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A Systematic Review On Synthesis Of Empagliflozin & Treatment Of Oral Hypoglycemic Drug

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Abstract:

Diabetes mellitus is a common disease affecting 5 and 7 percent of people living in Europe and the United States, respectively, but the prevalence of the disease may be between 20 and 25 percent in immigrants from South Asia. In Type 2 diabetes, multiple defects in insulin action and insulin secretio cause hyperglycemia and insulin effect on glucose absorption in skeletal muscle and adipose tissue, glucose urinary excretion, and glucose reabsorption in the kidneys. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are any type of drug for the treatment of type 2 diabetes. The drug's glucose reduction effect is independent of insulin. Empagliflozin can increase the diuretic activity of Amiloride. In the -C series, Cyclohexane Analogue 7 showed only moderate inhibition of SGLT2 and selective inhibition. Empiraglifloz can increase insulin resistance and cell function. The Drug's pharmacodynamic effects are independent of the insulin. In this paper, we summarize the current literature on the use of sodium-glucose cotransferer 2 inhibitors as a new treatment for diabetes.

Keywords: Empagliflozin, SGLT2 inhibitors, Type 2 diabetes, Kidneys, Insulin

Introduction:

The oral antidiabetic drugs are agents for the treatment of patients with type diabetes (non-insulin-dependent) mellitus. Type 2 diabetes mellitus (Type 2 DM) is a common disease affecting 5 and 7 percent of people living in Europe and the United States, respectively, but the prevalence of the disease may be between 20 and 25 percent in immigrants from South Asia. Type 2 diabetes mellitus is a heterogeneous disease with factors contributing to genetic and environmental factors. In Diabetes Mellitus, multiple defects in insulin action and insulin secretion cause hyperglycemia, and insulin effect on glucose absorption in skeletal muscle and adipose tissue, glucose production in the liver and kidney, and lipolysis in adipose tissue is impaired.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are any type of drug for the treatment of type 2 diabetes. Sodium glucose-transporter mediates the glucose reabsorption in the kidney. About 90% of the renal glucose reabsorption occurs in the first segment of the proximal tube and is mediated by SGLT2, a high-capacity low-affinity transporter, while the remaining 10% is eliminated in the diaphragm via SGLT1, a high-affinity low-capacity transporter. Since the inhibition of SGLT2 occurs through an insulin-independent mechanism, the risk of hypoglycemia is low.

Generic name: empagliflozin

Brand name: Jardiance

Dosage form: oral tablet (10 mg; 25 mg)

Drug class: SGLT-2 inhibitors

Side effects:

- Dehydration
- Skin rash
- Low blood sugar
- High cholesterol
- Increased urination
- Urinary tract infection
- Thirst

