WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 7, 448-472. Review Article ISSN 2277– 7105

SGLT INHIBITORS AS AN ANTIDIABETEC AGENTS

Ayodhya Tanaji Pardhe[1]*, Shubhangi Manikpuriya[2], Dr. Gajanan Sanap[3] and Pooja Dhamale[4]

Department of Pharmaceutical Chemistry, LBYP College of Pharmacy, India.

Article Received on
13 March 2023,

Revised on 02 April 2023,
Accepted on 23 April 2023

DOI: 10.20959/wjpr20237-28035

***Corresponding Author**
Ayodhya Tanaji Pardhe
Department of Pharmaceutical Chemistry, LBYP College of Pharmacy, India.

ABSTRACT

Diabetes Mellitus is the most common metabolic disorders that substantially contributes to increase in global health burden. DM is associated with various medical conditions, diseases such as hypertension, obesity, cardiovascular diseases and atherosclerosis. Diabetes mellitus classified in major 3 types that are Type1 DM, Type 2 DM and gestational diabetes. There are various classes of drugs which are used in the treatment or control the DM such as Insulin, Biguanides, Sulfonylureas, Metformin, DPP4 inhibitors, GLP-1 inhibitors and SGLT2 inhibitors. In this review, cover the study of diabetes mellitus with their type, anti-diabetes drugs, and main focus on the sodium/glucose co-transporter [SGLT2] inhibitors.

Sodium/glucose co-transporters [SGLT] are large of the proteins that improve the transport of sugars like fructose, fructose, galactose and also transport the sodium across the plasma membrane of cell from variety of tissues. SGLT receptors are promoted the reabsorption of glucose in the kidney. The inhibition of the SGLT2 inhibitors decreases the reabsorption of glucose and increases the excretion of glucose through the urine. There are various types of FDA approved drugs that are Canagliflozin, Dapagliflozin, Empagliflozin which are used in the management or control the diabetes mellitus.

KEYWORDS: Diabetes Mellitus, Oral Antidiabetic Agents, Sodium Glucose Co-Transporter Inhibitors 2 (SGLTI2).

INTRODUCTION

The ancient Indian physician, Sushruta, and the surgeon Charaka were able to identify the two types of diabetes mellitus that are Type 1 and Type 2 diabetes mellitus.[1] Cappadocian, who coined the term diabetes (Greek, ‘siphon’) are state that “ no essential part of the drink

is absorbed by the body while great masses of the flesh liquefied into urine". Indian it also called as the Madhumeha because it attracts the ants.[2] Avicenna the great Persian physician, in The Canon of Medicine observed diabetic mortify but also concocted a mixture of seeds (fenugreek, zedoary etc.) as a panacea.[3] The term mellitus (Latin, 'sweet like honey') was coined by the British Surgeon-General, John Rollo in 1798, to distinguish this diabetes mellitus from the other diabetes insipidus in which the urine was tasteless.[4]

In 1869, Paul Langerhans working on his medical doctorate, identified the cells are the 'islets of Langerhans'.[5] name is insulin for the secretions of the islets (Latin, insula = island), which could decreases blood glucose levels, was coined in 1910, individually by de Mayer and Schaefer, respectively.[6] In 1889, von Mering and Minkowski, when experimenting on dogs, found that removal of the pancreas led to diabetes.[7] In 1921, Banting and Best working in Macleod's laboratory, ligated the pancreatic duct, causes the destruction of the exocrine pancreas while leaving the islets intact. In their elegant animal experiments, by using canine insulin extracts to reverse induced diabetes, they conclusively established the deficiency of insulin was the cause of diabetes mellitus.[8]

DIABETES MELLITUS

The word diabetes mellitus means excessive excretion of sweet urine .It is group of metabolic disorder, characterised by hyperglycaemia due to defect in secretion of insulin. If the insulin is not secreted in sufficient amount or not stimulate the targeted cell or organ cause hyperglycaemia. The main symptoms of diabetes are the polyuria, polydipsia, polyphagia losing weight, feeling tired and weak, having blurry vision.[9] There is no cure for diabetes but it can be controlled by the pharmacotherapy and to require the normal insulin level to prevent the diabetes related problems. Diabetes mellitus (DM) is probably one of the oldest diseases known to man. The World Health Organization (WHO), there is a globally agreed target to halt the rise in diabetes and obesity by 2025.

About 422 million people worldwide have diabetes, the majority living in low-and middle-income countries, and 1.5 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades.[12]

Diabetes mellitus is diagnosed by.

-fasting blood glucose exceeds 6.1-7.0mmol/L

-Postprandial glucose >200mg/ dl.

-HbA1c > 6.5 gm%.

For giving the right therapy the diabetes mellitus classified in to major three types that are following.

1] Type 1.

2] Type 2.

3] Gestational diabetes mellitus (GDM)**.**

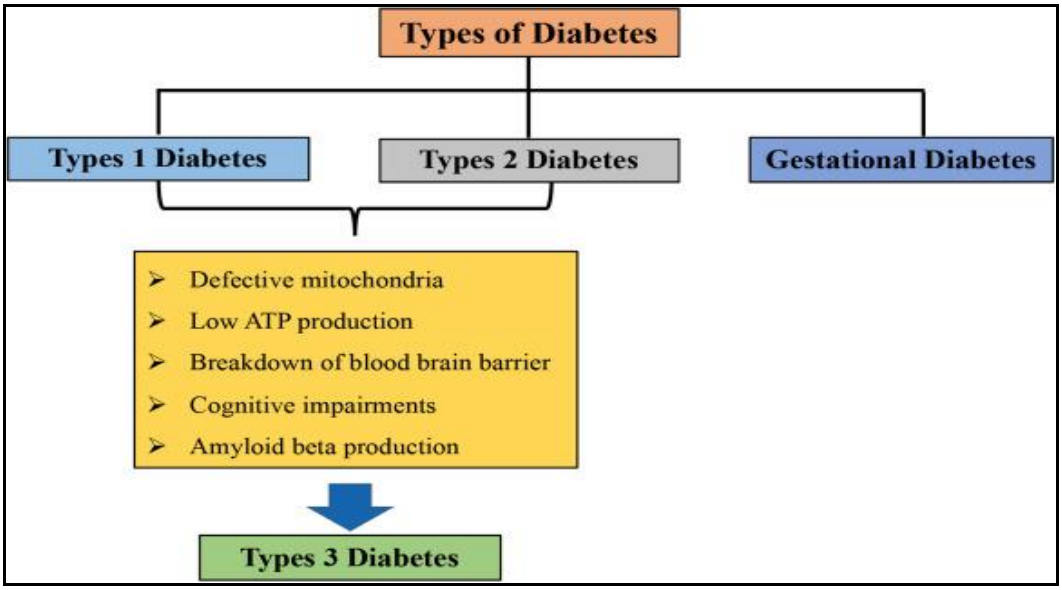

Fig. no. 1: Types of Diabetes.

Type 1 diabetes mellitus

It occurs due to destruction of autoimmune beta cells and result is deficiency of insulin. These DM is also called as insulin dependent diabetes mellitus (IDDM) or Juvenile diabetes. In these the patient required the periodic insulin dose in any age of the patient mainly in children. This diabetes only treat by the insulin.

Type 2 diabetes mellitus

In these diabetes progressively loss of beta cells of pancreas due to these insulin secretion frequently decrease.

These DM is also called as the noninsulin dependent diabetes mellitus (NIDDM) or Adult-onset diabetes. In these the insulin receptors on insulin responsive cells do not respond the normally to insulin therefore called “insulin resistant”. This diabetes treated by orally active drugs or injection.

Gestational diabetes mellitus (GDM)

In these the diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt prior to gestation. The risk factors associated with developing gestational diabetes. This diabetes treated with the insulin and Metformin in selected cases.[10]

Classification of anti-diabetics agents

1) Bigaunides- Metformin, Buformin, Phenoformin, Proguanil, Polyaminopropyl Biguanide
2) Sulfonylureas-

a) First Generation- Cholrpropamide, Tolbutanide, Acetohexamide, Metahexamide, Metahexamide.
b) Second Generation- Glipizide, Glibunuride, Glyclazide, Gliquidone.

