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AN AMALGAMATION OF SGLT-2 AND DPP-4 INHIBITORS: A PLAUSIBLE NOVEL TREATMENT FOR DIABETES MELLITUS

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ABSTRACT: Diabetes Mellitus is characterized as metabolic chronic disease spreading all over the world ata high pace. Due to its speedily wide population spreading it is termed as 3rd most populated country in the world since the number of individuals diagnosed with diabetes is just behind population of China and India. To date treatment therapy concerning diabetes majorly responds to insulin-dependent mechanisms. A newer activity regarding renal glucose mechanism highlights a novel treatment to curtail diabetes. Filtered glucose gets transported through the kidney, when reaches proximal tubules further reabsorbed through sodium glucose co-transporter-2 [SGLT-2] and elevates blood glucose level. SGLT-2 inhibition provokes a new treatment for diabetes and Empagliflozin, a novel, potent SGLT-2 inhibitor class drug and compare to other drugs of this class, Empagliflozin exerts a favorable once-daily dose and negligible risk of hypoglycemia. On the other hand, Sitagliptin is a DPP-4 inhibitor and has a significant role in the improvement of activity of GLP-1 situated in the myocardium pathway, an incretin hormone which got released from intestinal L cells of the distal part with a glucose-dependent release that consequently results in postprandial secretion of insulin. Briefly elaborating the synergistic effect of SGLT-2 inhibitor and DPP-4 inhibitor is the elevated secretion of incretin inhibited glucagon synthesis which consequently decreased blood glucose level. This novel mechanism of admixing SGLT-2 inhibitor and DPP-4 inhibitor is a reasonable prospective target for treating hyperglycemia.

INTRODUCTION: Diabetes is a multi-systemic, endocrine disorder characterized by high levels of blood glucose concentration in fasting as well as post-prandial conditions [1]. Diabetes is speedily prevailing all over the globe like an unstoppable train. In 2017, it has been stated that there were 425 million adults diagnosed with diabetes which is further expected to rise up to 629 million by 2045. About 79% of adult individuals having diabetes are situated in low-income and developing countries. It has also been surveyed that 4 million deaths were caused by diabetes and around 352 million were at risk of developing Type 2 diabetes. Diabetes has

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been expensive too as at least 727 billion US dollars was spent in 2017 on health expenditure concerning diabetes [2]. As far as the relationship between India and diabetes is concerned, India is stated as the Diabetes capital of the World with a figure of 62 million or more diagnosed with diabetes in India in 2014 and likely to increase bya double by 2030 [3]. It had been evaluated that around 85% of diabetic death occurred in the middle as well as low-income countries. A fact also states that 95% of the total diabetic patient accounts Type-2 class of hyperglycemia [4, 5] **Fig. 1.**

