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AN ENZOINFORMATICS STUDY ON SGLT2 INHIBITORS AS DUAL THERAPEUTIC AGENTS AGAINST DIABETES AND ALZHEIMER'S DIASEASE

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ABSTRACT : Alzheimer's disease (AD) is an escalating nervous disorder, and its link with diabetes mellitus (DM) has amplified its complexities several folds. Thus, simultaneous targeting of both associated maladies with a single drug is quite promising. This study evaluates newer anti-DM belonging to the class of Sodium Glucose Co-transporters 2 (SGLT2) for potential anti-AD properties. The screening for the potential pose properties of natural SGLT2 inhibitors (acerogenin B, formononetin, (-)-kurarinone, (+)-pteryxin, quinidine) with AD targets (acetylcholinesterase, beta-secretase and glycogen synthase kinase 3 beta) was done by computer aided docking study. The results of the study indicated that acerogenin B indicated superior binding with nearly all AD targets in comparison to other SGLT2 inhibitors. Acerogenin B binding affinity towards the kinase domain of glycogen synthase kinase 3 beta was even better than positive control 6-Bromoindirubin-32 -oxime. The study concluded SGLT2 inhibitors based platforms could be considered as potential agents to treat ford dual therapy against DM and AD.

Key words : Alzheimer's disease, diabetes mellitus, enzoinformatics, sodium glucose co-transporters 2, molecular docking.

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INTRODUCTION

Dementia is a common term for loss of memory, analytical skills and other reasoning abilities that significantly affect normal functioning of with daily life. Alzheimer's disease (AD) is the most common cause of dementia that afflicts geriatric population worldwide. World Alzheimer's Report 2018 (https://www.alz.co.uk/research/WorldAlzheimerReport2018.pdf.) indicates around fifty million people suffer from AD and other associated memory impaired ailments with the patient count expected to reach 152 million by end of 2050. AD associative links with other disease like type 2 diabetes mellitus (DM) further complicate the disease condition (Rizvi *et al*, 2015; Caberlotto *et al*, 2019). DM is one of the primary prompting factor for rapid progression of AD, with reports indicating 1.6 times higher risk of AD in such patients (McIntosh *et al*, 2019). DM is highly debilitating disease affecting 425 million people globally with the case count expected to reach 629 million by end of 2045 (https://diabetesatlas.org/IDF_Diabetes_Atlas_8e_interactive_EN/.). Mortality rate is reported to be one in seven seconds with half the death count being in the age group below 60 years. Effective treatment of both these chronic debilitating disorders is a matter of priority to the scientific community globally. Thus, the present research is focused on trying to manage the situation with alternate newer treatment strategies.

Sodium glucose co-transporter 2 (SGLT2) is one of the recently approved (2013) category of antidiabetic drug (https://www.fda.gov/media/87579/download). This class acts in proximal convoluted tubules of kidneys that are responsible for ~90% uptake of filtered glucose. They decrease the reabsorption of glucose regulating the blood glucose levels. Hence are being actively considered for diabetic treatment (Scheen *et al*, 2015; Hsia *et al*, 2017).

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