3) Glucagon- Like Peptide-1 (Glp-1) Receptor Agonists- Exenatide, Liraglutide, Lixisenatide
4) Glucose Co-Transportar 2 Inhibitor (SGLT-2)- Canagliflozin, Dapagliflozin, Empagliflozin
5) Alpha Glycosidase Inhibitors -Acarbose, miglitol
6) Meglitinides- Nateglidnide, Repaglinide, Mitiglinide.
7) DPP-4 Inhibitors- Sitagliptin, Saxagliptin, Linagliptin, alogliptin
8) Thiazolidiones (Tzds)- Rosaglitazone, Pioglitazone.[11]

1) Biguanides

Three drugs of biguanides are reported for the antidiabetic activity that are. phenoformin, buformin, and metformin. The use of phenoformin and buformin have been discontinued due to lactic acidosis the worldwide used biguanides is the metformin.

Metformin is first line drug for treatment of DM. Metformin is the insulin sensitizing drug that maintain its antihyperglycemic effects by the gluconeogenic gene expression. Metformin inhibits the mitochondrial respiratory chain in the liver, leading to activation of AMPK, enhancing insulin sensitivity and lowering CAMP, thus reducing the expression of gluconeogenic enzyme. Metformin absorb orally and not causes the lactic acidosis. Proguanil and chlorproguanil are biguanides used as antimalarials Chlorhexidine and polyhexanide are disinfectants.[12] [13]

2) Sulfonylureas

This is most widely used as oral anti-diabetic agents. Sulfonylureas stimulate insulin release by binding to the SUR-1 subunit of ATP sensitive potassium channel (KATP) of pancreatic b-cells and inducing channel closure. Therefore potassium flow across the plasma membrane is inhibit leading to depolarisation this open the calcium channel there is uptake of extracellular calcium which activate cytoskeletal system which causes translocation of secretary granules to cell surface and extrusion insulin through exocytosis this results fusion of secretary granules with plasma membrane causes release of insulin into the extracellular space to reach the capillary blood flow therefore sulfonyl ureas administered carefully since it causes hypoglycaemia and hyperinsulinemia. Sulfonylureas have multiple formulation at minimum side effect with low cost with maximum efficacy in controlling hyperglycemia. It gives in combination with insulin and other oral agent of antidiabetes. Second generation drugs (glipizide, gliburnuride, glyclazide, gliquidone) are more potent than first generation drugs (cholrpropamide, tolbutamide) and fewer side effects. Must sulfonylureas metabolised in liver and excreted through the urine.

First generation sulfonylureas causes disulfiram like reaction.[14]

3) Glucagon – like peptide 1 (GLP-1) receptor agonists

GLP1 receptor are present on the many tissue of the body, but their effect on the GIT to make the suitable for type 2 diabetes. GLP1 increase the glucose mediated release of insulin and decrease the release of glucagon after meals. GLP1 degraded by the enzyme DPP4 hence the half-life of this is 1 to 2 min.[15] GLP1 stimulate the glucose dependent insulin release from the pancreatic islet. It also shown to gastric empty, it inhibit the inappropriate post meal glucagon release and reduced the food intake. GLP1 stimulate insulin secretion by several mechanisms, include direct inhibition of ATP dependent potassium channel, like sulphonylureas, this causes to increase the intracellular level of calcium and increase ATP synthesis wich leads depolarization and it causes insulin granule exocytosis from pancreatic cells.[16]

4) Alpha glycosidase inhibitors (AGIs)

This are group of antidiabetes drugs wich are used in the treatment of type 2 diabetes. AGIs mostly decreases the glycosylated haemoglobin level and help in reducing postprandial insulin concentration.[17] The mode of action of AGIs is it delaying and inhibiting the absorption of carbohydrates from small intestine. they competatively inhibit the sucrose,

maltase, iso-maltase enzymes in brush border of enterocytes wich involved In converting non absorbable oligo into absorbable form by delaying absorption of carbohydrates in gut.[18] Alpha glucosidase consume orally and that are first line drug for type 2 DM. It taken three time a day before consuming meal. AGIs most common side effect is GI disturbance, diarrhea.[19]

5) DDP 4 inhibitors drugs

Sitagliptin, Vitagliptin, Saxagliptin.

These are the newer group of antidiabetes used in the treatment of type 2 diabetes.[20]

DPP4 are responsible for breakdown of the incretins those are release by the intestinal cells after meals wich increase the insulin secretion. It gives in combine with metformin and sulfonylureas to treatment of type 2diabetes and diabetes ketoacidosis.[21]

6) Thaizolidinediones (TDZs)

Thaizolidinediones are the orally active antidiabetes agents. These are consider as the insulin sensitizer like biguinoids.[22] The Troglitazone is the first TZDs drug is available in market. But now days these drug are not formulated or not available in market due to hypatotoxycity.[23]

TDZs are the potent synthetic activators of nuclear receptor PPAR these are aboundently present in the adipose tissue, muscle, liver and pancreatic cells.[24] TDZs are contraindicated in the wich have hearts disease due to fluid retention by TDZs. It also increase the bone fracture in the women when long term used of TDZs.[25]

7) Meglitinides

Drugs-Nateglinide, repaglinide, mitiglinide.

These are the newer class of the antidiabetes agents wich increase the insulin secretion by blocking the ATP sensitive potassium channels.[26] Meglitinides are short duration of action and it treat the type 2 DM. The adversed effect of the meglitinide is hypoglycaemia due to the increase in insulin secretion. These class of drug contraindicated in the patients with renal failure, liver dysfunction. The oral antidiabetes agents are shown in bellow (table no. 1)[46]

Table 1: Oral anti-diabetes agent.

Class of Oral Antidiabetic Medication	Mechanism To Control Glucose Levels	Generic Name	Brand Name
Sulfonylureas	Improve Insulin Production	Chlorpropamide Glimepiride Glipizide	Diabinese Amaryl Glucotrol
Mglitinides	Improve Insulin Production	Repaglinide Nateglinide	Prandin Starlix
Biguanides	Reduce Hepatic Glucose Output And Increase Uptake Of Glucose By The Periphery Including Skeletalmuscle	Metformin	Glucophage
Thiazolidinediones	Substantially Attenuated Nsulin Resistance	Rosiglitazone	Avandia
DPP4 Inhibitors	Inhibition Of DPP4 Enzyme Prolongs And Enhance Activity Of Incretins That Play An Important Role In Insulin Secretion And Control Bloodglucose Level	Sitagliptin	Januvia
Alpha Glucosidase	Slow The Digestion Of Starch	Acarbose	Precose

8) Sodium- glucose co-transporter 2 inhibitors (SGLT2 inhibitors)

Sodium glucose cotransporter-2 (SGLT2) in the kidney has become a play major role for the treatment of type 2 diabetes mellitus (T2DM). Smith et al. reported in 1933 the reabsorption of filtered glucose was completely inhibited by intravenous phlorizin (phloretin-2'-β-D-glucopyranoside)[27] In the half a century, DeFronzo and his colleagues found "phlorizinising" diabetic rats diminished their hyperglycemia and restored their insulin sensitivity and suggest phlorizin could be used for T2DM[28] At first phlorizin was used for treatment of malaria, fever or other incetion diseases. Cana is the derivative of the phalozin with more inhibitory activity for SGLT2 than SGLT1.[29]

SGLTs (Sodium Glucose Like Co- factors)

The scientist Crane was represent the active cotransport concept by describing the deposition of glucose molecules at brush border of epithelium cells of intestine. That associated transport of sodium ions downward their gradient.[30] The first co-transport sodium/glucose and sodium/ prolin found on intestinal brush border of the rabbit.

