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COMPARATIVE STUDY OF PHARMACOLOGICAL PROPERTIES AND PREDICTIONS FOR REPURPOSING OF GLIPTINS: A COMPUTATIONAL APPROACH

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ABSTRACT

Dipeptidyl peptidase-IV (DPP-IV) inhibitors are widely used drugs of choice for treating Type 2 Diabetes Mellitus (T2DM). These are mostly gliptin molecules. DPP-IV is responsible for the degradation of Glucagon-like polypeptide -I which is responsible for the enhancement of the activity of the insulin. So, the therapeutic strategy is to use these drugs to inhibit DPP-enzyme, hence prohibiting the degradation of GLP-I. A series of DPP-IV inhibitors are used for the effective management of T2DM. Many DPP-IV inhibitors are still in clinical trials. The discovery and the need for developing novel DPP-IV inhibitors is the newer approach. These

drugs have shown pharmacological effects in various metabolic disorders like controlling T2DM majorly and showing anti-parkinsonism, Anti-obesity, Anti-neoplastic, cardioprotective action, anti-inflammatory, and analgesic in diabetic neuropathy. The comparative study of pharmacological properties and predictions of 20 gliptins which are widely used as DPP-IV inhibitors helps to repurpose the same in different biological diseased conditions. It will save time and expenditure on the development of the new drug and the study of drug profiles through clinical investigations. The analysis method and prediction studies are beneficial for the prospects of this class of drugs specifically.

Keywords: DPP-IV inhibitors, Anti-diabetic agent, Anti-obesity agent, Anti-parkinson agent, activity predictions

INTRODUCTION:

Diabetes affects people of all ages, genders, and ethnicities and is one of the world's major causes of death and disability. Worldwide, 529 million individuals (95% uncertainty interval [UI] 500–564) acquired diabetes in 2021, and the age-standardized overall prevalence of diabetes was 6·1% (5·8–6·5). It is estimated that over 1·31 billion (1·22–1·39) people will have diabetes by 2050, with age-standardized overall diabetes prevalence rates likely to be higher than 10%. Diabetes continues to constitute a serious problem for public health. Most diabetes occurrences are type 2 diabetes, which is mostly avoidable and may even be reversible in certain circumstances if detected and treated early in the course of the illness **[1]**. There are economic ramifications to this health burden. According to estimates by Bommer *et al*. (2017), the cost of diabetes worldwide in 2015 was 1.8% of the world's gross domestic product ($1.3 trillion US) **[2]**. The occurrence of Type 2 diabetes has doubled the cases of Type 1 diabetes in the last two decades **[3]**. Currently used medication includes biguanides, thiazolidinediones, GLP-1 agonists, glucose-dependent insulinotropic polypeptide (GIP) agonists, Dipeptidyl peptidase-IV inhibitors, Peroxisome proliferator-activated receptor, etc. **[4]**. Dipeptidyl peptidase IV (DPP IV) is a widely distributed, multipurpose, serine protease enzyme and receptor that regulates immune system and endocrine function, cell proliferation, adhesion, and metabolism. The incretin hormones glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 are broken down into their N-terminal dipeptide by the enzyme DPP IV. As a result, the hormones become inactive and

lose their prandial insulinotropic impact. The creation of DPP IV inhibitors has been one method of treating Type 2 diabetes by restoring incretin function **[5]**. Dipeptidyl peptidase IV (DPP-IV, DPP4, CD26, adenosine deaminase complexing protein 2, EC 3.4.14.5) is a homodimeric type II transmembrane glycoprotein that is made up of a large extracellular domain (amino acids 29–766), a short cytoplasmic region (amino acids 1–6), and a transmembrane domain that is 22 amino acids long. The catalytic triad formed in the human protein by Ser630, Asp708, and His740 is found in the catalytic portion of the protein **[6]**. DPP-IV is involved in multiple physiological processes, such as immune system function, endocrine function, inhibition of cancer cell development, cell adhesion, and enzymatic incretin deactivation in diabetes mellitus. In diabetes mellitus, the insulin receptors are not able to interact with insulin, or the pancreas is unable to secret the insulin as per the requirement of the body. Hence the body's glucose level increases and leads to several complications. DPP-IV inhibitors play a vital role in lowering blood glucose levels. DPP-IV inhibitors are devoid of side effects like weight gain, hypoglycemia, and fatigue as that other traditional drug therapies **[7]**. DPP-IV inhibitors are promising targets for designing novel molecules. In the field of drug discovery, DPP-IV inhibitors are privileged targets that offer a variety of chances for investigating this target to create compounds as antidiabetic medicines. DPP-IV lowers blood glucose levels by blocking the activity of incretins with little adverse effects **[8]**. DPP-IV inhibitor drugs like Sitagliptin, vildagliptin, linagliptin, and other medications have been licensed globally for the management of diabetes mellitus. The basic heterocyclic nuclei utilized for the preparation of DPP-IV inhibitors are Pyrrolidines; Fluorobenzenes; Ketones; Pyrazines, Triazoles, Cycloparaffins; Nitriles; Polycyclic bridged compounds, Piperidines; Pyrimidinones etc.

Need for Drug Repurposing:

Finding new applications for medications that were once created for a different therapeutic purpose is known as drug repurposing, drug repositioning, or drug reprofiling. Repurposing already existing drugs saves expenses for the discovery of novel molecules and saves time **(Figure 1)**. As the safety profile of the drugs is already studied, it lowers the risk of adverse effects leading to the streamlined regulatory approval process. These molecules can enter the market easily and the availability of the drug to patients is also easier. Sometimes

these drugs may address the unmet medical needs and allow the researchers to explore alternative uses of existing drugs. Repurposing of drugs leads to the discovery of novel mechanisms of action and it can be used in combination with existing drugs which can improve the quality of a patient's life. Even repositioning orphan diseases is possible that are valuable. Resources can be allocated efficiently and optimization of the use of drugs can be possible by pharmaceutical companies. Drug repurposing contributes the environmental sustainability and one can quickly address the need for public health. In conclusion, drug repurposing plays a critical role in the pharmaceutical industry and healthcare by offering an efficient and cost-effective means of identifying new therapeutic uses for existing drugs. It can lead to the development of treatments for unmet medical needs, provide alternative treatment options, and accelerate the availability of effective therapies, all while reducing the risks and costs associated with drug development.

