ORIGINAL ARTICLE

Irbesartan protects against aluminium chloride induced amyloidogenesis and cognitive impairment

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Abstract

Background: Activation of brain renin angiotensin system is associated with neurodegenerative disorders like Alzheimer's disease (AD). AD is the most common type of dementia. Angiotensin Receptor Blockers (ARBs) like Telmisartan, Azilsartan, Valsartan and Losartan have shown efficacy against animal models of AD. The efficacy of Irbesartan in AD has not been thoroughly investigated. Aluminium chloride ($AlCl_3$) induces AD like pathology in rats. *Aim and Objectives:* The present work evaluates the efficacy of Irbesartan against $AlCl_3$ induced amyloidogenesis and cognitive impairment. *Material and Methods:* Wistar albino rats were divided into four groups containing six each. Group I (saline 10 ml/kg p.o.) and Group II ($AlCl_3$ 100 mg/kg p.o.) served as normal control and toxic control respectively. Both the groups were dosed daily for 42 days. Group III and Group IV received Irbesartan (10 mg/kg) and Telmisartan (10 mg/kg) respectively with $AlCl_3$ daily for 42 days. The drugs were given 1 hour before the administration of $AlCl_3$. Y-maze, elevated plus maze and radial arm maze were used to evaluate memory functions on day 0 and 42. Amyloid β (Aβ) content and enzymatic anti-oxidant status in both plasma and brain homogenate were measured and histological studies of brain tissues were done on day 43. *Results:* $AlCl_3$(100 mg/kg, p.o.) significantly ($p<0.05$) reduces the cognitive function, increases the concentration of Aβ and causes oxidative stress. Irbesartan (10 mg/kg, p.o.) and Telmisartan (10 mg/kg, p.o.) significantly ($p<0.05$) reverses $AlCl_3$ induced amyloidogenesis and cognitive impairment. *Conclusion:* So, Irbesartan may be useful against AD and other forms of dementia.

Keywords: Alzheimer's, memory, neuroprotective, amyloid-beta, $AlCl_3$, angiotensin

Introduction

Progressive loss of synapses and neurons in the hippocampus area of brain leads to Alzheimer's Disease (AD). AD is the most common form of dementia and cognitive impairment. Currently used drugs against AD are mostly anti-cholinesterase drugs based on cholinergic hypothesis. These drugs improving cholinergic function can only provide symptomatic relief without any impact on the disease progression. Drugs based on amyloid cascade and other hypotheses show limited efficacy clinically. Recent findings suggest the role of brain Renin Angiotensin System (RAS) in learning and memory. Many brain RAS components have been identified and targeted for the treatment of AD [1-6].

Angiotensin Receptor Blockers (ARBs) are the prominent inhibitors of RAS system and have been recently studied for their efficacy against cognitive impairment. These drugs are found to be neuroprotective [7-11]. Telmisartan possesses anti-oxidant, anti-inflammatory and anti-apoptotic

actions. It also prevents extracellular deposition of Amyloid beta (Aβ) protein. In addition to AT1 receptor blockade, the efficacy of telmisartan in AD is also attributed to Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ) agonist activity [12-14]. Valsartan ameliorates amyloid β-mediated cognitive dysfunction in the Tg 2576 mouse model of AD [15]. There are also reports of memory enhancing effects of Losartan because of Aβ-reducing and anti-inflammatory effects [16]. Azilsartan shows improvement in cognitive impairment and possesses antioxidant activity [17].

Many studies based on various neurotoxicological, analytical, and epidemiological findings have revealed that chronic administration of Aluminium (Al) results in AD like symptoms. Al is a neuro-toxin that is accumulated in the hippocampus, significantly decreases Acetyl Choline (ACh) content in mice and rat brain. It also causes accumulation of Aβ protein in the rat brain. Aluminium (Al) induced neurotoxicity also develops oxidative stress in the hippocampus [18-23]. Telmisartan and Azilsartan have shown efficacy against Aluminium Chloride ($AlCl_3$) induced AD like pathology in rats [13, 17]. Irbesartan has 70% bioavailability which is highest amongst the ARBs [6]. Thorough literature review does not reveal the efficacy of Irbesartan against cognitive impairment. So, the present study is undertaken to evaluate efficacy of Irbesartan and to compare its efficacy with Telmisartan against $AlCl_3$ induced amyloidogenesis and cognitive impairment.

Material and Methods

Animals

Wistar albino rats of both sex (120-200 g) were raised from the Central Animal House, Facility of School of Pharmaceutical Sciences, Siksha O Anusandhan (Deemed to be University), Bhubaneswar. The rats were housed under standard environmental conditions like 25±3^{0}C temperature, 45-55% relative humidity and light and dark cycle of 12 hr. Food and water were provided *ad libitum*. All the experimental protocols were approved by Institutional Animal Ethics Committee of School of Pharmaceutical Sciences, Siksha O Anusandhan University (Approval No-IAEC/SPS/SOA/13/2020) in accordance with strict ethical guidelines. Prior to experimentation the animals were acclimatized for 48 hours for adaptation to new environment.

Chemicals

Irbesartan and Telmisartan were received as gift samples from Aurobindo (Telengana, India), Alkem (Sikkim, India) respectively. All the chemicals used for experimental purpose are of laboratory grade.

