In the venture towards the development of potent multi-target ligands, a series of twelve benzothiazole derivatives were synthesized employing synthetic hybrid compounds, logically designed to integrate into a single molecular framework consisting of at least two different pharmacophoric moieties. **Enzyme based drug screening** assays specific for Alzheimer's disease were performed. All derivatives showed **Acetylcholine esterase (AChE)** inhibitory activity. Compounds **11** (IC_{50} = 0.421 μM) and **13** (IC_{50} = 3.641 μM) were potent, mixed-type and selective AChE inhibitors, binding at the both catalytic and peripheral anionic site of the enzyme. Treatment with compounds **11** and **13** at 50 μM with Aβ reduced the aggregation propensity of Aβ by 80.708% and 74.49% respectively, observed by the reduced **fluorescence** intensity of Thioflavin T. **Confocal** laser scanning microscopy**, Transmission electron** microscopy, and **Infrared** spectroscopic analysis also substantiated the Aβ fibril formation hampering ability of the compounds. Furthermore, disaggregation assay showed decrease in the fluorescence intensity after treatment with compounds **11** and **13** with Aβ fibrils, suggesting these can also disaggregate the matured fibrils. Besides, these derivatives were found to be non-neurotoxic agents in human neuroblastoma **SHSY5Y cells**.

Further, **in vitro** and **in vivo** investigations are under study. These results support our assertion that these compounds may constitute novel multi-functional agent for AD treatment.

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P32.85

Evaluation of the role of ellagic acid on spatial memory activity and oxidative responses in pentylenetetrazole chronic epileptic rat model

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Ellagic acid (EA) is a natural flavonoid abundant in plants and fruits that offers neuroprotection in animals. This study assessed the effect of pretreatment with EA (15, 30 and 60 mg/kg) in pentyleneterazole (PTZ)-kindled rats and its role in memory using the Y-maze and elevated plus maze for memory. The effects of the pre-treatment with the EA on kindling – induced memory impairment, oxidative stress and neurotransmitters were evaluated. Male Wistar rats (weighing 200–300 kg) were injected with PTZ (35 mg/kg, s.c) once every alternate day (48 ± 2) until they were kindled. Memory impairment was assessed using the elevated plus maze and Y-maze tests. Oxidative stress biomarkers (malondialdehyde, MDA), antioxidant enzymes (superoxide, SOD and catalase, CAT) and neurotransmitters (Glutamate and Y-aminobutyric acid, GABA) of the whole brain were assayed at the end of the experiments using relevant kits. One way ANOVA followed by Tukey post hoc analysis were used for statistical analysis. In the present study, PTZ increased ($P < 0.05$) glutamate and MDA with consequent reduction ($P < 0.05$) in GABA. EA showed anti-seizure ability in all treated groups and increased ($P < 0.05$) antioxidant enzymes activities. In conclusion, our study suggests that EA has anti-epileptogenic like effect on PTZ-induced kindling in rats and improved memory. The mechanism of action of EA could be due to its antioxidant properties.

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P32.86

Neuroprotective role of pioglitazone in reversing hippocampal insulin resistance in Amyloid-β fibrils induced animal model of Alzheimer's disease

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Background: Complications of the Alzheimer's disease (AD) have made the development of its therapeutic intervention quite a challenging task. Numerous studies have supported the hypothesis that central insulin resistance plays a significant role in AD. Serine phosphorylation of Insulin Receptor Substrate-1 (IRS-1) has been found to be a contributing factor in neuronal insulin resistance. Pioglitazone (PIO) is a peroxisome proliferator-activated receptor gamma (PPAR-γ) activator, known for its significant anti-diabetic functions, has also demonstrated neuroprotective actions.

Methods: In the present study, AD was induced by i.c.v administration of amyloid-β (1-42) fibrils in Wistar rats. After 7 days of recovery, rats were treated with 10 mg/kg and 20 mg/kg of PIO orally for 28 days. Behavioral analysis was done in the last week of our experimental study. On the 36th day, rats were sacrificed and their hippocampus was separated from the whole brain, then homogenized and stored for biochemical estimations.

Results: PIO significantly reversed the cognitive and memory impairment, as assessed by Morris water maze test, in Aβ (1-42) fibrils infused Wistar rats. PIO also significantly attenuated Aβ (1-42) level, IRS-S307 activity, GSK-3β activity, TNF-α level, AChE level, nitrite level and oxidative stress in the hippocampus. Histopathological evaluation, done through H&E and Congo red staining, also demonstrated neuroprotective and anti-amyloidogenic effects of PIO in the hippocampus.

Discussions: Our study concludes protective action of pioglitazone against hippocampal insulin resistance and Alzheimer's disease complications, supporting the potential role of hippocampal insulin resistance targeting against the AD.

