Protective Effect of Hyperforin on β Amyloid Protein Induced Apoptosis in PC12 Cells and Colchicine Induced Alzheimer’s Disease: An Anti-oxidant and Anti-inflammatory Therapy

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Abstract: The current investigation aimed to scrutinize the neuro-protective effect of hyperforin on β-amyloid peptide (Aβ)₁₋₄₂ and H₂O₂ induced injury in PC12 cells and colchicine induced Alzheimer’s disease (AD). PC12 cells were treated with H₂O₂ and (Aβ)₁₋₄₂ in the presence of hyperforin. The cell viability was determined via using the MTT assay; malondialdehyde (MDA) and lactate dehydrogenase (LDH) levels were also scrutinized. Colchicine induced the destruction of memory and learning which was exhibited in neurobehavioral theory (passive avoidance and Morris water maze) connected with reduced activity of acetylcholinesterase (AChE). Anti-oxidant and inflammatory parameters also estimated. Hyperforin dose dependently increased the cell viability and reduced the MDA and LDH release via PC12 cell injured with H₂O₂ and (Aβ)₁₋₄₂. Hyperforin treatment lead to a considerable enhance in TLT in the retention trials as comparison to acquisition trial suggesting as boosting memory and learning in rats. Hyperforin treatments significantly increase the AChE and reduced the superoxide dismutase, glutathione, MDA, protein carbonyl, glutathione peroxidase, catalase, NF-kB and IL-1β at dose dependent manner. In summary, the model of H₂O₂ and (Aβ)₁₋₄₂ induced PC12 cell injury was successfully developed and dose dependently treatment of hyperforin showed the neuroprotective effect against the H₂O₂ and (Aβ)₁₋₄₂ induced cell damage. These finding clearly exhibited that hyperforin reverted the colchicine induced neuro-chemical and behavioural alteration via potent anti-inflammatory and anti-oxidant activity.

Key words: hyperforin, Alzheimer’s disease, anti-oxidant effect, colchicine, amyloid β, anti-inflammatory

1 Introduction

Alzheimer’s disease (AD), represents the one of the most reasonably disease Worldwide. AD is neurodegenerative disorder characterized via expansion the cortical neurons and degeneration of hippocampal that show the way to memory impairment and cognitive ability¹,². First clinical symptoms is destruction of short term memory, whereas retrieval of distant memories preserved relatively well into the course of disease. Pathophysiology hallmark of AD is senile plaques, where are deposition of protein β-amyloid escorted via degeneration processes of neuronal and neurofibrillary tangles, helical filaments and other proteins³,⁴. This communicates to the clinical symptoms of marked destruction of memory and abstract reasoning, with preservation of vision and movement. The clinical symptom of AD is dysfunction cognition and memory loss and conclusion is death. Till date no effective treatment is available due to pathogenesis and etiology of disease is unknown⁵. The

Abbreviations: AD = Alzheimer’s disease, H₂O₂ = Hydrogen peroxide, MDA = malondialdehyde, LDH = Lactate dehydrogenase, AChE = Acetylcholinesterase, NF-kB = Nuclear transcription factor, IL-1β = Interleukin-1β, SOD = Superoxide dismutase, CAT = Catalase, DMEM = Dulbecco’s modified Eagle’s medium, ELISA = Enzyme-linked immunosorbent assay, MTT = (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide), ICV = intracerebroventricularly, GSH = Glutathione, ROS = Reactive oxygen species, ChAT = choline acetyltransferase

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2 Material and methods

2.1 Cell culture

The PC12 rat pheochromocytoma cell lines were cultured in Dulbecco’s modified Eagle’s medium (DMEM) containing penicillin (100 U/mL), fetal bovine serum (10%), streptomycin (100 U/mL) in an incubator (having temperature 37°C) containing CO2 (5%) and air (95%). In order to determine the intrusion of drug itself on the expansion of PC12 cells, a toxicity experimental study was carried out. Briefly, PC12 cells were propagated in the 96 well plates and incubated overnight at 37°C. After that, discarding the supernatant and added the DMEM (200 μL) in black group and cells were treated with hyperforin (3.12, 6.25, 12.5, 25, 50 100 and 200 μg/mL) and incubated the cells at room temperature 37°C for 2 days and MTT solution (20 μL) was added in each well and re-incubated at 4 h. Afterwards, the supernatant was removed and dimethylsulfoxide (150 μL) was added in each well, followed via agitation for 10 min. Enzyme-linked immunsorbent assay (ELISA) plate reader was used for the estimation of optical density at 490 nm.