In bacterial cells and animal cells, more than 220 members of SGLTs family (gene symbol, SLC5A) identified. In humans from epithelial cells to nerve cells eleven genes coding members of SGLT family identified.[31] Sodium- glucose cotransporters (SGLTs) belongs to a membrane protein family, SGLTs facilitate transport of compounds that are glucose, amino

acids, various ions and vitamins by the Proximal convoluted tubule and intestinal epithelium.[32]

SGLT1 (Sodium Glucose Like Co- factors 1)

SGLT1 also known as solute carrier family 5 member 1 is a protein in humans that encoded by SLC5A1 gene. SGLT1 is the membrane bound protein and have mass of 75 k Dalton. It is mostly found in the cell membranes of small intestine, kidney (renal proximal convoluted tubule), in S3 segment and heart. The transportation of sodium and glucose by SGLT1 protein occurs at ratio of 2:1. The SGLT1 have a higher affinity for galactose and glucose but possess a low capacity to transports them. In the gastrointestinal tract SGLT1 assist as a vital transporter for glucose uptake, but its effect on the kidneys found less significant (approximately 10% reabsorption of glucose is observed). Mutations in the SGLT1 gene causes genetic disorder called as glucose-galactose malabsorption (GGM). In newborn infants, rare autosomal recessive disease cause to life-threatening diarrhea. removed of the dietary sugars such as glucose, galactose, and lactose then stops the diarrhea, in humans without this disorder, SGLT1 is key to operation of oral rehydration therapy by adding glucose and sodium to water this transporter allow to transport sodium, glucose and water by helping to speed up water absorption. Researchers developed the interest in SGLT1 receptor because it has been hypothesized that the inhibition of this transporter, decreases the gastrointestinal glucose uptake and also induce weight loss or reduce postprandial hyperglycemia.[33] the SGLT1 protein also Plays a role in the maintaining normal glucose level in the body and they does not use ATP as energy source. SGLT1 has been shown to interact with the PAWR. The structure of SGLT1 is classified as an integral membrane protein that made up of 14 alpha helices constructed from the folding of 482- 718 amino acid residues with N and C- terminalresiding upon the extracellular side of the plasma membrane. (Shown in fig.2)[34]

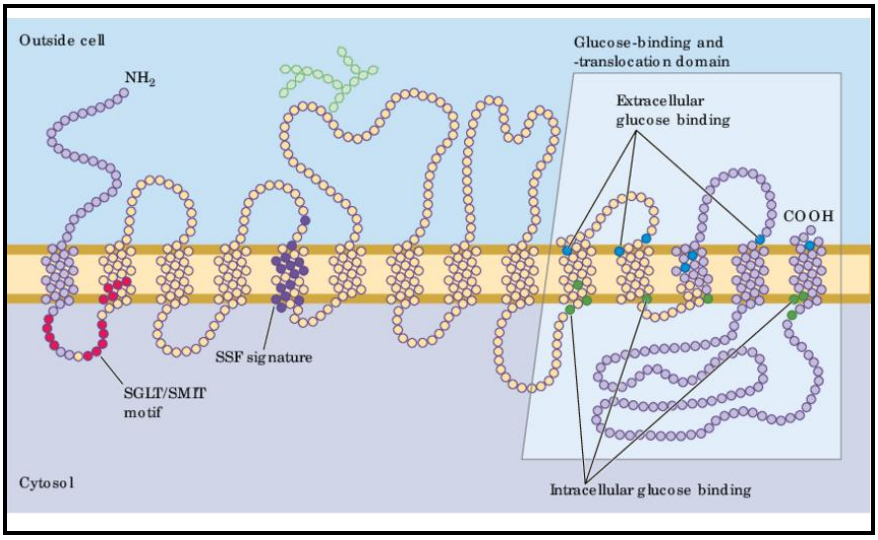

Fig. no. 2: Structure of SGLT1.

SGLT2 (Sodium Glucose Like Co- factors 2)

SGLT2 is the second membrane-bound SGLT family member that is encoded by the SLC5A2 in humans. SGLT2 has a high capacity but low affinity for glucose and galactose, the transport occurs at a stoichiometric ratio of the 1:1 of the sodium ion to the sugar molecule, which differentiates SGLT2 from SGLT1. This is the major co-transporter mostly expressed in the kidneys where it functions as the reabsorption of 90% glucose. This receptor found in the apical membrane of S1 and S2 segment of proximal tubule in kidneys, (shown in fig.3)[35] glucose transport is occurred during tubular filtration by the reabsorption of sodium ions along their electrochemical gradient by the mechanism that is called secondary active transport. This transporter has much interest in the diabetes mellitus because of its higher involvement in the glucose reabsorption process inside the kidneys.[36]

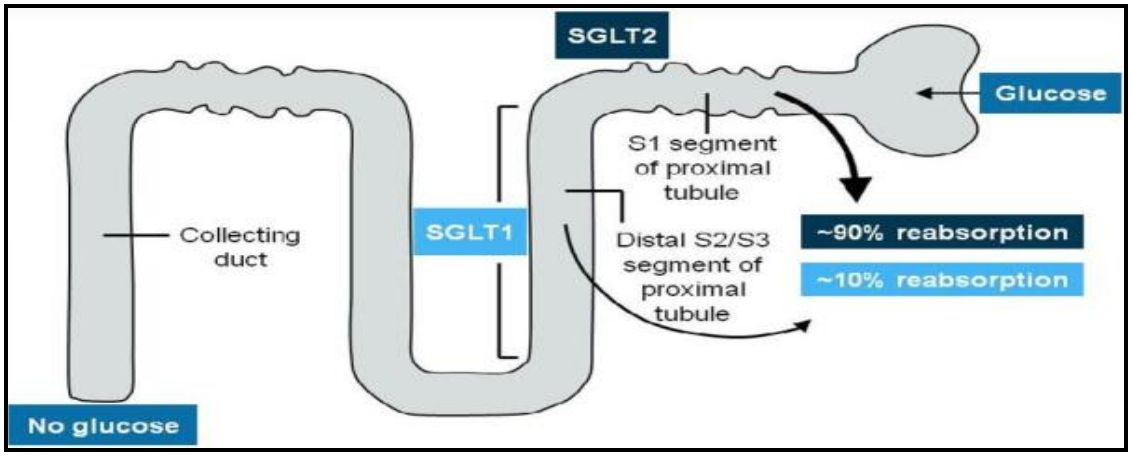

Fig. no. 3: Location of SGLT2 in Nephron.

SGLT3 (Sodium Glucose Like Co- factors 3)

SGLT3 is the third membrane-bound protein, which encoded by the SLC5A4 gene family that was first identified by chromosome 22 genome project. This is mostly found in skeletal muscles, the small intestine, the kidneys, and nicotinic acetylcholine receptor. Human SGLT3 is a basic glucose-gated ion channel present in the cell membranes of the muscles and the neuronal membranes but observed on the functional studies by using laevis oocyte expression that showed it does not act as a sodium/glucose transporter. SGLT3 is not sodium/ glucose sensor in plasma membrane of skeletal muscle, cholinergic neuron and other tissues.[37] The SGLT4, SGLT5, and SGLT6 proteins available information is still insufficient. The SGLT member, substrate, tissue distribution, encoding genes, function discussed below (table no.2).[47]

Table no. 2: The SGLT4, SGLT5, proteins available information is still insufficient. The SGLT member, substrate, tissue distribution, encoding genes with function.

SGLT member	Human gene	Substrate	Distribution in human tissue	Function: transport of
SGLT1	SLC5A1	Glucose,galactose	intestine,trachea,kidney,heart,brain,testis	Na,glucose, galactose
SGLT2	SLC5A2	Glucose	Kidney,liver,brain, thyroid, muscle,heart	Na,glucose
SGLT3	SLC5A4	Glucose	Intestine,testis,uterus,lung, thyroid	Na
SGLT4	SLC5A8	Glucose,mannose	Intestine, kidney,trachea, pancreas,uterus	Glucose,mannose
SGLT5	SLC5A9	Glucose, galactose	Kidney	Unknown

- **Pathophysiology of disease (GGM) cause by mutation occurs in SGLT1**

Glucose- galactose malabsorption (GGM) is a genetic disorder that is linked to the SGLT family of genes. It is a rare autosomal recessive disease occurs in new-born infants, where mutations in SGLT1 gene cause life-threatening diarrhoea. GGM is a condition in which the body cannot absorb sugar glucose and galactose, and cause severediarrhoea. Diarrhoea can be managed by removed of dietary sugars, but it can quickly recur after the reintroduction of these sugars.[33] SGLT2 transporter found in the kidneys, which are associated with glucose reabsorption, hence, confirming why autosomal recessive renal glycosuria occurs in diabetes patients. DNA sequencing was conduct on two younger brothers and their parents for investigating the formation of two mutations, homozygous nonsense mutation and a heterozygous mutation, which both occurred in exon 11 of SGLT2.[36] Patient suffering from GGM then removed the sugar containing foods from their diet because of sugar containing foods leads diarrhoea and other health problems. Glucose and galactose are handled by the SGLT1 receptor and fructose is transport across the brush border by its own carrier, the

facilitated fructose transporter (GLUT5). The glucose, galactose and fructose transfer across the cell membrane into the blood by SLUT2 in basolateral membrane (shown in fig.4.)[38]