Experimental design

All the rats were divided into four groups (n=6). Group I (Control) rats received normal saline (10 ml/kg) once daily for 42 days. Group II received $AlCl_3$ (100 mg/kg, p.o.) once daily for 42 days. Irbesartan (10 mg/kg, p.o.) and Telmisartan (10 mg/kg p.o.) were administered 1hr prior to the administration of $AlCl_3$ (100 mg/kg, p.o.) once daily for 42 days to Group III and Group IV animals respectively. Behavioural tests were done on day 1 and day 42. Following to this animal were sacrificed on day 43 for the biochemical estimations and histological studies.

Behavioral study

Y-maze

The spatial working memory was measured through the spontaneous alternation of behavior in rats by using Y-maze. The instrument comprises of three equal arms settled at equal angles and named A, B, C. Animals were placed at the edge of one arm followed by free walk between arms for 8 minutes. Arms were cleaned well between each rat to get rid of any remaining odors. Complete arm entry is counted when the rat totally entered its hind paws inside the maze arm. The alternation was regarded to a consecutive entry on overlapping triplet combination pattern (CAB, ABC, etc.) in the three arms. We recorded both number of alternations and total arm entries to obtain the percentage Spontaneous Alternation Behavior (SAB) by using following equation [24, 25].

SAB (%) = [(Number of alternations) / (total arm entries-2)]* 100

Radial arm maze

The radial arm maze (INCO) consisting of 8 arms was employed to study the number of correct responses for each rat. Individually the rats were placed on the centre and allowed to enter arms freely for 10 minutes. Entry into an arm which it had not visited previously recorded as a correct response whereas re-entry was counted as an error. The number of correct responses before committing the first error was calculated as the index of radial arm maze performance [25].

Elevated plus maze

In this maze, the time taken by the animal to enter a closed arm with all four limbs when placed at the end of one open arm facing away from central platform was recorded as the initial transfer latency. A 60 seconds cut off was set. The rat was then allowed to move freely in the maze regardless of open and closed arms for another 10 seconds. Twenty-four hours later, retention transfer latency test was performed in the same way as in the acquisition trial. If the rat did not enter the enclosed arm within 60 seconds on second trial, the transfer latency (day 1) was assigned 60 seconds [25-26]. The rats were again put into the elevated plus maze on day 42 to evaluate the transfer latency.

Biochemical estimations

Following to completion of all behavioral models, rats from each group were decapitated under anesthesia with Ketamine (87.5 mg/kg)/ Xylazine (12.5 mg/kg) cocktail. The plasma and serum were collected by cardiac puncture method for biochemical estimations. The brain tissues were immediately removed and cleaned with cold saline over the ice and were immediately stored in 10% formalin solution for further studies.

Enzymatic antioxidant assay

Preparation of homogenates

For preparation of brain homogenates, 0.3 M of phosphate buffer at pH 7.4 was added 3 times to the weight of hippocampus and homogenized using a homogenizer at oscillation frequency of 180-1800 per minutes. The obtained homogenates were centrifuged at 10,000 rpm for 15 minutes at 4°C using a cooling centrifuge. The supernatant was collected and stored at -80°C till the assay was to be performed.

Superoxide Dismutase (SOD) assay

SOD assay was done using JASCO (V-630) UV spectrophotometer. The blank preparation was made by adding 0.5 ml of EDTA (1mM) to 1.5 ml of Tris buffer (0.05M). For control solution 1 ml of

Pyrogallol (0.2mM) was added to the identical blank preparation. The test preparation consists of reagent blank and 50 µl of serum or brain homogenate in a separate test tube. Change in absorbance was recorded against reagent blank at 420 nm. The percentage protection was calculated using following equation:

$$\% \text{ Protection} = (A_{control} - A_{test}) / A_{control} \times 100$$

The SOD content was determined by putting each % protection in the standard curve (Y= 56.53×-0.1198, $R^2 = 0.99$) and expressed as mmol/l [25-26].

Lipid peroxidation activity

Estimation of Malondialdehyde (MDA) is considered as indices for lipid peroxidation activity. This was estimated by UV spectrophotometer. The reagent blank was prepared by mixing 2 ml of trichloroacetic acid (15%), 2 ml of thiobarbituric acid (0.37%) and 2 ml of 0.25 N HCl. Test solutions were prepared by adding 100 µl of plasma or brain homogenate to the identical blank solution separately. Following to this, the reaction mixture were heated for 60 minutes at 90 ^{0}C over water bath and centrifuged at 3000 rpm for 15 minutes after gradual cooling to room temperature. The change in absorbance of supernatant was measured at 532 nm against reagent blank. The extent of MDA content was determined from the standard curve and expressed as nmol/l [27].

Detection of amyloid-β content by ELISA test

A sandwich ELISA kit (Elabscience) was used for the determination of amyloid-β in the brain. The whole brain of control, $AlCl_3$ and test drugs were taken and homogenized in PBS at a ratio 1:9 using a tissue homogenizer. The brain homogenates were centrifuged at 10000 rpm for 15 minutes and the supernatants were collected. Prior to estimation of amyloid-β, the standard solution was prepared using serial dilution method to obtain a standard calibration curve. The protein concentration was assayed by BCA method and about 100µl containing 250µg of protein from soluble fraction of $A\beta_{1-42}$ were incubated at 37°C for 90 minutes in the microplate pre-coated with their corresponding antibodies and added sample solution. Following to this the microplate well was washed with 350µl of wash buffer solution and incubated with 100µl of biotinylated detection antibody for 60 minutes at 37°C. After incubation samples were washed and HRP-labeled conjugate was added to each well and incubated for 30 minutes, washed again and incubated with a substrate reagent of 50µl for 15 minutes at 37°C and finally 40µl of stop solution was added to stop the reaction. Then it is heated for some time at same temperature and optical density was measured by ELISA reader at a wavelength of 450 nm [28-29].

