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Machine Learning Prioritizes the Development of Novel 1,3,5-Triazine-Thiazolidinedione Hybrids as Protective Agent Against Diabetic Nephropathy in Rats via Hypoglycemic Effect and Activating Nrf-2/Ho-1 Pathway

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Objectives : Diabetic nephropathy (DN) is presently the primary cause of end-stage renal disease in the Western world and poses a significant challenge to public health necessitating the development of effective strategies for prevention and treatment. Thiazolidinediones (TZDs) are a group of drugs that decrease insulin resistance in individuals with type 2 diabetes, resulting in decreased blood glucose levels. Furthermore, accumulating evidence indicates that TZDs have many advantageous impacts on DN, extending beyond their influence on glucose management by avoiding renal damage and decreasing urinary albumin excretion. The current investigation aimed to create a new 1,3,5-triazine-thiazolidinedione (TATD) combination using machine learning techniques and assess its effectiveness against Streptozotocin (STZ)-induced diabetic nephropathy in rats.
Methods : We have used the Support Vector Machines machine learning method to perform the quantitative structure-activity relationship (QSAR) study on the various TATD derivatives. After the prioritization, the most active molecule was synthesized and administered to STZ-DN rats in various doses. Numerous biochemical parameters were analyzed, and a western blot study was conducted to determine the effect of TATD on numerous biomarkers.
Results : The currently adopted machine learning model yielded a highly accurate statistical model ($R^2 = 0.842$), and the resulting molecule showed significant hypoglycaemic activity in STZ-DN rats as compared to the control. The level of pro-inflammatory (TNF-α, IL-1β, and IL-6) and BUN, SCr, TC, and TG were also found reduced in a dose-dependent manner. It also reduces LRG1, TGFβ1, ALK1, and VEGF proteins in rat kidneys The western blot analysis suggests that TATD upregulated the expression of Nrf-2 and HO-1 in the DN rats.
Conclusions : The present study is the first to adopt the machine learning approach toward the development of a novel protective agent against DN. The developed compound has a significant clinical benefit against DN owing to its anti-inflammatory and reno-protective effects.