



RESEARCH ARTICLE



Integrated Bioinformatics Approach Showed Linagliptin as Potential Drug for Prevention of Cardiac Arrest and Cancer

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Abstract: The availability of Linagliptin as a dipeptidyl peptidase-4 (DPP4) inhibitor for the management of type 2 diabetes in individuals has been a recent development. The primary aim of the present investigation is to gain insights into the biological, physiological, and pharmacological mechanisms of action of the substance, as well as its impact on the cellular structure of human organisms. In this study, a range of genomics approaches and *in silico* tools were employed, including PASS, SwissTargetPrediction, SwissADME, SEA, CLC-Pred, and DIGEP-Pred, to ascertain the physicochemical characteristics, pharmacokinetic attributes, biological targets, and biological activity of Linagliptin. Linagliptin is employed as a novel DPP4 inhibitor for the purpose of assisting those diagnosed with type 2 diabetes in managing their body's glycemic control. Nevertheless, our study revealed that Linagliptin has affinity for other molecular targets in humans, such as *CHRM1*, *FAP*, *ALDH1A1*, and *PDE6D*, thereby modulating their gene expression patterns. Prior studies have demonstrated that the administration of the medicine exerts an influence on renal and cardiovascular problems. Based on our research findings, we have developed a solid hypothesis that Linagliptin could potentially serve as an effective pharmaceutical intervention for the treatment of blood cancer and cardiac arrest.

Keywords: Linagliptin, DPP4 inhibitor, diabetes, pharmacokinetics, chemoinformatics

1. Introduction

Over the world, type 2 diabetes is rising. Diabetes affects an estimated 463 million people worldwide, and that number is expected to climb to 700 million in the next 20 years, according to the diabetes atlas (9th edition) [1]. By 2040, there would be 123.5 million diabetic patients in India, up from the current 69.2 million [2]. Effective and secure treatments are required to lessen the effects of type 2 diabetes. A dipeptidyl peptidase-4 (DPP4) inhibitor called Linagliptin has just recently been employed as a therapeutic molecule to treat type 2 diabetes and diabetes mellitus. DPP4 inhibitors are a class of oral medications with an incretin-based mechanism of action. Easy-to-use medications that do not require frequent glucose testing or dosage modifications are favorable in this regard [3]. Drugs in the DPP4 inhibitor class, which were first developed in 2006, appear to meet these criteria. Boehringer Ingelheim, a scientist, developed the medication. DPP4 inhibitors are also well tolerated and have an excellent safety profile. In

practice, patients have exhibited strong adherence to the fixed-dose combos of DPP4 inhibitors and metformin, and these fixed-dose combinations are technically feasible [4]. As a result, this pharmacological class has been seen as a crucial advancement in oral anti-diabetic therapy.

DPP4 regulates the secretion of glucagon and insulin in the human body. Following a meal, the L- and K-cells located in the intestines secrete the digestive hormones known as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) [5, 6]. Approximately 70% of insulin secretion following a meal is attributed to these entities, which also exhibit an ability to enhance insulin secretion in the presence of elevated blood glucose levels. DPP4 is the principal enzyme accountable for the initial cleavage of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). The ingestion of glucose through oral consumption elicits a greater insulin response compared to the administration of glucose intravenously at an equivalent glycemic level [7, 8]. This disparity in insulin response can be attributed to the incretin effect, which is mediated by the hormones GLP-1 and GIP [9]. Despite the reduced influence of incretins in individuals with type 2 diabetes, exogenous GLP-1 still demonstrates insulinotropic and glucagonostatic actions that are reliant on glucose levels. On the other hand, GIP no longer

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exhibits its insulinotropic function. The biological half-life of GLP-1 in vivo is limited to a range of 1–2 minutes due to the presence of DPP4 activity. The inhibition of DPP4 prevents the degradation of GLP-1, resulting in increased levels of endogenous GLP-1 in the plasma. This elevation in GLP-1 levels significantly enhances its glucose-dependent insulinotropic and glucagonostatic effects [6, 10, 11]. The initial evidence supporting the effectiveness of DPP4 inhibition in individuals with type 2 diabetes was observed in 2002 [12].

Linagliptin belongs to the class of medications known as gliptins or DPP4 inhibitors. The medication is employed for the management of type 2 diabetes, a condition characterized by reduced secretion of the insulin hormone [13]. Linagliptin is described chemically as 1H-purine-2, 6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-(8-butyn-1-yl)-3, 7-dihydro-3-methyl-1-[(4-methyl-2quinazoliny)methyl]). The empirical formula, C₂₅H₂₈N₈O₂, has a molecular weight (MW) of 472.54 g/mol, as indicated in Figure 1.

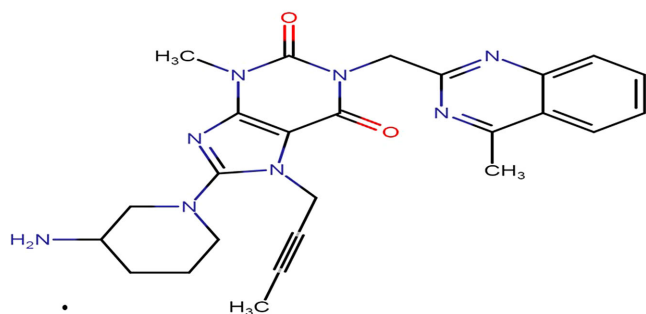


Figure 1. Two-dimensional structure of Linagliptin molecule

The medicine Linagliptin is marketed under the trade name Tradjenta. In investigations on rats and monkeys, Linagliptin has an oral bioavailability of 51%, and its biological half-life is roughly 36 hours [12]. Only a little amount of Linagliptin is metabolized in living organisms, and 90% of the drug is eliminated intact through the feces via the hepatobiliary pathway [12, 14]. Endocrine cells in the digestive system release the incretin hormones GLP-1 and GIP in response to food consumption to promote insulin production. DPP4 normally breaks down the incretin hormones within a few minutes of their release, and as a result, it is crucial in controlling how long the incretin hormones remain active. Linagliptin extends the half-life of the incretin hormones by inhibiting DPP4 enzymatic activity. This, in turn, promotes pancreatic beta-cells to secrete more insulin and less glucagon. These processes work together to reduce blood sugar levels [15].

Due to its involvement with various glucose-lowering medications [16], type 2 mellitus diabetes is frequently linked to cardiovascular illness [17, 18], which increases the risk of heart failure and its consequences [19]. The high risk of heart failure state is unaffected by the medication [20, 21]. Numerous studies have shown that the administration of Linagliptin results in enhanced vascular functions, a reduction in the concentration of pro-inflammatory factors, an increase in the anti-inflammatory factors, as well as the prevention of aberrant proliferation [22]. The drug

alters a variety of cellular and molecular mechanisms or signaling pathways, including the NO signaling pathway, GLP-1-dependent and -independent effects, immune and inflammatory mechanisms, FGF23/klotho signaling, and stromal cell-derived factor-1/CXCR4 signaling, to modulate cell–cell interaction [23]. According to reports, Linagliptin is a DPP4 inhibitor but has had little to no impact on kidney and heart conditions. In the present investigation, we examined the possibility that the medicine promotes cytotoxicity, activation of biological processes, and gene expression in conditions other than type 2 diabetes. We discovered that Linagliptin exhibits a comparable affinity for binding to CHRM1 and FAP, two different prolyl endopeptidases. FAP is essential for the modeling of tissue during development and wound repair. The ligand for Linagliptin has demonstrated affinity to CHRM1 receptors. A G-protein of class Gq called CHRM1 activates signaling pathways involving inositol triphosphate (IP₃) and DAG kinase to cause the upregulation of phospholipase C. Based on some possible in silico analyses, we discovered that Linagliptin also exhibits biological activity for the target proteins and controls gene expression, suggesting a role for Linagliptin in the treatment of leukemia and heart failure as well as other cancers.

2. Materials and Methods

2.1. Selection of drug

Linagliptin is a DPP4 inhibitor used to treat diabetes mellitus type 2. Nowadays, the Linagliptin drug compound is used vastly for various types of studies. The Canonical SMILES format for Linagliptin was obtained from PubChem.