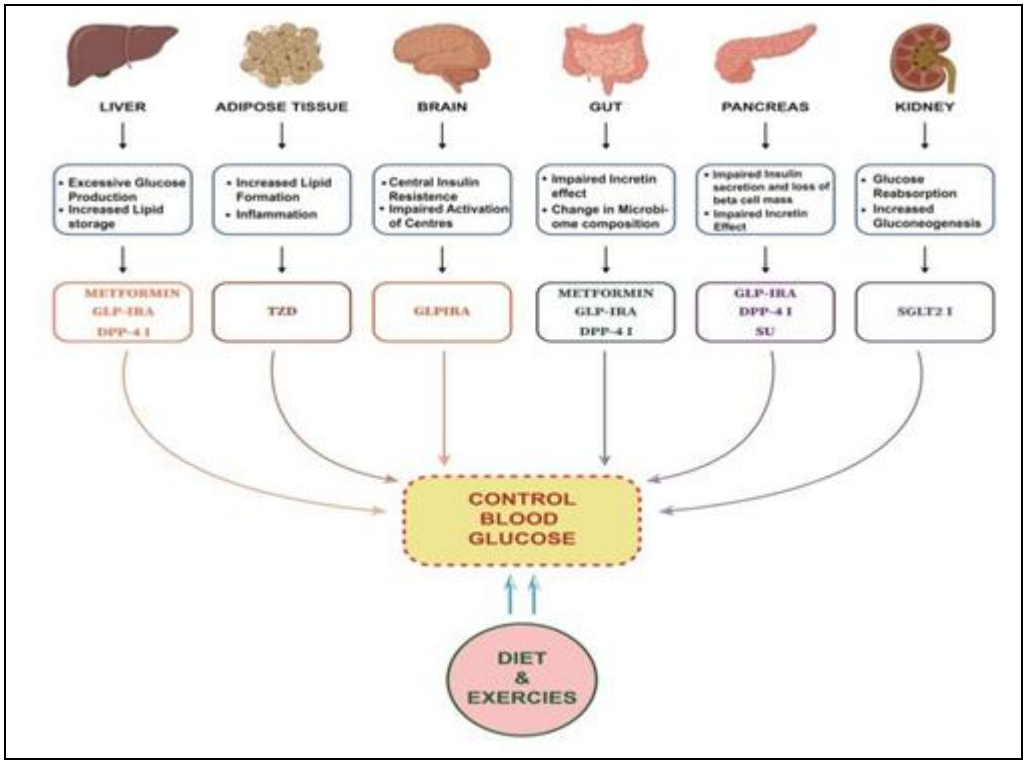

FIG. 1: DIABETIC PATHOPHYSIOLOGY AND PLEIOTROPIC DRUGS

The current need in the management of diabetes type II is the novel therapeutic approach, as the current therapeutic options do not address all pathophysiological mechanisms as well as targeted glycemic level goals. While correlating with Type 2 diabetes, kidneys offer a main therapeutic target for treatment. Among the filtered glucose, it is anticipated that 90% of it gets reabsorbed by the kidney through SGLT-2 which is situated in the proximal tubules' region of nephron [6]. SGLT-2 inhibitors are categorized as a novel oral hyperglycemic drug that concluded independency with beta cell and insulin release and reduction in hyperglycemia through increased urinary excretion of glucose with a reduction in glucose reabsorption [7]. Few cases of risk of hypoglycemia were reported with the additional profit of a reduction in weight loss and blood pressure [8, 9]. SGLT-2 inhibitors consist of drugs commonly called *gliflozins*. Drugs of this class are *Canagliflozin, Dapagliflozin, Empagliflozin, Ipragliflozin etc*. Empagliflozin is a potent, orally active, selective inhibitor of SGLT-2 inhibitor [10]. It was among the recently approved SGLT-2 inhibitors for the treatment of Type -2 diabetes [11]. It has been reported that single doses of empagliflozin result in a dose-dependent increment in urinary glucose excretion and a fall in glucose levels of blood [12]. On the other hand, multiple-dose of empagliflozin also states a reduction in blood glucose [fasting] and glycated hemoglobin [HbA1C] and improves insulin sensitivity in ZDF rats [12]. In streptozotocin-induced diabetes positive curtailment of blood glucose, alone and with insulin amalgamation is reported [13].

To understand glucose homeostasis, it is essential to know about the incretin hormone. Glucagon-like peptide-1[GLP-1] is a major incretin hormone that is present at α and β cells in the kidney, pancreas, GIT, brain, heart and lungs and functionally increases incretin hormone post-prandially [14-16].

B cell regeneration, differentiation as well as prevention of apoptosis through the activation of

GLP-1 receptor has been reported by GLP-1 [17, 18]. An enzyme named dipeptidyl peptidase-4 [DPP-4] was reported to degrade the action of GLP-1. DPP-4 enzymes are expressed in brain, liver, pancreas, intestine, kidney, lymphocytes and adrenal gland *etc* [19, 20]. Drugs used to inhibit the action potential of DPP-4 enzymes are termed as DPP-4 inhibitors and several studies states that they decreased β cell death as well as increase regeneration in hyperglycemic animals [21-23].