2.2 Aβ1-42 induced PC12 cell damage

Aβ1-42 peptide was procured form the Shanghai, China and solubilized in 100 μg/mL water and incubated for 4 days at 37°C and kept at 4°C for further use. 96 well plates was used for seeded the PC12 cell lines. After culture for 24 h for adherence, Aβ1-42 (50 μL) and various concentration of hyperforin (0.125, 0.25, 0.5, 1, 1.5 and 2 μM) dissolved in DMEM (serum free) and incubated for various time interval (24, 48, 72 and 96 h). MTT assay was used for the estimation of cell viability. Different concentration of hyperforin (5, 25 and 50 μg/mL) was treated with PC12 cell lines in the presence of Aβ1-42 (0.5 μM) for 24 h and the cell viability was estimated via using the MTT assay.

2.3 H2O2 induced PC12 cell damage

Briefly, different concentration of hyperforin (0-500 μM) and H2O2 dissolved in the DMEM in the presence or absence of 0.1 mol/L phosphate buffer saline (PBS) and incubated at 37°C for 24 h. MTT assay was used for the estimation of cell viability. Various concentrations of hyperforin (0, 0.5, 5, 25 and 50 μM) were treated with PC12 cells. Afterwards, the cell culture and PC12 cells were treated with H2O2 (100 μL) and dissolved in the DMEM along with PBS in the presence of hyperforin for 24 h and (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) (MTT) assay was further used for the determination of cell viability.

2.4 Lactate dehydrogenase (LDH) release assay

LDH kit was used for the estimation of cell injury via measured the LDH activity in the PC 12 cell supernatant via using the manufacture’s instruction. Briefly, pyruvic acid, coenzyme I buffer, double distilled water and matrix buffer were added in the sequence after the hyperforin treatment and incubated for 15 min at 37°C and added the 2,4-dinitro-phenylhydrazine. Afterwards, NaoH (250 μL) was added in each well and after 30 min the supernatant was collected and again incubated at 37°C. The microplate reader was used for estimation the LDH activity at 450 nm.

2.5 MDA content

Commercial available MDA kit was used for the estimation of MDA content in PC12 cell supernatant. Briefly, the kit reagents and dehydrated alcohol were added and incubated at water bath for 1 h at 100°C. The prepared sample was centrifuged at 15,000 rpm for 15 min and left for the cooling. The supernatant was used for estimation the MDA content at 532 nm via using the microplate reader.

2.6 Experimental animal

For the current experimental study, the animal were carried out from the Institutional animal house and kept in the single polythene cages. The Wistar rats (150-185 g,
body weight) sex – male, was used for the current experimental study. The rats were kept in the standard experimental condition (22 ± 5°C, 12 h light/dark natural circle) with free accesses to standard rodent and water ad libitum. All the experimental investigation was approved from the institutional ethical committee.

2.7 Experimental study
The rats were divided into following groups and each group contain 12 rats as follow-Group I: received vehicle only; Group II treated with colchicine (15μg/ 5 μL icv); Group III received colchicine (15μg/ 5 μL icv) + hyperforin (5 mg/kg); Group IV received colchicine (15μg/ 5 μL icv) + hyperforin (10 mg/kg); Group V received colchicine (15 μg/ 5 μL icv) + hyperforin (20 mg/kg) and Group IV received colchicine (15 μg/ 5 μL icv) + memantine HCL (2.5 mg/kg), respectively.