2.2. Analysis of physicochemical and pharmacokinetics properties using the SwissADME

When using the SwissADME online browser, the submission page, where molecules can be entered as Canonical SMILES, is immediately visible. In the beginning, it shows a two-dimensional structure. In relation to the input, it displays a number of properties (see Computational Methods). Additionally, bioavailability radar is shown. Lipophilicity, size, polarity, solubility, flexibility, and saturation are six physicochemical characteristics that are taken into consideration [24, 25]. The radar plot of the molecule has to completely fall into a pink area on each axis representing a physicochemical range in order to be classified as drug-like. This section compiles physicochemical characteristics such as simple molecular descriptors like MW, molecular refractivity, count of particular atom kinds, and polar surface area (PSA). Topological polar surface area (TPSA), a fragmentary method, is used to determine the PSA [26]. The tool also displays the estimated molecular pharmacokinetic properties. These characteristics explain how a substance interacts with cytochrome P450 isoenzymes and whether it is a substrate or non-substrate of the permeability glycoprotein (P-gp) [27].

2.3. Biological activity prediction using PASS

A computer algorithm called prediction of activity spectra for substances (PASS) can be used to evaluate a compound's broad biological potential based on its structural formula [28]. A

compound's projected activity spectrum is estimated by PASS software as having two possible states: probable activity (P_a) and probable inactivity (P_i). Conical SMILES was used to submit the compounds. The PASS user receives output data in the form of a list of anticipated activity kinds, along with an estimated probability for each activity type: "to be active", P_a , or "to be inactive", P_i [29]. P_a and P_i 's probabilities of being active or inactive range from 0.000 to 1.000, and generally speaking, $P_a + P_i = 1$ [30]. It might turn out to be a compound of a recognized pharmacological drug if we choose the highest forecast P_a value. We chose the compound for the prediction in this study that falls above the cut-off value and set the cut-off value of P_a "to be active" as $P_a > 0.2$.

2.4. Biological target prediction using SwissTargetPrediction and similarity ensemble approach (SEA)

SwissTargetPrediction is based on the finding that targets in three different species are more comparable to similar physiologically active compounds [31, 32]. Therefore, using a known compound that is extremely close to the query molecule, the targets of a molecule can be predicted. The accuracy similarity between the query molecule and the known substance is a significant prospect. A chemical receives a maximum likelihood score of 1 whenever it exhibits robust binding interactions with targets that are similar to it. The target probability value ranges from 0 to 1, with the query molecule having the highest possibility of being a known compound of the target [33]. Users of the revised SwissTargetPrediction application can select between the human, mouse, or rat organisms. The selection and addition of an organism occur once Linagliptin has submitted in a SMILE format. Each target's probability score is based on its similarity scores to its most similar ligands. Target molecules are organized based on how likely it is that they will bind to Linagliptin. The columns show the target name, classes, and their Uniprot ID. The upper right side of the page's pie chart displays a summary of the top 15 anticipated target classes (Figure 2).

You can predict specific chemical targets using the SEA search service. The maximum Tanimoto similarity (MaxTC) and significant values are used to express the sequence similarity or structural

similarity between targets based on the similarity of the molecule that binds to them. The relationships between chemicals were stronger in the values [34].

2.5. Prediction of cytotoxic effects of Linagliptin using CLC-Pre

To analyze cytotoxicity effect of the Linagliptin on the basis of the input file, CLC-Pred (cell line cytotoxicity prediction) was performed using online server (www.way2drug.com/PASSonline) (accessed date 22 May 2019). The prediction is based on PASS technique. It allows predicting cytotoxicity against various human cell lines represented with P_a and P_i values if P_a value is >0.5 ; the probability of action is considerably high whereas P_i value indicates inactivity [35].

2.6. Protein and mRNA-based prediction of changes in gene expression pattern using DIGEP-Pred

To analyze gene expression that is induced by Linagliptin can be performed using DIGEP-Pred, which is a web service for in silico prediction of drug-induced changes of gene expression profiles. The predictions are based on mRNA and protein expression [36]. The gene expression induced by the Linagliptin was either up or downregulated.

3. Results

3.1. Physicochemical and pharmacokinetic properties

Using the Swiss ADME bioinformatics tool, physicochemical and pharmacokinetic features were analyzed. Using this method, we can forecast ADME characteristics including pharmacokinetics, physiochemistry, lipophilicity, and water solubility. For each of the six physicochemical properties – lipophilicity, size, polarity, solubility, flexibility, and saturation – the prediction's 2D structure and bioavailability radar are shown (Figure 3).

The area in pink displays the radar plot of the molecule to be drug-like. The colored zone is suitable for the physicochemical space for oral bioavailability [37]. According to SwissADME

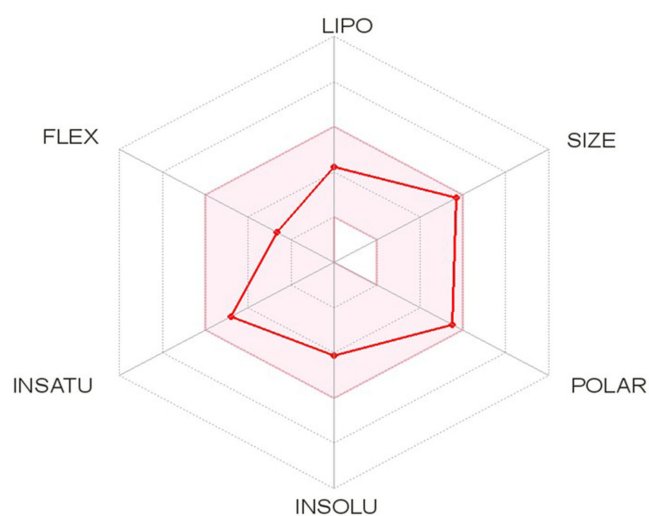


Figure 2. Bioavailability radar showing and signifying the drug-likeness of Linagliptin

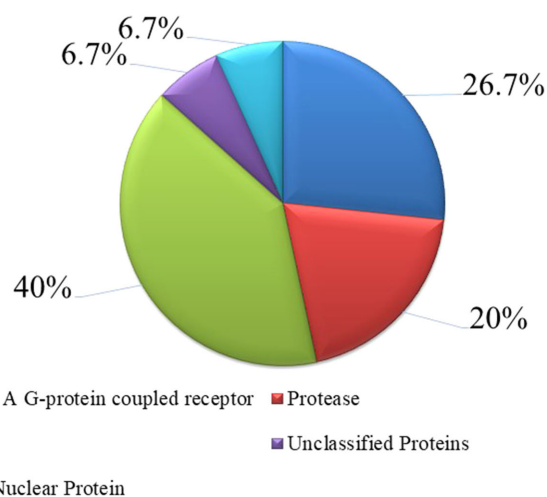


Figure 3. The pie chart of top 15 target compounds of Linagliptin

server, oral bioavailability of the compound was evaluated based on the threshold value of certain physicochemical descriptors, namely lipophilicity ($-0.7 < \text{XLOGP3} < +5.0$), size ($150 \text{ g/mol} < \text{MV} < 500 \text{ g/mol}$), polarity ($20 \text{ \AA}^2 < \text{TPSA} < 130 \text{ \AA}^2$), insolubility ($0 < \text{Log S (ESOL)} < 6$), instauration ($0.25 < \text{Fraction Csp3} < 1$), and flexibility ($0 < \text{Num. Rotatable bonds} < 9$) [38]. The physicochemical and pharmacokinetic properties of the compound are represented in Table 1.

Table 1. Computed parameter values such as physicochemical properties, lipophilicity, solubility, and pharmacokinetics using SwissADME web browser

Physicochemical properties	
Formula	C25H28N8O2
Molecular weight	472.54 g/mol
Num. heavy atoms	35
Num. arom. heavy atoms	19
Fraction Csp3	0.4
Num. rotatable bonds	4
Num. H-bond acceptors	6
Num. H-bond donors	1
Molar refractivity	139.33
Lipophilicity	
Log Po/w (XLOGP3)	1.91
Water solubility	
Log S (ESOL)	-4.11
Solubility	3.66e-02 mg/ml; 7.75e-05 mol/l
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes

Any medication molecule's biological activity and lipophilicity are connected. This is the cause of the target protein's greater binding. Numerous other pharmacokinetic characteristics of pharmacological molecules are impacted by lipophilicity, including lower water solubility, increased permeability across the blood-brain barrier (BBB) and other tissue membranes in the gastrointestinal system, increased protein binding, etc. [39]. Due to lipophilicity's significance, many approaches could be used to acquire the numbers experimentally and calculate the log *p*-value [40]. We noted in the article that the value of log Po/w is determined by the XLOGP program, version 3.2.2 (courtesy of CCBG, Shanghai Institute of Organic Chemistry), using an atomistic and knowledge-based methodology. A chemical compound must meet at least three of the following conditions in order to be orally active in humans, according to Lipinski's rule of five: (a) MW 500, (b) XLOGP3 3.5, (c) hydrogen bond acceptor 10, and (d) hydrogen bond donor 5 [41]. As a result, it can be seen that the RO5 rule is followed by our target medicine, Linagliptin. Also shown in Table 1 are the compound's pharmacokinetic characteristics related to its GI absorption, BBB permeation, drug metabolism, and permeability glycoprotein action. It is clear from Table 1 that Linagliptin has a high rate of gastrointestinal absorption and can thus enter the

bloodstream with ease. According to predictions, those biological barriers contain the most significant active efflux mechanism [42]. Linagliptin minimizes potential neurological side effects because it does not penetrate the BBB [43]. An essential pharmacokinetic parameter of the drug compound is the drug's metabolic clearance from the body [44]. For the criteria, the cytochrome P450 metabolic enzymes are crucial [45]. In these studies, the chemical inhibitors CYP2C9, a key player in drug metabolism and a member of the cytochrome P450 family of oxidizing enzymes. The metabolic clearance of the medication from the body depends on the proper operation of these CYP enzymes.