Sitagliptin is known as one of the first, well tolerated and most widely used DPP-4 inhibitors all over the world. Around 130 countries had been using Sitagliptin for diabetes treatment either as a monotherapy or as a combined fixed dose regimen [24]. An adverse effect from sitagliptin is mild and withinan acceptable range. Sitagliptin is reported to prevent GLP-1 degradation quickly, furthermore, GLP-1 and insulin concentration in serum is enhanced to lower the blood glucose level [25-27]. Fixed dose combination [FDC] is a boon for the patient with the therapy of several medications. It reducesthe pill burden effect and the combo of more API itself produces a synergistic effect in Drug interaction [28]. An example regarding FDC: *Atripla* is an HIV drug used with having a combination of 3 drugs i.e. Efavirenz, Emtricitabine and Tenofovir DF. Various combinations of diabetic drugs too present in the market like *Synjardy* [Empagliflozin and Metformin], *Janumet* [Sitagliptin and Metformin], *Sepamet XR* [Sitagliptin and Metformin]. Now it has been hypothesized that the combination of Empagliflozin and Sitagliptin will be a major prospective novel approach in treating diabetes. The mechanism of action of DPP-4 inhibitor tends to synergize the action potential of SGLT-2 inhibitor which in conclusion restrict down the blood glucose level.

SGLT-2 Inhibitors: A new class of glucose-lowering agents came into the therapeutic field and was termed as SGLT-2 inhibitors. It is a novel class that reduces body sugar by having a mechanism of action independent to insulin [29, 30]. The specific target is on kidney, and they impede glucose reabsorption which consequently results in urinary glucose excretion [UGE] more than ever in case of hyperglycemia [31, 32].

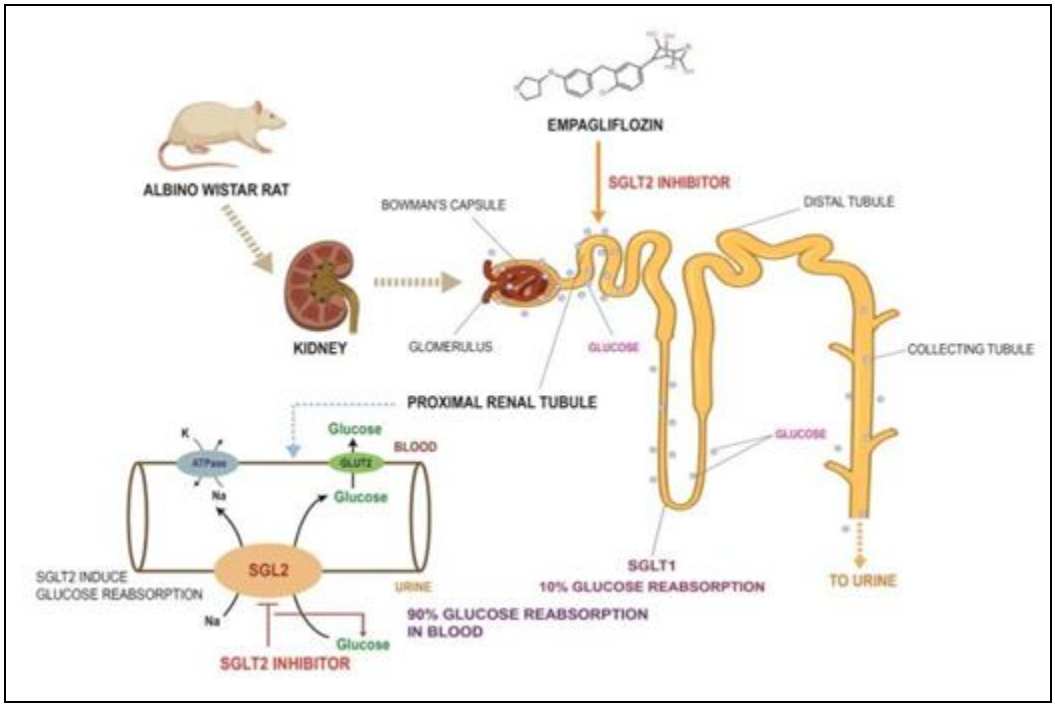

FIG. 2: SCHEMATIC REPRESENTATION OF ACTION SITE OF SGLT2 INHIBITORS

It was reported that SGLT-2 mediates the first segment of the proximal tubule which stands for about 90% of renal glucose reabsorption **Fig. 2**, with diet remodeling, SGLT-2 Inhibitor got prescribed either as a monotherapy drug or in combination with other glucose-lowering agents [33, 34]. The par excellence regarding the selection of SGLT-2 inhibitors over other hyperglycemic

medicaments is its pharmacokinetic activity. Its characteristics ensure excellent bioavailability, longer t1/2, negligible renal excretion as well as active metabolite production and above all risk of drug-drug interaction is almost zero [35-37].

