydrogen Bond	Hydrogen Bond
	SER170	2.395	Conventional Hydrogen Bond	Hydrogen Bond
	GLN514	1.989	Conventional Hydrogen Bond	Hydrogen Bond
	GLN514	2.638	Conventional Hydrogen Bond	Hydrogen Bond
	ASN671	2.467	Conventional Hydrogen Bond	Hydrogen Bond
	HIS701	2.916	Conventional Hydrogen Bond	Hydrogen Bond
	CYS512	2.482	Conventional Hydrogen Bond	Hydrogen Bond
	PHE318	4.381	Pi-Pi Stacked	Hydrophobic
	TYR508	5.282	Pi-Pi Stacked	Hydrophobic
1,7-bis(4′-Hydroxy-3′-methoxyphenyl)-3,5-diacetate heptane (Compound-IV) (-7.1 kcal/mol)	ARG86	2.026	Conventional Hydrogen Bond	Hydrogen Bond
	ARG86	2.390	Conventional Hydrogen Bond	Hydrogen Bond
	SER591	2.436	Conventional Hydrogen Bond	Hydrogen Bond
	TYR592	2.482	Conventional Hydrogen Bond	Hydrogen Bond
	TYR623	2.687	Conventional Hydrogen Bond	Hydrogen Bond
	HIS701	2.425	Conventional Hydrogen Bond	Hydrogen Bond
	GLU167:O	3.690	Carbon Hydrogen Bond	Hydrogen Bond
	GLU167	4.546	Pi-Anion	Electrostatic
	TYR508	3.806	Pi-Pi Stacked	Hydrophobic

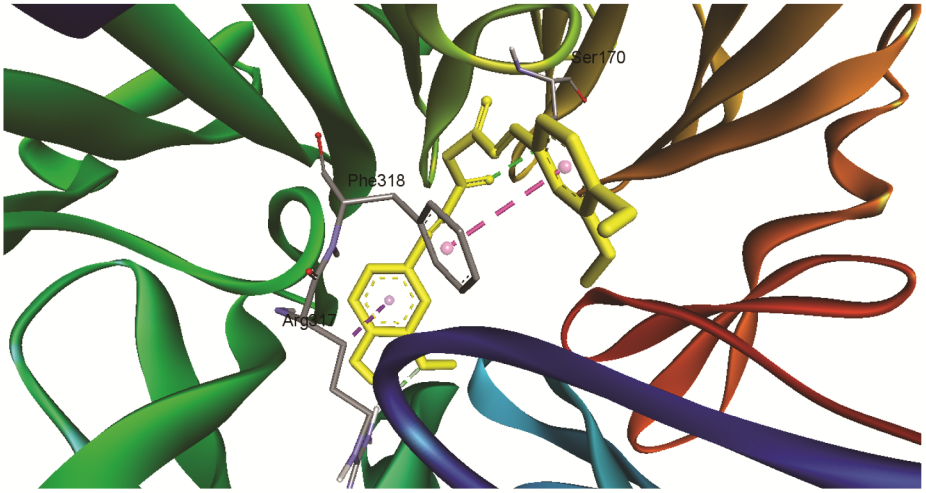

Figure 2 — Visualization of three-dimensional interactions of Compound-I with DPP4