3.2. Biological activity of Linagliptin

A list of likely biological activities for Linagliptin can be obtained as an output from the PASS program's prediction of biological activity. *Pa* and *Pi* values, which can be expressed correspondingly as the probabilities of a molecule belonging to the classes of active and inactive molecules, are obtained for each activity. Linagliptin appears to be a very attractive candidate for further investigation because no substantial unfavorable or hazardous consequences are predicted for this chemical, even at $Pa > Pi$. We chose $Pa > 0.2$ as the biological active threshold value for observation. The query chemical, Linagliptin, has pharmacological activity against about 26 target molecules. The current study focuses on a few active target substances, including DPP4 inhibitors, antagonists of the acetylcholine M1 receptor, etc. In addition, Linagliptin was discovered to be a possible vasodilator, antiparkinsonian molecule, phosphodiesterase inhibitor, and ophthalmic medication. These findings are displayed in Table 2.

Table 2. Predicted activity spectrum for Linagliptin at threshold value $Pa > 0.2$

S. No.	Target	<i>Pa</i>	<i>Pi</i>
1	Acetylcholine M1 receptor antagonist	0.620	0.003
2	Nootropic	0.499	0.132
3	Acetylcholine muscarinic antagonist	0.475	0.004
4	Dipeptidyl peptidase inhibitor	0.474	0.002
5	Cognition disorders treatment	0.431	0.027
6	Transplant rejection treatment	0.414	0.014
7	HCV IRES inhibitor	0.412	0.023
8	Cholinergic antagonist	0.411	0.005
9	Vasodilator, peripheral	0.398	0.083
10	Acetylcholine antagonist	0.393	0.006
11	Anti-diabetic	0.382	0.048
12	Male reproductive dysfunction treatment	0.326	0.021
13	erectile dysfunction treatment	0.293	0.018
14	Cyclic GMP phosphodiesterase inhibitor	0.279	0.020
15	Antiemetic	0.277	0.013
16	Ophthalmic drug	0.254	0.088
17	Polarization stimulant	0.247	0.175
18	Antiparkinsonian	0.245	0.103
19	Neurodegenerative diseases treatment	0.240	0.203
20	Cyclic AMP phosphodiesterase inhibitor	0.230	0.164
21	Adenosine receptor antagonist	0.223	0.011
22	Rhinitis treatment	0.222	0.199
23	Antiviral (Influenza A)	0.218	0.169
24	Phosphodiesterase inhibitor	0.214	0.013
25	Diuretic	0.207	0.086
26	Dipeptidyl peptidase IV inhibitor	0.204	0.003

3.3. Biological targets of Linagliptin

In SwissTargetPrediction, we ranked the target based on the probability and estimated the accuracy of the predictions [33]. A probability is computed from the 2D similarity with the compound [37]. In our observation, the higher probability was exhibited by gene CHRM1, DPP4, and FAP as the potential target for Linagliptin (maximum probability=1). The target classes of CHRM1, DPP4, and FAP are family A G-protein coupled receptor, protease, and protease, respectively (Table 3). The pie chart shows the top 15 target compounds (Figure 2).

The SEA search server is used to predict structural similarity and biological target molecule in different species. In the current study, we observed the structural similarity and active biological target molecules in the human species. The higher probability compounds in human species are highlighted in Table 4. The significant values expressed that DPP4, FAP, CHRM1, ALDH1A1, and PDE6D are target molecules for Linagliptin (Figure 4).

3.4. Cytotoxicity analysis

To analyze the cytotoxicity effect of the Linagliptin molecule, CLC-Pred (cell line cytotoxicity prediction) was run. The CLC-Pred showed that the Linagliptin molecule does not exhibit any cytotoxicity effect. Previous clinical studies on human lymphocytes cells concluded that Linagliptin has no cytotoxic, pro-oxidative, and genotoxic effects, although the treatment with Linagliptin drug was safe and tolerant [46–48].

3.5. Pattern of gene expression induced by Linagliptin

Observations through DIGEP-prediction demonstrated that the Linagliptin molecule induces gene expression patterns such as upregulations and downregulations of number of genes (Table 5).

The observation as in Table 5 shows that Linagliptin either up or downregulated the mRNA-based gene expression [36]. ALD18A1 (aldehyde dehydrogenase family 18 member 1), EV128 (ecotropic viral integration site 2B), SLC15A1 (solute carrier family 15 member 1), CTPS1 (CTP synthase 1), and H6PD (hexose-6-phosphate dehydrogenase) are only a few of the genes that Linagliptin causes to downregulate (Figure 5).

Gamma-glutamyl kinase and phosphate reductase activities are both present in the ATP and NADPH-dependent enzyme that ALD18A1 encodes. L-glutamate is changed into delta-1-pyrroline-5-carboxylate, which is then used metabolically to create proline, ornithine, and arginine. Non-essential amino acids include proline, ornithine, and arginine [49]. Linagliptin caused the gene expression to be downregulated, which could result in glutamate buildup in the body. The overexcitation of nerve cells caused by the elevated glutamate content can result in increased cellular activity and cell death.

A regulator of myeloid cell development, enhancer binding protein alpha (C/EBP), targets the gene EV12B (ecotropic viral integration site 2B) [50]. Acute or chronic myelogenous leukemia is caused by changes in myeloid cells, which result in aberrant proliferation of mature myeloid cells [51].

Carrier proteins that are used to absorb and take in dietary protein are encoded by the SLC15A1 gene. Small peptides made up of two or three amino acids are the primary form in which digested proteins are absorbed. Only one transport system – the proton-coupled peptide transporter-1 (PepT1) encoded from the soluble carrier protein Slc15a1 – mediates the intestinal absorption of short peptides [52]. A protein deficiency disorder results from downregulation of the SLC15A1 gene, which reduces the absorption of dietary proteins. In the de novo pyrimidine biosynthesis route, cytidine triphosphate (CTP) is converted to uridine triphosphate by the CTP synthase enzyme, which is encoded by CTPS1 [53, 54]. The two mechanisms that produce CTP – the salvage pathway and the de

Table 3. Predicted molecules targeted by Linagliptin

Target	Common name	Uniprot ID	Target class	Probability*
Muscarinic acetylcholine receptor M1	CHRM1	P11229	Family A G protein-coupled receptor	1
Dipeptidyl peptidase IV	DPP4	P27487	Protease	1
Fibroblast activation protein alpha	FAP	Q12884	Protease	1

Table 4. Target molecules for Linagliptin in different species

Target key	Target name	Description	P-Value	MaxTC
DPP4_HUMAN	DPP4	Dipeptidyl peptidase 4	1.51E-77	1
SEPR_HUMAN	FAP	Prolyl endopeptidase FAP	7.92E-32	1
SEPR_MOUSE	Fap	Prolyl endopeptidase FAP	9.63E-10	1
ACM1_HUMAN	CHRM1	Muscarinic acetylcholine receptor M1	2.40E-09	1
Q8MHZ5_SHEEP		Ghrelin/growth hormone secretagogue receptor	8.83E-37	0.34
DPP4_BOVIN	DPP4	Dipeptidyl peptidase 4	4.68E-25	0.39
DPP4_PIG	DPP4	Dipeptidyl peptidase 4	3.53E-23	0.56
AA2AR_RAT	Adora2a	Adenosine receptor A2a	9.69E-20	0.4
AL1A1_HUMAN	ALDH1A1	Retinal dehydrogenase 1	4.44E-16	0.33
AA1R_RAT	Adora1	Adenosine receptor A1	1.37E-12	0.4
PDE6D_HUMAN	PDE6D	Retinal rod rhodopsin-sensitive cGMP 3',5'-cyclic phosphodiesterase subunit delta	1.12E-10	0.31
DPP4_RAT	Dpp4	Dipeptidyl peptidase 4	2.85E-08	0.54