A list of SGLT-2 inhibitors either available on the market or in a clinical trial is long. The four major SGLT-2 inhibitors are *Canagliflozin, Dapagliflozin, Empagliflozin, Ipragliflozin*. Few others in trials namely *Remigliflozin, Sergiflozinetabonate, T-1095, Phlorizin* [38].

Canagliflozin: Canagliflozinchemically known as ([1S]-1, 5 – anhydro – 1 - [3-[[5-[4 - fluorophenyl]-2-thienyl) methyl] – 4 - methylphenyl] - D-glucitolhemihydrate; molecular formula: $C_{24}H_{25}FO_5S$. ½ H_2O]. Canagliflozin is one of the first discovered SGLT-2 inhibitors which is active orally and show reversible selectivity on SGLT-2 inhibitor. FDA approved Canagliflozin in March 2013. It stands with CAS no. 842133-18-0. *Invokana, Invokamet* are the branded Canagliflozin. Itis administered orally, rapidly absorbed and in 1–2 hours achieve peak plasma concentrations. The $t_{1/2}$ of Canagliflozin at a concentration of 100mg is 10.6 h whereas it is 13.1 h with a concentration exceeding to 300mg, both in healthy individuals. Approximately 60% of the administered dose is eliminated through feces and 33% through urine. Canagliflozin achieves a steady state within 4 days, with minimal accumulation observed upon repeated dosing [39]. The sodium-glucose co-transporter 2 (SGLT-2), located in the proximal renal tubules, is primarily responsible for reabsorbing most of the filtered glucose from the tubular lumen. By inhibiting the action of SGLT-2, canagliflozin reduces glucose reabsorption, lowering the renal threshold for glucose (RTG). Consequently, UGE is increased [40].

Dapagliflozin: Dapagliflozin is another type of approved SGLT-2 inhibitors class of anti-diabetic drugs. The molecular formula and weight of dapagliflozinare $C_{21}H_{25}ClO_6$ and 408.87 respectively. It is chemically termed as [2S,3R,4R,5S,6R]-2-[4-chloro-3-[4-ethoxybenzyl] phenyl]-6-[hydroxy methyl]tetrahydro-2H-pyran-3,4,5-triol]. Dapagliflozin is a Biopharmaceutics Classification System [BCS] Class I, II compound with Class-Ilike characteristics and is approved by FDA in January 2014 [41]. *Edistride, Qtern, Xigduo* are few among marketed drug of Dapagliflozin. It act as a competitive inhibitor of the SGLT-2 protein, prevents glucose reabsorption in the kidney and eliminating blood glucose through the urine. Dapagliflozincauses a high level of glucose elimination through urine. Not prescribed in Type-1 diabetes and diabetic ketoacidosis which can lead to weight loss and tiredness.

The Pharmacokinetic stand of Dapagliflozin is as it attains t½ of 13.8 hours with the consumption of a 50 mg dose. The C_{max} is about 1 hour and 1.6% of unchanged dapagliflozin is found in urine. The plasma protein binding of dapagliflozin is 91%. *Dapagliflozin 3-O-glucuronide* is the primary metabolite of dapagliflozin, with 61% of the dapagliflozin dose recovered in the urine as this metabolite. Oral plasma clearance of 4.9 mL/min/kg, and renal clearance of 5.6 mL/min[42].

Empagliflozin: Unlike SGLT-2 present in the proximal tubule, SGLT-1 is extensively expressed in small intestine region where it plays an importment involvement in glucose absorption. It's too an important factor for SGLT-2 inhibitors to have high selectivity for SGLT-2 v/s SGLT-1 which consequently results in glucose malabsorption. A.J. Scheen reported that empagliflozin had the highest selectivity for SGLT-2 over SGLT1 [2,500 folds] compared with other SGLT-2 inhibitors canagliflozin [250 folds], dapagliflozin [1,200 folds] and ipragliflozin [550 folds] [43].