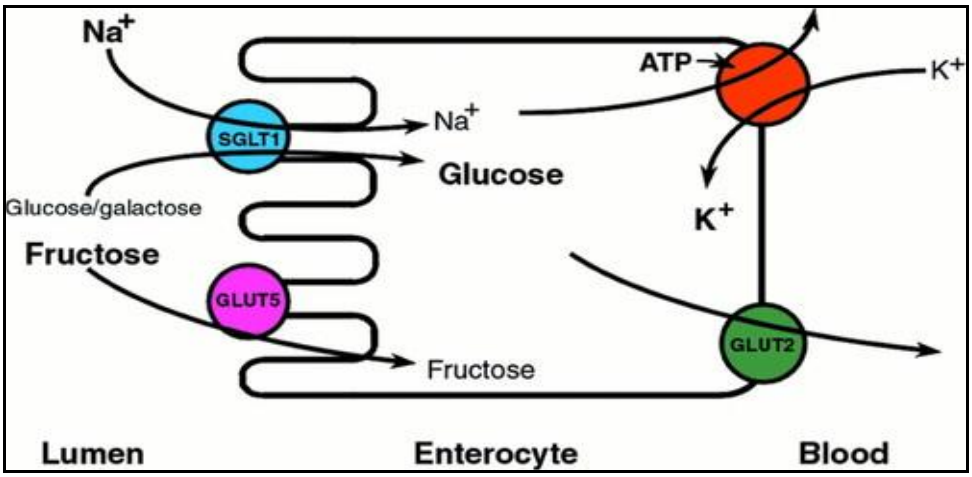

Fig. no. 4: Model for transport of sugar by SGLT1 and GLUT5 transporters and basolateral sodium potassium pumps and sugar transporter GLUT2.

- **Structure and functions of SGLT**

A. Crystal structure: The crystal structure of SGLT was derived from Vibrio parahaemolyticus it shows 60% similarity to human SGLT1. The model of the SGLT structure anticipate 14 transmembrane α-helices (TMH) and features NH2-terminal and a COOH-terminal halves. Studies on this type of transporters indicate the NH2-terminal half carries the sodium ion while COOH-terminal half carries the sugar moiety. NH2-terminal binding to sodium ions and induces a conformational change in the proteins to permit sugar binding and translocation. This studies postulated that the TMHs numbered 10–13 are critical for maintaining the sugar translocation pathway in SGLT1.[39]

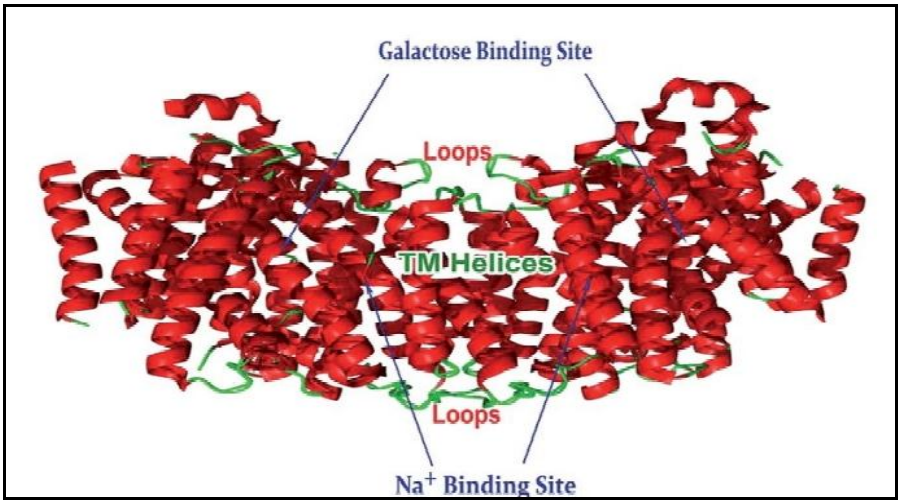

Fig. no. 5 Crystal structure of the SGLT protein.

Researchers identified two important binding sites in crystal structure, that are: Galactose and Na+ binding sites- The function of this site is to identify the precise point of reference and location of the sugar molecule. This binding site located in between the hydrophobic residues of the intracellular and extracellular gates. Owing to the densitometric similarity in between the Na+ and water, is difficult to locate the sodium binding site precisely on vSGLT. Sodium binding site located at the crossing of TM2 and TM9 helices and is 10 Å away from the substrate-binding site on the basis of sequence alignment studies on the LeuT structure.[40]

B. Functions: In a mutagenesis analysis of SGLT1 the residues at positions 457, 468, and 499 were replaced by cysteines, which make the transporter susceptible to methanethiosulfonate (MTS) when the transporter is in the C2 conformation. If the MTS reaction is performed with glucose/phlorizin in presence or absence of sodium ions or in the presence of sodium ions alone (when depolarization of the membrane potential), the accessibility of the cysteine residues to MTS is blocked. The probability of proteins to adopt the C2 conformation is directly proportional to accessibility of these residues (457, 468, and 499) to MTS. The main conclusion of these experiments was the transporter residues 457, 468, and 499 are critical for maintaining the translocation pathway, which is accessible in C2 conformation. MTS reagents react with these critical residues, but phlorizin block the entry of sugar derivatives towards them. It is suggested that the sodium ion creates a large conformational change by rotating one or more TMHs in the 10–13 helical bundle. In cell, the translocation of sugar generally needs a substantial change in the helical rotation, which results in the cotransportation of water and urea. Under these conditions, the stoichiometry of sodium ions:glucose: water in a such transport found to be 2:1:250. SGLT1 is responsible for the absorption of glucose and galactose in the small intestine and SGLT2 responsible for the reabsorption of glucose in the kidney.[41]

Role in diabetes: kidney utilised various mechanisms to maintain glucose levels, this occurs by glomerular filtration and reabsorption mechanisms in the kidney. To determine urinary glucose excretion (UGE) the absorbed glucose is subtract from the total amount of filtered glucose. It has observed in a healthy adult person approximately 180 g per day of glucose is filtered. After filtration, the glucose gets completely reabsorbed and very low amount (below 1%) eliminated in the urine.

Glucose reabsorption consists of various steps by various mechanisms. Tubular epithelial cells carry filtered glucose from the tubule. This filtered glucose further carried into the

peritubular capillary through basolateral membranes. Loss of glucose does not occurs through the urine under the non-diabetic conditions (when the glucose load is normal). But, whenever the renal glucose threshold passed then UGE occurs. To trigger this process, there is no set value for plasma glucose which in most found approximately 200 mg dL. During the reuptake from urine by the SGLTs glucose is transported to tubular or luminal epithelial cells. various members of the SGLT protein family present in the cell membrane they facilitate the movement of several constituents like glucose, amino acids, ions or vitamins through the renal tubules and luminal epithelial cells. The SGLT transporter i.e. SGLT1 and SGLT2 transporters are important members of SGLT. SGLT1 transporter in the GIT responsible for glucose absorption in the kidneys (it present in S3 segment of proximal convoluted tubule), SGLT1 reabsorbs only 10% of the glucose. SGLT2 as another transporter which have high capacity and a low affinity for the glucose and galactose. SGLT2 is found in the kidneys and this approximately 90% of glucose is reabsorbed. SGLT2 transporter interacts and binds with glucose molecules and sodium ions of the tubular filtrate to facilitate the secondary active transport. This type of glucose transport across the membrane is couplet to movement of sodium ions, which drive the transport along with electrochemical sodium ion gradient between the tubular filtrate and cells.[42] SGLT2 mediated glucose transport into the luminal epithelial cells, after glucose molecules are passed through the basolateral cell membrane by facilitated diffusion and again back into the peritubular capillary. Glucose transporters (GLUTs) such as GLUT1 and GLUT2 are the main transporters involved in this facilitated diffusion. It has been previously reported that glucose reabsorption is higher in insulin-treated diabetic patients than in healthy person. In addition, diabetic patients show increased SGLT2 expression in renal proximal tubular cells. SGLT activity mediates apical sodium and glucose transport across the cell membrane. Co-transport is driven by active sodium extrusion by basolateral sodium potassium ATPase, thus facilitating glucose uptake against an intracellular up-hill gradient.[43]

SGLT inhibitors: SGLT inhibitors are class of prescription medicines that are inhibit the SGLT1 and also SGLT2 and maintain the blood glucose level.