ARG317; 2.342 Å), one carbon-hydrogen bond (ARG; 3.482 Å), and two hydrophobic interactions (ARG317 3.771 Å, PHE318 4.029 Å) (Fig. 2). The Compound-III with DPP4 docked complex showed the nine hydrogen bonds (ARG86; 2.154 Å, ARG86; 2.147 Å, ARG86; 2.572 Å, SER170; 2.395 Å, GLN514; 1.989, GLN514; 2.638 Å, ASN671; 2.467 Å, HIS701; 2.916 Å, CYS512; 2.482 Å) and two hydrophobic bond formation (PHE318; 4.381 Å, TYR508; 5.282 Å). The diarylheptanoid of Compound-IV displayed the six hydrogen bonds (ARG86; 2.026 Å, ARG86; 2.39 Å, SER591; 2.436 Å, TYR592; 2.482 Å, TYR623; 2.687 Å, HIS701; 2.425 Å), one C-H bond (GLU167; 3.69 Å), one electrostatic attraction (GLU167; 4.546 Å) and one hydrophobic bond formation (TYR508; 3.806 Å). Compared to other bioactive candidates, the diarylheptanoid of compound-III exhibited a significant bond formation to the target DPP4 amino acid residues. Sajal *et al*. reported that *Ocimum tenuiflorum*'s phytocompounds 1S-α-pinene, β-pinene, and dehydro-p-cymene as potential DPP4 inhibitors with the binding affinity of −6.2 kcal/mol −6.2 kcal/mol and −6.4 kcal/mol respectively[28]. The diarylheptanoid of Compound-II exhibited tight bond interactions with DPP4 amino acid residues (H-bond: SER170; 2.967 Å, ARG317; 2.353 Å, ARG317; 2.2 Å, ARG319; 3.056 Å, VAL168; 2.413 Å, C-H bond: SER170; 3.714 Å, Electrostatic: GLU167; 3.953 Å, Hydrophobic: ARG317; 3.842 Å). Kalhotra *et al*. reported that garlic extract at 70.9 µg/mL inhibits 50% of DPP-4 activity, and in docking Garlic bioactives such as Calenduloside E, Caffeic acid 3-glucoside, Malonylgenistin had a strong binding affinity of −10.172 kcal/mol, −7.436 kcal/mol, and −7.438 kcal/mol by forming strong hydrogen-bonding, carbon-hydrogen bonding, hydrophobic, and negative electrostatic interactions with DPP-4[29]. Active sites of DPP-4 includesASN85, ASN150, ASN281, ASN229, ARG147, HIS740, SER86, VAL178, ILE194, TRP187, THR231, TYR631, TYR547, GLU205 & 206, GLU232, VAL711, VAL289, SER630, TYR662 & 666, VAL656 and ASP708 &709[23,30]. All four selected compounds have not formed interaction with the amino acid in the active site of DPP4 rather it interacted with ARG317, PHE318, ARG319, VAL168, GLU167, ARG86, SER170, GLN514, ASN671 HIS701, CYS512, TYR508, SER591 and TYR592. One possibility is that these ginger bioactive compounds may act as allosteric modulators, binding to alternative regions of the DPP4 and inducing conformational changes that affect the overall activity.

GCK

The Liver regulates cell metabolic functions, GCK is one among the four members of the hexokinase family that catalyzes the breakdown of glucose to glucose-6-phosphate. In the pancreas, it acts as a glucose sensor, increasing insulin secretion in hyperglycemic conditions and releasing glucagon in hypoglycemic states, thereby maintaining glucose levels in homeostatic conditions. GCK in the liver processes and stores excess glucose as glycogen, which can be utilized for fat synthesis and regulating blood glucose levels between meals. GCK's regulatory activity relies on insulin and Glucokinase Regulatory Protein (GCKRP). Insulin controls GCK activation via the PI3K/Akt pathway, crucial for glucose homeostasis. GCKRP, a liver-specific protein, forms the GCK/GCKRP complex in normal conditions[2,31]. In

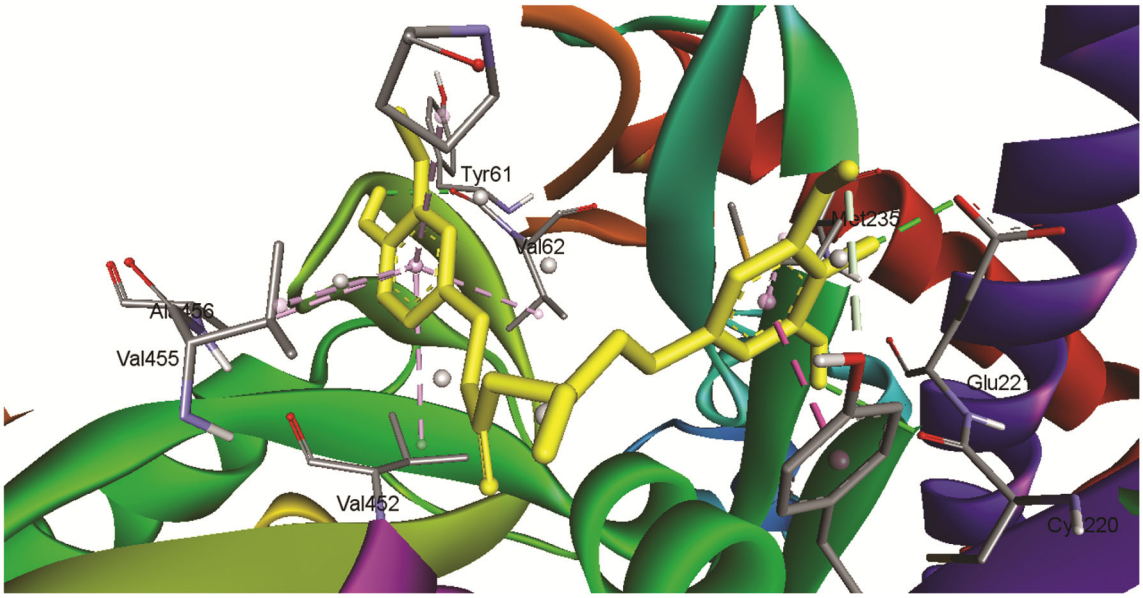

Figure 3 — Binding pose and interactions of Compound-II with GCK

hyperglycemic conditions, this complex dissociates, activating GCK. An effective molecule that activates GCK is essential for managing diabetes[5,32].