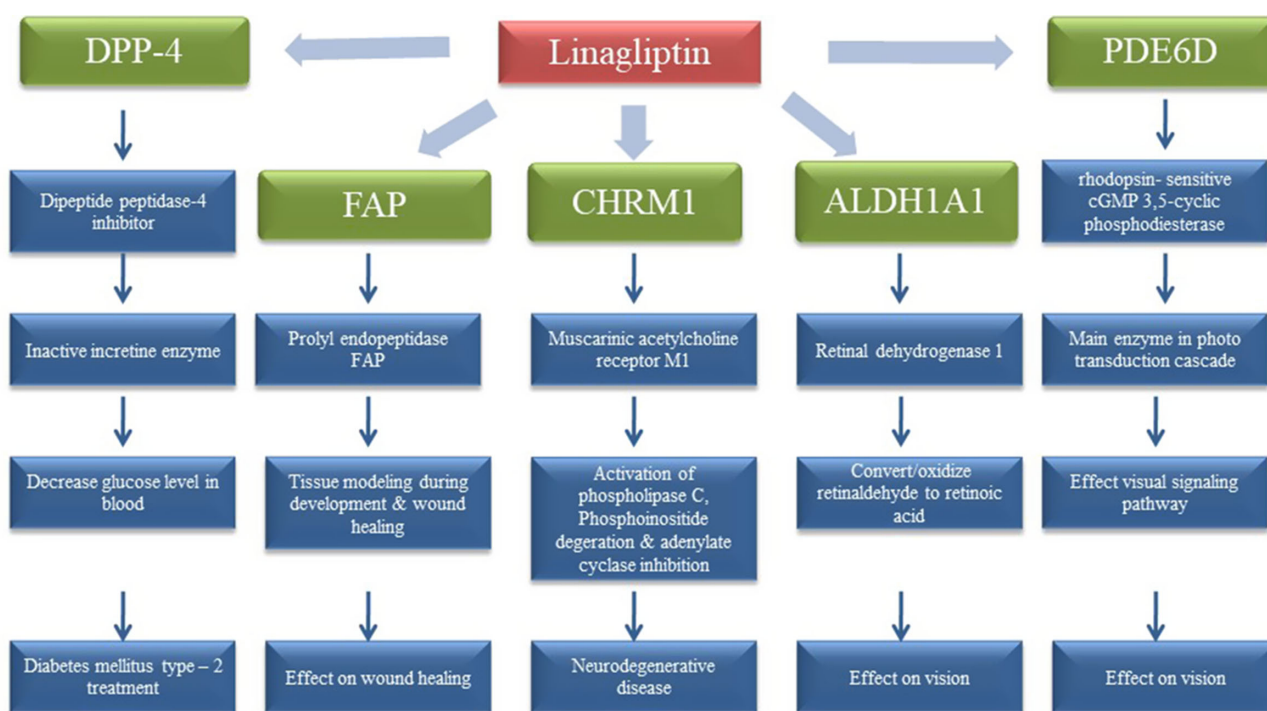


Figure 4. Biological targets and activities of Linagliptin

Table 5. Linagliptin-induced changes in the cellular gene expression patterns. Upward arrows show upregulation of gene, while downward arrows show downregulation of gene.

S. No.	<i>Pa</i>	<i>Pi</i>	Regulation	Up/Down
1	0.948	0.004	ALDH18A1	↓
2	0.78	0.024	EVI2B	↓
3	0.757	0.037	SLC15A1	↓
4	0.721	0.034	CTPS1	↓
5	0.561	0.104	H6PD	↓
1	0.921	0.017	LST1	↑
2	0.646	0.089	SFRP1	↑
3	0.599	0.095	NPPB	↑
4	0.521	0.075	ID1	↑

novo synthesis pathway – are controlled by the enzymes CTP synthase (CTP1 and CTP2) [55]. In lymphocytes, CTP synthase activity may be a crucial step in the synthesis of DNA [56, 57]. Immunodeficiency is brought on by a decrease in CD3-mediated T-cell proliferation, which is caused by downregulation of CTPS1 expression [58].

The pentose phosphate pathway uses H6PD. In the endoplasmic reticulum lumen, the H6PD gene reduces NADPH by converting glucose 6-phosphate to 6-phosphogluconate. The first step of the pentose phosphate pathway, glucose-6-phosphate dehydrogenase (G6PD), carries out the same reaction in the cytosol [59]. Reduced total ATP generation and reduced cell proliferation are both associated with downregulation of the H6PD gene in murine cancer cell lines [60]. H6PD regulates calcium homeostasis, redox balance, and protein response in cancer cells [61].

In addition, as shown in Figure 6, Linagliptin causes the upregulation of genes such as leucocyte-specific transcript 1

protein (LST1), secreted frizzled-related protein 1 (SFRP1), inhibitor of DNA binding HLH protein (ID1), and natriuretic peptide B (NPPB).

LST1 gene encodes membrane protein that inhibits the proliferation of the lymphocytes. Upregulation of the gene expresses inhibited growth of lymphocytes. LST1/A is a potential negative regulator of myeloid cell signaling [62]. SFRP1-encoded frizzled-related protein acts as a modulator of the Wnt signaling pathway. The protein binds with the Wnt signaling molecules in the cytoplasm and downregulates the Wnt signaling by the formation of the inhibitory complex [63]. The signaling pathway is essential for the embryonic development or cell proliferation. DNA binding protein inhibitor, ID1, regulates the ETS transcription factor, ELK-1 and ELK-4 [64]. NPPB encodes a secreted protein that functions as a cardiac hormone. It stimulates the activity of guanylate cyclase that activates protein kinase G, which leads to a decreased Ca²⁺ concentration in cytosol resulting in the relaxation of the heart smooth muscles and vessel dilation, a condition which potentially avoids cardiac arrest.

4. Discussion

With significant binding to proteins like DPP4, Linagliptin has distinct physiochemical, pharmacokinetic, and biological characteristics. The Linagliptin medicines were categorized as drug-like compounds because they exhibit greater oral bioavailability and comply with Lipinski’s rule of five (RO5) [41] based on observation of physiochemical features. The pharmacokinetic action is crucial for the human body to process and eliminate the medicinal ingredient [45]. For these requirements, the CYPs are crucial [65]. Inhibitory action of Linagliptin is seen for CYP2C9 and CYP3A4. However, Linagliptin is not hampering the functioning of other CYPs enzymes like CYP1A2, CYP2C19, and CYP3D6. A non-P-gp