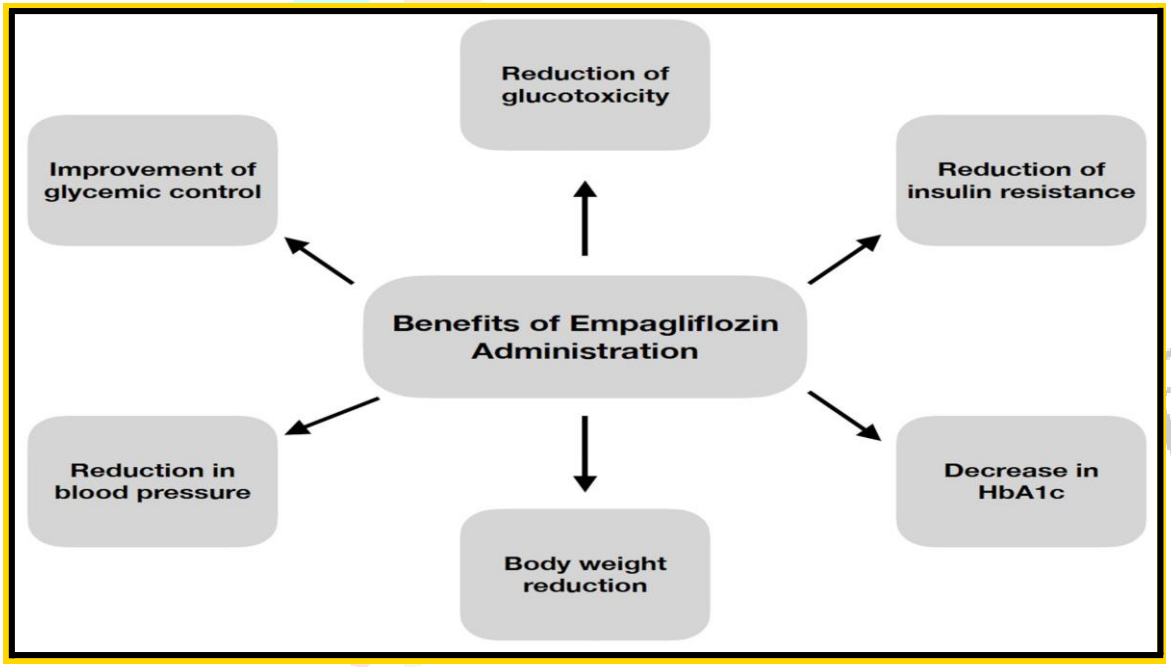

Fig.1 Benifits of Empagliflozin

Structure:

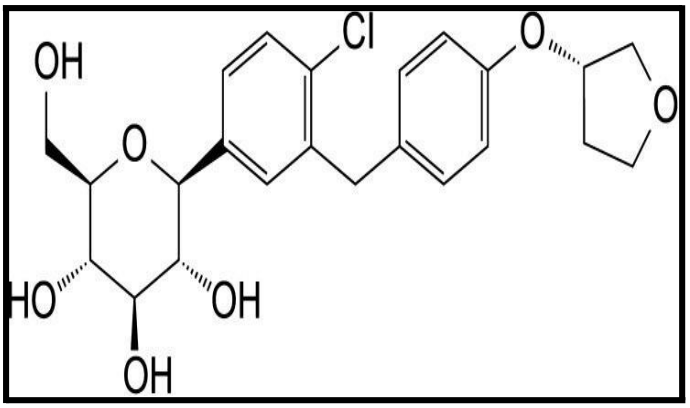

Fig.2 Structure of Empagliflozin

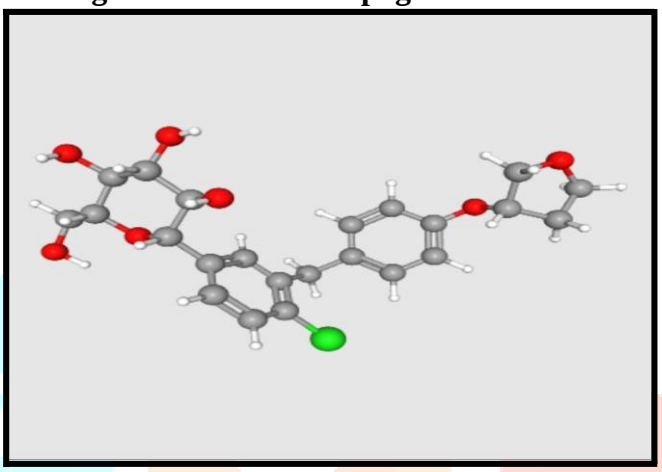

Fig.3 3D Structure of Empagliflozin

Physical-chemical properties:

- IUPAC name:

(2S,3R,4R,5S,6R)-2-[4-Chloro-3-[[4-[(3S)-oxolan-3-yl]oxyphenyl]methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol

- Hydrogen bond acceptors - 6
- Chemical Formula -$C_{23}H_{27}ClO_7$
- Molar mass - 450.91 g·mol−1
- Colour - yellow, white to off-white powder
- Shape - round, oval
- Boiling point - 664.5°C at 760 mmHg
- Melting point -151-153°C
- Density -1.4g/cm3
- Solubility - It is very slightly soluble in water, slightly soluble in acetonitrile and ethanol, rarely soluble in methanol, and practically soluble in toluene.

Treatment:

Empagliflozin is used to treat type 2 diabetes. It works in the feathers to help the immersion of glucose(blood sugar). This helps lower the blood sugar position. Empagliflozin doesn't help cases who have insulin-dependent or type 1 diabetes. Type 1 diabetic cases must use insulin injections.

Empagliflozin is also used to reduce the risk of heart disease in patients with type 2 diabetes and heart or blood vessels. This medicine is also used to reduce the risk of heart failure and heart failure in patients whose heart cannot supply enough blood to other parts of the body.