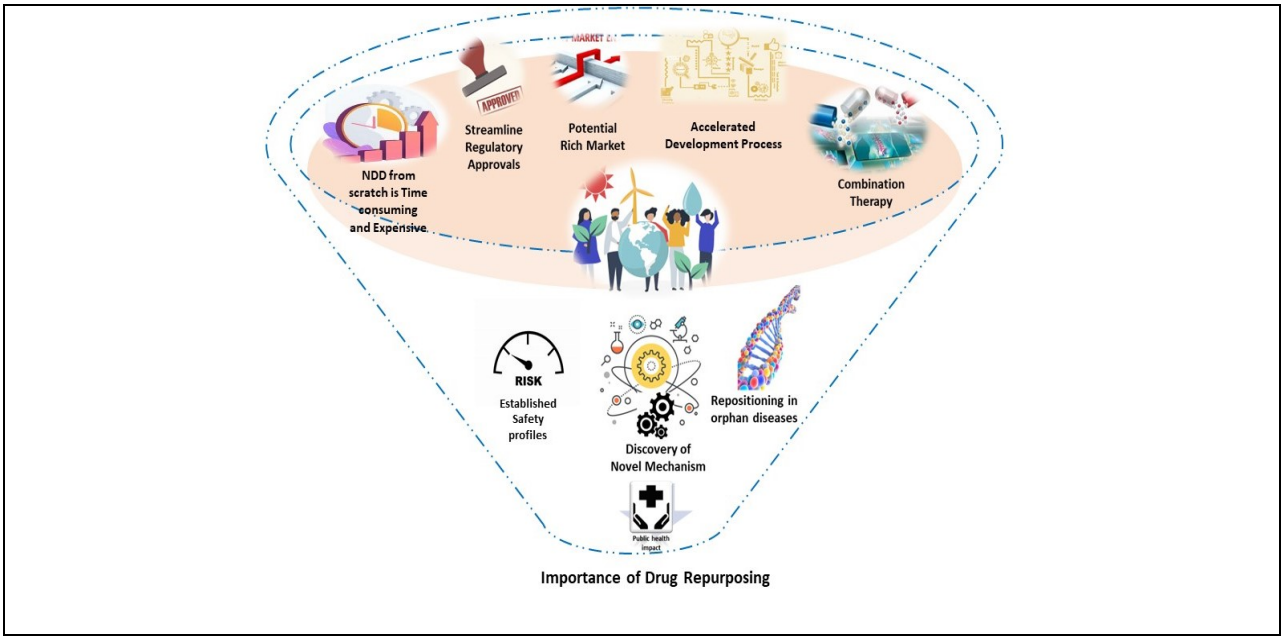

Figure 1: Importance of Drug Repurposing

Mechanism of action of Dipeptidyl peptidase-IV (DPP-IV):

In response to calorie intake, the intestinal mucosa's enteroendocrine L cells secrete the peptide hormone known as glucagon-like peptide-1 (GLP-1), which is a potent insulin secretagogue that may enhance insulin activity while simultaneously suppressing

glucagon secretion in a glucose-dependent manner and also delaying gastric emptying time **[9]**. GLP-1 has its biological effects through N-terminal amino acids and inactivation of the GLP-1 is carried out via the action of DPP-IV which removes these N-terminal amino acids **[10]**. The glucose-lowering capacity of GLP-1 agonists and DPP-IV inhibitors differs widely; hence the inhibition of the DPP-IV enzyme is an essential pathway for effective hypoglycemic action **[11]**. Essentially, DPP-4 inhibitors raise levels of the two active incretin hormones (secreted by the enteroendocrine L and K cells, respectively, which are substrates for DPP-4): GLP-1 and glucose-dependent insulinotropic polypeptide **(Figure 2)**. As a result, glucagon production is suppressed and β-cell responsiveness to current glucose concentrations is enhanced. By blocking DPP-IV, GLP-1 and GIP degradation is avoided **[12]**. DPP-IV is available throughout the body on endothelial cells and they are expressed as ectoenzymes, also present on T lymphocyte surface as well as in circulating form **[13]**.

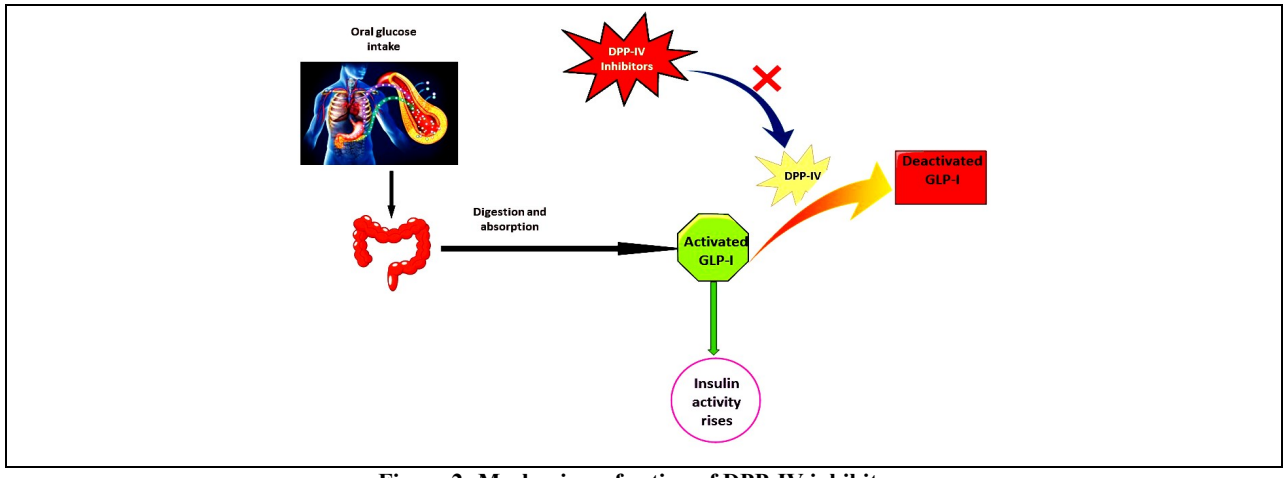

Figure 2: Mechanism of action of DPP-IV inhibitors

Classification of DPP-IV inhibitory drugs:

Compared to non-substrate-like inhibitors, substrate-like inhibitors are more universal. These are proline mimetic, meaning that they occupy the P1-substituent and S1-pocket in their fundamental structure. Substrate inhibitor containing cynopyrrolidine shows interaction with the nitrile group, serine hydroxyl group, and amino group which is protonated **[14]**. The interacting amino acids are Glu205, Glu206, Tyr662. They are given below in **Table 1 and Table 2** detailed classification of DPP-IV inhibitors. The inhibitor group contains fluorobenzene as one of the most active moieties. Pyrrolidine heterocycle is present in most of the

molecules of DPP-IV inhibitors. At the same time, it is observed that 'N' containing heterocycles like piperazine, pyrrole, nitriles, pyrazoles, and amides are found to be contributing functional groups present in the DPP-IV inhibitors **[15]**.

Current Status of DPP-IV Inhibitors:

About 22 molecules of DPP-IV inhibitors as a derivative of gliptin are available either in the market for therapeutic use or in the clinical and preclinical phases for further study **Table 3**. Sitagliptin is a widely used DPP-IV inhibitor. These drugs are useful as monotherapy and adjunctive therapy with traditional hypoglycaemic agents like Metformin, Glibenclamide, Gliclazide, etc. Along with this DPP-IV inhibitors are also under research as dual targets with other novel targets like GPR119 in the treatment of T2DM. The respective data like synonyms, originator, developer, and current status of the drug was collected from the web server https://adisinsight.springer.com/ **[16]**. This web server provides very useful information related to the discovery of the new drug, development information, safety, patents, and clinical trials.