The experimental rodents were intracerebroventricularly (icv) infused with either artificial cerebrospinal fluid (ACSF) or 15 lg colchicine dissolved in ACSF. After the ICV, the rodents were further used for the neurochemical and neurobehavioral estimation.

2.8 Post operative procedures
After successfully complete the surgery, we also maintained the aseptic conditions and provide the food and water to the experimental rodents. For prevention the sepsis, the rodents received the intraperitoneal injection of gentamicin (5 mg/kg) for 3 days and further experimental investigation was started after 3 days of surgery and continued till the end of the experimental investigation.

2.9 Behavioural study
For the behavioural study, Morris maze method was used via using the reported method of Bhatt et al., with minor modification. Morris maze method was used for measure the memory and learning capability in rodent. Briefly, in the Morris water maze method a circular pool (60 cm in height and 180 cm in diameter) with completely filled with water. All rodent put into the any quadrant during retention and acquisition phase.

2.10 Probe trial
On the last day of training session, the platform was successfully removed from the pool and rodents were free to swim in the pool for 2 min. The time travel via the rodents in the target quadrant was compared to different groups and result has been presented as latency time ± SEM.

2.11 Passive avoidance paradigm
For the estimation of memory and learning ability of rodents, passive avoidance paradigm was used. Briefly, the rodents were kept in the shuttle box, which have 2 compartments (dark and light) and separated guillotine door.

Firstly, rodent was kept in the light chamber for 30 s and guillotine door was opened and rodent was transferred into the dark chamber and door was closed and 0.5 mA (low intensity foot shock) was given for next 10s.

2.12 Neurochemical parameters
Neurochemical parameters such as acetylcholinesterase, lipid peroxidation and protein carbonyl content were estimated via using the reported method with minor modification.

2.13 Anti-oxidant parameters
Anti-oxidant parameters such as superoxide dismutase (SOD), glutathione (GSH) and catalase (CAT) in hippocampus were assessed via using the reported method with minor modification.

2.14 Inflammatory mediators
Pro-inflammatory cytokines such as IL-1β and inflammatory mediator including NF-kB was estimated via using the standard kits.

2.15 Statistically analysis
One way ANOVA was used for the estimation the statistical analysis. Graphpad Prism was used for the statistically analysis. All the data performed in triplicate and presented as mean ± SEM. Date compared between the treated and untreated group were made via Dunnett post tests. The data presented as *p<0.05, **p<0.01 and ***p<0.001.

3 Results
3.1 Effect on PC12 cells viability
Figure 1 showed the effect of the hyperforin on PC12
3.2 Effect of hyperforin on Aβ1-42 induced PC12 cell injury

Figure 2 demonstrated the effect of Aβ1-42 on PC12 cell injury. On the comparison with the control group, Aβ1-42 exhibited the cell viability (72.84%) at dose of 0.5 μM. Concentration dependent treatment of Aβ1-42 (1, 1.5 and 2 μM) significantly (p > 0.001) reduced the cell viability injury in PC12 cell group. On the basis of result, we can say that Aβ1-42 (0.5 μM) exhibited the optimal condition for invitro model for AD.

Figure 3 revealed the effect of hyperforin on the PC12 cells treated with Aβ1-42 (0.5 μM). Hyperforin (50 μg/mL) treated group did not showed the any effect of the cells. Concentration dependent treatment of hyperforin significantly (p < 0.001) rescued the cell viability on PC12 cell treated with Aβ1-42 and suggest the neuro-protective effect.

3.3 Effect of hyperforin on LDH activity

Figure 3a and b demonstrate the increased LDH activity in the supernatant of damaged PC12 cells. Figure 3a demonstrated the increased H2O2 LDH leakage in H2O2 group and concentration treatment of hyperforin reduced the LDH leakage in PC12 cells. Hyperforin (50 μg/mL) demonstrated the significantly (p < 0.001) down-regulation the LDH leakage (61 ± 1.89).

A similar momentum was observed in the LDH leakage in Aβ1-42 group and dose dependent treatment of hyperforin significantly (p < 0.001) reduced the LDH leakage in Aβ1-42 group (Fig. 3b).