SGLT1 inhibitors

SGLT1 inhibitors are new diabetes mellitus medications that delay and reduce the absorption of glucose in the small intestine. SGLT1 treatment improve diabetes control and reducing the sugar level after eating. SGLT1 inhibitors work on a different transport proteins, sodium-

glucose like co-transporter1 this co-transporter 1 also play important roles in the reabsorption of glucose, and minor role play in the kidneys, to down the working in tubules to reabsorb glucose. It is responsible for the 5% of glucose reabsorbed in the kidneys, about 10 g/day. That does not very much, but SGLT1s also work to reabsorb glucose in the small intestine. By blocking the SGLT1 action reduces the blood glucose level and improve glycaemic control, basically after meals. SGLT1 inhibitors are helpful for the patients with renal dysfunction, than SGLT2 inhibitors this are less effective. By delaying and reducing glucose absorption in small intestine, they reduces glucose impale after eating and improve glycaemic control after meals. The drug "Sotagliflozin" is the first oral SGLT1 inhibitor developed for the treatment of adult patients with type 2 diabetes mellitus in combination with insulin, which is reviewed by the FDA. This drug also inhibit the SGLT2. The studies have shown that people with type 2 diabetes mellitus who take sotagliflozin in addition to optimized insulin therapy have lower haemoglobin A1c levels and weight and a low incidence of severe hypoglycaemia ayear of treatment.(shown in fig.6).[44]

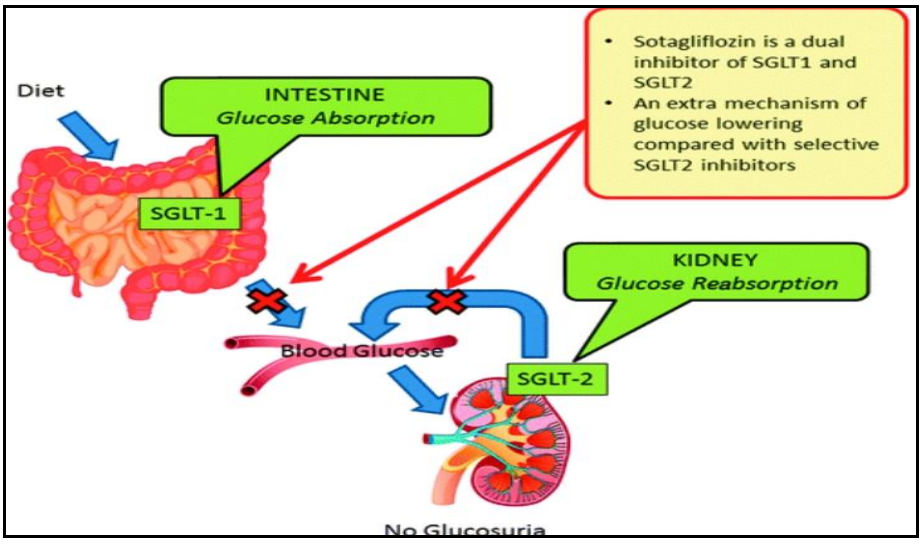

Fig. no. 6: Mechanism of action of Sotagliflozin.

SGLT2 Inhibitors

SGLT2I are a class of prescription medicines that are FDA approved for use with diet and exercise to lower the blood glucose level in adult with type 2 diabetes mellitus. The SGLT2I drug sincludecanagliflozin, dapagliflozin and empagliflozin. Table 3 is list of worldwide available and FDA or EMA (European Medicines Agency) approved SGLT2 inhibitors.[48]

Table no. 3: world wide available and FDA and EMA approved SGLT2 inhibitors.

SGLT2 inhibitors	Body of approval for diabetics	Year of approval	Trade name	Dose (mg)	Frequency
Dapagliflozin	FDA EMA	2014 2012	Farxiga	5;10	Once daily
Canagliflozin	FDA EMA	2013 Pending	Invokana	100;300	Once daily,before first meal of day
Empagliflozin	FDA EMA	2014 2014	Jardiance	10;25	Once daily
Ertugliflozin	FAD EMA	2017 2017	Steglaro	5;15	Once daily

This inhibitors, are also called as gliflozin drugs, they are a new class of diabetic medications for the treatment of type 2 diabetes. They have also shows cardiac benefits in patients with diabetes. They work by reducing the absorption of glucose via the kidneys so that excess glucose is excreted through urination. SGLT2 is a protein in humans that facilitates glucose reabsorption in the kidney. SGLT2 inhibitors block the reabsorption of glucose in the kidney, increase glucose excretion, and lower blood glucose levels.(shown in fig.7). Inhibition of SGLT2 leads to the decrease in blood glucose level due to increase in renal glucose excretion. The mechanism of action of this class of drugs are control glucose by increasing insulin sensitivity and uptake of glucose in the muscle cells decreases gluconeogenesis and increase first phase insulin release from the beta cells.[35]

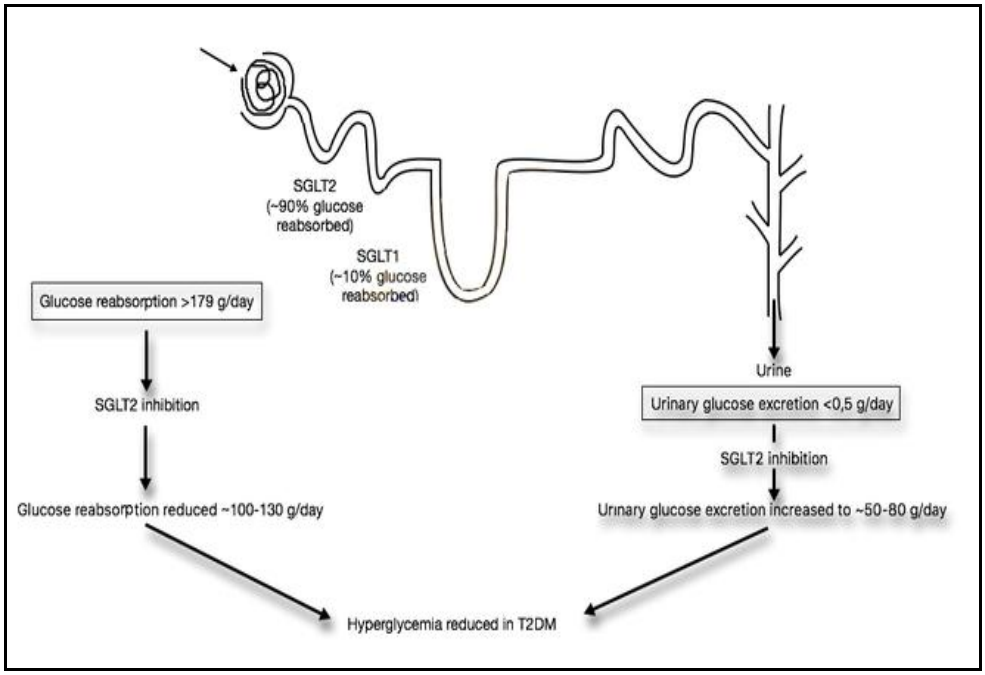

Fig. no. 7 Reabsorption of glucose in nephron.

Beneficial effects of SGLT2 inhibitors in clinical and preclinical studies

SGLT2 inhibitor therapy to treat type 2 diabetes mellitus unexpectedly it reduced all causes mortality and hospitalization for heart failure by ~30% and decreases the risk of cardiovascular death. If the patient have atherosclerosis, chronic kidney disease or heart failure most preferntial the SGLT2i. There are various beneficial effect of SGLT2 inhibitor that are: lowers the blood pressure, increase diuresis or natriuresis, improvecardiac energy metabolism, prevent inflammation, weight loss, improved glucose control. The action of SGLT2 inhibitor on renal excretion of glucose and is independent of the insulin action. The action of SGLT2i reduces hypoglycemia and liver disease adverse effects, of older drugs. The newer class of antihyperglycemic medications have beneficial effects.(shown in fig.7).

Hemoglobin A1c Levels: The drugs such as Canagliflozin, dapagliflozin, and empagliflozin reduces hemoglobin A1c (HbA1c) levels. Inagaki and his colleagues found the significant reductions in HbA1c and weight gain is > 100 mg canagliflozin compared with thatplacebo when used for the 12 weeks. In the study where 2.5mg, 5mg and 10mg dapagliflozin was compared with the placebo, mean HbA1c change from baseline was 0.23% with placebo; -0.58% at 2.5 mg; -0.77% at 5 mg; and -0.89% at 10 mg. Empagliflozin was more effective for reducing HbA1c levels than sitagliptin. When patients were treated with 10mg empagliflozin, 25mg empagliflozinand sitagliptin, HbA1c levels decreased 1.44%, 1.43% and 1.04% respectively.