Table 1: Substrate-like and non-substrate-like inhibitors

Sr. No.	Category	Properties	Drugs example
1	Substrate like inhibitors	Proline mimetics occupy the S1 pocket and P1-substituent	Vildagliptin, Saxagliptin, Denagliptin
2	Non-substrate like inhibitors	Non-covalent inhibitors with aromatic ring occupies the S1 pocket	Sitagliptin, Linagliptin, Alogliptin

Table 2: Based on the Chemical components present in the structure:

Sr. No.	Component	Drug molecule	Heterocyclic moieties present
1	Inhibitor group	Sitagliptin,	Fluorobenzene; Ketones; Pyrazines, Triazoles
		Retagliptin,	Carboxylic acids; Fluorobenzene; Imidazole; Pyrazines
		Gemigliptin,	Piperidines; Pyrimidines,
		Omarigliptin,	Fluorobenzene; Pyrazoles; Pyrrolidines, Sulphonamides
		Evogliptin	Amides, Fluorobenzene; Piperazines
2	Boronic acid	Dutogliptin,	Pyrrolidines
		Carmegliptin	3-ring heterocyclic compounds, Pyrrolidinones
3	Cynopyrrolidine	Vildagliptin	Cycloparaffins; Nitriles; Polycyclic bridged compounds; Pyrrolidines
		Anagliptin	Nitriles; Pyrazoles; Pyrimidines; Pyrrolidines
		Denagliptin	Aromatic amino acids; Pyrrolidines
		Melogliptin	Nitriles; Pyrrolidines, Triazoles
4	Dipropyl	Teneligliptin,	Ketones; Piperazines; Pyrazoles, Thiazolidines
		Gosogliptin	Pyrrolidines
5	Pyrimidinedione	Alogliptin,	Benzonitrile; Piperidines; Pyrimidinones
		Trelagliptin	Amines, Fluorobenzene; Nitriles; Piperidines; Pyrimidinones, Succinates
6	Xanthine	Linagliptin	Alkynes; Amines, Ketones; Piperidines; Purines; Quinazolines

Table 3: Status of Gliptin derivates as DPP-IV inhibitors

Sr. No.	DPP-IV Inhibitors	Status	Synonym	Name of Originator	Current Status	Source
1	Sitagliptin	Approved drug 2006	Sitagliptin phosphate ZITUVIO	Zydus Cadila	On 23rd October 2023 US FDA approved a New Drug Application	https://adisinsight.springer.com/drugs/800067004
2	Vildagliptin	Approved drug 2007	Equa; Galvus; Jalra; LAF 237; LAF 237A; NVP LAF 237; NVP LAF 237A; Vysov; Xiliarx	Novartis, Developed by Cipla; Hanmi Pharmaceutical; Novartis; Samsung Medical Center; University of Sao Paulo	Marketed drug, • In clinical phase III for Type I DM • On 27 December 2022 clinical phase II was discontinued in South Korea • On 20 May 2021 Committee for Medicinal Products for Human Use (CHMP) approved changes in the label and to be used as an adjunct to diet, exercise in adults with T2DM	https://adisinsight.springer.com/drugs/800017333
3	Saxagliptin	Approved drug 2009	BMS-477118; Onglyza; OPC-262 NCT03199053	Bristol-Myers Squibb Developed by: AstraZeneca; Bristol-Myers Squibb; Otsuka Pharmaceutical	Marketed Drug • Till 08 March 2022 it was clinical phase III as adjunctive treatment in T2DM patients in USA, Australia, Argentina, United Kingdom, Ukraine, Turkey, Thailand, Taiwan, Russia, Romania, Philippines, New Zealand, Mexico, Malaysia, South Korea, Italy, Israel, India, Colombia, Chile, Brazil, Canada, Finland, Poland	https://adisinsight.springer.com/drugs/800016588
4	Linagliptin	Approved drug 2011	BI 1356; BI 1356 BS; Ondero; Tradjenta; Trajenta; Trayenta; Trazenta	Boehringer Ingelheim Developed by: Boehringer Ingelheim; Eli Lilly and Company	Marketed Drug • It is in clinical phase III for Diabetic nephropathies • Till 27 July 2022 it was in clinical phase III DINAMO trial for T2DM in the US, Argentina, Colombia, Portugal South Korea, Russia, Mexico, Canada, New Zealand, United Kingdom, Thailand, Puerto Rico, Netherlands, Israel, Germany, Colombia, China, Brazil (PO) (NCT03429543)	https://adisinsight.springer.com/drugs/800022743
5	Teneligliptin	Approved drug 2012	--	Mitsubishi Pharma Corporation Developed by: Handok Inc; Mitsubishi Tanabe Pharma Corporation	Marketed Drug • On 17 Aug 2022 enrolled in clinical phase III in South Korea (NCT05504239) • On 10 Feb 2022 launch in China	https://adisinsight.springer.com/drugs/800022757
6	Gemigliptin	Approved drug 2012	Gemigliptin tartrate sesquihydrate; Gemiglo®; LC-150444; Zemiglo •	LG Life Sciences Developed by: LG Chem; Sanofi	• On 24 June 2023 clinical phase III trial efficacy and adverse events data was released at the American Diabetes Association (ADA-2023) annual scientific session	https://adisinsight.springer.com/drugs/800024128
7	Anagliptin	Approved drug 2012	Beskoa; CWP-0403; SK-0403; Suiny	Kyowa Hakko; Sanwa Kagaku Kenkyusho	Marketed Drug • Since 2019 there no development reported from the clinical phase III trial in South Korea	https://adisinsight.springer.com/drugs/800018710

				Developed by: JW Pharmaceutical; Kowa Pharmaceutical; Sanwa Kagaku Kenkyusho	• In USA and EU, it is in the pipeline for clinical trials	
8	Alogliptin	Approved drug 2013	Alogliptin benzoate; NESINA; Nesina; SYR-322; TAK-322; Vipidia	Syrrx Inc Developed by: Takeda	Marketed Drug • On 14 Feb 2022 Takeda Pharmaceutical company completed a clinical phase III trial in T2DM patients in Brazil, Germany, Israel, Italy, Mexico, and Poland (NCT02856113)	https://adisinsight.springer.com/drugs/800019992
9	Evogliptin	Approved drug 2015	DA-1229; RNV-1001; SUGANON; Sugarnon,	Dong-A Pharmaceutical Developed by: Alkem Laboratories; Dong-A ST; Eurofarma; GEROPHARM; Luye Pharma Group; REDNVIA; Tobira Therapeutics	Marketed Drug • In clinical phase II/III for Aortic valve stenosis • In pre-clinical phase for Non-alcoholic steatohepatitis • On 24 Feb 2023 Dong-A ST plans a phase I trial in Healthy volunteers in South Korea (PO, Tablet) (NCT05739851)	https://adisinsight.springer.com/drugs/800026700
10	Omarigliptin	Approved drug 2015	Marizev; MK-3102	Merck & Co	Marketed Drug • On 6th March 2017 Merck terminated the clinical phase III trial due to some business reasons from the USA, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Lithuania, the Netherlands, Norway, Slovakia, Poland, Spain and Sweden (NCT01703208)	https://adisinsight.springer.com/drugs/800031846#disabled
11	Trelagliptin	Approved drug 2015	SYR-472; SYR111472 succinate; TAK-472; Trelagliptin succinate; Zafatek	PPD; Syrrx Inc, CSPC ZhongQi Pharmaceutical Technology Developed by: 3SBio; Takeda	Marketed Drug On 22 Feb 2023 clinical phase III trial was discontinued in Japan and the preclinical trial was discontinued in China	https://adisinsight.springer.com/drugs/800026744 https://adisinsight.springer.com/drugs/800054799
12	Retagliptin	Clinical Phase II	Preregistration Type 2 diabetes mellitus	Phenomix Corporation; RECARDIO	• Pre-registration on 20 Sep 2023 • Jiangsu HengRui Medicine planned a clinical phase I trial for Diabetes mellitus (PO) in September 2023 (NCT06035406)	https://adisinsight.springer.com/drugs/800039203
13	Dutogliptin	Clinical Phase III	Dutogliptin tartrate; PHX-1149; PHX1149T; REC-01	RECARDIO	• It is in a clinical phase II trial for Myocardial infarction. On 31 May 2023 Recardio plans a clinical phase III trial for Myocardial infarction (NCT05881382)	https://adisinsight.springer.com/drugs/800024092
14	Melogliptin	Clinical Phase III	EMD 675992; GRC 8200	Glenmark Pharmaceuticals Ltd	Clinical Phase III trial	https://adisinsight.springer.com/drugs/800021640
15	Carmegliptin	Clinical Phase II	DPP-IV(3); R 1579; RG 1579; RO 4876904-001 Roche	Developed by: Chugai Pharmaceutical; Roche	Discontinued for T2DM	https://adisinsight.springer.com/drugs/800025180
16	Denagliptin	Clinical Phase III	823093; GW 823093; GW823093C; Redona	GlaxoSmithKline	On 20 April 2015, GSK withdrew a clinical phase II/III in T2DM in USA and Finland Discontinued for T2DM	https://adisinsight.springer.com/drugs/800025180
17	Gosogliptin	Clinical	PF-00734200; PF-	Developed by: Pfizer; SatRx	Till 01 August 2019, it was not available in Russia In	https://adisinsight.springer.com/drugs/800025