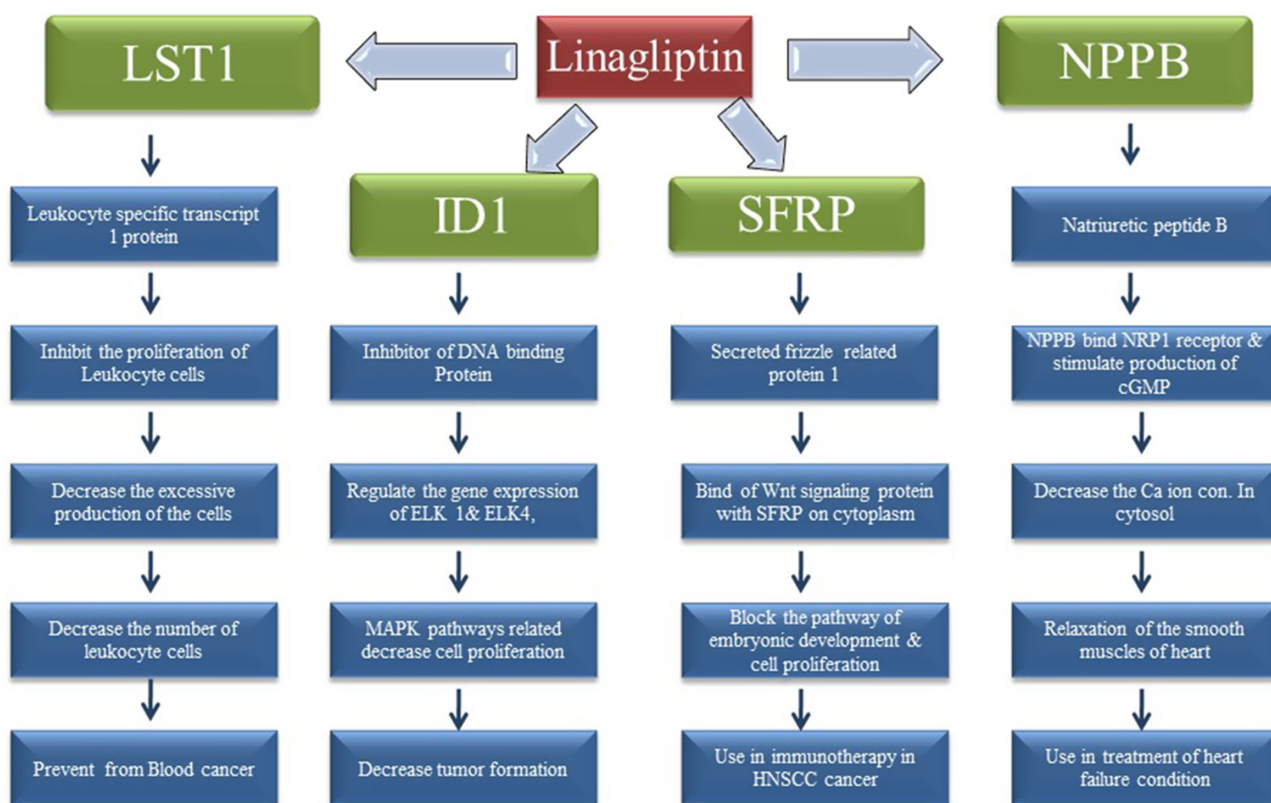


Figure 5. Linagliptin’s downregulation of genes

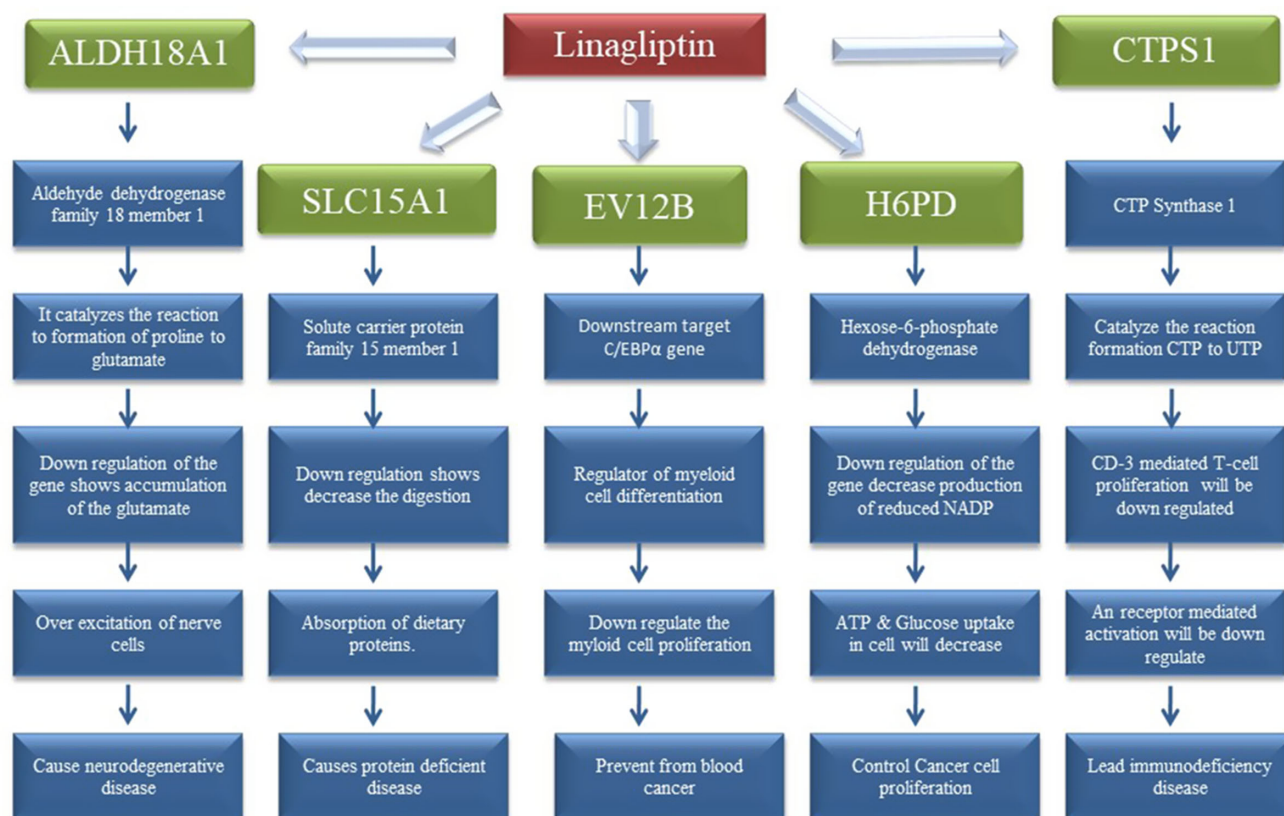


Figure 6. Upregulation of genes by Linagliptin

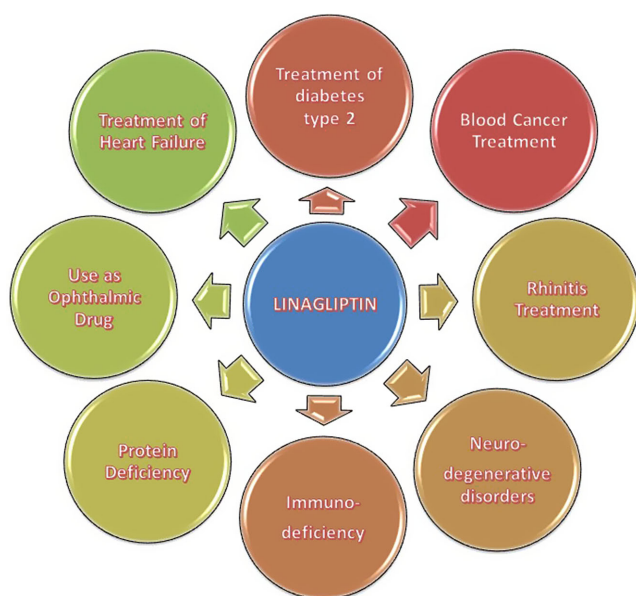


Figure 7. Linagliptin drug model suggesting its cytotoxic effects in treatment of various diseases

protein substrate chemical exhibits low absorption and issues with multidrug resistance [27]. The Linagliptin molecules in this situation are P-gp substrates and have a high bioavailability. Because of all these characteristics, Linagliptin is used as a medication to treat type 2 diabetes in people [66]. With Linagliptin, DPP4 as a target molecule has strong binding activity. We came to the conclusion that Linagliptin causes various types of gene expression either by upregulation or downregulation on the basis of mRNA and proteins from our predictions made using various bioinformatic methods. In the human body, gene expression has both positive and negative effects.

The drug Linagliptin may be employed in immunotherapy for the treatment of heart failure in accordance with the detected gene expressions. In the spontaneously hypertensive rat, the natriuretic peptide precursor A (NPPA) and B (NPPB) genes are potential genes for hypertension and cardiac hypertrophy [67]. Activation of the NPPB gene results into expression of the encoded secreted protein that serves as a cardiac hormone. The guanylyl cyclase is stimulated, and more cGMP is produced, which stimulates protein kinase-G and phosphorylates myosin phosphate, causing the smooth muscles of the heart to relax [68]. Rapid cell division and migration are induced by the Wnt signaling system, which plays a role in embryonic development [69]. Cancer can result from improper cell regulation and unrestrained cell division [70]. Frizzles-related protein, which is encoded by SFRP1, functions as a regulator of the Wnt signaling pathway. The protein interacts with cytoplasmic Wnt signaling molecules to downregulate the signaling by forming an inhibitory complex that causes beta catenin to be degraded by ubiquitin and blocks the pathway [71]. Linagliptin can upregulate the ID4 gene, which in turn can cause the MAPK cascade reaction to downregulate, so reducing excessive cell proliferation. Leukocyte growth is inhibited by LST1 upregulation. When the ALDH18A1 gene is downregulated, glutamate builds up; this high concentration of glutamate may cause nerve cells to get overexcited, which can result in neurodegenerative disorders. SLC15A1 and CTPS1 are additional genes that are downregulated, whereas CHRM1, PDE6D, and ALDH1A1 are targeted genes. Through its non-incretin effects on immune cells, DPP4 may also contribute to the emergence of

neurological diseases with a neuroinflammatory component [71]. The medicine Linagliptin has cytotoxic effects and may be used to treat a number of illnesses, including type 2 diabetes (Figure 7).