Histopathology

Fixed tissues were dehydrated in different mixtures of ethanol and water followed by cleaning with xylene. The clean tissues were embedded in paraffin and prepared 5-6 µm thick sections. This was further stained with haematoxylin and eosin dyes followed by mounting in DPX medium for microscopic observations [30].

Statistical analysis

For statistical analysis of results One-way ANOVA followed by Tukey's post hoc test was used. The experimental data was presented as mean ± SD. Value of p was established at 5% level of significance.

Results

Y-maze

Y-maze (INCO, INDIA) was used to measure the spatial working memory through SAB in rats. Administration of $AlCl_3$ for 42 days significantly decreased % SAB ($p<0.05$) when compared to control group. The group treated with Irbesartan (10 mg/kg) and Telmisartan (10 mg/kg) significantly increased the % SAB ($p < 0.05$) when compared with $AlCl_3$. There was no significant difference between % SAB of Telmisartan and Irbesartan (Figure 1).

Radial arm maze

Administration of $AlCl_3$ for 42 days showed significant ($p < 0.05$) decrease in number of correct responses as compared to control animals. Treatment groups (Irbesartan, Telmisartan) given together with $AlCl_3$ improved number of correct responses significantly ($p < 0.05$). Telmisartan showed significantly ($p < 0.05$) more protective effect than Irbesartan (Figure 2).

Elevated plus maze

Significant increase ($p < 0.05$) in transfer latency was observed after treatment with $AlCl_3$ for 42 days as compared to control group. Group III and Group IV treated with Irbesartan (10 mg/kg) and Telmisartan (10 mg/kg) respectively given together with $AlCl_3$ improved transfer latency significantly ($p < 0.05$). Telmisartan (10 mg/kg) showed significantly ($p < 0.05$) more protective effect than Irbesartan (10 mg/kg) (Figure 3).

Enzymatic antioxidant status

SOD and MDA

After 42 days of administration of $AlCl_3$, impaired antioxidant status was observed in group II animals i.e., decreased SOD level and increased MDA content as compared to control group. However, Telmisartan and Irbesartan showed significantly ($p < 0.05$) increased SOD level (Figure 4) and decreased level of lipid peroxidation (Figure 5) as compared to $AlCl_3$ group. Telmisartan showed significantly ($p < 0.05$) more protective effect than Irbesartan.

Amyloid β estimation

After chronic administration of $AlCl_3$ for 42 days it was found that there is significant increase in the levels of Aβ 1-42. Both Irbesartan and Telmisartan produced significant ($p < 0.05$) protective effect against $AlCl_3$ and decreased the amount of Aβ 1-42 produced in the brain cells. However, Telmisartan produces significantly more protection than Irbesartan (Figure 6).

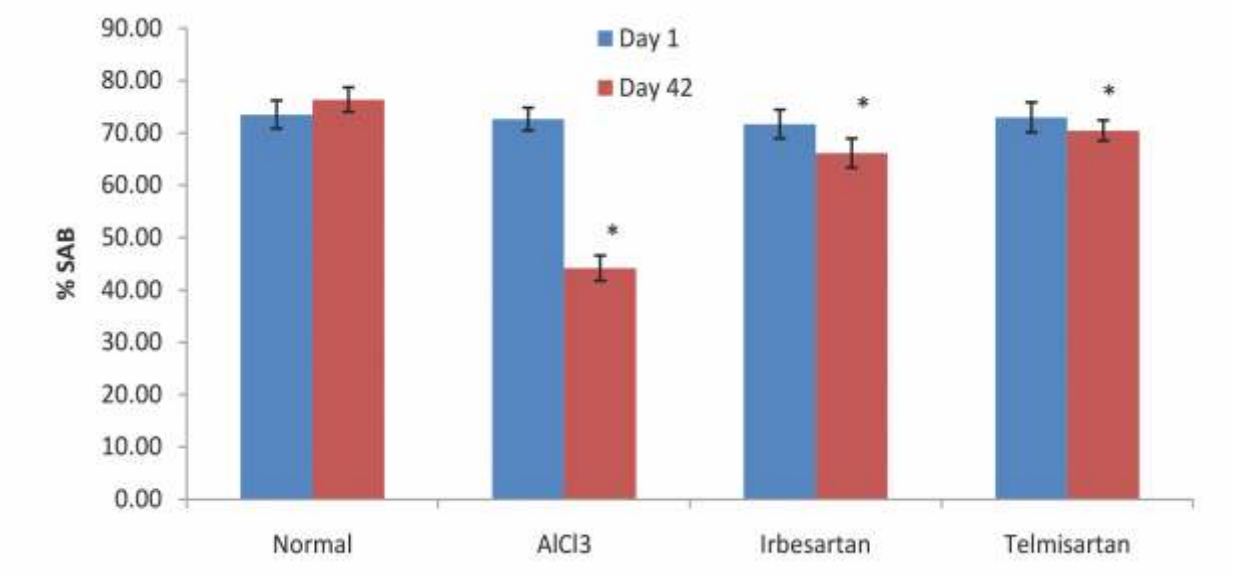


Figure 1: Effect of Irbesartan on % SAB in $AlCl_3$ administered rats using Y-Maze