		Phase II	**734,200; SatRx**		**June 2016 registered for global approval for T2DM**	**571**
18	**Besigliptin**	**Clinical Phase II**	**Besigliptin tosylate, SHR 117887 free base, 2K789YO4JJ, 1177459-85-6**	**Jiangsu Hansoh Pharmaceutical Co.Ltd.**	**The clinical phase is currently pending.**	**NA**
19	**Imigliptin**	**Clinical Phase II**	**Imigliptin hydrochloride, KBP-3853**	**Shandong Xuanzhu Pharmaceutical Technology Co. Ltd.Beijing Sihuan Pharmaceutical Co. Ltd.**	**Till 2020 no development was reported in China. The clinical phase II is pending**	**https://adisinsight.springer.com/drugs/800041472**
20	**Cetagliptin**	**Clinical Phase I**	**Cetagliptin phosphate,CGT-8012, GT8012, CGT 8012, Shengtagliptin phosphate**	**CGeneTech**	**Till 28 June 2023, no development in the Clinical Phase I Trial was reported in China**	**https://adisinsight.springer.com/drugs/800066087**
21	**Yogliptin**	**Clinical Phase I**	**NA**	**Easton Biopharmaceuticals**	**Till 01 January 2022 Clinical Trial phase III in China is going on**	**https://adisinsight.springer.com/drugs/800048731**
22	**Augliptin**		**NA**	**--**		**NA**
23	**Fotagliptin**	**Clinical Phase III**	**FCN-005; Fotagliptin benzoate; Futagliptin benzoic acid**	**Chongqing Fochon Pharmaceutical**	**As of July 2022, Clinical Phase III is going on in China**	**https://adisinsight.springer.com/drugs/800045073**

MATERIAL AND METHODS:

DPP-IV is one of the validated targets for anti-diabetic activity, and many are well-established drugs that are used for their better therapeutic efficacy and related comparative studies are performed **[17]**. These gliptin molecules are also under consideration for repurposing as anti-obesity agents, for the treatment of myocardial infarction, non-alcoholic steatohepatitis, and various types of cancers **[18]**. In silico strategies can be implemented for validating these molecules and identifying the potential of these molecules for repurposing multiple diseases, and disorders, or even as anti-infective agents **[19, 20]**. **Table 4** provides the structures and canonical smiles of all the molecules. The structures were drawn in ChemDraw software professional 15.0 and canonical smiles file format was obtained **[21]**.

The interactive biomolecules show their pharmacological effects via interaction with the target protein **[22]**. These biomolecules also interact with the other proteins in the biological system and exert their actions. As these gliptin molecules are well established as DPP-IV inhibitors in the effective management of T2DM, these drugs are also incorporated for the utilization of other disorders. Hence probable targets or target proteins were predicted using the Swiss Target Prediction web tool ChEMBL23 version which is free of charge (www.swisstargetprediction.ch) **[23]**. This free web tool for computer-aided drug design was prepared by the SIB Swiss Institute of Bioinformatics. Using this website, one can determine the likely macromolecular targets of a small molecule that is thought to be bioactive. The prediction is based on a combination of 3D and 2D similarity on over 3000 proteins from three distinct species and a library of 370'000 known actives. These predictions are based on the similarity principles. The predictions available in this software 03 species can be studied (a) Homo sapiens (b) Mus musculus (c) Rattus norvegicus as per the requirement of the study. Here we have studied it with Homo sapiens species. SMILE (simplified molecular-input line-entry system) file format is given as input, in the system and predictions were initiated. The output file is generated which describes the scientific and common name of the target/macromolecule, Uniprot ID, ChEMBL ID, Target Class, and the probability of forming the interaction with the molecule and the known 2D and 3D activities are also given. A pie chart can be obtained which can show the Top 15, 25, 50, and 100 targets, which can have a quick view on the percentage of the drug target

interaction. The results can be obtained in CSV format, and PDF formats as well as we can take the printout of the results. The top 50 target classes presented in the pie chart include protease, Family A G protein-coupled receptor, Oxidoreductase, electrochemical transporter, Kinase, Family C G protein-coupled receptor, enzyme, phosphodiesterase, enzymes, Lyase, voltage-gated ion channel, etc. **[24]**.

A single drug molecule may have different biological activity spectra, that were studied by using the Way2drug portal, with its web services as PASS online. This PASS online server gives predictions for more than 4000 types of biological activities including interactions, adverse effects, mechanisms of action, and pharmacological effects **[25]**.

