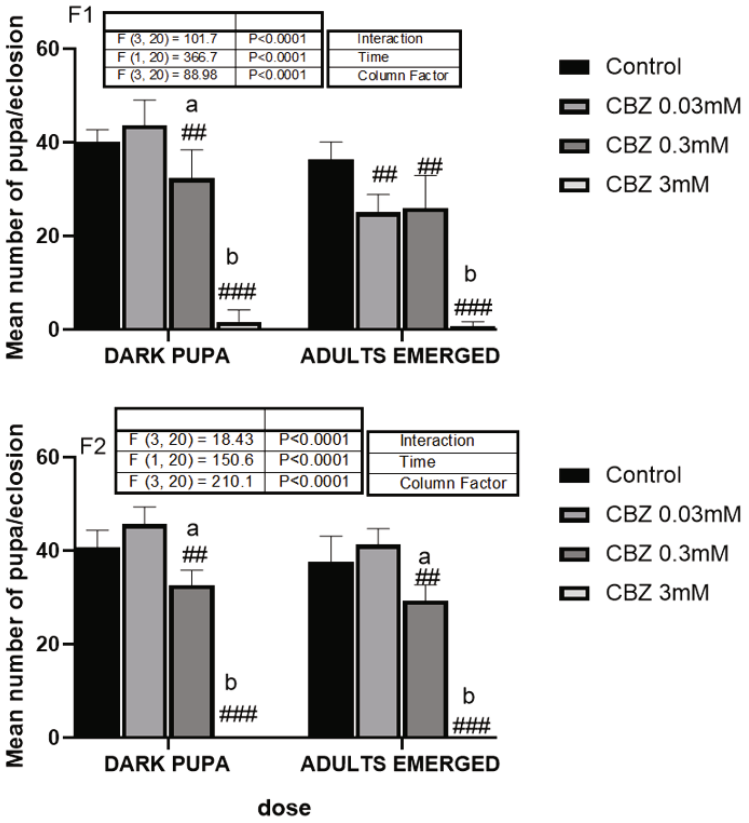

FIGURE 1 Effect of carbamzepine (CBZ) on dark pupa eclosion to adult flies. Values are expressed as mean±SD, ##p<0.01, ###p<0.001 versus vehicle control, [a]p<0.01 versus CBZ 0.03mM, [b]p<0.001 versus CBZ 0.3mM

318 | Cognition-enhancing and neuroprotective potential of steroid sulfatase inhibitors Irosustat and STX140 in a scopolamine-induced Alzheimer's disease rat model

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline and neuroinflammation. As per the World Health Organization, 2025, it is the most common type of dementia among the elderly population, making up approximately 60%–70% of all dementia cases globally [1]. Acetylcholinesterase inhibitors are currently used for Alzheimer's disease treatment; however, these medications are associated with many side effects and limited efficacy. This study evaluates the therapeutic potential of steroid sulfatase (STS) inhibitors, Irosustat and STX140 [2], in a rat model of AD.

Methods

Male Wistar rats (n = 13/group) were divided into five groups: normal control (CMC only), scopolamine [3] (4 mg/kg/day, i.p.), and three treatment groups that received oral donepezil (1 mg/kg), Irosustat (25 mg/kg) or STX140 (15 mg/kg) for 30 days. Open-Field, Elevated Plus Maze, Morris Water Maze (MWM) and Marble Burying tests were among the behavioural evaluations. Cholinergic, inflammatory and oxidative stress markers were measured using biochemical analysis (ELISA). In addition to amyloid beta 1–40 (Aβ-40) and amyloid beta 1–42 (Aβ-42) in brain tissue, immunohistochemical investigations, Western blotting and qPCR were used to assess the expression of genes and proteins linked to AD.

Results

STX140 significantly decreased escape latency (Day 5: 22.3 ± 2.1 s vs. scopolamine: 42.1 ± 3.5 s; P < 0.001) and path length (3.6 ± 0.4 m vs. 6.5 ± 0.6 m; P < 0.01) in the MWM. Irosustat also reduced latency (27.4 ± 2.9 s; P < 0.01). Irosustat extended marble play time in the Marble

Burying Test to 96.2 ± 5.3 s, while the disease group's play time was 45.1 ± 4.8 s (P < 0.001). STX140 increased open-field central activity by 41% (global activity index: 0.52 ± 0.04 vs. 0.37 ± 0.03; P < 0.05), indicating a decrease in anxiety.

Biochemical assays revealed significantly decreased AChE levels in the Irosustat group (4.8 ± 0.6 mU/ml vs. 7.9 ± 0.7 mU/ml in disease; P < 0.01) and reduced MDA levels (1.92 ± 0.17 ng/ml vs. 3.84 ± 0.32 ng/ml; P < 0.001). Total antioxidant capacity (T-AOC) increased markedly with Irosustat (4.5 ± 0.3 U/mg vs. 2.1 ± 0.2 in disease; P < 0.001). NF-κB levels were significantly reduced with STX140 (0.76 ± 0.08 μg/ml vs. 1.49 ± 0.09; P < 0.0001). Aβ-42 levels decreased in all treatment groups, with STX140 showing the greatest reduction (147 ± 15 pg/ml vs. 296 ± 22 in disease; P < 0.001). ADAM10 expression increased 2.8-fold in Irosustat-treated rats (P < 0.01). STX140 reduced pro-caspase-9 expression by 41% vs. disease group (P = 0.0267).

Conclusions

Irosustat and STX140 significantly improved cognitive function and reduced AD pathology in scopolamine-induced rats. Their antioxidant, anti-inflammatory and anti-amyloid properties were comparable or superior to donepezil. These findings support the repositioning of STS inhibitors as promising disease-modifying agents in Alzheimer's disease.

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