Cholesterol: SGLT 2 inhibitors have beneficial effect to reduced vascular disease risk factors. The study by Hayashi and his colleagues found dapagliflozin decreases harmful atherogenic small, low-density lipoprotein-cholesterol (LDL-C), increases the less atherogenic large, buoyant LDL-C and increase high-density, lipoprotein-2 cholesterol (HDL-2C). Empagliflozin can cause a small dose-dependent increase in HDL-C and LDL-C.Although there is increase in serum LDL-C level., empagliflozin induces the decreasing intestinal absorption of cholesterol, thus promoting fecal excretion of LDL-C and macrophage-derived cholesterol.

Weight Loss: The study by Weber and his colleagues found the SGLT2 inhibitor dapagloflozin leads to a reduction in body weight from 1.0 kg -0.3 kg compared with placebo. Cefalu and his colleagues found the daily prescribing of 100 mg or 300 mg of canagliflozin evidenced dose-dependent loss of weight. Neel and his colleagues found that

empagliflozin utilization results less adiposity indices in 3,300 subjects. The beneficial effect of SGLT2I given in (fig. no. 8).[49]

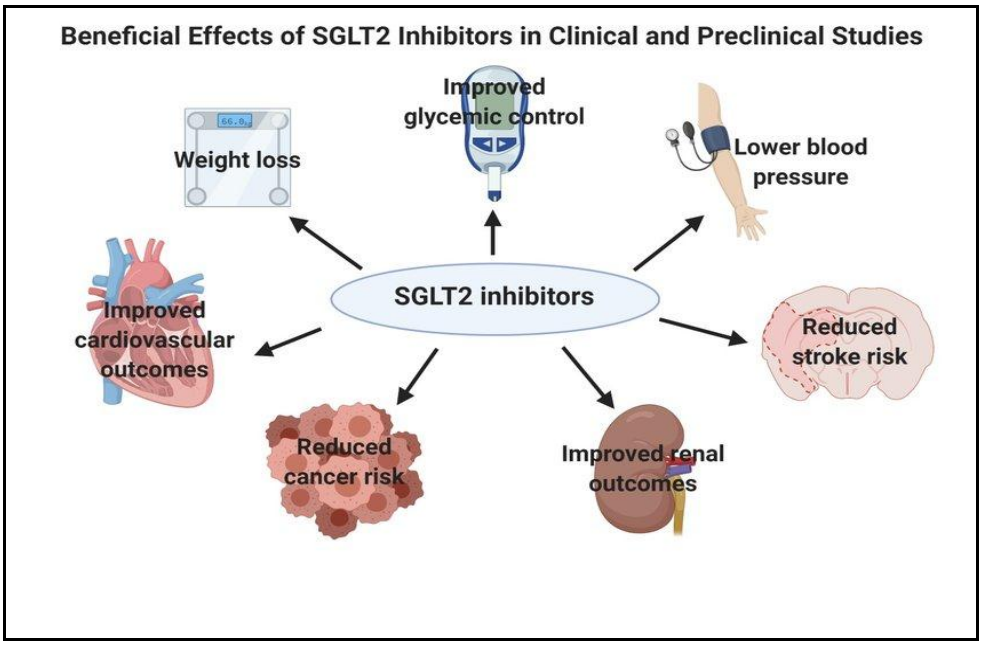

Fig. no. 8 beneficial effect of SGLT2 inhibitors.

RISKS factor of SGLT2i

There are various adverse effects or factors of the SGLT2I such as nausea, vomiting, fatigue, polyuria, polydipsia and xerostomia. The use of SGLT2 inhibitors can induce other more serious adverse effect. Increased Risk for Amputations the Canagliflozin Cardiovascular Assessment Study (CANVAS) and the Canagliflozin Cardiovascular Assessment Study-Renal (CANVAS-R) documented that canagliflozin doubled the incidence of leg and foot amputations in research participants compared with placebo (6.3 vs 3.4 per 1,000 patient-years). Therefore, canagliflozin should be prescribed with caution in persons with prior history of foot ulceration, neuropathy, or vascular diseases. Acute Renal Injury is the mechanism of kidney damage by SGLT2 inhibitor drugs is not completely understood. About in 100 patients observed kidney failure after the intake of SGLT2 inhibitor drugs. Among them, more than half reported symptom onset within a month of starting the medication and their symptoms improved after the discontinuing the SGLT2 medication. As result, the FDA issued a warning to monitor kidney function before initiating and during such pharmacotherapy.

Ketoacidosis: SGLT2I leads to elevated ketone body levels and glycemic ketoacidosis however, this risk reportedly is negligible. Use of SGLT2 inhibitors is not recommended for

the patients evidencing the presence of precipitating factors like acute gastroenteritis and insulin pump failure. Genitourinary Infections About 10% - 15% of women taking SGLT2 inhibitor medications developed urinary tract infections and vulvovaginitis. This is because of glycosuria effect caused by SGLT2 inhibitors.

Hypotension Sodium: The glucose co-transporter 2 inhibitors causes contraction of intravascular volume therefore, patients taking SGLT2 inhibitors are the risk for hypotension, caused dizziness and potentially dangerous falls. When patients already taking volume-depleting medications such as diuretics, then advised in the patients for use of this groups of medications with precaution and report there adverse effects.

Bone Fractures - In a clinical trial revealed that SGLT2 inhibitors such as canagliflozin, decrease bone mineral density and leading to bone fractures. Bone fractures occurred in about 1.5% of cases of patients taking 100 mg and 300 mg of canagliflozin as compared with 1.1% fracture rate among the placebo group.[49] Risk factors with beneficial factors (shows bellow in fig.9).[45]

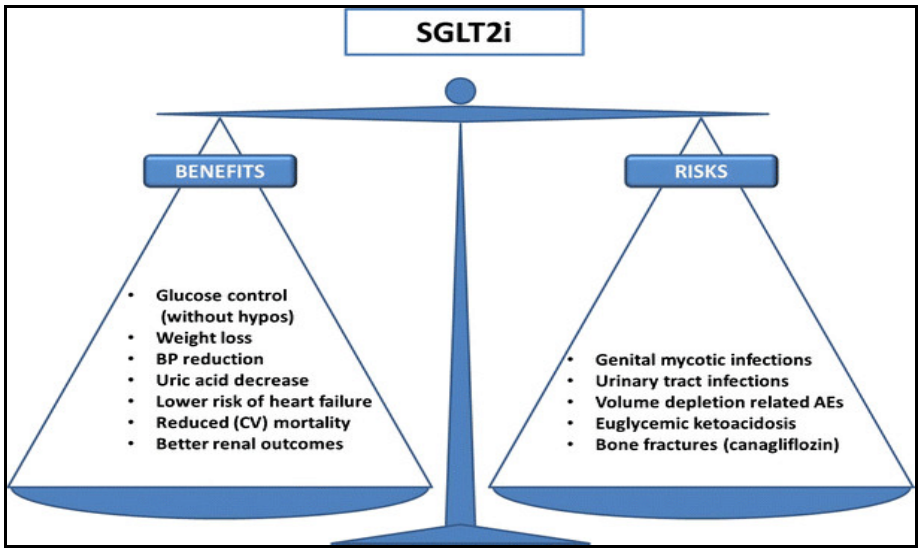

Fig. no. 9: Risk factors with beneficial factors of SGLT2 inhibitors.

Role of SGLT 2 inhibitors in current clinical practice

In January 2015 issue of Diabetes Care, ADA as well as EASD given the update of 2012 ADA guidelines regarding the use of SGLT2i. Metformin still remains drug of choice for mono therapy in type 2 diabetes, but SGLT2i can be given as a second or third line drug for type 2 diabetes. SGLT2I can be added to metformin or sulfonylurea drugs with metformin if glycemic goals are not met. Trials have also shows the combination of SGLT-2 inhibitors and

dipeptidyl peptidase inhibitors produces a good reduction in HbA1c. There is also propensity to use SGLT-2 inhibitors along with insulin in both type 1 and type 2 diabetes Mellitus.[50]

Current drugs in the market

Recently, the FDA approved several types of SGLT2 inhibitors, such as canagliflozin, empagliflozin, dapagliflozin and ertugliflozin. The treatment with these drugs should be accompanied by improved diet and exercise regimen to reduce the blood sugar levels in Type 2 diabetes patients. These medicines are available as a single therapy and also in combination therapy with other anti-diabetic agents such as metformin.