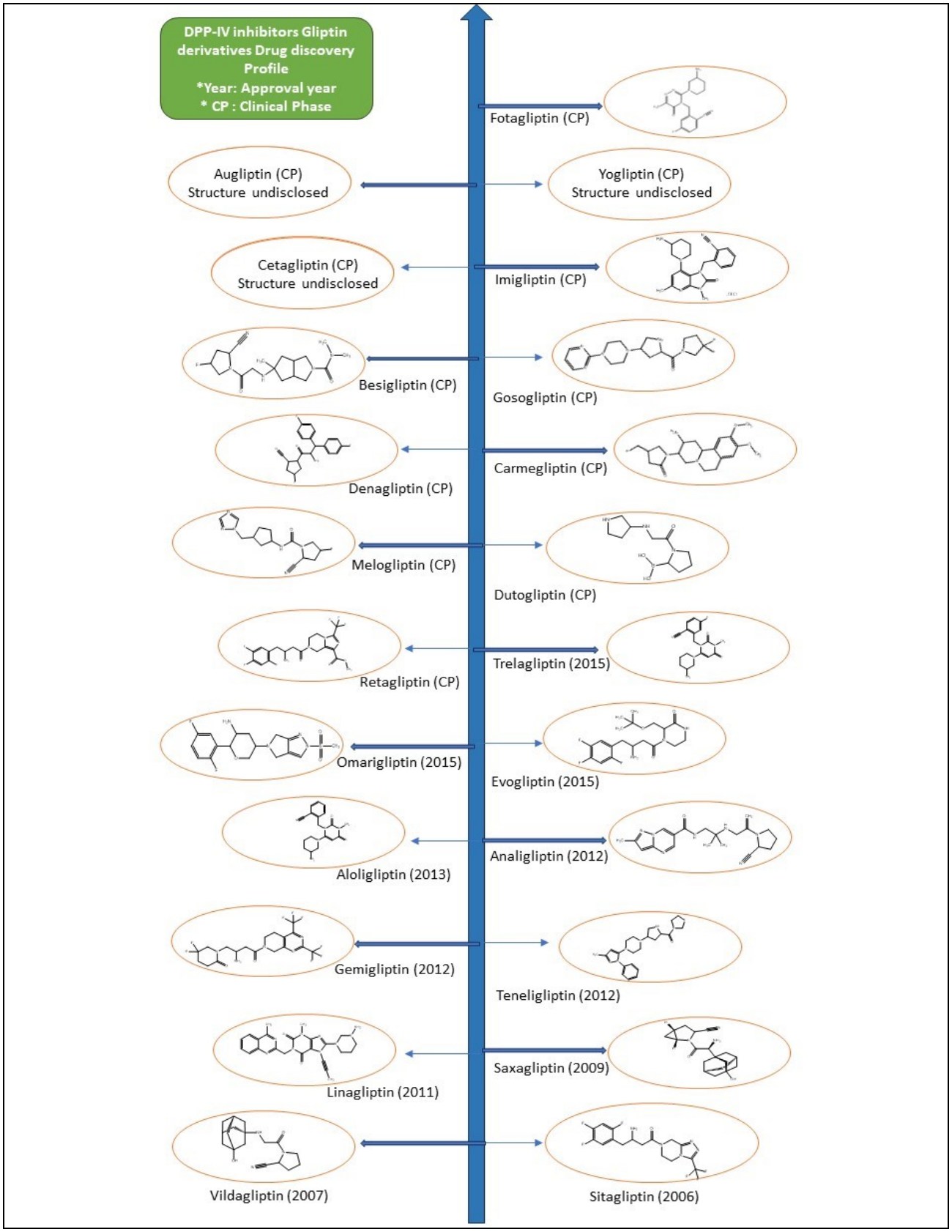

Figure 4: Discovery Gliptin Derivatives

RESULT AND DISCUSSION:

The Canonical smiles obtained from the ChemDraw structures were used as input file format for the Swiss Predictions and PASS online predictions of Pharmacological activities of gliptins which are widely used as Anti-diabetic agents for the management of T2DM.

Table 4: Smile file format of gliptin derivatives for input files to softwares

Sr. No.	Molecule	Name of Drug	Canonical Smiles
1	Molecule 1	Sitagliptin	NC(Cc1cc(F)c(cc1F)F)CC(=O)N1CCn2c(C1)nnc2C(F)(F)F
2	Molecule 2	Vildagliptin	N#CC1CCCN1C(=O)CN[C@]12CC3C[C@@H](C1)CC(C2)(C3)O
3	Molecule 3	Linagliptin	CC#Cn1c(nc2c1c(=O)n(Cc1nc(C)c3c(n1)cccc3)c(=O)n2C)N1CCCN(C1)N
4	Molecule 4	Saxagliptin	N#CC1C[C@@H]2[C@H](N1C(=O)[C@H]([C@]13C[C@@H]4C[C@H](C1)C[C@](C3)(C4)O)N)C2
5	Molecule 5	Teneligliptin	O=C(N1CSCC1)C1NCC(C1)N1CCN(CC1)c1cc(nn1c1ccccc1)C
6	Molecule 6	Gemigliptin	NC(CN1CC(F)(F)CCC1=O)CC(=O)N1CCc2c(C1)nc(nc2C(F)(F)F)C(F)(F)F
7	Molecule 7	Alogliptin	N#CC1=C(CN2C(N3CCCC(N)C3)=CC(N(C)C2=O)=O)C=CC=C1
8	Molecule 8	Anagliptin	N#CC1CCCN1C(=C)CNC(CNC(=O)c1cnc2n(c1)nc(c2)C)(C)C
9	Molecule 9	Evogliptin	NC(Cc1cc(F)c(cc1F)F)CC(=O)N1CCNC(=O)C1COC(C)(C)C
10	Molecule 10	Omarigliptin	Fc1ccc(c(c1)C1OCC(CC1N)N1Cc2c(C1)cn(n2)S(=O)(=O)C)F
11	Molecule 11	Retagliptin	COC(=O)c1nc(n2c1CN(CC2)C(=O)CC(Cc1cc(F)c(cc1F)F)N)C(F)(F)F
12	Molecule 12	Trelagliptin	N#Cc1ccc(cc1Cn1c(cc(=O)n(c1=O)C)N1CCCC(C1)N)F
13	Molecule 13	Dutogliptin	OB(C1CCCN1C(=O)CNC1CNCC1)O
14	Molecule 14	Melogliptin	N#CC1CC(CN1C(=O)NC1CCC(C1)Cn1cncn1)F
15	Molecule 15	Denagliptin	N#CC1CC(CC1C(=O)C(C(c1ccc(cc1)F)c1ccc(cc1)F)N)F
16	Molecule 16	Carmegliptin	FCC1CC(=O)N(C1)C1CN2CCc3c(C2CC1N)cc(c(c3)OC)OC
17	Molecule 17	Gosogliptin	O=C(N1CCC(C1)(F)F)C1NCC(C1)N1CCN(CC1)c1ncccn1
18	Molecule 18	Besigliptin	N#CC1CC(CN1C(=O)CNC1(C)CC2C(C1)CN(C2)C(=O)N(C)C)F
19	Molecule 19	Imigliptin	NC1CN(C2=C(N(CC3=C(C#N)C=CC=C3)C(N4C)=O)C4=NC(C)=C2)CCC1
20	Molecule 20	Fotagliptin	FC1=CC=C(C#N)C(CN2C(C(C)=NN=C2N3CC(N)CCC3)=O)=C1
21	Molecule 21	Cetagliptin	Structure undisclosed
22	Molecule 22	Augliptin	Structure undisclosed
23	Molecule 23	Yogliptin	Structure undisclosed

In SWISS Target Predictions represents the 100 most probable targets with which this particular gliptin molecule can interact. To name a few of them are protease, Family A G Protein Coupled Receptor, kinases, protease, enzymes, oxidoreductase, phosphodiesterase, electrochemical transporters, membrane receptors, lyases, voltage-gated ion channels, Cytochrome P450, Ligand-gated ion channel, phosphodiesterase, nuclear receptor, oxidoreductase, phosphatase, hydrolases, other nuclear protein, Eraser, Writer, enzymes etc. There is cleavage in a single polypeptide bond in a zymogen to generate enzymatic function. This function activation is the ultimate result of this activity. When proteins in any form are synthesized (hormone, enzymes, proteins) they are in inactive form. Selective enzymatic cleavage is responsible for converting them in the active form **[26]**.