Structure-activity relationship:

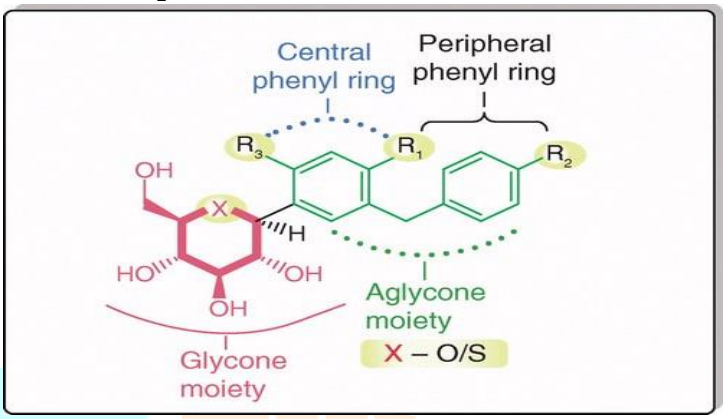

Fig.4 General structure of Empagliflozin

study A cell 14C--methyl-D-glucopyranoside (14C-AMG) absorption test was used to evaluate the inhibitory activity of SGLT2/SGLT1 in our carboxyl phenol analogy.

In general, the -C series is more active than the -C series, suggesting that the configuration of C-1 is essential for inhibitory activity.

However, in the -C series, Cyclohexane Analogue 7 showed only moderate inhibition of SGLT2 and selective inhibition of SGLT2/SGLT1; Cyclohexane Analogue 8 showed nanomolar inhibition of SGLT2 and selective inhibition of SGLT2/SGLT1.

The excellent capability and selectivity of SGLT2 and the improved stability of 8 due to its dual C-C connection suggest that it is a highly promising lead compound as a clinically useful SGLT2 inhibitor.

Synthesis:

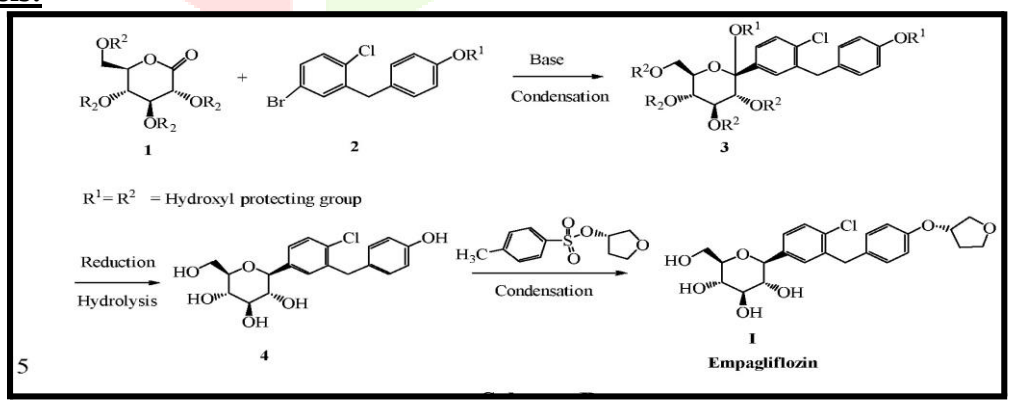

Fig.5 Synthesis of Empagliflozing

General method of preparation :

Empagliflozin film coating tablets are prepared with a wet granulation technique.

Preparation of granules :

All ingredients have been carefully measured as shown in Table 4. Empagliflozin, lactose monohydrate, and microcrystalline cellulose were sifted with sieve no. 30. The binding solution was prepared for 30 minutes by stirring the mixture of hydroxypropyl cellulose with a 20% w/vcleanwater using a mechanical mixer (Remi

Electrotechnik Ltd.).The sifted mass was placed in a fast mixer granulator (Sams Techno Mesh Pvt. Ltd.) and mixed for 15 minutes at a speed of 100 rpm. The addition of the binder solution was carried out in the next 5 min at the same speed. Then Kneading was performed for 5 min at the impeller speed of

100 rpm and chopper speed of 2100 rpm. These wet granules were dried in a fast dryer (Pharma Fab Engineers)until the moisture content of the granules reaches 1%. The dried grains were passed through sieve no. 30. The retained hard granules are milled in the QuadroR Co-mill(QuadroEngineering)to obtain uniform granules that can pass through sieves.30. These uniform granules were mixed with extragranular parts(previously passed through sieve number).30)with the exception of mg stearate in the cage blender (Pharma Fab Engineers) for 30 min at 12 rpm. Then, the lubricated granules with magnesium stearate are mixed into a blender at 12 rpm for 5 min.