The polyphenol derivative of Compound-I bound to the GCK with a minimum binding affinity (-8.0 kcal/mol) and showed one hydrogen bond (TYR214; 3.567 Å) and seven hydrophobic bond interactions (TYR214; 3.9 Å, MET235; 5.058 Å, PRO66; 5.315 Å, ILE159; 5.064 Å, VAL452; 5.286 Å, VAL455; 4.602 Å, ALA456; 4.913 Å). The Compound-II with GCK docked complex explored the three hydrogen bonds (GLU221; 2.884 Å, CYS220; 2.557 Å, TYR61; 2.472 Å), one C-H bond (TYR214; 3.509 Å) and seven hydrophobic bond formation (TYR214; 3.776 Å, MET235; 5.181 Å, VAL62; 4.491 Å, PRO66; 5.036 Å, VAL452; 4.958 Å, VAL455; 4.416 Å, ALA456; 5.399 Å) (Fig. 3). The docked complex of Compound-III and GCK showed the five hydrogen bonds (HIS50; 2.229 Å, ASN166; 2.189 Å, SER263; 2.213 Å, GLN287; 2.073 Å, GLU51; 2.195 Å), two electrostatic attraction (LYS56; 4.736 Å, GLU51; 3.765 Å) and two hydrophobic bond interactions (LEU165; 3.455 Å, ALA259; 3.621 Å). The receptor-ligand complex of GCK and Compound -IV exhibited three hydrogen bonds (LYS56; 2.241 Å, ARG155; 1.919 Å, ASN166; 1.820 Å), one C-H bond (ASN166; 3.642 Å), one electrostatic (GLU51; 3.420 Å) and two hydrophobic interactions (LEU165; 3.646 Å, ALA259; 3.520 Å) results are shown in Table 2. Elekofehinti *et al*. reported that the phytochemicals 5, 7-dihydroxy-6–4-dimethoxyflavanone, luteolin of *C. odorata* showed more favourable binding energies of – 9.476 kcal/mol, -8.813 kcal/mol with glucokinase and –10.055 kcal/mol , – 9.305 kcal/mol with Keap1 than other compounds investigated[33]. Hao *et al*., reported that the active binding sites of GK are ILE211, PRO66, THR65, TYR214, VAL62, VAL455, TYR215, GLU67 and MET235 [(Ref. 32)]. Similarly, to their findings, the screened phytocompounds interacted with active sites of glucokinase such as compound I(-8.0) with MET235, VAL455, TYR214 and compound II(-7.4) with MET235, VAL455, TYR214. Khan *et al*., reported that bioactive compounds of *Enicostemma littorale,* such as Apigenin, Ferulic acid, and p-Coumaric acid showed interaction with the following active amino acid residues of GCK such as ILE211, TYR215, VAL455, VAL62, TYR214, PRO66,VAL452, ALA456 and TYR61[20]. As expected, similar to their findings ginger compounds I& II exhibited the interaction with amino acids like TYR214, VAL452&455, PRO66, ALA456 and TRY6 of GCK. Therefore, the compound I&II exhibited strong interaction with the active sites of GCK.

PPAR-γ

Peroxisome proliferator-activated receptors (PPARs) are a subfamily of the nuclear hormone receptor (NHR) superfamily. It regulates several biological processes, such as cellular differentiation and metabolic homeostasis. It is of three forms: PPAR-α, PPAR-β/δ, and PPAR-γ; each of these has its own function and distribution. PPAR-α and PPAR-β/δ mostly aid in energy expenditure, whereas PPAR-