The family of A G protein-coupled receptors have similarities in their structural and functional characteristics. Any drug molecule binds to the hydrophobic packet to give desired effects either agonist or antagonist found in the transmembrane layers **[27]**. G protein–coupled receptors (GPCRs) are targets for a considerable amount of medicinal treatments and transduce numerous significant physiological signals. Family A, which is the biggest family of GPCRs, is considered to self-associate as dimers and higher-order oligomers; however, only a few number of these quaternary structures' importance for signaling or receptor trafficking are known **[28]**. GPCRs are believed to be the largest class of pharmacological targets that are approved **[29]**. G protein-coupled receptors (GPCRs), one of the most effective therapeutic target families, have transitioned from arbitrary ligand discovery to knowledge-driven drug design **[30]**. The enzyme catalyses the transfer the transfer of phosphate group from high energy molecule to low energy molecule that to a specific substrate. The process is known as phosphorylation. Kinases belong to the wider family of enzymes called phosphotransferases. Kinases are of different types like protein kinase (Cyclin dependant kinase, Mitogen activated protein kinase), lipid kinase (Phosphotidylinositol kinase, Sphingosine kinase, carbohydrate kinase), Carbohydrate kinase (Hexokinase, phosphofructokinase), Riboflavin kinase, Thymidine kinase, etc. which are responsible for various cellular processes. The drugs interacting with kinase either improve the activity or give an inhibitory effect. Multikinase inhibitors have become one of the promising targets in oncology treatment **[31]**. Proteases are the enzymes that catalyzes breakdown of proteins known as proteolysis in to smaller proteins or amino acids. The peptide bonds are broken by hydrolysis. Multiple biological pathways are controlled by these enzymes. Basically, Proteases are of two different types serine and cysteine proteases forms covalent enzyme complexes, while another is aspartic and metalloproteases that do not form covalent enzyme complexes. Other proteases are threonine protease, glutamic proteases, asparagine peptide lyases **[32, 33]**. Many aspects of cell and organism function, such as nutrition, protein turnover, growth, adaptability, regulation, sporulation and germination, disease, and death, are impacted by proteases, which are widely distributed in biology. Many processes in the human body, such as the vital cellular processes of differentiation, motility, division, and cell

death, are regulated by proteases **[34]**. All the gliptins show more interaction with the Family A-G Protein coupled receptor, kinase, protease and other enzymes. The target predictions studies performed indicated that the Vildagliptin is having highest affinity for Family A-G Protein coupled receptors is 46%, while the Denagliptin is having lowest affinity.

Dutogliptin and Denagliptin shows highest affinity of 58% with kinase also Evogliptin shows the activity of 48% for kinase protein and Vildagliptin is showing lowest affinity for kinase. Teneligliptin with 28% show highest affinity for protease. For enzymes all the gliptins are showing average 8% affinity. Depending on the affinity of the drugs for the particular protein the drugs can be repurposed as per the need and severity of the diseased condition.

PASS online predictions:

Molecular weight comparison indicates that all the molecules are having molecular weight ranging from 241gm/mol (Dutagliptin) to 489 gm/mol (Gemigliptin). The PASS online prediction results indicates that out of these 20 gliptin derivatives, of which structures are available, Dutagliptin is showing highest possible activity of value 978, Saxagliptin 933, Besigliptin 926 and Vildagliptin 827 as Dipeptidyl peptidase IV inhibitor for hypoglycaemic effect. These all molecules are primarily used for its anti-diabetic activity, and the predictions indicates the multipurpose use or the repurposing of the established, clinical approved drugs for the rare, complicated diseases/disorders. Vildagliptin, Teneligliptin, Gemigliptin, Melogliptin, Gososgliptin, Besigliptin possesses anti-obesity activity **[35-38]**. Anti-Parkinsonian activity is observed with Vildagliptin, Linagliptin, Saxagliptin, Teneligliptin, Anagliptin, Gosogliptin **[39-41]**. Even these gliptins can show their use in the treatment of neurodegenerative diseases. Linagliptin, Saxagliptin, Teneligliptin, Anagliptin, Carmegliptin can be used for neuronal disorders **[42-49]**. Some of the gliptin molecules also show considerable values of predictions with prominent activity like Analgesic effects (Sitagliptin, Gemigliptin, Gosogliptin) **[50-51]**, Anti-viral effects (Vildaglitpin, Saxagliptin, Imigliptin) **[52-53]**, Anti-neoplastic/anti-cancer activity (Besigliptin, Anaglitptin, Alogliptin) **[54-56]**, to support the anti-diabetic action by another mechanism such as Glucagon-Like Peptide-1 agonistic activity (Saxagliptin, Anaglitpin, Besigliptin), cardiovascular effects like anti-ischemic agent (Vildagliptin, Linaglitpin, Carmeglitpin) **(Figure 6) [55-59]**.

Table 5 indicates the percentage activities of 20 gliptin derivates with different major targets, that helps to understand the highest probability of interaction with the macromolecules to have agonistic/antagonistic, inhibitory effects etc. and the values are mentioned in **Table 6**.

The average value shows that all the gliptin shows 27% average possible interaction with Family A-G Protein coupled receptor, 29% kinase interaction that is the highest one, 18% of protease interaction and about 8% of other enzyme interactions.

Table 5: Highest possible target prediction of gliptins

Sr. No.	Name of the drug molecule	Family A-G Protein-coupled receptor	Kinase	Protease	Enzyme
1	Sitagliptin	18%	14%	18%	4%
2	Vildagliptin	46%	4%	10%	8%
3	Linagliptin	30%	32%	14%	12%
4	Saxagliptin	38%	14%	18%	8%
5	Teneligliptin	38%	30%	10%	4%
6	Gemigliptin	20%	16%	28%	6%
7	Alogliptin	24%	34%	12%	6%
8	Anagliptin	34%	8%	22%	6%
9	Evogliptin	20%	48%	12%	2%
10	Omarigliptin	40%	18%	26%	4%
11	Retagliptin	34%	28%	10%	--
12	Trelagliptin	20%	28%	16%	14%
13	Dutogliptin	10%	58%	10%	16%
14	Melogliptin	20%	34%	12%	18%
15	Denagliptin	6%	58%	10%	10%
16	Carmegliptin	32%	32%	8%	6%
17	Gosogliptin	26%	32%	20%	8%
18	Besigliptin	40%	20%	8%	6%
19	Imigliptin	22%	30%	14%	10%
20	Fotagliptin	24%	34%	22%	6%
	Average values	27%	29%	18%	8%