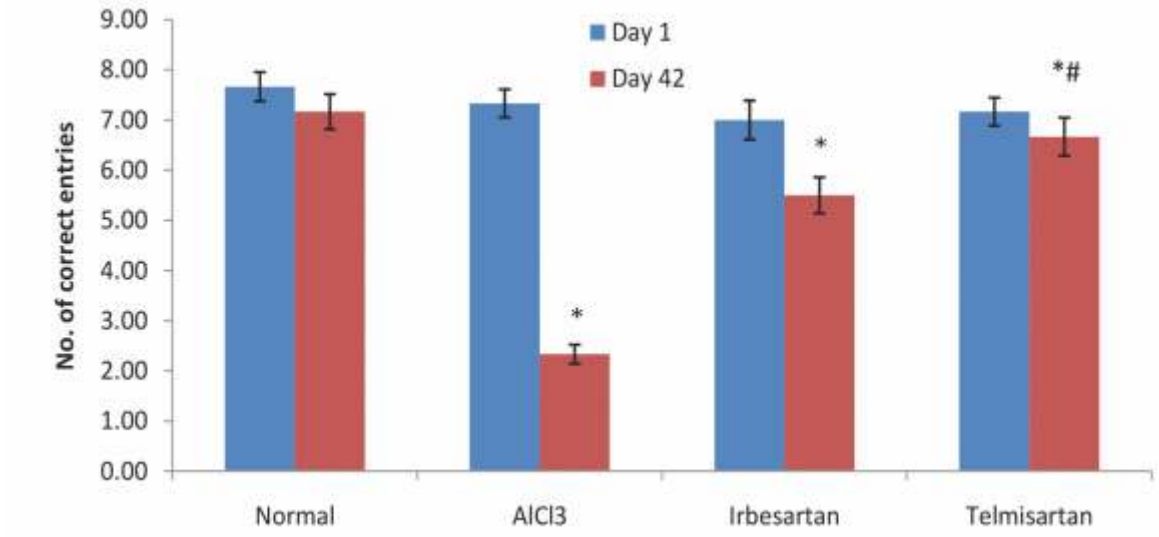


Figure 2: Effect of Irbesartan on number of correct responses in $AlCl_3$ administered rats using radial arm maze

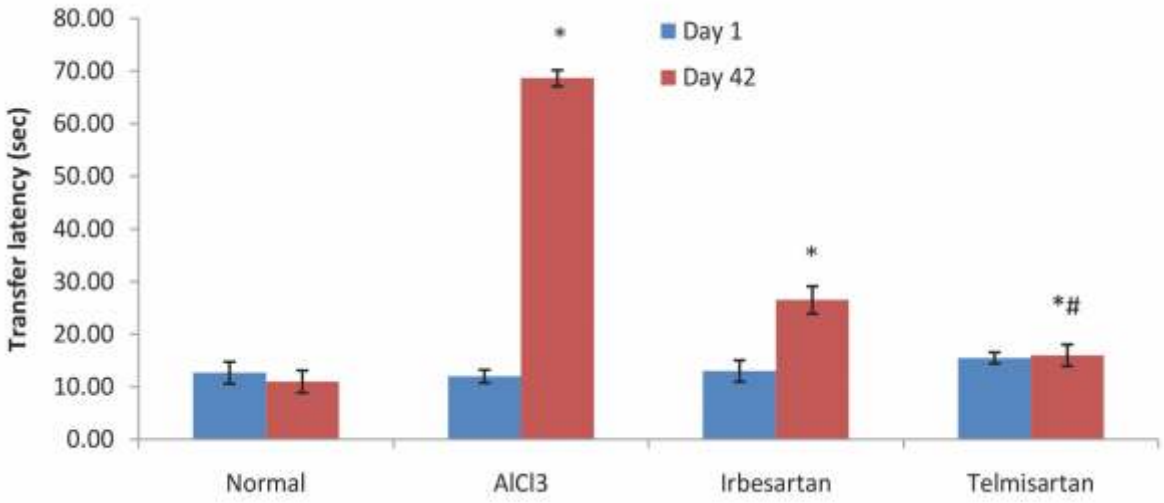


Figure 3: Effect of Irbesartan on transfer latency in $AlCl_3$ administered rats using elevated plus maze