Table 2 — Molecular docking of selected bioactive compounds with GCK protein

Compound name	Binding site of amino acids	Distance	Type of interactions	Category of bonding
Curcumin (Compound-I)	TYR214	3.567	Carbon Hydrogen Bond	Hydrogen Bond
	TYR214	3.900	Pi-Pi Stacked	Hydrophobic
(-8.0 kcal/mol)	MET235	5.058	Pi-Alkyl	Hydrophobic
	PRO66	5.315	Pi-Alkyl	Hydrophobic
	ILE159	5.064	Pi-Alkyl	Hydrophobic
	VAL452	5.286	Pi-Alkyl	Hydrophobic
	VAL455	4.602	Pi-Alkyl	Hydrophobic
	ALA456	4.913	Pi-Alkyl	Hydrophobic
7-(3′,4′-Dihydroxy-5′-methoxyphenyl)-5-hydroxy- 1-(4″-hydroxy-3″-methoxyphenyl)heptan-3-one (Compound-II)	GLU221	2.884	Conventional Hydrogen Bond	Hydrogen Bond
	CYS220	2.557	Conventional Hydrogen Bond	Hydrogen Bond
	TYR61	2.472	Conventional Hydrogen Bond	Hydrogen Bond
	TYR214	3.509	Carbon Hydrogen Bond	Hydrogen Bond
	TYR214	3.776	Pi-Pi Stacked	Hydrophobic
(-7.4 kcal/mol)	MET235	5.181	Pi-Alkyl	Hydrophobic
	VAL62	4.491	Pi-Alkyl	Hydrophobic
	PRO66	5.036	Pi-Alkyl	Hydrophobic
	VAL452	4.958	Pi-Alkyl	Hydrophobic
	VAL455	4.416	Pi-Alkyl	Hydrophobic
	ALA456	5.399	Pi-Alkyl	Hydrophobic
1,7-bis(3′,4′-Dihydroxyphenyl)-3,5-diacetate heptane (Compound-III)	HIS50	2.229	Conventional Hydrogen Bond	Hydrogen Bond
	ASN166	2.189	Conventional Hydrogen Bond	Hydrogen Bond
	SER263	2.213	Conventional Hydrogen Bond	Hydrogen Bond
	GLN287	2.073	Conventional Hydrogen Bond	Hydrogen Bond
(-7.2 kcal/mol)	GLU51	2.195	Conventional Hydrogen Bond	Hydrogen Bond
	LYS56	4.736	Pi-Cation	Electrostatic
	GLU51	3.765	Pi-Anion	Electrostatic
	LEU165	3.455	Pi-Sigma	Hydrophobic
	ALA259	3.621	Pi-Alkyl	Hydrophobic
1,7-bis(4′-Hydroxy-3′-methoxyphenyl)-3,5-diacetate heptane (Compound-IV)	LYS56	2.241	Conventional Hydrogen Bond	Hydrogen Bond
	ARG155	1.919	Conventional Hydrogen Bond	Hydrogen Bond
	ASN166	1.820	Conventional Hydrogen Bond	Hydrogen Bond
	ASN166	3.642	Carbon Hydrogen Bond	Hydrogen Bond
	GLU51	3.420	Pi-Anion	Electrostatic
(-7.1 kcal/mol)	LEU165	3.646	Pi-Sigma	Hydrophobic
	ALA259	3.520	Pi-Alkyl	Hydrophobic

γ promotes energy storage by enhancing adipogenesis and glucose metabolism[2,7]. PPAR-γ is found in white and brown adipose tissue, large intestine, and spleen. However, it is predominantly expressed in adipocytes and plays a vital role in the regulation of adipogenesis, energy expenditure, insulin sensitivity, lipid and glucose metabolism. Dysregulation of PPAR-γ has been associated with obesity, type 2 diabetes, atherosclerosis, and progression of disease conditions[8]. PPAR-γ activation is increasingly recognized for its role in managing diabetes, as it stimulates GLUT4 receptor activity, making it the primary target for diabetes treatment[6].

The diarylheptanoid derivative of Compound-II docked complex exhibited the minimum binding affinity (-7.8 kcal/mol) with three hydrogen bonds (GLU343; 3.265 Å, LEU228; 2.561 Å, SER342; 4.015 Å), one C-H bond (ILE326; 3.358 Å) and two hydrophobic bond interactions (LEU333; 3.488 Å, ILE341; 4.399 Å) (Fig. 4). The PPAR-γ with ginger Compound-III docked complex showed three hydrogen bonds (ARG288; 2.881 Å, LEU228; 2.759 Å, SER342; 4.130 Å,) and six hydrophobic interactions (MET329; 3.950 Å, CYS285; 3.625 Å, GLY284-CYS285; 5.378 Å, ALA292; 4.504 Å, ARG288; 3.701 Å, ILE341; 4.784 Å). The receptor-ligand complex of PPAR-γ with Compound-IV explored the four hydrogen bonds (SER342; 3.106 Å, GLU295; 1.921 Å, GLU295; 1.991 Å, LEU228; 2.164 Å) and four hydrophobic interactions (ALA292; 4.182 Å, PRO227; 5.462 Å, LEU228; 4.245 Å, LEU333; 5.404 Å). The