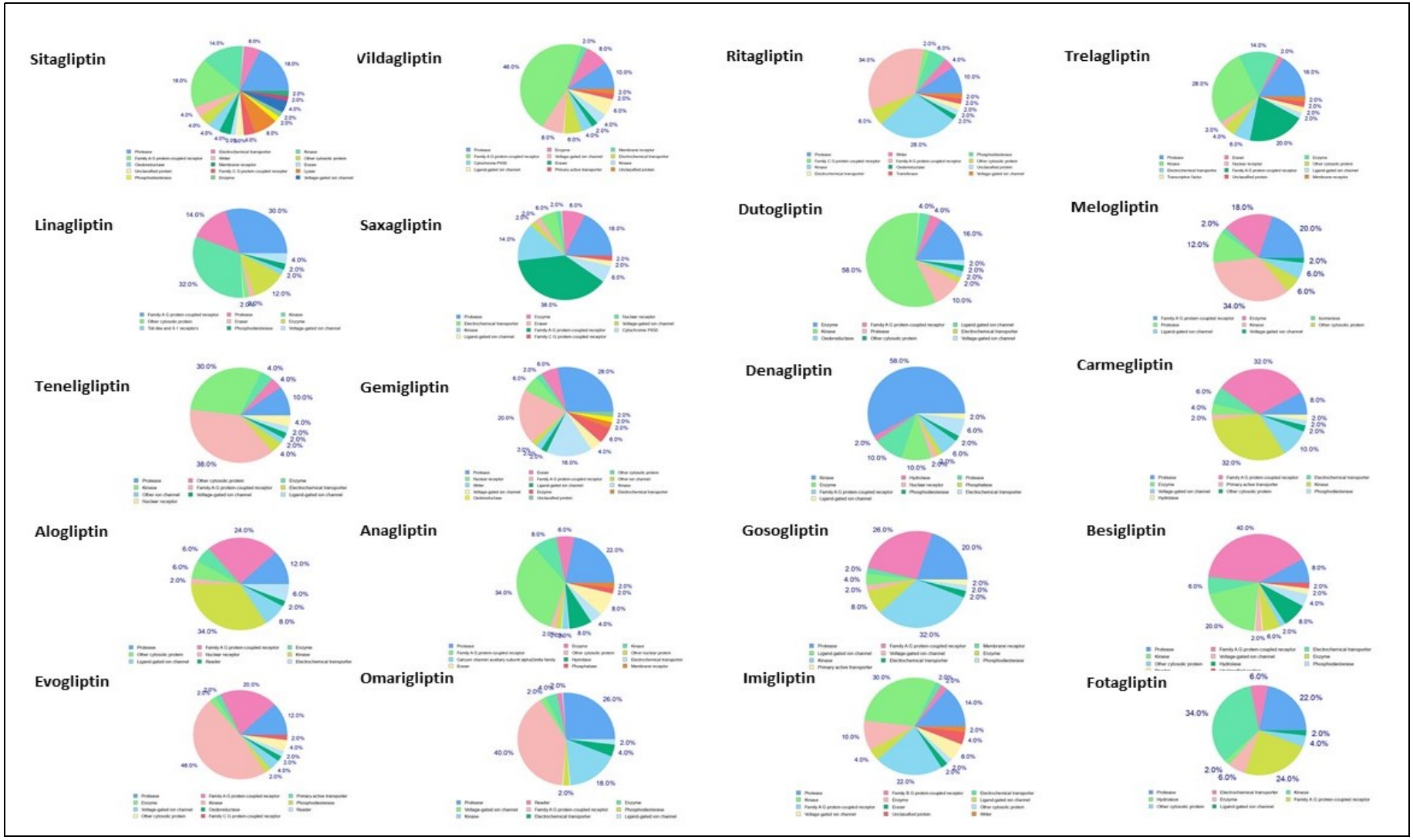

Figure 5: SWISS Target Predictions showing results for TOP 50 targets

Table 6: PASS Prediction Results

Sr. No.	Drug Molecule	Pharmacological Activity Predictions	Probably Active (Pa)	Probably Inactive (Pi)
1	Sitagliptin [Molecule 1]	Dipeptidyl peptidase inhibitor	0,892	0,001
		Analgesic, non-opioid	0,473	0,032
		Platelet aggregation inhibitor	0,448	0,013
		Analgesic	0,443	0,054
		3'-Demethylstaurosporine O-methyltransferase inhibitor	0,405	0,028
2	Vildagliptin [Molecule 2]	Dipeptidyl peptidase inhibitor	0,868	0,001
		Antiobesity	0,705	0,006
		Anti-ischemic, cerebral	0,698	0,029
		Dipeptidyl peptidase VIII inhibitor	0,642	0,001
		Pulmonary hypertension treatment	0,475	0,004
		Nicotinic alpha4beta4 receptor agonist	0,491	0,085
		Antiviral (Influenza A)	0,392	0,009
3	Linagliptin [Molecule 3]	CYP2C19 inducer	0,470	0,017
		Antiparkinsonian	0359	0,029
		Neurodegenerative diseases treatment	0,417	0,060
		Cyclic AMP phosphodiesterase inhibitor	0,361	0,078
		Nootropic	0,352	0,268
		Anti-ischemic, cerebral	0,310	0,284
4	Saxagliptin [Molecule 4]	Dipeptidyl peptidase inhibitor	0,907	0,001
		Antiparkinsonian	0,663	0,005
		Glucagon-like peptide 1 agonist	0,603	0,002
		Neurodegenerative diseases treatment	0,542	0,023
		Nicotinic alpha4beta4 receptor agonist	0,568	0,051
		Antiviral (Influenza)	0,312	0,082
5	Teneligliptin [Molecule 5]	Nootropic	0,833	0,012
		MAP3K5 inhibitor	0,713	0,002
		Dipeptidyl peptidase IV inhibitor	0,668	0,001
		Interleukin 2 agonist	0,572	0,008
		Antiobesity	0,508	0,020
		Neurodegenerative diseases treatment	0,489	0,034
		Antiparkinsonian	0,376	0,035
6	Gemigliptin [Molecule 6]	Dipeptidyl peptidase inhibitor	0,719	0,001
		Nootropic	0,541	0,106
		HIV attachment inhibitor	0,418	0,010
		Anaphylatoxin receptor antagonist	0,472	0,073
		Analgesic, non-opioid	0,384	0,059
		Antiobesity	0,324	0,059
		Analgesic	0,342	0,101
7	Alogliptin [Molecule 7]	Proteasome ATPase inhibitor	0,492	0,073
		HCV IRES inhibitor	0,435	0,017
		Muramoyl tetrapeptide carboxypeptidase inhibitor	0,453	0,053
		Dipeptidyl peptidase inhibitor	0,401	0,002
		Neurotransmitter uptake inhibitor	0,438	0,090
		Antineoplastic (multiple myeloma)	0,327	0,058
8	Anagliptin [Molecule 8]	MAP3K5 inhibitor	0,513	0,005
		Antiparkinsonian	0,506	0,012
		Neurodegenerative diseases treatment	0,484	0,035
		Antineoplastic (multiple myeloma)	0,348	0,045
		Cardiotonic	0,354	0,052
		Antianginal	0,329	0,148
9	Evogliptin [Molecule 9]	Antidiabetic (type 2)	0,557	0,008
		Nootropic	0,607	0,073
		3'-Demethylstaurosporine O-methyltransferase inhibitor	0,364	0,038
		Muramoyltetrapeptide carboxypeptidase inhibitor	0,359	0,093
		Cancer associated disorders treatment	0,315	0,077

