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Discovery of Natural SGLT2-Inhibitors for Type 2 Diabetes – Possible Way to Reduce Side Effects

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Abstract

The number of patients diagnosed with diabetes mellitus in all over the world has risen ominously in the past few decades, in which majority of cases belongs to type 2 diabetes. Previously, type 2 diabetes was known as adult-onset and noninsulin-dependent but now it can be seen at any stage including childhood. Various recent researches revealed that type 2 diabetes can be treated by inhibiting sodium-glucose co-transporter 2 (SGLT2), a protein which facilitates glucose reabsorption in the kidney. SGLT2 inhibitors can reduce the blood sugar level by blocking reabsorption of glucose in the kidney and increasing glucose excretion. In the past couple of years, many SGLT2 inhibitors have been discovered but owing to serious side effects, their use are completely banned. Hence, the discovery of natural SGLT2 inhibitors can be helpful in treating type 2 diabetes without any adverse effects.

Keywords: Antihyperglycemic drugs, Dapagliflozin,Insulin, Renal glucose, Sodium-Glucose Co-Transporter 2

Diabetes mellitus is most common lives threatening metabolic disorder, characterized by hyperglycemia, glycosuria, hyperlipidemia, negative nitrogen balance and sometimes by ketonemia. The prevalence of diabetes will be 5.4% by the year 2025, with the global diabetic population reaching to 300 million[2]. Among all the WHO regions, South East Asian region is highest affected with maximum global burden of the disease, and by year 2025 there will be nearly 80 million diabetic in the region. Despite a tremendous development in the field of medical science, diabetes is still challenging, and efforts are continued to conquer it. Management of type-2 diabetes has been revolutionized throughout the past several years which is still a big challenge of the hour because the patients are failing to maintain glucose level in their blood. Although several oral antihyperglycemic drugs are already available including metformin, glimepiride, repaglinide, pioglitazone, sitagliptin and acarbose, but these showed various side effects including weight gain and hypoglycemic stage[1,4]. So, the discovery for new drugs with an improved benefit-risk profile is still in progress.

Recently, the kidney has found to be a therapeutic target to treat type-2 diabetes because of increasing maximal renal glucose reabsorption. Every day, around 180g of glucose is filtered from the glomeruli of a healthy adult, which is reabsorbed from the glomerular filtrate and returned to the circulation. However, almost 90% of filtered glucose is reabsorbed in the bloodstream by the Sodium-Glucose Co-Transporter 2 (SGLT2), located primarily in the luminal membrane of the proximal renal tubules[3]. The co-transportation of sodium and glucose is driven by the active transport of sodium out of the basolateral cells by the Na/K-ATPase pump.

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Various studies confirmed that upregulation of SGLT2 increased renal glucose handling and transport in type-2 diabetes. Therefore, the reabsorption of filtered glucose as well as blood glucose concentration can be reduced by inhibiting SGLT2.

SGLT2 inhibitors can be reduced the reabsorption of filtered glucose as well as blood glucose concentration. This approach could be helpful in the management of type-2 diabetes by increasing urinary glucose excretion independently of insulin secretion or sensitization. The approach to investigate SGLT2 inhibitors from natural sources is although new but synthetic inhibitors are already studied in recent years. The research is being conducting with many SGLT2 inhibitors which are mostly synthetic in nature. A randomized clinical trial showed that a number of SGLT2 inhibitors caused adverse effects and the difference in HbA1c levels was found insignificant when compared to placebo group[5].

To date, only very few SGLT2 inhibitors such as dapagliflozin, canagliflozin and empagliflozin are known. However, dapagliflozin was refused by FDA due to possible cause of genital and urinary tract infections and bladder and breast cancer, whereas canagliflozin and empagliflozin are under clinical trial[6]. Therefore, a need of discovery of natural SGLT2 inhibitors to treat type-2 diabetes is the demand of the hour.

Nowadays, a variety of antidiabetic drugs are available with different chemistry and mechanism of action. These drugs either improve insulin sensitivity or enhance its secretion, and are associated to weight gain and hypoglycemia. Thus, the discovery of natural SGLT2 inhibitors, with novel mechanism which is independent of insulin secretion or sensitization, can be helpful in treating type 2 diabetes without any side effects.

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