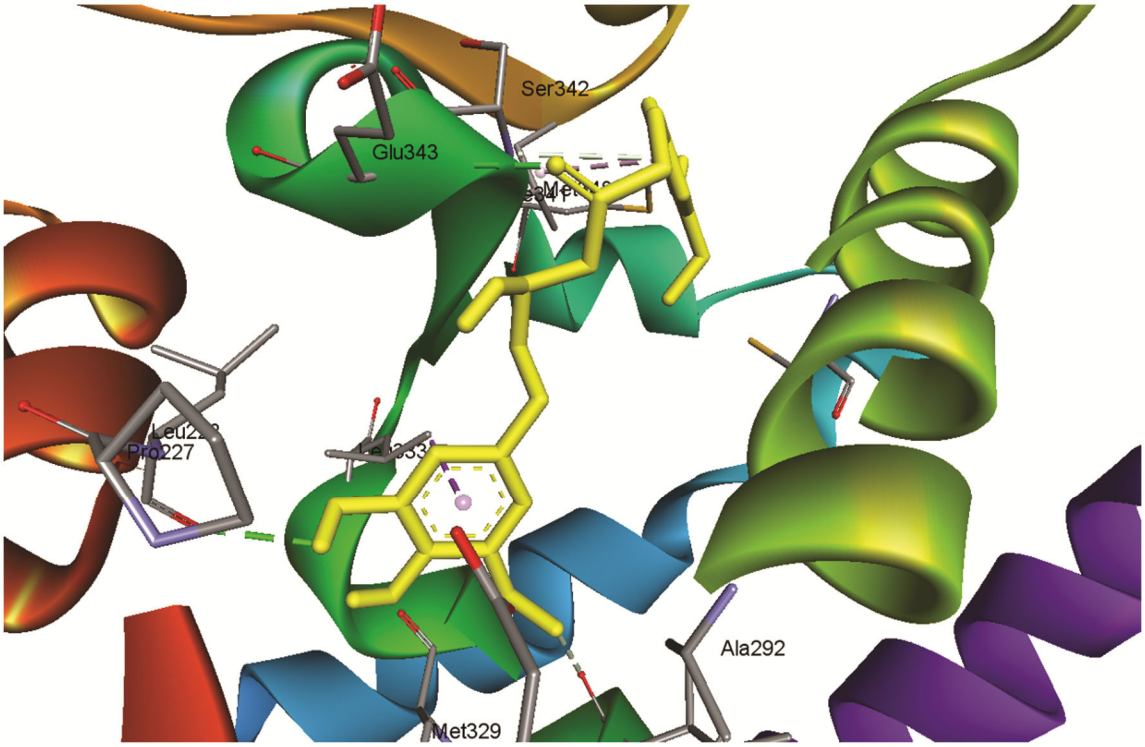

Figure 4 — Molecular docking pose and binding pose of Compound-II with PPAR-γ

Compound-I with PPAR-γ docked complex displayed the four hydrogen bond (GLU343; 2.83493 Å, MET329; 2.26474 Å, ILE326; 3.56018 Å, CYS285; 3.42911 Å) and three hydrophobic interactions (LEU333; 3.40535 Å, ILE341; 3.27758 Å, MET348; 5.3346 Å) detailed results are shown in Table 3. According to Selvaraj *et al*., the bioactive chemical protein 4-butyl pyridine 1-oxide *Rhizophora apiculata* has a better interaction with PPAR-γ (-5.1 kcal/mol) than TDZ (-4.3 kcal/mol)[7]. Ladokun *et al*. reported that 2,2′-Benzylidenebis (3-methylbenzofuran) from seed and 1-Methyl-3-phenylindole from leaves of *Hunteriaum bellata* exhibits minimized binding energy of −11.3 kcal/mol −8.9 kcal/mol, respectively[6]. According to Hao *et al*., the binding site for PPARγ includes ARG288, CYS285, MET364, LEU333, SER289, LEU330, LEU340 and VAL339[32]. Accordingly, compound I(-7.5) interacted with CYS285, LEU333, compound III(-7.5) with AGR288, CYS285, compound II & IV with LEU333 active sites of PPARγ. Sabapathy *et al*., reported that triterpenoid compounds from *C. fistula* stem bark exhibit strong interaction with amino acid residues ASP260, GLN283, GLU343 and SER342 of PPARγ[34]. In the present study, ginger phytocompounds such as compound I interacted with GLU343, compound II interacted with GLU343, SER342 compound III & IV interacted with SER342 the amino acid residues of PPARγ. Stalin *et al*. reported 14 amino acid residues in the active site of PPARγ, including ARG288, CYS285, GCN286, GLU295, GLU259, HIS323, ILE341, SER289, HIS449, TYR473, MET364, LEU330, SER273 and SER342[35]. Accordingly the selected ginger phytocompounds such as compound I interacted with CYS285, ILE341, compound II interacted with ILE341, SER342 compound III interacted with CYS285, ILE341, SER342, ARG288 and compound IV interacted with SER342, GLU295 the amino acid residues of PPARγ. Consequently, all four drugs displayed substantial interaction with active regions of PPARγ.