Sr. No.	Drug Molecule	Pharmacological Activity Predictions	Probably Active (Pa)	Probably Inactive (Pi)
10	Omarigliptin [Molecule 10]	Antidiabetic (type 2)	0,619	0,006
		Antipsychotic	0,309	0,050
		Cognition disorders treatment	0,311	0,066
11	Retagliptin [Molecule 11]	Nootropic	0,670	0,049
		Antidiabetic (type 2)	0,477	0,011
		CYP2H substrate	0,539	0,098
		3'-Demethylstaurosporine O-methyltransferase inhibitor	0,384	0,033
		Alzheimer's disease treatment	0,314	0,059
12	Trelagliptin [Molecule 12]	Dipeptidyl peptidase inhibitor	0,761	0,001
		Cytochrome P450 inhibitor	0,386	0,028
		HCV IRES inhibitor	0,379	0,033
		Antieczematic atopic	0,323	0,018
		Proteasome ATPase inhibitor	0,413	0,120
13	Dutogliptin [Molecule 13]	Dipeptidyl peptidase IV inhibitor	0,978	0,001
		Fibroblast activation protein alpha inhibitor	0,855	0,000
		Antineoplastic (non-Hodgkin's lymphoma)	0,854	0,002
		Serine protease unspecified inhibitor	0,622	0,002
		Chemoprotective	0,622	0,004
		Antineoplastic (pancreatic cancer)	0,517	0,005
14	Melogliptin [Molecule 14]	Antidiabetic (type 2)	0,579	0,005
		Antineoplastic (multiple myeloma)	0,515	0,001
		Dipeptidyl peptidase inhibitor	0,527	0,018
		Antiobesity	0,401	0,018
		Anti-infertility, female	0,343	0,010
15	Denagliptin [Molecule 15]	Antidiabetic	0,619	0,011
		Antimetastatic	0,434	0,037
		DNA polymerase I inhibitor	0,399	0,020
		Anti dyskinetic	0,453	0,078
		Ophthalmic drug	0,378	0,028
16	Carmegliptin [Molecule 16]	Antidiabetic (type 2)	0,768	0,004
		5 Hydroxytryptamine release stimulant	0,704	0,025
		Cognition disorders treatment	0,636	0,007
		UGT2B12 substrate	0,605	0,009
		Gluconate 2-dehydrogenase (acceptor) inhibitor	0,668	0,076
		Antidiabetic	0,571	0,015
17	Gosogliptin [Molecule 17]	Dipeptidyl peptidase IV inhibitor	0,734	0,001
		Neurodegenerative diseases treatment	0,629	0,013
		Alzheimer's disease treatment	0,557	0,009
		Antiobesity	0,562	0,014
		Analgesic, non-opioid	0,527	0,022
18	Besigliptin [Molecule 18]	Dipeptidyl peptidase inhibitor	0,950	0,001
		Anti-obesity	0,585	0,013
		Neurotransmitter uptake inhibitor	0,519	0,054
		Glucagon-like peptide 1 agonist	0,459	0,004
		Antineoplastic (multiple myeloma)	0,387	0,028
19	Imigliptin [Molecule 19]	Cytochrome P450 inhibitor	0,548	0,009
		CYP3A4 inhibitor	0,514	0,005
		Immunomodulator	0,327	0,056
		Neurotransmitter uptake inhibitor	0,361	0,144
		Antiviral (Picornavirus)	0,333	0,178
20	Fotagliptin [Molecule 20]	Dipeptidyl peptidase inhibitor	0,441	0,002
		CYP3A4 inhibitor	0,399	0,011
		HCV IRES inhibitor	0,398	0,027
		Chronic obstructive pulmonary disease treatment	0,371	0,014
		Antiasthmatic	0,397	0,049

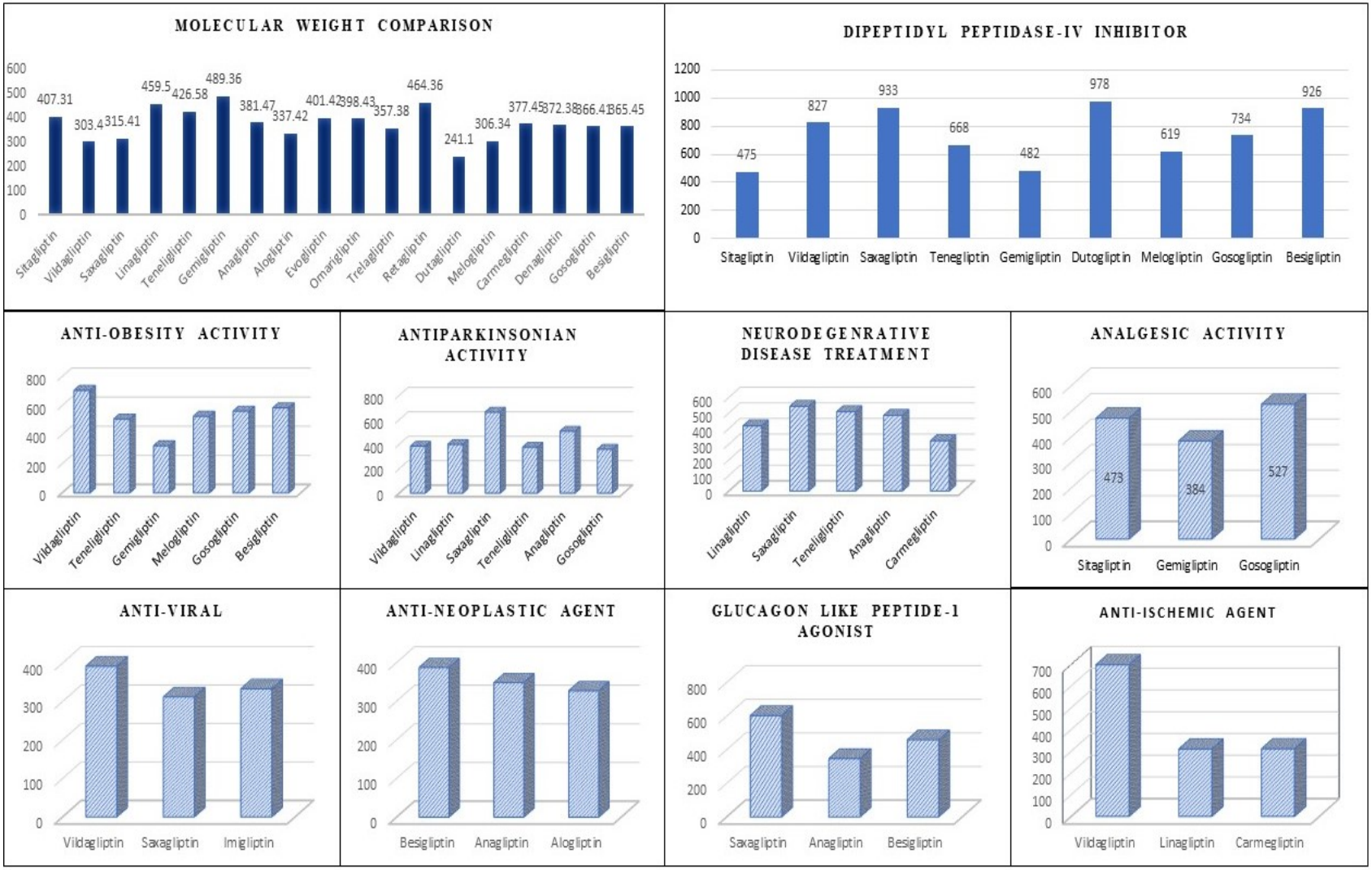

Figure 6: Repurposing possibilities of gliptin derivatives for various diseases and disorders

CONCLUSION:

Repurposing of the clinically approved drugs is need of hours. It has several benefits like economic benefits for pharma industry, time and energy of researchers and innovators for the discovery of the new drugs, clinical investigations for the determination of efficacy of the drug. It has been observed that Sitagliptin and Vildagliptin are widely used anti-diabetic agents with effective hypoglycaemic effect. Considering the dipeptidyl peptidase inhibitory action of these drugs several gliptin derivatives came into the market as well and many dipeptidyl peptidase inhibitors are under research for more effectiveness and fewer side effects. Amongst these all some are getting more attention due to their reliability and patient compliance. A patient suffering from diabetes mellitus manages the disease with many other complications, or a patient suffering from any life-threatening disease or disorder like cancer, ischemic disorders, or viral infections may be associated with diabetes complications. So, these predictions indicated the outstanding results for the probable repurposing of these gliptin derivatives. Vildagliptin is a wonderful drug molecule that can used as an anti-obesity agent, Parkinson's disease, anti-viral agent, and anti-ischemic agent. Teneligliptin, Saxagliptin may become a promising drug for the treatment of Parkinson's disease and neurodegenerative disorders. Analgliptin can have anti-neoplastic activity, effect in neurodegenerative disease treatment. The mechanistic pathways needs to studies and have to undergone research for the confirmation of these other activities for these gliptin derivatives. The future scope of these study is to evaluate these gliptin derivatives for repurposing possibility in clinical practice. This research article is very useful for researchers working with gliptin derivatives.

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