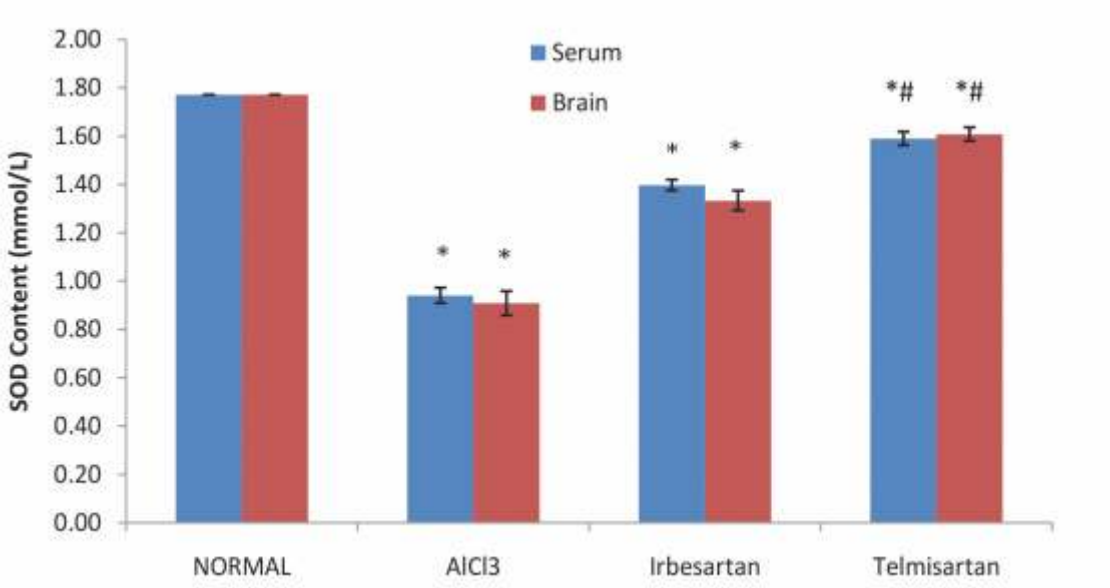


Figure 4: Effect of Irbesartan on SOD activity in $AlCl_3$ administered rats

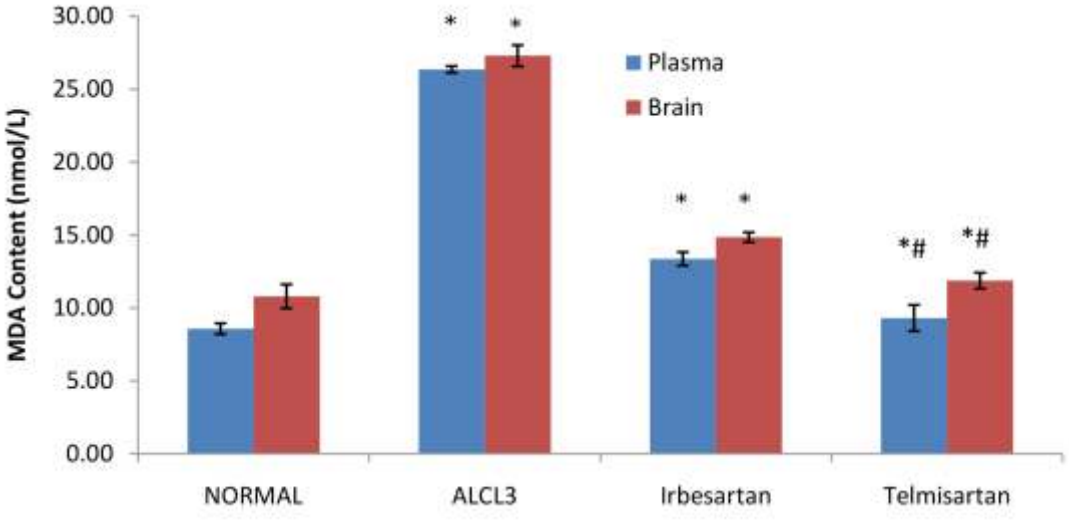


Figure 5: Effect of Irbesartan on MDA activity in $AlCl_3$ administered rats

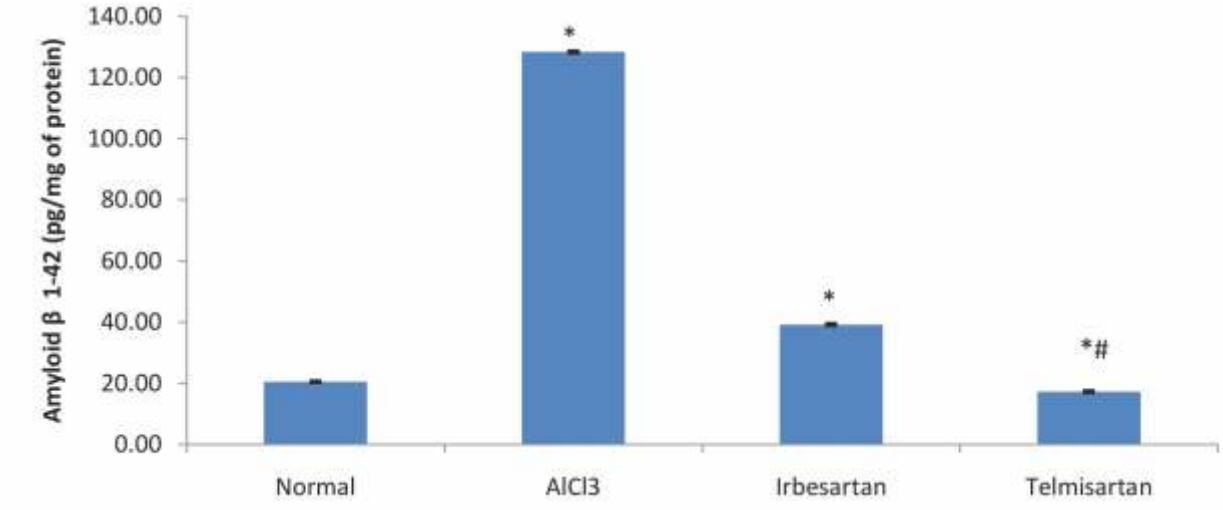


Figure 6: Effect of Irbesartan on Amyloid β activity in $AlCl_3$ administered rats