Scaffold analysis

All the four lead compounds are derivatives of diarylheptanoids, that exhibits significant interaction with the selected key targets such as DPP4, GCK, PPAR γ. It noteworthy to mention that p-hydroxybenzyl group is present in all four lead compounds. According to literature reports most of the diarylheptanoid with hydroxybenzyl group act as anti-diabetic agent. The diarylheptanoid-flavanone hybrids with p-hydroxybenzyl at C-6 position exhibit multi-targeting potential by inhibiting DPP4, GPa, α-glucosidase, and PTP1B activity[35]. Wang *et al*.,

Table 3 — Molecular docking of selected bioactive compounds with PPAR-γ protein

Compound name	Binding site of amino acids	Distance	Type of interactions	Category of bonding
7-(3′,4′-Dihydroxy-5′-methoxyphenyl)-5-hydroxy- 1-(4″-hydroxy-3″-methoxyphenyl)heptan-3-one (Compound-II)	GLU343	3.265	Conventional Hydrogen Bond	Hydrogen Bond
	LEU228	2.561	Conventional Hydrogen Bond	Hydrogen Bond
	ILE326	3.358	Carbon Hydrogen Bond	Hydrogen Bond
	SER342	4.015	Pi-Donor Hydrogen Bond	Hydrogen Bond
	LEU333	3.488	Pi-Sigma	Hydrophobic
(-7.8 kcal/mol)	ILE341	4.399	Pi-Alkyl	Hydrophobic
1,7-bis(4′-Hydroxy-3′-methoxyphenyl)-3,5-diacetate heptane (Compound-III)	ARG288	2.881	Conventional Hydrogen Bond	Hydrogen Bond
	LEU228	2.759	Conventional Hydrogen Bond	Hydrogen Bond
	SER342	4.130	Pi-Donor Hydrogen Bond	Hydrogen Bond
	MET329	3.950	Pi-Sigma	Hydrophobic
(-7.5 kcal/mol)	CYS285	3.625	Pi-Sigma	Hydrophobic
	GLY284 -CYS285	5.378	Amide-Pi Stacked	Hydrophobic
	ALA292	4.504	Pi-Alkyl	Hydrophobic
	ARG288	3.701	Pi-Alkyl	Hydrophobic
	ILE341	4.784	Pi-Alkyl	Hydrophobic
1,7-bis(3′,4′-Dihydroxyphenyl)-3,5-diacetate heptane (Compound-IV)	SER342	3.106	Conventional Hydrogen Bond	Hydrogen Bond
	GLU295	1.921	Conventional Hydrogen Bond	Hydrogen Bond
	GLU295	1.991	Conventional Hydrogen Bond	Hydrogen Bond
	LEU228	2.164	Conventional Hydrogen Bond	Hydrogen Bond
(-7.7 kcal/mol)	ALA292	4.182	Pi-Alkyl	Hydrophobic
	PRO227	5.462	Pi-Alkyl	Hydrophobic
	LEU228	4.245	Pi-Alkyl	Hydrophobic
	LEU333	5.404	Pi-Alkyl	Hydrophobic
Curcumin (Compound-I)	GLU343	2.83493	Conventional Hydrogen Bond	Hydrogen Bond
	MET329	2.26474	Conventional Hydrogen Bond	Hydrogen Bond
(-7.5 kcal/mol)	ILE326	3.56018	Carbon Hydrogen Bond	Hydrogen Bond
	CYS285	3.42911	Pi-Donor Hydrogen Bond	Hydrogen Bond
	LEU333	3.40535	Pi-Sigma	Hydrophobic
	ILE341	3.27758	Pi-Sigma	Hydrophobic
	MET348	5.3346	Pi-Sulfur	Other

reported that diarylheptanoids of *Kaempferia galangal* exhibits antidiabetic potential by inhibiting α-glucosidase, GPa activity and enhancing GLP-1 secretion in NCI-H716 cells[36]. *Aquilaria sinensis* diarylheptanoids effectively mitigates hyperlipidemia in AML12 cells by decreasing triglyceride levels and hyperglycemic conditions in C2C12 cells by enhancing AMPK-mediated GLUT 4 translocation in a dose-dependent manner[37]. *Alpinia officinarum* diarylheptanoid ameliorates oxidative stress and insulin resistance in HepG2 cells, additionally molecular docking indicated strong interaction with PI3K, AKT, and Nrf2[38].

ADMET properties

ADMET properties are crucial for developing lead compounds as drug molecules since most bioactive compounds fail clinical trials owing to adverse effects. Hence, much attention is required to assess the lead compound's ADMET properties before formulating it as a drug. The four lead bioactive compounds were subjected to pharmacokinetic properties analysis using pkCSM online server[21]. Absorption properties are assessed by solubility in water (log S), human intestinal absorption (HIA), Caco-2 permeability, and blood-brain barrier (BBB) penetration of lead compounds. To interact with cellular targets at different locations, the drug molecules should have the ability to get transported well to cross the cell membrane for exhibiting their maximal bioactivity at the site of action[39]. P-glycoprotein is a membrane transporter widely distributed across the body responsible for limiting the adsorption, and distribution of toxins and xenobiotics[21,22].