1. Canagliflozin: A division of Johnson & Johnson, licensed for marketing the first FDA-approved SGLT2 inhibitor is canagliflozin which was approved in 2013. This drug is categorized under the gliflozin class, the mechanism of action is based on the inhibition of glucose reuptake inside the proximal convoluted tubules of the kidneys. In extensive placebo-controlled trials, canagliflozin dose of 100 and 300 mg/day were evaluated as a single therapy and in combination therapy with other anti-diabetic agents. both doses of canagliflozin caused significant declines in HbA1c from the baseline relative to the placebo when used in a single therapy and combinations with sulfonylureas, metformin, metformin and pioglitazone and insulin. When used as a single therapy, there is reductions from the HbA1c baseline at a dose of 100 and 300 mg were 0.91 and 1.16, Treatment with canagliflozin and other SGLT-2 inhibitors have a some adverse effects, such as elevation in thirst, urination and LDL cholesterol, episodes of low blood pressure and the increased occurrence of urogenital infections. Therefore, canagliflozin is contraindicated in people with renal insufficiency, decreased glomerular filtration rate (GFR) or kidney problems.

The FDA has additional concerns about the cardiovascular safety of canagliflozin. More cardiovascular events are observed in canagliflozin-receiving patients (0.45%) during the initial 30 days of study compared to those in placebo-receiving patients (0.07%), suggested the increased cardiovascular risk during the early treatment period. further subjects receive canagliflozin appeared to have an increased the risk of stroke, this risk was not statistically significant. The FDA issued a warning in May 2015 canagliflozin and other certain SGLT2 inhibitors induce the development of ketoacidosis. In September 2015, the FDA also issued a drug safety communication for canagliflozin stating that decreased bone density can occurand results is risks of bone fracture. This fact was already included in the adverse reactions of

these drug and had been provided to health care professionals and patients to immediately report any fractures that occurred during therapy.

2. Empagliflozin: The Boehringer Ingelheim and Eli Lilly Company together developed empagliflozin that is another SGLT2 inhibitor belonging to the gliflozin class this drug was approved in 2014. Empagliflozin contains a C-glucoside with similar to the phlorizin (the glycone and aglycone part linked by a C-C bond for ensuring efficient oral administration and the bypassing of GIT degradation). In addition, these drug is more selective for SGLT2 and it have only few adverse reactions on the GIT.

According to the statistical data obtained from about the empagliflozin combination studies,a marked decreased in systolic blood pressure (SBP) and body weight was observed as compared to the placebo treatment. There are different combinations therapy such as metformin, metformin plus sulfonylurea, pioglitazone, were included in these combination studies. When empagliflozin with or without metformin at dose of 10 or 25 mg were included in a multidose regimen of insulin, it shows a marked loss in body weight and a decrease in SBP. However, in these combination studies, empagliflozin was linked to a minor elevation in LDL-C and HDL-C level. The post-marketing clinical trial "EMPA-REG OUTCOME" released in Aug 2015 and in Jan 2019 that indicated the inclusion of empagliflozin in standard care can reduce the risk of stroke, myocardial infarction, and cardiovascular death. Urogenital infections were the common adverse reactions found with the use of empagliflozin in the treatment of Diabetes mellitus.

3. Dapagliflozin: This is the member of the gliflozin class and which is used to treat Type 2 diabetes was developed by Bristol-Myers Squibb under the trade names Farxiga™ and Forxiga™. Initially, in July 2011, the FDA rejected the approval due to low data availability, and later, on January 8, 2014, the FDA approved dapagliflozin for glycemic control in diabetes patients, along with diet and exercise. In the October 2014, FDA also approved a combination therapy of dapagliflozin and metformin hydrochloride (Xigduo™).

There are some adverse effects associated with the treatment of dapagliflozin that are heavy glycosuria, which may be up to 70g/day, tiredness with rapid weight loss and an increased risk of diabetic ketoacidosis (DKA). Existing infections due to diabetes, mostly urinary tract infections and candidiasis, Canagliflozin, empagliflozin, dapagliflozin and ertugliflozin are now on the market in the US and EU. Ipragliflozin, tofogliflozin, and luseogliflozin drugs

approved in Japan as the first national approval granted in the world. Other drug candidates such as sotagliflozin had successfully completed the phase III clinical trial, but in early 2019, it was rejected as an adjunct to insulin for type 1 diabetes mellitus. In addition, various drugs combinations containing SGLT2 inhibitors along with the other oral antidiabetic agents are currently in clinical development and are being tested in clinical trials.[40]

4. Ertugliflozin: The Phase III study of ertugliflozin conducted by Merck in partnership with Pfizer met the initial endpoints for the development of oral SGLT2 inhibitor in treatment of type 2 diabetes mellitus. When compared to placebo, significant HbA1C reduction of 0.69% and 0.76% observed using a doses of 5 and 15 mg, respectively. Researchers also observed ertugliflozin give in combination with sitagliptin reduces the HbA1C to less than 7.0% compared to that of ertugliflozin or sitagliptin administrated individually. In 2017, ertugliflozin (Steglatro) approved from the FDA. There are some SGLT2I given in combination with other anti-diabetics with trade name (shown intable 4).[48]

Table No. 4: SGLT2I In Combination With Other Anti-Diabetes Agents.

Combination of SGLT2 inhibitor with other antidiabetes drugs	Trade name
Canagliflozin and Metformin	Invokamet
Dapagliflozin and Metformin extended release	Xiduo XR
Empagliflozin and Linagliptin	Glyxambi
Empagliflozin and Metformin	Synjardy

CONCLUSION

The Diabetes mellitus is major metabolic, chronic disease associated with metabolism. It affects the large proportion of the world population. It is linked to other medical conditions and disorders such as obesity, hypertension, cardiovascular diseases, and atherosclerosis. In most cases, the Diabetes mellitus management period includes the entire lifespan of a diabetic person, requiring a multidisciplinary approaches that involves lifestyle changes, medical treatments such as antidiabetic therapies. In this article cover the all published information on SGLTs as targets for Diabetes treatment and the compounds with inhibitory activity against the SGLTs, including current drugs in clinical development. In this review, a systematic overview of the research published over the last 5 years in the area of SGLT inhibition as an antidiabetic target is provided to serve as a comprehensive resource for the scientific community.

ACKNOWLEDGMENT

The authors would like to express since gratitude to the management of Late Bhagirathi Yashwantrao Pathrikar College of Pharmacy for their continuous support and encouragement in this work.

REFERENCES

1. Tipton MC. Susruta of India, an unrecognized contributor to the history of exercise physiology. J Appl Physiol, 2008; 108: 1553–6.
2. The History of Diabetes. From Ritu Lakhtakiya 3rd JUN 13.369.
3. Dobson M. Experiments and observations on the urine in diabetes. Med Obs Inq, 1776; 5: 298–316.
4. MacCracken J, Hoel D. From ants to analogues: Puzzles and promises in diabetes management. Postgrad Med, 1997; 101: 138–40. 143–5, 149–50.
5. Sakula A. Paul Langerhans (1847–1888): a centenary tribute. J R Soc Med, 1988; 81: 414–5.
6. Schafer E. An introduction to the study of the endocrine glands and internal secretions. Palo Alto, California: Stanford University, 1914; P. 84.p. 86.
7. Von Mehring J, Minkowski O. Diabetes mellitus Pancreas extirpation. Arch Exp Pathos Pharmacology, 1890; 26: 371–87.
8. Banting FG, Best CH, Collip JB, Campbell WR, Fletcher AA. Pancreatic extracts in the treatment of diabetes mellitus: preliminary report. CMAJ, 1922; 12: 141–6.
9. MERICAN Diabetes Association .diagnosis and classification of diabetes mellitus. Diabetes Care, 2014; 37Suppl 1: S81-S90.
10. Deborah, W. and Ncrna, R. (2019) Insulin Charts. Written by Heather Grey—Updated on March 4, 2019. https: //www.healthline.com/health/type-2-diabetes/insulin-chart.
11. Villa, C., Pan, D., Zaitsev, S., Cines, D., Siegel, D.andMuzykantov, V. (2015) Delivery od Drugs Bound to Erythrocytes: New Avenues for an Old Intravascular Carrier. Therapeutic Delivery, 6: 795-826. https: //doi.org/10.4155/tde.15.34.
12. Maria J. Meneses, Branca M. Silva, Antidiabetes Drugs: Mechanism of action and Potential outcomes on cellular metabolism. Current pharmaceutical Design, 2015; vol. 21, No. 25 3607.
13. Furqan UI Haq, AbuzarSiraj, Tanveer Hamid. Comparative review of drugs used in Diabetes mellitus- new and old. Journal of diabetes mellitus Vol. 11 No. 4, November 2021.