Preparation of tablets

Lubricated grains were poured into hoppersinforming holes and compacted using upper and lower punches with Tablet press® (Pharma Tools) to obtain core tablets. The coating solution was prepared by mixing OPADRY yellow mixture with purified water. This coating was sprayed onto the core table to obtain uniform coating using the Gansons automatic tablet coating machine.

Fig.6 Powder of Empagliflozin

Mechanism of action:

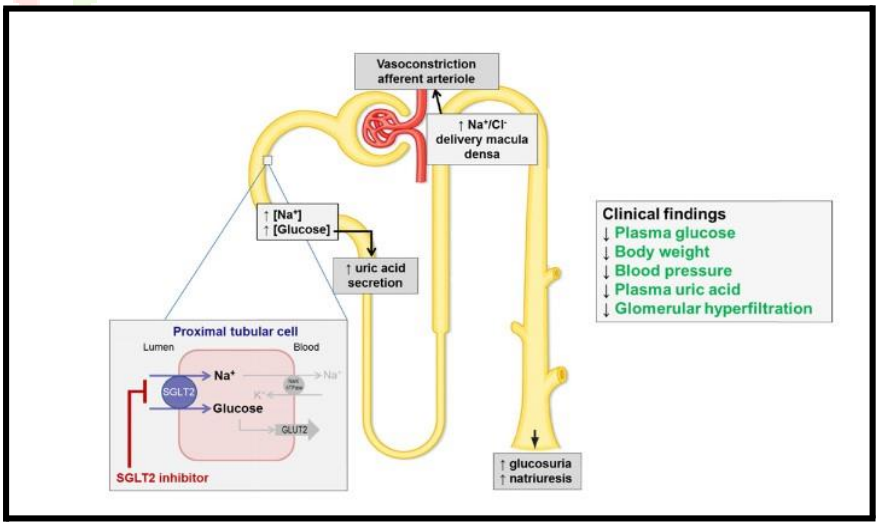

Fig.7 MOA of Empagliflozin

Empagliflozin works by inhibiting the sodium-glucose co-transporter-2 (SGLT-2) present in the proximal tubules of the kidneys. Through SGLT2 inhibition, empagliflozin reduces glucose reabsorption in the kidneys and increases glucose urinary excretion. The Drug's glucose reduction effect is independent of insulin. In type 2 diabetes patients, urinary glucose excretion increased by about 64 grams per day with 10 mg of Empagliflozin and 78 grams per day with 25 mg. Empagliflozin reduces the sodium and volume load, causing intravascular contraction due to its diuretic and natriuretic properties. In addition, empagliflozin is associated with weight loss, with blood pressure reduction without increasing heart rate. **Pharmacological properties:**

pharmacodynamic:

Empagliflozin Reduces Blood glucose levels by preventing glucose reabsorption in the kidneys and thus increasing the amount of glucose excreted in the urine. It has a relatively long duration of action requiring only a dose once a day. Patients should be carefully monitored for signs and symptoms of ketoacidosis regardless of blood glucose level since empagliflozin can cause diabetic ketoacidosis in the absence of hyperglycemia. As its mechanism of action depends on renal glucose excretion, empagliflozin can be retained in case of acute kidney injury and/or discontinued in patients with chronic kidney disease. Over-excessive glucose intake Creates a sugar-rich urogenital environment, which increases the risk of urogenital infection in both male and female patients - closely monitor the signs and symptoms of infection development.

Pharmacokinetic:

- Absorption - After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours.
- Distribution - Apparent steady-state volume distribution is estimated to be 73.8 L based on population pharmacokinetic analysis.
- Metabolism - The primary route of metabolism in humans is glucuronidation.
- Elimination - Expelled in feces or urine.

Preclinical safety data:

Non-clinical data do not show any particular hazard to humans based on conventional studies on safety pharmacology, genetic toxicity, fertility, and early embryonic development.