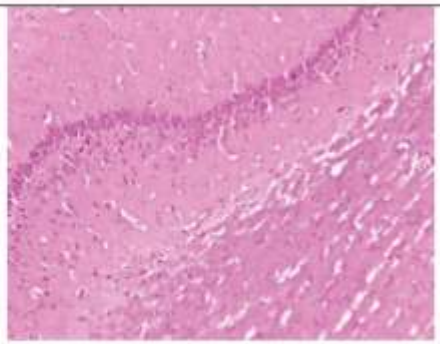
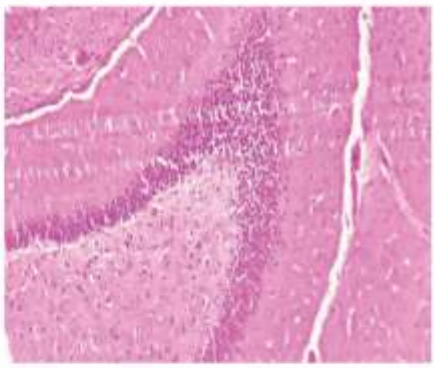
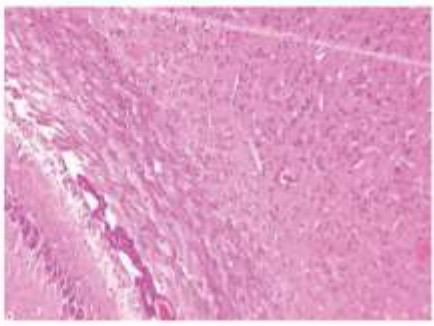
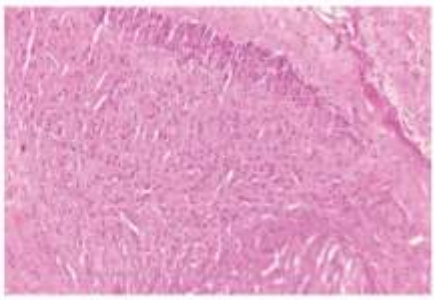
Group	Brain	Remarks
Control		Sections taken from brain cerebral cortex of normal rats showed normal appearance and organization of neuronal cells.
$AlCl_3$		Presence of pyramidal cells, pyknotic nuclei, dense and dead neuronal cell, and developed neuro fibrillary tangles with vacuolation, focal hemorrhage indicating neuronal degeneration.
Irbesartan		Histology revealed presence of pyramidal cells, presence of focal gliosis with focal hemorrhage but presence of normal neuronal cells indicating its partial neuroprotective effect.
Telmisartan		Histology of brain tissue of animals treated with Telmisartan (10 mg/kg for 42 days, p.o.) associated with little focal hemorrhage and reduction of neuronal cell layer and normal cytoarchitecture indicating its neuroprotective effect.

Figure 7: Effect of Irbesartan on brain tissue of $AlCl_3$ administered rats

Histopathology study

Histological examination further confirmed the results of this study. Normal-control group showed normal appearance and organization of neuronal cells whereas animals treated with $AlCl_3$ showed neurodegenerative changes. $AlCl_3$ treated rats showed presence of neurofibrillary tangles, neuronal dead cells, and pyknotic cells in histological studies when compared to normal group. Both Irbesartan and Telmisartan showed protection from neurodegeneration (Figure 7).

Histology of normal rat brain showed normal appearance and organization of neuronal cells. However, $AlCl_3$ treated rat brain was associated with presence of pyramidal cells, pyknotic nuclei, dense and dead neuronal cell, and developed neuro fibrillary tangles with vacuolation, focal Haemorrhage indicating neuronal degeneration. Irbesartan treated rat brain tissue had shown the presence of pyramidal cells, focal gliosis with focal haemorrhage, but the presence of normal neuronal cells implies its partial neuroprotective effect. Sections taken from brain cerebral cortex of rats treated with Telmisartan (10 mg/kg for 42 days, p.o.) were associated with little focal haemorrhage and reduction of neuronal cell layer and normal cyto-architecture indicating its neuroprotective effect.

Discussion

AD is characterized by amyloid plaques, phosphorylated tau proteins and neurofibrillary tangles in cerebral cortex and hippocampal region in the midbrain. Other factors like neuroinflammation, oxidative stress, genetics and environmental factors like Al toxicity are also responsible for AD. Symptomatic treatment is only possible with currently used drugs. No drug is available for modifying the pathogenesis [2]. Recently, repurposing of RAS inhibitors has been attempted by many researchers as over expression of RAS is associated with neurodegenerative disorders like AD [6].

There are many reports of ameliorative effects of Telmisartan against spatial memory [31-33], diabetes associated cognitive impairment [34-35], stress induced memory impairment [36], lipopolysaccharide-induced cognitive impairment [37, 38] and $AlCl_3$ induced cognitive impairment [13]. The mechanisms behind such action may be attributed to its anti-oxidant, anti-apoptosis, anti-inflammatory effects [12], anti-amyloidogenesis effect [34, 37], neuroprotective effect [38] and PPAR-γ agonist action [33, 35]. So, we have taken Telmisartan as standard. In our study, Telmisartan reduced amyloidogenesis, showed anti-oxidant and neuroprotective action and improved learning and memory. This is in agreement with earlier studies. The efficacy of Irbesartan was compared with that of Telmisartan against $AlCl_3$ induced amyloidogenesis and cognitive impairment.

Decrease in SAB, increase in transfer latency and decrease number of correct responses have been used as markers of cognitive impairment in rat models using Y-maze, elevated plus maze and radial maze respectively. Administration of $AlCl_3$ (100 mg/kg) for 42 days showed cognitive impairment [28-30]. Telmisartan (10 mg/kg) reversed $AlCl_3$ induced cognitive impairment which is in agreement with earlier findings [13]. Irbesartan (10 mg/kg) also showed amelioration of $AlCl_3$ induced cognitive impairment which is comparable to that of Telmisartan.

Irbesartan significantly reduced amyloidogenesis like Telmisartan in our study. Amyloidogenesis is

an important pathological feature in AD [39, 40]. Irbesartan is reported to be a neuroprotective. It reduces lipopolysaccharide induced inflammatory mediators in vessels of cerebral cortex by inhibiting NF-kB / MLCK / MLC pathway [41-43]. Our histological studies confirmed the neuroprotective effect of both Irbesartan and Telmisartan. Irbesartan also protected against oxidative stress as evident from significant increase in SOD and decrease in MDA levels. Its neuroprotective action may be attributed to its antioxidant action [6].