Empagliflozin is an approved, small molecule by FDA in August 2014 that is known as best effective and well tolerated among all other SGLT-2 inhibitors used for hyperglycemia. Empagliflozin is a potent, orally active, and highly selective inhibitor of SGLT-2.It is derived by *Boehringer Ingelheim* Pharmaceuticals [Ingelheim, Germany] with the name *BI 10773* which was later named Empagliflozin [40]. The IUPAC name of Empagliflozin is 1-chloro-4-[b-D-glucopyranos-1-yl]-2-[4-[[S]-tetrahydrofuran- 3-yl-oxy]-benzyl]-benzene; its molecular formula is $C_{23}H_{27}ClO_7$ and molecular weight 450.9. It majorly prevails in the market as *Jardiance, Glyxambi* and *Synjardy*. Empagliflozin confirmed cardio as well as reno-protective effects which are largely independent of

glycemic control in patients with T2DM and established Cardiovascular Disease [CVD] [44]. Empagliflozin is a novel marketed latest SGLT-2 inhibitor. Reduction in renal absorption and lowering in renal threshold results in increased UGE. Additional to other SGLT-2 inhibitors, Empagliflozin too reduces blood pressure and aid in weight loss. The Cmax of empagliflozin reached 1.5h. The plasma protein binding was found to be approx. 86% and the volume of distribution is 73.8L.After oral administration, Empaglifozin was 54.4% eliminated through urine 41.2% eliminated through feces. The t½ was reported to be 12.4 hours and clearance was found to be 10.6L/hours [45].

Ipragliflozin: Ipragliflozin is now being in clinical studies and not yet been commercialized but marketed in Japan as *Suglat* is being one of a kind of new oral hypoglycemic SGLT-2 inhibitor. Studies regarding ipragliflozin proved that Ipragliflozin has been shown to lowers blood glucose by selectively inhibiting SGLT-2, it enhances UGE, reduces fasting blood glucose and glycatedHb in type-2 diabetes. The chemical name of ipragliflozin is [1S]-1,5-anhydro-1 C-{-[[1-benzothiophen – 2 - yl]methyl] – 4 - flurophenyl}-D glucitol with molecular formula and weight as $C_{21}H_{21}FO_5S$ and 404.5 respectively. CAS number is identified as 761423-87-4. The total bioavailability is 90.2% and plasma protein binding is around 95%. The t½ is 15 hours and is eliminated mainly in the urine. Urine elimination holds 68% whereas feces holds 33% [46, 47].

DPP-4 Inhibitors: Dipeptidyl peptidase 4 inhibitors are prescription medicines that control elevated blood sugar levels in type-II diabetes-affected adults. Dipeptidyl peptidase 4 inhibitors have been introduced in 2006 for the treatment of diabetes type II by the introduction of the first drug sitagliptin by FDA approval [48]. Dipeptidyl peptidase 4 (DPP-4) inhibitors are an oral hypoglycemic medication family that inhibits the activity of the DPP-4 enzyme [49]. DPP-4 inhibitors reduce blood glucose levels by enhancing insulin synthesis while lowering glucagon levels [50] **Fig. 3**.