14. Tao, L., Vikas, B. and Matthew, S. (2021) first Aid for the USMLE Step 1 2021. 31st Edition, MCgraw- Hill Education, New York, 352-353.
15. Mcfarthing, Larson, D. and Simuni, T. (2020) Clinical Trail Highlits- GLP-1Agonist, Journal of Parkinsons Disease, 10: 355-368. https: //doi.org/10.3233/JPD-200002.
16. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastrienterology, 2007; 132: 2131-57.
17. Bell, D. S., O'Keefe, J. H. and Jellinge, P. (2008) Postprandial Dysmetabolism: The Missing Link between Diabetes and Cardiovasculat Events? Endocrine Practice, 14: 112-124.
18. Ceppa, E. P., Ceppa, D. P., Omotosho, P. A., D ickerson 2nd., J. A., Park, C. W. and Portenier , D. D. (2012) Algorithm to Daignose Etiology of Hypoglycemia after Rouxen-Y Gastric Bypass for Morbid Obesity: Case Series and Review of the Literature . Surgery for the Obesity and related Disease, 8, 641-647. 2011. 08. 008.
19. Reuser, A. J. and Wisselaar, H. A. (1994) An Evaluation of the Potential Side Effects of Alpha-Glucosidase Inhibitors Used for the Management of Diabetes Mellitus. European Journal of Clinical Investigation, 24: 19-24. https: //doi.org/10.1111/j.1365-2362.1994.tb02251.x.
20. Ahren, B. (2009) Clinical Results of Treating type 2 Diabetes Patients with Sitagliptin, Vildagliptin or Saxagliptin-Diabetes Control and Potential Adverse Events. Best Practice and Research Clinical Endocrinology and Metabolism, 23: 487-498.
21. Thornberry, N. A. and Gallwitz, B. (2009) Mechanism of action of inhibitors of DPP-4. Best Practice and Research Clinical Endocrinology and Metabolism, 23: 479-486. https: //doi.org/10.1016/j.beem.2009.03.004.
22. TominagaM, Igarashi M, Diamon M, et al. Thiazolidinediones (AD – 4833 and CS – 045) improve hepatic insulin resistance in streptozotocin- induced diabetic rats. Endocr J, 1993; 40: 343-9.
23. Gitlin N, Julie NL, Spurr CL, et al. Two cases of severe clinical and histological hepatotoxic associated with troglitazone. Ann In- term Med, 1998; 129: 36-38.
24. Ahmadian M, Suh JM, H ah N, et al. PPAR gamma signling and metabolism; the good, the bad and future. Nat Med, 2013; 19: 557-66.
25. R.W. Nesto, D. Bell, R. O. Bonow, V. Fonseca, S. M. Grundy, E. S. Horton, M. L. Winter, D. Porte, C.F. Semenkovich, S. Smith, L. H. Young and R. Kahn, Circulation, 2009; 108: 2941-2948.

26. Standl, E., Schernthaner, G., Rybka, J., Hanefeld, M., Raptis, S. A. and Naitch, L. (2001) Improved Glycaemic control with Miglitol in Inadequately- controlled Type 2 Diabetes. Diabetes Research and clinical practices, 51: 205- 213.
27. Chasis H, Jolliffe N, Smith HW: The action of phlorizin on the excretion of glucose, xylose, sucrose, creatinine and urea by man. J Clin Invest, 1933; 12: 1083–1090. 10.1172/JCI100559.
28. Rossetti L, Smith D, Shulman GI, Papachristou D, DeFronzo RA: Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest, 79: 1510–1515, 1987. 10.1172/JCI112981.
29. Grempler R., Thomas L., Eckhardt M., Himmelsbach F., Sauer A., Sharp D.E., Bakker R.A., Mark M., Klein T., Eickelmann P. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: Characterisation and comparison with other SGLT-2 inhibitors. Diabetes Obes. Metab, 2012; 14: 83–90.
30. R. K. Crane, D. Miller and I. Bihler, in Membrane transport and metabolism, ed. A. Kleinzeller and A. Kotyk, Academic Press, New York, 1961; pp. 439–449.
31. (a) OMIM182380, Solute carrier family-5 (sodium/glucose cotransporter), member1, SLC5A1, https: //www.omim.org/entry/182380, accessed April, 2019; (b) E. M. Wright and E. Turk, Eur. J. Physiol, 2004; 447: 510–518.
32. J. J. Neumiller, J. R. White and R. K. Campbell, Drugs, 2010; 70: 377–385.
33. (a) OMIM182380, Solute carrier family-5 (sodium/glucose cotransporter), member1, SLC5A1, https: //www.omim.org/entry/182380, accessed April, 2019; (b) E. M. Wright and E. Turk, Eur. J. Physiol, 2004; 447: 510–518.
    (c) A. Diez-Sampedro, B. A. Hirayama, C. Osswald, V. Gorboulev, K. Baumgarten, C. Volk, E. M. Wright and H. Koepsell, Proc. Natl. Acad. Sci. U. S. A, 2003; 100: 11753–11758.
34. Ernest M wright,Donald D Loo A review on Surprising Versatility ofsodium/glucose cotrasporters (SLC5) January 2005.physiology, 19(6): 371-6.
35. David L, Joffe, BSpharm. LDE, FACA SGLT2 inhibitors: A New class of Diabetes medication sep 19, 2018.
36. (a) E. M. Wright, Am. J. Physiol. Renal. Physiol., 2001; 280: F10–F18 (b) E. M. Wright, G. M. Martin and E. Turk, in Familial glucose–galactosemalabsorption and hereditary renal glycosuria, ed. C. R. Scriver, A. L. Beaudet, W. S. Sly and D. Valle, McGrow-Hill, New York, 8th edn, 2001, Metabolic basis of inherited disease, 4891–4908.

37. Ana Diez- Sampedro, BruceA, Hirayana,ChristinaOsswald., VelentinGorboulev glucose sensor hiding in family of transporters sep. 16, 2003.
38. ERNEST M. WRIGHT; Genetic disorder of membrane Transport I.GGM. Physiology Department University of California school of medicine, Los Angles, California 90095-175 G. 879-88039.
39. S. Faham, A. Watanabe, G. M. Besserer, D. Cascio, A. Specht, B. A. Hirayama, E. M. Wright and J. Abramson, Science, 2008; 321: 810–814.
40. Rahul P. Kshirsagar, Abhishek A. Kulkarni, Rashmi S. Chouthe. SGLT inhibitors as antidiabetes agents: a comprehensive review. 9th Jan 2020; 10: 1733-1756.
41. (a) D. D. F. Loo, B. A. Hirayama, A. K. Meinild, G. Chandy, Z. Zeuthen and E. M. Wright, J. Physiol, 1999; 518: 195–202 (b) A. C. Schoolwerth, B. C. Smith and R. M. Culpepper, Miner. Electrolyte Metab, 1988; 14: 347–361.
42. (a) G. A. Quamme and H. J. Freeman, Am. J. Physiol, 1987; 253: F151–F157 (b) A. Mather and C. Pollock, Kidney Int, 2011; 79: S1–S6.
43. H. Rahmoune, P. W. Thompson, J. M. Ward, C. D. Smith, G. Hong and J. Brown, Diabetes, 2005; 54: 3427–3434.
44. NazneenMemon, BHMS. PGDRR. Sarforoj Khan, BHMS PGD, How Do SGLT1 inhibitors work (in capital) Reviewed on.1-12-2022.
45. Andere'J. Scheen1,2,3 - SGLT2 inhibitors: Benifits/Risk Balance Cure Diab Rep., 2016; 16: 92.
46. Jun WU, Veronique Anne Lacombe, Rajesh Balkrishna. Statin medication Adherence and Associated outcomes in type 2 diabetes Medicaid Enrolled with comorbid Hyperlipidemia - Article 2010; 10.
47. Michael A Nauck, Department of Internal medicine, Diabeteszentrum Bad Lauterbery, Germany - Undate on development with SGLT2 inhibitors in management of type 2 diabetes. Drug design and development therapy, 2014; 8: 1337.
48. HaroonJakher, T. Chang, K. Mahaffey Canagliflozin review - safety and efficacy profile in patients with T2DM. 1 Feb 2019.
49. Shanti Pittampalli, MD; SatyaUpadyadyla, DmD; HemaMadhuriMekala: The Risks vsBenifits for SGLT2 inhibitors Medications. July 2018. FEDERA PRACTITIONER, 45-47.
50. PV Shij, AV Raveendran, PV Bhargavan. Review article SGLT2 inhibitors; A New Therapeutic Target and it is it's Role in current clinical practices, BMH medical journal, 2015; 2(4): 97-101.