All drug candidates showed greater absorption properties, Compound-I: 82.19%, Compound- II: 62.158%, Compound-III: 84.336%, Compound-IV:

Table 4 — Pharmacokinetics, toxicities and receptor binding properties of Ginger bioactive compounds from medicinal plants using pkCSM web server

Property	Model Name	I	II	III	IV	Unit
Absorption	Water solubility	-4.01	-3.409	-3.713	-3.222	log mol/L
	Caco2 permeability	-0.093	-0.389	-0.28	-0.695	log Papp in 10^{-6} cm/s
	Intestinal absorption (human)	82.19	62.158	84.336	70.081	% Absorbed
	Skin Permeability	-2.764	-2.735	-2.739	-2.735	log Kp
	P-glycoprotein I inhibitor	Yes	Yes	Yes	Yes	Yes/No
	P-glycoprotein II inhibitor	Yes	Yes	Yes	Yes	Yes/No
Distribution	VDss (human)	-0.215	0.418	0.097	0.526	log L/kg
	Fraction unbound (human)	0	0.1	0.116	0.26	Fu
	BBB permeability	-0.562	-1.249	-0.996	-1.672	log BB
	CNS permeability	-2.99	-3.294	-3.192	-3.267	log PS
Metabolism	CYP2D6 substrate	No	No	No	No	Yes/No
	CYP3A4 substrate	Yes	Yes	Yes	Yes	Yes/No
	CYP1A2 inhibitor	Yes	No	No	No	Yes/No
	CYP2C19 inhibitor	Yes	Yes	Yes	No	Yes/No
	CYP2C9 inhibitor	Yes	No	Yes	No	Yes/No
	CYP2D6 inhibitor	No	No	No	No	Yes/No
	CYP3A4 inhibitor	Yes	Yes	Yes	Yes	Yes/No
Excretion	Total Clearance	-0.002	0.245	1.105	0.715	log ml/min/kg
	Renal OCT2 substrate	No	No	No	No	Yes/No
Toxicity	AMES toxicity	No	No	No	No	Yes/No
	Max. tolerated dose (human)	0.081	-0.052	-0.416	0.089	log mg/kg/day
	hERG I inhibitor	No	No	No	No	Yes/No
	hERG II inhibitor	No	Yes	Yes	Yes	Yes/No
	LD50	1.833	1.959	1.823	2.157	mol/kg
	LOAEL	2.228	2.609	1.867	2.279	log mg/kg_bw/day
	Hepatotoxicity	No	No	No	No	Yes/No
	Skin Sensitization	No	No	No	No	Yes/No

Intestinal absorption (30 % <), skin permeability (2.5 cm/h <), Caco2 permeability (<0.9 cm/s), log VDss (0.45 <), BBB membrane permeability, log BB >0.3 to < 1, CNS permeability, log PS > 2 to < 3, Cytochrome P450 enzymes (CYP2D6, CYP2A4, CYP2C9, CYP2C19, CYP2D6 and CYP3A4).

70.08%, respectively, as well as greater aqueous solubility (Compound-I: -4.01 mol/L, Compound-II: -3.409 mol/L, Compound-III: -3.713 mol/L, Compound-IV: 3.222 mol/L) as shown in Table 4. The selected ginger derivatives showed acceptable Caco-2 permeability (<0.9 cm/s) and skin permeability (>2.5 cm/h). P-glycoprotein inhibitors are helpful to enhance the drug adsorption and bioavailablity[39]. All lead drug molecules were predicted to be an inhibitor of P-glycoprotein. The theoretical VDss scores are an important factor for drug distribution. The high VDss values (> 0.45 L/kg) influence the higher distribution rate, affecting renal failure and dehydration. Compound-I showed a lesser VDss (-0.215 L/kg), and Compound-IV (0.526 L/kg) was predicted to be higher VDss. Compound-II (0.418 L/kg) and Compound-III (0.097 L/kg) showed moderate VDss scores. All the bioactive compounds were poorly distributed to the brain (log BB scores: Compound-I: -0.562, Compound-II: -1.249, Compound-III: -0.996, Compound-IV: -1.672) and unable to pass through the nervous system (log CNS scores: Compound-I: -2.99, Compound-II: -3.294, Compound-III: -3.192, Compound-IV: -3.267). CYP450 in the liver plays vital role in drug metabolism. All the drug candidates were predicted as a CYP3A4 substrate in drug metabolism and predicted to be an inhibitor for CYP2C19 (Compound- I, II, III), CYP2C9 (Compound-I, II), and CYP3A4 (compound-I, II, III & IV) combination of hepatic and renal clearance[39]. Total drug clearance is determined by hepatic and renal clearance, indicating drug concentration in the body. Bioactive compounds total clearance scores range from -0.002 to 1.1 mL/min/kg. Toxicity is a crucial factor in drug discovery[21]. All the ginger drug candidates have not expressed any skin sensitization, AMES toxicity, and hepatotoxicity effect. The lead drug candidates are