Empagliflozin is not genotoxic. In a two-year study on carcinogenicity, empagliflozin did not increase the incidence of tumors in female rats to the maximum dose of 700 mg/kg/day, which corresponds to about 72 times the highest clinical exposure to AU with empagliflozin. In male rats, benign vascular proliferative lesions(hemangiomas) related to the treatment of the mesenteric lymph node were observed at the highest dose, but not at 300 mg/kg/day, which corresponds to about 26 times the maximum clinical exposure to empagliflozin. Interstitial cell tumors in the testicles were observed with a higher incidence in rats with a frequency of 300 mg/kg/day and above, but not 100 mg/kg/day, which corresponds to about 18 times the maximum clinical exposure of empagliflozin. Both Tumors Are common in rats and are unlikely to be related to humans. Empagliflozin did not increase the incidence of tumors in female mice at doses of up to 1000 mg/kg/day, equivalent to about 62 times the maximum clinical exposure of empagliflozin. Empagliflozin induces renal cancer in male mice at 1000mg/kg/day but not at 300 mg/kg/day, which corresponds to approximately 11 times the maximum clinical exposure of empagliflozin. The mechanism of action of these tumors depends on the natural predisposition of male mice to renal pathology andona metabolic pathway that does not reflect humans. Malemouse renal tumors are considered not relevant to humans.

Drug interactions:

Empagliflozin Can Increase the diuretic activity of Amiloride. Aminosalicylic acid can increase the hypoglycemic activity of Empagliflozin. The risk or severity of hypoglycemia may increase when Amiodarone is combined with Empagliflozin. Amitriptyline Can reduce the hypoglycemic activity of Empagliflozin.

Interactions with other medicines:

- Satifloxacin
- Other Sulphonylureas
- Insulin
- Gemfibrozil
- Probenecid
- Medicine used to lower blood pressure (Diuretics)

Resistance:

Empagliflozin significantly improved insulin sensitivity indexes, but did not affect insulin resistance and-cell function. After The end of the drug, all indexes returned to the initial level. The insulin sensitivity index was inversely correlated with the left ventricular mass at baseline.

Precautions:

- Pregnancy
- Breastfeeding
- Alcohol
- Driving

Contraindications:

- Allergy to this medicine
- Serious kidney disease (end-stage renal disease or dialysis

Adverse effects:

- Hypotension
- Ketoacidose
- Acute Kidney Damage in Renal Function
- Urosepsis and Pyelonephritis
- Hypoglycemia with simultaneous use of insulin and secretagogues Insulin
- MycoticGenital Infections
- Increased Low-density lipoprotein cholesterol(LDL-C)

Toxicity:

The most common side effects reported were urinary tract infections, genital mycotic infections, and dyslipidemia. Due to its diuretic properties related to volume depletion, dehydration, hypotension, low oxygenation, and syncope were also reported. The FDA issued a warning for the gangrene Fournier, a type of vascular fasciitis of the perineum. Twelve cases were reported, all twelve of which were hospitalized and needed surgical debridement. If suspected, stop the drug and submit a timely report to the ED for surgical evaluation.

Dosage:

Recommended dose:

Empagliflozin is an oral medication dosed at either 10 mg daily or 25 mg daily. The recommended dose is 10 mg once daily in the morning, taken with or without food. If tolerated initially, dosing may increase up to 25 mg. Correct volume depletion, if present, before starting the drug

Overdose:

- If You think you have taken too much of this drug, seek emergency medical attention.
- this overdose can cause serious problems.
- Moreover, the blood sugar levels can be very low resulting in hypoglycemia.
- It is essential to take food or drinks containing glucose, so have some juice, eat sugar or chocolate immediately, and then go to your doctor.

Uses:

- Empagliflozin is used with appropriate diet and exercise programs to control high blood sugar in people with type 2 diabetes.
- Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems.
- Empagliflozin is also used in patients with type 2 diabetes and heart disease to reduce the risk of death from heart attack sorstrokes.
- Empagliflozin works by increasing the sugar removal of your kidneys.
- Empagliflozin is also used to treat heart failure.
- It Reduces the risk of death due to heart disease and reduces the need to visit a hospital to treat heart failure.
- Empagliflozin works by increasing the removal of sodium by your kidneys.

Conclusion:

Empagliflozin improved insulin sensitivity indexes in patients with a recent coronary event and drug-induced glycemia. These results support the safe use of empagliflozin as the first line of glucose reduction therapy for patients at high cardiovascular risk with recently diagnosed diabetes.

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