DBT-THSTI study a new way to prevent diabetic complications

New Delhi, Feb 18: Diabetes is one of the leading causes of blindness, renal failure, and nerve damage. The progression of diabetic complications can be prevented by inhibition of aldose reductase. Unused glucose of cells enters the sorbitol–aldose reductase (AR) pathway of glucose metabolism and may result in a reduction of NADPH and oxidized NAD⁺, which are necessary cofactors for other processes of cellular metabolism. The progression of diabetic complications can be prevented by inhibition of AR. Among the AR inhibitors (ARIs), fidarestat is considered highly potent in the suppression of accumulation of erythrocytes sorbitol in diabetic patients.

A team of researchers from DBT-Translational Health Science and Technology Institute (DBT-THSTI), NIPER-Guwahati and CSIR-IICT, Hyderabad conducted a study on the characterization of hitherto unknown in vitro and in vivo metabolites of fidarestat using liquid chromatography-electrospray ionization tandem mass spectrometry (LC/ESI/MS/MS). The group identified 18 metabolites of fidarestat. The main in vitro phase I metabolites of fidarestat are oxidative deamination, oxidative deamination and hydroxylation, reductive defluroniation, and trihydroxylation. Phase II metabolites are methylation, acetylation, glycosylation, cysteamination, and glucuronidation. Aldose reductase activity was determined for oxidative deaminated metabolite (F-1), and it showed an IC50 value of 0.44 μM. The major metabolite, oxidative deaminated, did not show any cytotoxicity in H9C2, HEK, HEPG2, and Panc1 cell lines. However, in silico toxicity prediction results showed toxicity for skin irritation and ocular irritancy SEV/MOD versus MLD/NON (v5.1) model for fidarestat and its all metabolites. The results indicate that that active metabolites of fidarestat may have an advantage as drug themselves. However, detailed studies are needed further to confirm these findings.


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