3.4 Hyperforin reduce injury induced MDA production in PC12 cells

During the AD disease, the content of MDA was significantly increased and same result was observed in the supernatant of injured PC12 cells. The injured PC12 cells exhibited the enhanced production of MDA after H2O2 interference and concentration treatment of hyperforin significantly (p < 0.001) down-regulated (Fig. 4a).

A similar momentum was found in the MDA level after Aβ1-42 interference. Aβ1-42 group showed the increased level of MDA and concentration dependent treatment of hyperforin significantly (p < 0.001) reduced the MDA level (Fig. 4b).

Fig. 2  Dose screening of hyperforin to measure the most favourable dose to not affect cell viability. *p < 0.05, **p < 0.01 and ***p < 0.001.

Fig. 3  Screening of β amyloid peptide 1-42 damage conditions. *p < 0.05, **p < 0.01 and ***p < 0.001.

cell lines. Dose dependent treatment of Hyperforin exhibited the cell viability PC12 cells. Consequently, hyperforin (5, 25 and 50 μg/ml) demonstrated the no effect on the PC12 cell viability. On the basis of result, we can select the current dose for the further experimental investigation.

Fig. 4  Effect of hyperforin on the LDH release (a) H2O2 interference and (b) Aβ1-42 interference in an invitro model of AD. LDH = lactate dehydrogenase, Aβ = α amyloid peptide. *p < 0.05, **p < 0.01, ***p < 0.001 and #p < 0.05 vs control.
3.5 Hyperforin suppress the injury induced MDA release via PC12 cells

H$_2$O$_2$ induced group showed the increase MDA content in the PC12 cells, which was significantly ($p<0.001$) inhibited by hyperforin at concentration dependent manner (Fig. 5).

3.6 Platform quadrant time spent analysis

The Probe trial data analysis for rodent treated with colchicine demonstrated the significant down-regulation towards the target quadrant as compared to the control group spends time. Hyperforin treated group animal showed the significantly ($p<0.001$) increased time as compared to the colchicine treated group (Fig. 6).

3.7 Effect of hyperforin on Morris water maze

Colchicine induced group rats showed the higher escape latencies as compared to the normal group and dose dependent treatment of hyperforin exhibited the less escape latencies as compared to the colchicine induced group rats (Fig. 7).

3.8 Effect of hyperforin on P. carbonyl and AchE activity

Figure 8a and 8b showed the increased level of P. carbonyl and AchE activity in the colchicine induced and dose dependent treatment of hyperforin significantly ($p<0.001$) reduced the P. carbonyl and AchE activity. A similar result was observed in the memantine induced group rats.

3.9 Effect of hyperforin on BDNF and Aβ peptide activity

Figure 9a and 9b showed the activity of BDNF and Aβ peptide activity and colchicine induced group rats exhibited the reduce activity BDNF and increased activity of Aβ peptide and dose dependent treatment of hyperforin significantly ($p<0.001$) increased the activity of BDNF and reduced the activity of Aβ peptide.

3.10 Effect of hyperforin on antioxidant parameters

The antioxidant parameters such as GPx, SOD, GR and CAT, reduced in the colchicine induced group rats and dose dependent treatment of hyperforin significantly ($p<0.001$) increased the level of antioxidant parameters. A similar effect was observed in the memantine treated group rats (Fig. 10).

3.11 Effect of pro-inflammatory cytokines

Figure 11 exhibited the level of pro-inflammatory cytokines in the all group rats. colchicine induced group rats showed the increased level of NF-kB and IL-1β and concentration dependent treatment of hyperforin significantly ($p<0.001$) inhibited the pro-inflammatory cytokines level.

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**Fig. 5** Effect of hyperforin on the (a) H$_2$O$_2$ interference and (b) Aβ$_{1-42}$ interference in an invitro model of AD. MDA, malondialdehyde; Aβ, α-amyloid peptide. *$p<0.05$, **$p<0.01$, ***$p<0.001$ and #$p<0.05$ vs control.