5. Conclusion

The collection and analysis of data from millions of species, possibly billions of individuals, and many trillions of base pairs from multiple species are required for biological inquiry to be considered a true science [72–77]. As tools for high-throughput data processing, computers are perfectly suited to help this business. New kinds of inquiries and analyses have also become available as biological data analysis techniques and the capacities of electronic computers have advanced. Computational techniques are developed and used in the interdisciplinary field of computational biology and bioinformatics to analyze large-scale biological data sets, such as genetic sequences, cell populations, or protein samples, in order to generate novel hypotheses or identify novel biological processes.

We performed a computational analysis on Linagliptin for the current investigation. According to the findings, it may have an impact on the gene's signaling pathways, which may result in less serious side effects such as protein deficiency sickness, immunodeficiency disease, and vision loss. In general, we did the research to learn how Linagliptin could be used for purposes other than the management of type 2 diabetes. By inducing the expression of the genes ID1, LST1, SFRP1, EV12B, and NPPB, respectively, Linagliptin may be used to treat cancer by reducing the growth of cancer cells and relaxing smooth muscles. Linagliptin is a possible medication that can be used to treat cardiac arrest and cancer.

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Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

The structures used in this study are openly available at <https://pubchem.ncbi.nlm.nih.gov>.

References

- [1] International Diabetes Federation. (2009). *IDF Diabetes Atlas 4th edition*. Retrieved from: <https://diabetesatlas.org/atlas/fourth-edition/>
- [2] International Diabetes Federation. (2015). *IDF Diabetes Atlas 7th edition*. Retrieved from: <https://diabetesatlas.org/atlas/seventh-edition/>
- [3] Chawla, A., Chawla, R., & Jaggi, S. (2016). Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian Journal of Endocrinology and Metabolism*, 20(4), 546–551. <https://doi.org/10.4103%2F2230-8210.183480>

- [4] Halimi, S., Schweizer, A., Minic, B., Foley, J., & Dejager, S. (2008). Combination treatment in the management of type 2 diabetes: Focus on vildagliptin and metformin as a single tablet. *Vascular Health and Risk Management*, 4(3), 481–492. <https://doi.org/10.2147/vhrm.s2503>
- [5] Kim, W., & Egan, J. M. (2008). The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacological Reviews*, 60(4), 470–512. <https://doi.org/10.1124/pr.108.000604>
- [6] Singh, A. K. (2014). Dipeptidyl peptidase-4 inhibitors: Novel mechanism of actions. *Indian Journal of Endocrinology and Metabolism*, 18(6), 753–759. <https://doi.org/10.4103%2F2230-8210.141319>
- [7] Larsen, M. P., & Torekov, S. S. (2017). Glucagon-like peptide 1: A predictor of type 2 diabetes? *Journal of Diabetes Research*, 2017(1), 7583506. <https://doi.org/10.1155/2017/7583506>
- [8] Vardarli, I., Nauck, M. A., Köthe, L. D., Deacon, C. F., Holst, J. J., Schweizer, A., & Foley, J. E. (2011). Inhibition of DPP-4 with vildagliptin improved insulin secretion in response to oral as well as “isoglycemic” intravenous glucose without numerically changing the incretin effect in patients with type 2 diabetes. *The Journal of Clinical Endocrinology & Metabolism*, 96(4), 945–954. <https://doi.org/10.1210/jc.2010-2178>
- [9] Deacon, C. F., & Ahrén, B. (2011). Physiology of incretins in health and disease. *The Review of Diabetic Studies*, 8(3), 293–306.
- [10] Gallwitz, B. (2012). Linagliptin – A novel dipeptidyl peptidase inhibitor for type 2 diabetes therapy. *Clinical Medicine Insights: Endocrinology and Diabetes*, 5, 1–11. <https://doi.org/10.4137/CMED.S7274>
- [11] Röhrborn, D., Wronkowitz, N., & Eckel, J. (2015). DPP4 in diabetes. *Frontiers in Immunology*, 6, 386. <https://doi.org/10.3389/fimmu.2015.00386>
- [12] Gallwitz, B. (2013). Emerging DPP-4 inhibitors: Focus on linagliptin for type 2 diabetes. *Diabetes, Metabolic Syndrome and Obesity*, 6, 1–9. <https://www.tandfonline.com/doi/full/10.2147/DMSO.S23166>
- [13] Fisman, E. Z., & Tenenbaum, A. (2015). Antidiabetic treatment with gliptins: Focus on cardiovascular effects and outcomes. *Cardiovascular Diabetology*, 14(1), 129. <https://cardiab.biomedcentral.com/articles/10.1186/s12933-015-0294-0>
- [14] Scheen, A. J. (2011). Linagliptin for the treatment of type 2 diabetes (pharmacokinetic evaluation). *Expert Opinion on Drug Metabolism & Toxicology*, 7(12), 1561–1576. <https://doi.org/10.1517/17425255.2011.628986>
- [15] Ropa, J., & Broxmeyer, H. E. (2020). An expanded role for Dipeptidyl peptidase 4 in cell regulation. *Current Opinion in Hematology*, 27(4), 215–224. <https://doi.org/10.1097%2FMOH.0000000000000590>
- [16] Nissen, S. E., & Wolski, K. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *The New England Journal of Medicine*, 356(24), 2457–2471. <https://doi.org/10.1056/NEJMoa072761>
- [17] Rawshani, A., Rawshani, A., Franzén, S., Eliasson, B., Svensson, A. M., Miftaraj, M., . . . , & Gudbjörnsdóttir, S. (2017). Mortality and cardiovascular disease in type 1 and type 2 diabetes. *The New England Journal of Medicine*, 376(15), 1407–1418. <https://doi.org/10.1056/NEJMoa1608664>
- [18] Wen, C. P., Chang, C. H., Tsai, M. K., Lee, J. H., Lu, P. J., Tsai, S. P., . . . , & Wu, X. (2017). Diabetes with early kidney involvement may shorten life expectancy by 16 years. *Kidney International*, 92(2), 388–396. <https://doi.org/10.1016/j.kint.2017.01.030>
- [19] Ofstad, A. P., Atar, D., Gullestad, L., Langset, G., & Johansen, O. E. (2018). The heart failure burden of type 2 diabetes mellitus—A review of pathophysiology and interventions. *Heart Failure Reviews*, 23, 303–323. <https://doi.org/10.1007/s10741-018-9685-0>
- [20] McGuire, D. K., Alexander, J. H., Johansen, O. E., Perkovic, V., Rosenstock, J., Cooper, M. E., . . . , & Marx, N. (2019). Linagliptin effects on heart failure and related outcomes in individuals with type 2 diabetes mellitus at high cardiovascular and renal risk in CARMELINA. *Circulation*, 139(3), 351–361. <https://doi.org/10.1161/CIRCULATIONAHA.118.038352>
- [21] Rosenstock, J., Perkovic, V., Johansen, O. E., Cooper, M. E., Kahn, S. E., Marx, N., . . . , & McGuire, D. K. (2019). Effect of Linagliptin vs Placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: The CARMELINA randomized clinical trial. *JAMA*, 321(1), 69–79. <https://doi.org/10.1001/jama.2018.18269>
- [22] Wiciński, M., Socha, M., Malinowski, B., Wódkiewicz, E., Walczak, M., Górski, K., . . . , & Pawlak-Osińska, K. (2019). Liraglutide and its neuroprotective properties—Focus on possible biochemical mechanisms in Alzheimer’s disease and cerebral ischemic events. *International Journal of Molecular Sciences*, 20(5), 1050. <https://doi.org/10.3390/ijms20051050>
- [23] Aroor, A. R., Habibi, J., Kandikattu, H. K., Garro-Kacher, M., Barron, B., Chen, D., . . . , & DeMarco, V. G. (2017). Dipeptidyl peptidase-4 (DPP-4) inhibition with linagliptin reduces western diet-induced myocardial TRAF3IP2 expression, inflammation and fibrosis in female mice. *Cardiovascular Diabetology*, 16, 61. <https://doi.org/10.1186/s12933-017-0544-4>
- [24] Lovering, F., Bikker, J., & Humblet, C. (2009). Escape from flatland: Increasing saturation as an approach to improving clinical success. *Journal of Medicinal Chemistry*, 52(21), 6752–6756. <https://doi.org/10.1021/jm901241e>
- [25] Ritchie, T. J., Ertl, P., & Lewis, R. (2011). The graphical representation of ADME-related molecule properties for medicinal chemists. *Drug Discovery Today*, 16(1–2), 65–72. <https://doi.org/10.1016/j.drudis.2010.11.002>
- [26] Ertl, P., Rohde, B., & Selzer, P. (2000). Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. *Journal of Medicinal Chemistry*, 43(20), 3714–3717. <https://doi.org/10.1021/jm000942e>
- [27] Amin, M. L. (2013). P-glycoprotein inhibition for optimal drug delivery. *Drug Target Insights*, 7(1), 27–34. <https://doi.org/10.4137/DTI.S12519>
- [28] Poroikov, V. V., & Filimonov, D. A. (2002). How to acquire new biological activities in old compounds by computer prediction. *Journal of Computer-Aided Molecular Design*, 16, 819–824. <https://doi.org/10.1023/A:1023836829456>
- [29] Kurashov, E. A., Fedorova, E. V., Krylova, J. V., & Mitrukova, G. G. (2016). Assessment of the potential biological activity of low molecular weight metabolites of freshwater macrophytes with QSAR. *Scientifica*, 2016(1), 1205680. <https://doi.org/10.1155/2016/1205680>
- [30] Filimonov, D. A., Lagunin, A. A., Glorizova, T. A., Rudik, A. V., Druzhilovskii, D. S., Pogodin, P. V., & Poroikov, V. V. (2014). Prediction of the biological activity spectra of organic compounds using the PASS online web resource. *Chemistry of Heterocyclic Compounds*, 50(3), 444–457. <https://doi.org/10.1007/s10593-014-1496-1>
- [31] Campillos, M., Kuhn, M., Gavin, A. C., Jensen, L. J., & Bork, P. (2008). Drug target identification using side-effect similarity.