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P32.87

The role of DNA damage in TDP-43-associated-Amyotrophic Lateral Sclerosis (ALS)

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Almost all cases of ALS (97%) are associated with pathological forms of TAR-DNA binding protein 43 (TDP-43), which mislocalizes from the nucleus to the cytoplasm and forms inclusions containing misfolded TDP-43. However, it remains unclear how TDP-43

pathology is induced in ALS. Furthermore, no single molecular pathway has been confirmed as causative of disease pathogenesis in ALS. DNA damage has been implicated in the etiology of several neurological disorders, but its role in ALS is still emerging. In this study, I investigated whether DNA damage is involved in the pathogenesis of TDP-43-associated ALS. Upon induction of DNA damage in NSC-34 cells using etoposide, TDP-43 was found to mislocalize into the cytoplasm, where it formed significantly more inclusion-like structures compared to the control cells which were treated with DMSO. These TDP-43 inclusion-like structures displayed immunoreactivity to stress granule marker HuR, suggesting recruitment of TDP-43 into stress granules. Overexpression of TDP-43 with a deleted nuclear localization signal (NLS), which results in the production of TDP-43 mis-localized into the cytoplasm, also induced DNA damage in NSC-34 cells. DNA damage was then examined in a mouse model of TDP-43 in which the pathological cytoplasmic human TDP-43 (hTDP-43) were overexpressed (Walker et al., 2015). Using immunoblot techniques, upregulation of DNA damage was detected in the cortex of these animals compared to age matched control mice. DNA damage was first detected one week after cytoplasmic TDP-43 expression, corresponding to one week before development of symptoms and TDP-43 pathology. Importantly, the extent of DNA damage increased during disease progression, but significantly less damage was present when expression of hTDP-43 was inhibited, during the 'recovery' disease phase. These studies therefore demonstrate that DNA damage is closely linked to the formation of TDP-43 pathology in ALS, and they reveal DNA damage as a disease mechanism in TDP-43-associated ALS.

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P32.88

Fingolimod improves the functional recovery of optic pathway and alleviates the expression level of histone deacetylase/sphingosine 1 phosphate receptor 1 in focal demyelination model of rat's optic chiasm

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Fingolimod (FTY720) as a sphingosine 1-phosphate (S1P) receptor agonist, has been introduced as the first oral medicine for relapsing-remitting multiple sclerosis (MS). Besides immunomodulatory role, FTY720 exerts beneficial effects on remyelination process in central nervous system (CNS). In this study, the effect of FTY720 on conductivity of visual signals, myelin repair, glial activation and expression levels of histone deacetylase 1 (HDAC1)/S1P1R has been evaluated in lysolecithin (LPC)-induced demyelination model in optic chiasm. In order to induce demyelination model, LPC (1%, 2 μl) was injected into rat's optic chiasm. Visual evoked potential recording (VEP) was used to measure the latency of visual waves. The extent of demyelination area and levels of glial activation were assessed using immunostaining. Gene expression analysis was performed to evaluate the expression levels of HDAC1, S1P1R and Olig2 in the optic chiasm. Analysis of electrophysiological data showed that injection of LPC increased the latency of visual signals and application of FTY720 significantly improved the functional recovery of visual pathway and alleviated the levels of glial activation in the optic chiasm. FTY720 enhanced the myelin repair and upregulated the expression level of Olig2. Additionally, the expression levels of HDAC1/S1P1R were significantly reduced in animals treated with FTY720. Cumulatively, the results of the present study demonstrate that FTY720 application improves the functional recovery of optic pathway through enhancement of remyelination, alleviation of glial activation and downregulation of S1P1R/HDAC1.

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P32.89

Ursin reduce neuronal loss and astrocytes activation in chemical kindling model of epilepsy

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Background: Epilepsy is one of the most common chronic neurological disorders, which provoke progressive neuronal degeneration and memory impairment. In recent years, application of herbal compounds with anti-inflammatory properties, such as Ursin has been introduced as useful agent in reducing of the epilepsy symptoms. In this study, the effect of Ursin application on spatial memory improvement, neuronal density and astrocyte activation were evaluated in pentylenetetrazol (PTZ)-induced kindling model.

Methods: Male NMRI mice have received the daily injection of Ursin at dose of 25 and 50 mg/kg. All interventions were injected intraperitoneally (i.p.), 10 days before PTZ administration and the injections were continued until 1 h before each PTZ injection. Spatial learning and memory was evaluated using Morris water maze test after the 11th PTZ injection. Animals have received 13 injections of PTZ and then, brain tissues were removed. Immunostaining against NeuN and GFAP respectively as mature neuronal and astrocyte markers were performed on brain sections.

Findings: Our results showed that Ursin administration reduced the seizures behavior and prevented cognitive impairment in fully kindled animals. Immunostaining data demonstrated that the level of neuronal loss and astrocyte activation were reduced in animals under treatment of Ursin.

Conclusion: Overall, the results of this study suggest that Ursin administration effectively ameliorates memory impairment and alleviates the level of neuronal death and astrocyte activation in PTZ-induced kindling model.

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