**Fig. 6** Effect of hyperforin on colchicine impaired memory and learning in rats scrutinize via probe trial in water maze. Data presents mean ± SEM. *$p<0.05$, **$p<0.01$ and ***$p<0.001$. 

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Fig. 7  Effect of hyperforin on colchicine impaired memory and learning in rats scrutinize via water maze. Data presents mean ± SEM. *p < 0.05, **p < 0.01 and ***p < 0.001.

Fig. 8  Effect of hyperforin on acetylcholinesterase and P. carbonyl activity in hippocampus of rats to estimate the neuroprotective activity in colchicine induced memory impairment. Data presents mean ± SEM. *p < 0.05, **p < 0.01 and ***p < 0.001.

Fig. 9  Effect of hyperforin on BDNF and Aβ peptide activity in hippocampus of rats to estimate the neuroprotective activity in colchicine induced memory impairment. Data presents mean ± SEM. *p < 0.05, **p < 0.01 and ***p < 0.001.
Neuroprotective Role of Hyperforin

Alzheimer’s disease (AD) is a age interrelated neurodegenerative diseases regarded as early cognitive dysfunction connected later via social and behavioural deterioration. The neuropathologic character of AD such as intracellular neurofibrillary, extracellular senile plaques as well as losses of neurons in some part of brain viz., hippocampus region. The hippocampus region is the primary damage region, which is involved in the pathophysiology of disease. Several researches suggest that the formation of amyloid plaques and deposition of β amyloid are considered as the well-known feature of AD. Aβ(39-43 amino acids) peptide that are the result of proteolysis of amyloid precursor protein via γ and β-secretases. In the current experimental investigation, intrahippocampal injection of the summative Aβ(1-42) considerably induced the destructions in cognitive ability in the rodent brain. in the current study, was have observed that the hyperforin can boost the cognitive function (memory and learning) in AD model of rodent.

The production of free radical, reactive oxygen species (ROS) and oxidative damage are take part in the pathogenesis of neurodegenerative disorders. Several researchers confirm that the oxidative stress play an imperative role in underlying mechanism of Aβ arbitrated neurotoxicity in AD. Previous literature indicates that oxidative stress induces early in the expansion of AD, long before the growth of senile plaques. The correlation between redox transition metals, oxidative stress and unusual mitochondria contributes to the production of ROS in diseased neurons. Now, the researcher mainly focus on the anti-oxidant mechanism to reduce the Aβ deposition in both invitro and in-vivo model. Moreover, targeting the free radical production or oxidative stress may be the best approach for the treatment of AD. In the current experimen-
tal investigation, we established the invitro model for AD and comprising the H2O2 and Aβ1-42 induced PC12 cell damage model\textsuperscript{36, 37}. The result showed that the concentration dependent treatment of hyperforin significantly (p<0.001) enhanced the cell viability and reduced the MDA and LDH production in PC12 cells injury model. On the basis of result, we can say that hyperforin having the neuroprotective effect on PC12 cells.

The injury induced by the Aβ1-42 in PC12 cells showed the increased level of oxidative stress via boosting the production of free radicals\textsuperscript{36, 38}. The injury induced via Aβ1-42 was also affected through certain parameters such as product quality, incubation time and solvent. Aβ1-42 induced the toxicity via boosting the deposition of Aβ through increase the production of free radicals and our drug (hyperforin) reduced the Aβ production and improves the anti-oxidant enzymes activity.

In the current time, a huge demand of functional and novel food due to lot of health human benefits. Several investigation suggest that amplify the age start the outflow of proteins and fibrin from the blood brain barrier\textsuperscript{36, 40}. Insight the brain, fibrin stick together the Aβ and start the formation of clots. These generated clots impede the blood flow and start the injury in brain, inflammation and AD in brain. A later investigation exhibited that break down the fibrin down-regulated the deposition of amyloid present in the brain blood vessels of AD rodent and also contribute the enhancing the memory\textsuperscript{35, 41}. Although the proof that reducing the inflammation and fibrin can down-regulate the symptom of AD, hyperforin has not yet been scrutinize for the intention.