Conclusion

Irbesartan shows protection against $AlCl_3$ induced amyloidogenesis and cognitive impairment which is comparable to that of Telmisartan. Hence, like other ARBs, Irbesartan can be used potentially against AD. However, further clinical studies are needed to validate its efficacy in AD and other forms of dementia.

References

1. Wright JW, Kawas LH, Harding JW. A role for the brain RAS in Alzheimer's and Parkinson's diseases. Front Endocrinol 2013;4:158.
2. Sahu PK, Tiwari P, Prusty SK, Subudhi BB. Past and present drug development for Alzheimer's disease. In: Rahman A (Ed), Frontiers in clinical drug research – Alzheimer disorders, Vol 7. Bentham Science Publishers. 2018: 214-253.
3. Savaskan E. The role of the brain renin-angiotensin system in neurodegenerative disorders. *Curr Alzheimer Res* 2005; 2(1):29-35.
4. Indumathy S, Kavimani S, Raman KV. Role of angiotensin antagonists in memory enhancement. *Int J Pharm Bio Sci* 2010; 1(3):1-4.
5. Mohapatra D, Jena S, Prusty SK, Sahu PK. Biomarkers of Alzheimer's disease: A review.*Syst Rev Pharm* 2020;11(6): 151-158.
6. Prusty S K, Sahu P K, Subudhi B. Angiotensin mediated oxidative stress and neuroprotective potential of antioxidants and AT1 receptor blockers. *Mini Rev Med Chem* 2017;17(6):518-28.
7. Subudhi BB, Sahu PK, Singh VK, Prusty S. Conjugation to ascorbic acid enhances brain availability of losartan carboxylic acid and protects against Parkinsonism in rats. *AAPS J* 2018;20(6):110.
8. Atlas SA. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. *J Manag Care Pharm* 2007; 13(8 Suppl B):9-20.
9. Horiuchi M, Mogi M. Role of angiotensin II receptor subtype activation in cognitive function and ischaemic brain damage. *Br J Pharmacol* 2011; 163(6):1122-1130.
10. Ciobica A, Bild W, Hritcu L, Haulica I. Brain renin-angiotensin system in cognitive function: pre-clinical findings and implications for prevention and treatment of dementia. *Acta Neurol Belg* 2009; 109(3):171-180.
11. Li NC, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE, *et al*. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. *BMJ* 2010; 340:b5465.
12. Jung KH, Chu K, Lee ST, Kim SJ, Song EC, Kim EH, *et al*. Blockade of AT1 receptor reduces apoptosis, inflammation, and oxidative stress in normotensive rats with intracerebral hemorrhage. *J Pharmacol Exp Ther* 2007; 322(3):1051-1058.
13. Khalifa M, Safar MM, Abdelsalam RM, Zaki HF. Telmisartan protects against Aluminium-induced Alzheimer-like pathological changes in rats. *Neurotox Res* 2020; 37(2):275-285.
14. Sodhi RK, Singh N, Jaggi AS. Neuroprotective mechanisms of peroxisome proliferator-activated receptor agonists in Alzheimer's disease. *Naunyn Schmiedebergs Arch Pharmacol* 2011;384(2):115-124.
15. Wang J, Ho L, Chen L, Zhao Z, Zhao W, Qian X, *et al*. Valsartan lowers brain β-amyloid protein levels and improves spatial learning in a mouse model of Alzheimer disease. *J Clin Invest* 2007;117(11):3393-3402.
16. Danielyan L, Klein R, Hanson LR, Buadze M, Schwab M, Gleiter CH, *et al*. Protective effects of intranasal losartan in the APP/PS1 transgenic mouse model of Alzheimer disease. *Rejuvenation Res* 2010;13(2-3):195-201.