- Science*, 321(5886), 263–266. <https://doi.org/10.1126/science.1158140>
- [32] Keiser, M. J., Roth, B. L., Armbruster, B. N., Ernsberger, P., Irwin, J. J., & Shoichet, B. K. (2007). Relating protein pharmacology by ligand chemistry. *Nature Biotechnology*, 25(2), 197–206. <https://doi.org/10.1038/nbt1284>
- [33] Gfeller, D., Michielin, O., & Zoete, V. (2013). Shaping the interaction landscape of bioactive molecules. *Bioinformatics*, 29(23), 3073–3079. <https://doi.org/10.1093/bioinformatics/btt540>
- [34] Lounkine, E., Keiser, M. J., Whitebread, S., Mikhailov, D., Hamon, J., Jenkins, J. L., . . . , & Urban, L. (2012). Large-scale prediction and testing of drug activity on side-effect targets. *Nature*, 486(7403), 361–367. <https://doi.org/10.1038/nature11159>
- [35] Chinnasamy, P., & Arumugam, R. (2018). In silico prediction of anticarcinogenic bioactivities of traditional anti-inflammatory plants used by tribal healers in Sathyamangalam wildlife Sanctuary, India. *Egyptian Journal of Basic and Applied Sciences*, 5(4), 265–279. <https://doi.org/10.1016/j.ejbas.2018.10.002>
- [36] Lagunin, A., Ivanov, S., Rudik, A., Filimonov, D., & Porokov, V. (2013). DIGEP-Pred: Web service for in silico prediction of drug-induced gene expression profiles based on structural formula. *Bioinformatics*, 29(16), 2062–2063. <https://doi.org/10.1093/bioinformatics/btt322>
- [37] Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*, 7(1), 42717. <https://doi.org/10.1038/srep42717>
- [38] Hassan, S. A., & Tayubi, I. A. (2017). Computational approaches to identify a derivative of Galardin as an inhibitor of mycobacterial peptide deformylase. *VAWKUM Transactions on Computer Sciences*, 5(1), 45–55. <https://doi.org/10.21015/vtcs.v12i2.452>
- [39] Stocks, M. (2013). The small molecule drug discovery process – From target selection to candidate selection. In R. Ganellin, S. Roberts & R. Jefferis (Eds.), *Introduction to biological and small molecule drug research and development* (pp. 81–126). Elsevier. <https://doi.org/10.1016/B978-0-12-397176-0.00003-0>
- [40] Armstrong, M. S., Finn, P. W., Morris, G. M., & Richards, W. G. (2011). Improving the accuracy of ultrafast ligand-based screening: Incorporating lipophilicity into ElectroShape as an extra dimension. *Journal of Computer-Aided Molecular Design*, 25, 785–790. <https://doi.org/10.1007/s10822-011-9463-8>
- [41] Lipinski, C. A. (2004). Lead-and drug-like compounds: The rule-of-five revolution. *Drug Discovery Today: Technologies*, 1(4), 337–341. <https://doi.org/10.1016/j.ddtec.2004.11.007>
- [42] Montanari, F., & Ecker, G. F. (2015). Prediction of drug–ABC-transporter interaction—Recent advances and future challenges. *Advanced Drug Delivery Reviews*, 86, 17–26. <https://doi.org/10.1016/j.addr.2015.03.001>
- [43] Carpenter, T. S., Kirshner, D. A., Lau, E. Y., Wong, S. E., Nilmeier, J. P., & Lightstone, F. C. (2014). A method to predict blood-brain barrier permeability of drug-like compounds using molecular dynamics simulations. *Biophysical Journal*, 107(3), 630–641. <https://doi.org/10.1016/j.bpj.2014.06.024>
- [44] Testa, B., & Krämer, S. D. (2006). The biochemistry of drug metabolism – An introduction: Part 1. principles and overview. *Chemistry & Biodiversity*, 3(10), 1053–1101. <https://doi.org/10.1002/cbdv.200690111>
- [45] Sigel, A., Sigel, H., & Sigel, R. K. O. (2007). *The ubiquitous roles of cytochrome P450 proteins*. USA: John Wiley & Sons.
- [46] Çadirci, K., Türkez, H., & Özdemir, Ö. (2019). The in vitro cytotoxicity, genotoxicity and oxidative damage potential of the oral dipeptidyl peptidase-4 inhibitor, linagliptin, on cultured human mononuclear blood cells. *Acta Endocrinologica (Bucharest)*, 15(1), 9–15. <https://doi.org/10.4183%2Faeb.2019.9>
- [47] Schernthaner, G., Barnett, A. H., Emser, A., Patel, S., Troost, J., Woerle, H. J., & von Eynatten, M. (2012). Safety and tolerability of Linagliptin: A pooled analysis of data from randomized controlled trials in 3572 patients with type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism*, 14(5), 470–478. <https://doi.org/10.1111/j.1463-1326.2012.01565.x>
- [48] Taskinen, M. R., Rosenstock, J., Tamminen, I., Kubiak, R., Patel, S., Dugi, K. A., & Woerle, H. J. (2011). Safety and efficacy of Linagliptin as add-on therapy to metformin in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled study. *Diabetes, Obesity and Metabolism*, 13(1), 65–74. <https://doi.org/10.1111/j.1463-1326.2010.01326.x>
- [49] Puigserver, P. (2018). Signaling transduction and metabolomics. In R. Hoffman, E. J. Benz, L. E. Silberstein, H. E. Heslop, J. I. Weitz, J. Anastasi, M. E. Salama & S. A. Abutalib (Eds.), *Hematology* (pp. 68–78). Elsevier. <https://doi.org/10.1016/B978-0-323-35762-3.00007-X>
- [50] Zjablovskaja, P., Kardosova, M., Danek, P., Angelisova, P., Benoukraf, T., Wurm, A. A., . . . , & Alberich-Jorda, M. (2017). EVI2B is a C/EBP α target gene required for granulocytic differentiation and functionality of hematopoietic progenitors. *Cell Death & Differentiation*, 24(4), 705–716. <https://doi.org/10.1038/cdd.2017.6>
- [51] Kawamoto, H., & Minato, N. (2004). Myeloid cells. *The International Journal of Biochemistry & Cell Biology*, 36(8), 1374–1379. <https://doi.org/10.1016/j.biocel.2004.01.020>
- [52] Okamura, A., Koyanagi, S., Dilxiat, A., Kusunose, N., Chen, J. J., Matsunaga, N., . . . , & Ohdo, S. (2014). Bile acid-regulated peroxisome proliferator-activated receptor- α (PPAR α) activity underlies circadian expression of intestinal peptide absorption transporter PepT1/Slc15a1. *Journal of Biological Chemistry*, 289(36), 25296–25305. <https://doi.org/10.1074/jbc.M114.577023>
- [53] Evans, D. R., & Guy, H. I. (2004). Mammalian pyrimidine biosynthesis: Fresh insights into an ancient pathway. *Journal of Biological Chemistry*, 279(32), 33035–33038. <https://doi.org/10.1074/jbc.R400007200>
- [54] Higgins, M. J., Graves, P. R., & Graves, L. M. (2007). Regulation of human cytidine triphosphate synthetase 1 by glycogen synthase kinase 3. *Journal of Biological Chemistry*, 282(40), 29493–29503. <https://doi.org/10.1074/jbc.M703948200>
- [55] Kassel, K. M., Au, D. R., Higgins, M. J., Hines, M., & Graves, L. M. (2010). Regulation of human cytidine triphosphate synthetase 2 by phosphorylation. *Journal of Biological Chemistry*, 285(44), 33727–33736. <https://doi.org/10.1074/jbc.M110.178566>
- [56] Fairbanks, L. D., Bofill, M., Ruckemann, K., & Simmonds, H. A. (1995). Importance of ribonucleotide availability to proliferating T-lymphocytes from healthy humans: Disproportionate expansion of pyrimidine pools and contrasting effects of de novo synthesis inhibitors. *Journal of Biological Chemistry*, 270(50), 29682–29689. <https://doi.org/10.1074/jbc.270.50.29682>
- [57] van den Berg, A. A., van Lenthe, H., Kipp, J. B. A., de Korte, D., van Kuilenburg, A. B. P., & van Gennip, A. H. (1995). Cytidine triphosphate (CTP) synthetase activity during cell cycle progression in normal and malignant T-lymphocytic cells. *European Journal of Cancer*, 31(1), 108–112. [https://doi.org/10.1016/0959-8049\(94\)00442-8](https://doi.org/10.1016/0959-8049(94)00442-8)
- [58] Martin, E., Palmic, N., Sanquer, S., Lenoir, C., Hauck, F., Mongellaz, C., . . . , & Latour, S. (2014). CTP synthase 1 deficiency in humans reveals its central role in lymphocyte