Oxidative stress is frequently described as an imbalance between the endogenous anti-oxidant and pro-oxidants and can be determined via estimation the redox state in the plasma\textsuperscript{34, 39}. It also induces the apoptosis and cell death, which may take part to scavenge the free radicals depend on the level of CAT and SOD. CAT and SOD, both are the primary endogenous anti-oxidant and scavenge the hydroxyl radicals.

Malonakdehyde (MDA) is the marker of lipid peroxidation and also contributes the oxidative stress and is consider as the end product of polyunsaturated fatty acid (PUFA)/lipid peroxidation\textsuperscript{42, 43}. The level of the MDA reflects the overall oxidative stress status in the body. In the current experimental study, the MDA level was extant and dose dependent treatment of hyperforin significantly (p<0.001) reduced the MDA level. Various investigations suggest that the oxidative stress related generation of ROS in psychiatric and neurological disorder has been widely acknowledged. In the current investigation increase level of protein carbonyls, lipid peroxidation and reduce concentration of SOD, GSH and CAT was observed in the hippocampus region of colchicine induced group rats and dose dependent treatment of hyperforin significantly (p<0.001) altered the anti-oxidant parameter at dose dependently manner. A opposite momentum was observed in the SOD, CAT and GR level in colchicine induced group rats and dose dependently treatment of hyperforin significantly (p<0.001) increased the level of SOD, GPx, CAT, GR and reduced the oxidative stress in the brain. On the basis of result, we can conclude that hyperforin having neuroprotective effect via anti-oxidant mechanism.

Colchicine induced AD model is very popular model and various researcher used this model. Colchicine induced memory and learning impairment connected with neurodegeneration in different area of brain with maximum severity in the hippocampus region. In the current experimental study, we have found the reduction in the AChE content in colchicine induced group rats and several previous investigation suggest that AChE activity linked with the impaired the memory and learning ability in rodent\textsuperscript{44, 45}. Previous studies claim the anti-inflammatory and anti-oxidant effect of hyperforin in various model rodents. Pathogenesis of AD, two factors such as oxidative stress and inflammation may contribute the progression of disease. So, on the basis of potential effect, we can say that both mechanisms may provide the potential effect in the AD. During the AD, the rigorousness of accumulation of Aβ cerebral and memory dysfunction is related with the marked cholinergic function. Several researches exhibited that marked reduction of Ach in specific area of brain start the memory and learning deficits\textsuperscript{44, 46}. Marked reduction of choline acetyltransferase (ChAT) and boosting the AChE activity may resultant sown-regulation of Ach level. Many experimental investigation suggest that reduction of neuronal AChE activity in experimental rodent start the enhancing the AChE concentration and as a resultant enhance the cognitive function.

Nuclear transcription factor (NF-kB), firstly identified into the B cell of nuclear. It also possesses the capability to join the sequence specific enhancers of immunoglobulins K light chain gene. During the AD, NF-kB going to activate in the senile plaques\textsuperscript{37, 48}. The pathogenesis of AD suggests that the activation of NF-kB and NF-kBp65 level may directly or indirectly linked to the severity of AD. Interleukin-1β (IL-1β) is pro-inflammatory cytokine that mediates the inflammation reaction and also generate the various range of immune-modulatory effects including memory loss, fever and learning impairment\textsuperscript{49}. IL-1β activated during the activation of NF-kB and the activation of IL-1β may be extent the inflammatory reactions. During the AD, the level of NF-kB and IL-1β boosted and dose dependently treatment of hyperforin significantly (p<0.001) reduced the level of inflammatory mediators and claim the anti-inflammatory effects.
Conclusion

On the basis of result, we can say that dose dependently treatment of hyperforin significantly reduced the oxidative stress in Aβ1-42 induced PC12 cell injury via improved the anti-oxidant status. Colchicine induced AD model, hyperforin significantly (p < 0.001) altered the endogenous anti-oxidant status and reduced the inflammatory reaction via alteration of NF-κB pathway.

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Author contribution

All the authors equally contributed for performing the experimental study and proof reading.

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