17. Alzahrani YM, Sattar MA, Kamel FO, Ramadan WS, Alzahrani YA. Possible combined effect of perindopril and Azilsartan in an experimental model of dementia in rats. *Saudi Pharm J* 2020; 28(5):574-581.
18. Kawahara M, Kato-Negishi M. Link between aluminium and the pathogenesis of Alzheimer's disease: the integration of the aluminium and amyloid cascade hypotheses. *Int J Alzheimers Dis* 2011;2011: 276393.
19. Blaylock RL. Aluminium induced immunoexcito-toxicity in neurodevelopmental and neurodegenerative disorders. *Curr Inorg Chem* 2012; 2(1):46-53.
20. Walton JR. A longitudinal study of rats chronically exposed to aluminium at human dietary levels. *Neurosci Lett* 2007; 412(1):29-33.
21. Wu YH, Zhou ZM, Xiong YL, Wang YL, Sun JH, Liao HB, *et al*. Effects of aluminium potassium sulfate on learning, memory, and cholinergic system in mice. *Acta Pharmacol Sin* 1998; 19:509-512.
22. Platt B, Fiddler G, Riedel G, Henderson Z. Aluminium toxicity in the rat brain: histochemical and immunocytochemical evidence. *Brain Res Bull* 2001;55(2):257-267.
23. Singh NA, Bhardwaj V, Ravi C, Ramesh N, Mandal AK, Khan ZA. EGCG nanoparticles attenuate aluminium chloride induced neurobehavioral deficits, beta amyloid and tau pathology in a rat model of Alzheimer's disease. *Front Aging Neurosci* 2018; 10:244.
24. Mishra SK, Rout K, Prusty SK, Sahu PK. Shodhana decreases nootropic activity of Semecarpus anacardium. *Asian J Pharm Clin Res* 2016; 9(Supp 2):294-297.
25. Prusty SK, Pati AK, Subudhi BB, Sahu PK. Chronic forced swimming induced stress alters behavioural, histological and anti-oxidant status. *Indian Drugs* 2017;54(6): 58-64.
26. Das MK, Tiwari P, Prusty SK, Sahu PK. Neuroprotective potential of metformin against forced swimming induced neurodegeneration Wistar albino rats. *Asian J Biol Sci* 2018; 11(2):89-97.
27. Salissou MT, Mahaman YA, Zhu F, Huang F, Wang Y, Xu Z, *et al*. Methanolic extract of Tamarix Gallica attenuates hyperhomocysteinemia induced AD-like pathology and cognitive impairments in rats. *Aging (Albany NY)* 2018; 10(11):3229-3248.
28. Mohapatra D, Kanungo S, Pradhan SP, Jena S, Prusty SK, Sahu P. Captopril is more effective than perindopril against aluminium chloride induced amyloidogenesis and cognitive dysfunction. *Heliyon* 2022; 8(2): e08935.
29. Pradhan SP, Sahoo S, Behera A, Sahoo R, Sahu PK. Memory amelioration by hesperidin conjugated gold nanoparticles in diabetes induced cognitive impaired rats. *J Drug Deliv Sci Tech* 2022; 69:103145.
30. Tiwari P, Prusty SK, Das MK and Sahu PK. Metformin prevents Phenytoin induced cognitive impairment. *Indian Drugs* 2020; 57(1): 66-71.
31. Shindo T, Takasaki K, Uchida K, Onimura R, Kubota K, Uchida N,*et al*. Ameliorative effects of telmisartan on the inflammatory response and impaired spatial memory in a rat model of Alzheimer's disease incorporating additional cerebrovascular disease factors. *Biol Pharm Bull* 2012;35(12):2141-2147.
32. Haruyama N, Fujisaki K, Yamato M, Eriguchi M, Noguchi H, Torisu K, *et al*. Improvement in spatial memory dysfunction by telmisartan through reduction of brain angiotensin II and oxidative stress in experimental uremic mice. *Life Sci* 2014;113(1-2):55-59.
33. Haraguchi T, Iwasaki K, Takasaki K, Uchida K, Naito T, Nogami A, *et al*. Telmisartan, a partial agonist of peroxisome proliferator-activated receptor γ, improves impairment of spatial memory and hippocampal apoptosis in rats treated with repeated cerebral ischemia. *Brain Res* 2010; 1353:125-132.
34. Du GT, Hu M, Mei ZL, Wang C, Liu GJ, Hu M, *et al*. Telmisartan treatment ameliorates memory deficits in streptozotocin-induced diabetic mice via attenuating cerebral amyloidosis. *J Pharmacol Sci* 2014; 124(4): 418-426.
35. Singh B, Sharma B, Jaggi AS, Singh N. Attenuating effect of lisinopril and telmisartan in intracerebro-ventricular streptozotocin induced experimental dementia of Alzheimer's disease type: possible involvement of PPAR-γ agonistic property. *J Renin Angiotensin Aldosterone Syst* 2013;14(2):124-136.
36. Wincewicz D, Juchniewicz A, Waszkiewicz N, Braszko JJ. Angiotensin II type 1 receptor blockade by telmisartan prevents stress-induced impairment of memory via HPA axis deactivation and up-regulation of brain-derived neurotrophic factor gene expression. *Pharmacol Biochem Behav* 2016; 148:108-118.

37. Khallaf WA, Messiha BA, Abo-Youssef AM, El-Sayed NS. Protective effects of telmisartan and tempol on lipopolysaccharide-induced cognitive impairment, neuroinflammation, and amyloidogenesis: possible role of brain-derived neurotrophic factor. *Canadian J Physiol Pharmacol* 2017;95(7):850-860.
38. Yamada K, Uchida S, Takahashi S, Takayama M, Nagata Y, Suzuki N, *et al*. Effect of a centrally active angiotensin-converting enzyme inhibitor, perindopril, on cognitive performance in a mouse model of Alzheimer's disease. *Brain Res* 2010;1352:176-186.
39. Nixon RA. Autophagy, amyloidogenesis and Alzheimer disease. *J Cell Sci* 2007;120(23):4081-4091.
40. Shishido H, Kishimoto Y, Kawai N, Toyota Y, Ueno M, Kubota T,*et al*. Traumatic brain injury accelerates amyloid-β deposition and impairs spatial learning in the triple-transgenic mouse model of Alzheimer's disease. *Neurosci Lett* 2016; 629:62-67.
41. Yang Q, Yu J, Qin H, Liu L, Di C, Zhuang Q, Yin H. Irbesartan suppresses lipopolysaccharide (LPS)-induced blood–brain barrier (BBB) dysfunction by inhibiting the activation of MLCK/MLC. *Int Immunopharmacol* 2021; 98:107834.
42. Dwivedi A, Sharma R, Purkayastha A, Kakria N. Imaging findings of a survivor of avalanche without any life support at very high altitude and extreme low temperatures. *J Krishna Inst Med Sci* 2016;5(4): 107-112.
43. Pradhan SP, Sahu PK. Antidepressant and anticataleptic effects of Eucalyptus tereticornis in rats and mice. *J Krishna Inst Med Sci* 2020;9(4): 58-71.

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