Table 5 — Bioactivity score prediction of selected bioactive compounds from Ginger using Molinspiration cheminformatics online software

Compounds	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
C-I	0.2	0.21	-0.06	0.33	0.24	0.3
C-II	-0.06	-0.2	-0.26	0.12	-0.14	0.08
C-III	0.14	0.04	-0.51	0.73	0.07	0.51
C-IV	0.16	0.07	-0.17	0.17	0.2	0.33

Highly active (more than 0.00); abstemiously active (between -0.50 and 0.00); inactive (less than -0.50).

predicted to be a non-inhibitor of hERG-I (hERG-related to cardiotoxicity). However, compound-II, III, and IV showed inhibitor for hERG-II excerpt compound-I. According to modern drug development, the drug molecule should not impede the hERG channel[40]. To address this issue, analogs with modified structures will be formulated to reduce hERG inhibition activity while retaining the therapeutic activity of the drug. According to Kottarapat *et al*., oral administration of ginger oil at a dose of 500 mg/kg to Wistar rats for 13 weeks had no adverse consequences[41]. Following OECD guidelines, Tullayakorn *et al*. reported that *Zingiber officinale* Roscoe does not cause any adverse effects or death in acute and sub-acute toxicity test in mouse models[42]. Jianwei *et al*. found that Ginger's antioxidant and anti-inflammatory properties alleviates the severity of cardiac infarction in rats provoked by isoproterenol[43]. Ginger offers numerous health benefits, but excessive consumption may have mild side effects. Overall, the ginger bioactive compounds are found to be safe for consumption according to the results of ADMET analysis.

Bioactivity score prediction

The bioactivity scores analysis was performed for four bioactive compounds. The drug candidates with score values more than 0.00 were determined to be very active, values between -0.50 and 0.00 were considered moderately active, and values less than -0.50 were considered inactive[19]. The lead bioactive compounds (I, III, IV) exhibited promising bioactivity scores (0.04 to 0.73), and Compound- II was predicted to be a moderate bioactivity score (-0.06 to 0.12). Especially, all three compounds(I, III, IV) were found to have potential bioactive scores (GPCR ligand, enzyme inhibitor, protease inhibitor, ion channel modulator, and nuclear receptor ligand activities). The bioactivity score prediction results are summarized in Table 5. These findings indicate that ginger bioactive compounds possess potential therapeutic properties and play significant roles in various biochemical pathways, supporting their further exploration in drug development.

Conclusion

Diabetes mellitus is a chronic metabolic disorder diagnosed by abnormal blood glucose levels caused either by the destruction of pancreatic beta cells or by insulin resistance. It is closely associated with elevated reactive oxygen species (ROS) formation, chronic inflammation, and obesity, all of which contribute onset and progression of diabetes. Therefore, the selection of drug candidates with multiple pharmacological actions is essential to ameliorate the conditions. This present study mainly focused on screening the lead drug candidate from ginger against diabetes since it has proven poly-pharmacological effect like antioxidant, anti-inflammatory activities. Although numerous studies have been conducted, only a few have focused on screening phytocompounds that confer multiple pharmacological activities, leaving this area largely unexplored. Based on Druglikness, molecular docking and network analysis present study identified that the ginger bioactive compounds such as curcumin (C-I), 7-(3′,4′-Dihydroxy-5′-methoxyphenyl)-5 hydroxy-1-(4″-hydroxy-3″-methoxyphenyl) heptane-3-one (C-II), 1,7-bis(4′-Hydroxy-3′-methoxyphenyl)-3,5-diacetate heptane (C-III) and 1,7-bis(3′,4′ Dihydroxyphenyl)1, 7-bis(4′-Hydroxy-3′-methoxyphenyl)-3,5-diacetate heptane (C-IV) as therapeutic compound against predominant diabetes targets PPAR-γ, GCK, and DPP4. All four compounds interacted with the active sites of PPAR-γ, followed by compound I & II with active GCK. Four compounds showed significant intestinal adsorption rates without skin sensitization, AMES toxicity, or hepatotoxicity effects. These phytochemicals may serve as potential drug candidates for diabetes medication as they improve insulin secretion, glucose, and lipid metabolism. Further study on *in vivo* models is required to explore and validate the mechanisms of action of these polyphenols in the treatment of diabetes.

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Conflict of interest

The authors declared that they have no conflict of interest.

Supplementary Information

Supplementary information is available on the website http://nopr.niscpr.res.in/handle/123456789.

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