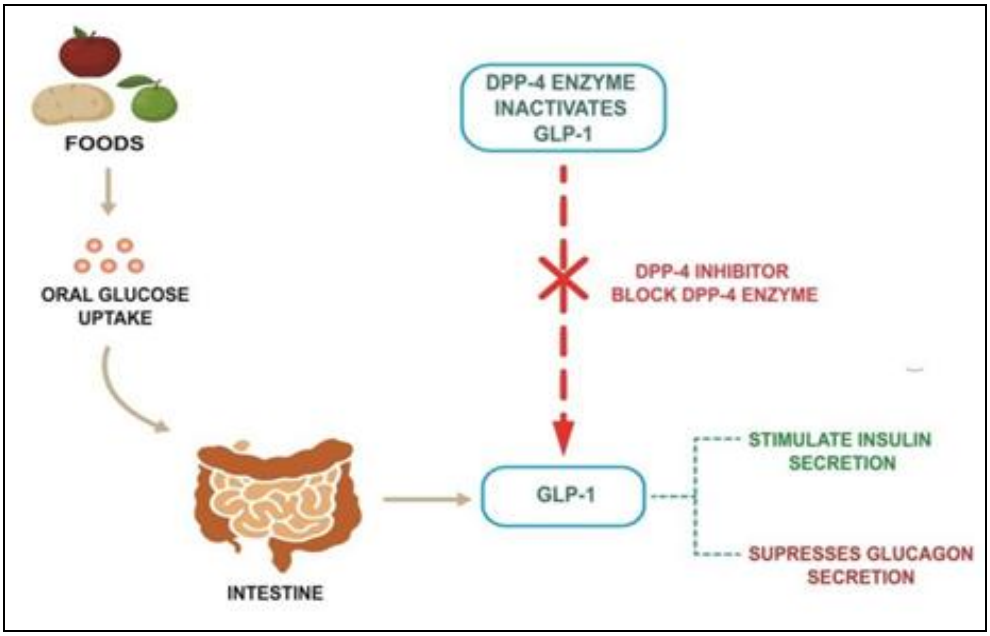

FIG. 3: SCHEMATIC REPRESENTATION OF ACTION SITE OF DPP-4 INHIBITORS

These drugs are not indicated for individuals with type I diabetes. These drugs are contraindicated in individuals with pancreatitis and should be discontinued if pancreatitis is suspected [51]. Dosage modification is necessary for patients with renal inefficiency as it may cause hypoglycemic conditions without dose reduction [52]. The progressive outcome of glycemic control seen in Type 2 diabetics is significantly attributed to a progressive decrease in β-cell mass. Restoring β-cell mass, which is normally decreased throughout Type 2 diabetes's natural course, is one of the main objectives of diabetes research [53, 54]. Metformin, sulphonylurea, and insulin are currently used

treatments; nevertheless, they do not stop the loss of beta cells, and studies on cultured human islets have revealed that sulphonylurea therapy causes beta cell apoptosis [55]. Type 2 diabetes reduces the incretin action. In type 2 diabetic individuals, increasing intact GLP-1 concentrations can decrease or even normalise plasma glucose. DPP-4, a large endothelium-localized enzyme that can also be detected in the bloodstream, degrades GLP-1 very quickly [53]. Peptides with an N-terminal alanine or proline amino acid residue are broken down by DPP-4. Both of the GLP-1 fragments produced by DPP 4 activity are biologically inert; in some investigations, the GLP-1 amide fragment has even been said to have GLP-1 antagonistic characteristics. Intact GLP-1 plasma concentrations are increased by DPP-4 inhibition to those seen in the stimulated state following a meal [56, 57]. DPP-4 inhibitors have been examined in combination with other medications, such as insulin, and have improved blood sugar levels. A combination approach to treating type II diabetes may be considered a better option to minimize the side effects with improved efficacy [58, 59].

Mechanism of Action of DPP-4I: DPP-4 inhibitors block the activity of DPP-4 enzyme which increases the level of in cretins glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP).These Incretins inhibit the glucagon release thus ultimately helping the increased concentration of insulin level in blood which in turn assists the decreased level of glucose in the blood. Their efficacy in reducing the HbA1c range from 0.5 to 1% and possess a favorable safety profile [60, 61].

Sitagliptin: A dipeptidyl peptidase inhibitor called sitagliptin, also known as a DPP-4 inhibitor, has recently been licenced for the treatment of type 2 diabetes. Chemical name for sitagliptin is MK-0431 (2R) -4-Oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4] triazolo[4,3-a] pyrazin-7(8H)-yl] -1-(2,4,5-triflorophenyl)butan-2-amine with an IC_{50} of 18 nM, exhibits extremely excellent DPP-4 selectivity. There is no affinity toward other DPP enzymes (DPP- 8 and DPP-9) [62]. Seventy-five percent of an oral dose is excreted mostly through the kidneys, and the remaining portion is processed by the cytochromes CYP 3A4 and CYP 2C8. Clinical investigations on sitagliptin therapy did not find any drug-drug interactions, and type 2 diabetic patients, in particular, did not experience any such interactions with other antihyperglycemic medications. 12 to 14 hours pass between rounds of elimination. Once daily doses of 50–200 mg/d of sitagliptin result in plasma concentrations of the drug of >100 nM and a 24-hour DPP-4 inhibition of ≥80%. As a result, postprandial GLP-1 concentrations are 2-3 times higher when it is biologically active and intact [56, 63].