- proliferation. *Nature*, 510(7504), 288–292. <https://doi.org/10.1038/nature13386>
- [59] Clarke, J. L., & Mason, P. J. (2003). Murine hexose-6-phosphate dehydrogenase: A bifunctional enzyme with broad substrate specificity and 6-phosphogluconolactonase activity. *Archives of Biochemistry and Biophysics*, 415(2), 229–234. [https://doi.org/10.1016/S0003-9861\(03\)00229-7](https://doi.org/10.1016/S0003-9861(03)00229-7)
- [60] Marini, C., Ravera, S., Buschiazzo, A., Bianchi, G., Orengo, A. M., Bruno, S., . . . , & Sambuceti, G. (2016). Discovery of a novel glucose metabolism in cancer: The role of endoplasmic reticulum beyond glycolysis and pentose phosphate shunt. *Scientific Reports*, 6(1), 25092. <https://doi.org/10.1038/srep25092>
- [61] Tsachaki, M., Mladenovic, N., Štambergová, H., Birk, J., & Odermatt, A. (2018). Hexose-6-phosphate dehydrogenase controls cancer cell proliferation and migration through pleiotropic effects on the unfolded-protein response, calcium homeostasis, and redox balance. *The FASEB Journal*, 32(5), 2690–2705. <https://doi.org/10.1096%2Fj.201700870RR>
- [62] Draber, P., Stepanek, O., Hrdinka, M., Drobek, A., Chmatal, L., Mala, L., . . . , & Brdicka, T. (2012). LST1/A is a myeloid leukocyte-specific transmembrane adaptor protein recruiting protein tyrosine phosphatases SHP-1 and SHP-2 to the plasma membrane. *Journal of Biological Chemistry*, 287(27), 22812–22821. <https://doi.org/10.1074/jbc.M112.339143>
- [63] Janssens, N., Janicot, M., & Perera, T. (2006). The Wnt-dependent signaling pathways as target in oncology drug discovery. *Investigational New Drugs*, 24, 263–280. <https://doi.org/10.1007/s10637-005-5199-4>
- [64] Kasza, A., O'Donnell, A., Gascoigne, K., Zeef, L. A., Hayes, A., & Sharrocks, A. D. (2005). The ETS domain transcription factor Elk-1 regulates the expression of its partner protein, SRF. *Journal of Biological Chemistry*, 280(2), 1149–1155. <https://doi.org/10.1074/jbc.M411161200>
- [65] Veith, H., Southall, N., Huang, R., James, T., Fayne, D., Artemenko, N., . . . , & Auld, D. S. (2009). Comprehensive characterization of cytochrome P450 isozyme selectivity across chemical libraries. *Nature Biotechnology*, 27(11), 1050–1055. <https://doi.org/10.1038/nbt.1581>
- [66] McGill, J. B. (2012). Linagliptin for type 2 diabetes mellitus: A review of the pivotal clinical trials. *Therapeutic Advances in Endocrinology and Metabolism*, 3(4), 113–124. <https://doi.org/10.1177/2042018812449406>
- [67] Ye, P., & West, M. J. (2003). Cosegregation analysis of natriuretic peptide genes and blood pressure in the spontaneously hypertensive rat. *Clinical and Experimental Pharmacology and Physiology*, 30(12), 930–936. <https://doi.org/10.1111/j.1440-1681.2003.03937.x>
- [68] Denninger, J. W., & Marletta, M. A. (1999). Guanylate cyclase and the NO/cGMP signaling pathway. *Biochimica et Biophysica Acta (BBA) – Bioenergetics*, 1411(2–3), 334–350. [https://doi.org/10.1016/S0005-2728\(99\)00024-9](https://doi.org/10.1016/S0005-2728(99)00024-9)
- [69] Lindsley, R. C., Gill, J. G., Kyba, M., Murphy, T. L., & Murphy, K. M. (2006). Canonical Wnt signaling is required for development of embryonic stem cell-derived mesoderm. *Development*, 133(19), 3787–3796. <https://doi.org/10.1242/dev.02551>
- [70] Nusse, R. (2005). Wnt signaling in disease and in development. *Cell Research*, 15(1), 28–32. <https://doi.org/10.1038/sj.cr.7290260>
- [71] Clevers, H. (2006). Wnt/β-catenin signaling in development and disease. *Cell*, 127(3), 469–480. <https://doi.org/10.1016/j.cell.2006.10.018>
- [72] Al-Badri, G., Leggio, G. M., Musumeci, G., Marzagalli, R., Drago, F., & Castorina, A. (2018). Tackling dipeptidyl peptidase IV in neurological disorders. *Neural Regeneration Research*, 13(1), 26–34. <https://doi.org/10.4103%2F1673-5374.224365>
- [73] Dakal, T. C., Kala, D., Dhiman, G., Yadav, V., Krokhotin, A., & Dokholyan, N. V. (2017). Predicting the functional consequences of non-synonymous single nucleotide polymorphisms in IL8 gene. *Scientific Reports*, 7(1), 6525. <https://doi.org/10.1038/s41598-017-06575-4>
- [74] Dakal, T. C., Kumar, R., & Ramotar, D. (2017). Structural modeling of human organic cation transporters. *Computational Biology and Chemistry*, 68, 153–163. <https://doi.org/10.1016/j.compbiolchem.2017.03.007>
- [75] Dhakar, R., Dakal, T. C., & Sharma, A. (2022). Genetic determinants of lung cancer: Understanding the oncogenic potential of somatic missense mutations. *Genomics*, 114(4), 110401. <https://doi.org/10.1016/j.ygeno.2022.110401>
- [76] Mathur, R., Sharma, L., Dhabhai, B., Menon, A. M., Sharma, A., Sharma, N. K., & Dakal, T. C. (2021). Predicting the functional consequences of genetic variants in co-stimulatory ligand B7-1 using in-silico approaches. *Human Immunology*, 82(2), 103–120. <https://doi.org/10.1016/j.humimm.2020.12.001>
- [77] Menon, A. M., & Dakal, T. C. (2020). Genomic scanning of the promoter sequence in osmo/halo-tolerance related QTLs in *Zygosaccharomyces rouxii*. *Meta Gene*, 26, 100809. <https://doi.org/10.1016/j.mgene.2020.100809>

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