Sitagliptin is an effective, reversible inhibitor of the DPP-4 enzyme, and is the first agent in DPP-4 inhibitors category to be launched. Evidence from a Cochrane review and meta-analysis of 14 trials/study arms suggests that it lowers glycated Hb by 0.7% in sitagliptin versus placebo trials [64, 65].

Saxagliptin: As dipeptidyl peptidase-4 inhibitors, Saxagliptin, coupled with its active metabolite M2, helps to regulate blood sugar levels by preventing the deactivation of incretin hormones such glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic polypeptide.This inhibits postprandial glucagon and glucose levels, raises GLP-1 levels, and promotes insulin secretion. For individuals with moderate or severe renal impairment (creatinine clearance [CrCl] ≤ 50 mL/min), the recommended dose of saxagliptin is 2.5 mg once daily. For the majority of patients, the recommended dose is 5 mg once day [66]. Saxagliptin is a novel and efficacious treatment that will be added to the current range of antidiabetic drugs available for individuals suffering from type 2 diabetes mellitus [67]. The current scenario of DPP-4inhibitors for implication in clinical **Table 1**, renal and hepatic disease **Table 2** and metabolic activities **Table 3** is provided below.

TABLE 1: CLINICAL IMPLICATION OF DPP-4 INHIBITORS

Clinical Trials	Drugs	Company	References
Phase II	BI 1356 BS	BoehringerIngelheim	68
	Melogliptin	Glenmark Pharmaceuticals Ltd.	69
	AMG 222	Amgen	70
	MP 513	Mitsubishi Tanabe Pharma Corporation	71

	PHX 1149	Phenomix Corporation	[72]
	PSN 9301	Prosidion	[73]
	R 1579	Roche	[74]
	SYR 472	Takeda San Diego	[75]
	TA 6666	Mitsubishi Tanabe Pharma Corporation	[76]
Phase III	Denagliptin	GlaxoSmithkline	[77]
	Saxagliptin+Metformin	Bristol Myers Squibb	[78]

TABLE 2: EFFECT OF DPP-4 INHIBITOR IN RENAL AND HEPATIC DISEASE

DPP-4 Inhibitors in renal and hepatic impairment				
DPP-4I Drugs	**Renal Impairement**	**Hepatic Impairment**	**Renal & Liver function monitoring**	**References**
Sitagliptin	50mg: Moderate OD 25mg: Severe OD	Yes	Yes	[79]
Vidagliptin	50mg Moderate and Severe OD	No	Yes	[80]
Saxagliptin	2.5mg OD	Yes	Yes	[81]
Alogliptin	12.5mg: Moderate OD 6.25mg: Severe OD	Yes	Yes	[82]
Linagliptin	-	Yes	No	[83]

TABLE 3: EFFECT OF DPP-4 INHIBITOR IN METABOLIC ACTIVITY

Effect of DPP-4 Inhibitors		
Action	**DPP-4 Inhibitors Effect**	**References**
Insulin Secretion	Increased	[84]
Glucagon Secretion	Decreased	
Appetite	No effect	
Satiety	No effect	
Gastric Emptying	No effect	
Body Weight	Neutral	

CONCLUSION: Controlling Type II Diabetes mellitus requires efforts to reduce blood glucose levels through various mechanisms. Recent advancements in medication therapy offer both actively and passively administered options, providing efficient and contemporary treatment for diabetes. Additionally, combination therapy, observed as the latest approach in antidiabetic treatment, is available. The review suggests that the combination of SGLT-2 and DPP-4 inhibitor oral anhihyperglycemic drug is more productive in managing hyperglycemic condition compared to the currently used standalone drugs.

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