IJBPAS, December, 2022, 11(12): 5648-5661

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

# PIRACETAM PHARMACOLOGICAL EFFECTS: A REVIEW

**KUMAR A*, MISHRA GP, DHAMA N AND VERMA V**

Department of Pharmaceutical Chemistry, Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University Meerut, 250005, Uttar Pradesh, India

***Corresponding Author: Mr. Aadesh Kumar: E Mail: adesh.adi.chaudhary@gmail.com**

**Received 6th Jan. 2021; Revised 25th Feb. 2022; Accepted 12th April 2022; Available online 1st Dec. 2022**

https://doi.org/10.31032/IJBPAS/2022/11.12.6612

## ABSTRACT

Piracetam is a nootropic substance that has been used in clinical trials for decades but is still a mystery due to a lack of knowledge of its mechanism of action. Its effects like multifactorial therapy in the treatment of brain atrophy, extinction impairments in experimental paradigms of post-traumatic stress disorder, Pharmacokinetics in Focal Cerebral Ischemic Rats,as a metabolic enhancer, Effect on Breath-holding spells, binge eating disorder in rats, effects on the fluidity of the membranes of human blood cells and role in Alzheimer's illness is dealt in this review article.

**Keywords: Nootropic, Antihypoxic, Neurodegeneration, Piractam**

## INTRODUCTION

UCB Pharma first introduced piractam in 1971 as a cyclic derivative of the neurotransmitter-aminobutyric acid (GABA). It was the first "nootropic" drug, a substance that improves cognitive performance without sedating or stimulating the user. While the mechanisms of action of piracetam are still being studied, it has an impact on neuronal and vascular functions. Furthermore, vascular effects are both peripheral and central, implying that piracetam's clinical value extends beyond its nootropic properties. Indeed, in addition to age-related cognitive impairments, piracetam is now approved for the treatment of vertigo, dyslexia, cortical myoclonus, and sickle cell anaemia.

Piracetam is a racetam nootropic medication with the chemical name 2-oxo-1-pyrrolidine acetamide. It is a cyclic derivative of the neurotransmitter -

aminobutyric acid and has the same 2-oxo-pyrrolidone base structure as pyroglutamic acid (GABA) **[1]**.

Piracetam (2-oxo-1-pyrrolidine acetamide) is a GABA (gamma-aminobutyric acid) cyclical derivative. It was initially synthesised in the 1950s by a group of scientists namely Corneliu E. Giurgea, Corneliu E. Giurgea, Corneliu E. There have been instances of it being used for in the 1950s, there was a lot of talk about epilepsy. Piracetam has a number of advantages like improved brain function and has an impact on impaired brain function,without operating as a neural and cognitive function boosting blood flow and acting as a sedative or stimulant **[2]**.

Piracetam is the first example of the class of medications known as 'nootropics.' In experimental animals, it protects brain functioning from externally applied brain 'aggressions' such as hypoxia, electroconvulsive treatment, and barbiturate intoxication. It has been shown to aid learning and memory in a variety of animal models, including elderly animals. It improves cerebral inter- and intrahemispheric connectivity in electrophysiological and behavioural models, implying that it may improve information transit in the brain. Piracetam improves microcirculation by lowering platelet activity, increasing red blood cell deformability, and decreasing endothelial cell adhesion to damaged erythrocytes. Under some conditions, the medication improves recollection of learnt material, verbal capacity, and mental functioning in healthy individuals. In rat cortical slices, piracetam accelerates the glucose degradation, increases 31p incorporation into brain phospholipids, and stimulates adenylate cyclase. Despite its structural similarity to GABA, it appears to have no GABA-like actions in animals. It appears to work by stimulating central cholinergic activity, however it's possible that other neurotransmitters are involved as well **[3]**.

**Piracetam has recently been used in paediatric neurology to treat brain atrophy.**

Piracetam has lately been found to be used as part of multifactorial therapy in the treatment of brain atrophy. In a very severe form of spastic cerebral palsy associated with evidence of significant brain atrophy, multifactorial therapies including intramuscular piracetam, intramuscular cerebrolysin, citicoline (oral and intramuscular), oral pyritinol, and intramuscular nandrolone decanoate were used with a beneficial effect **[4]**.

**Table 1: Summary of piracetam [2]**

| | | |
|---|---|---|
| **A double-blind study compared the effect of piracetam treatment with that of a placebo in postconcussional syndrome suggested that piracetam can be a new drug for the treatment of postconcussional syndrome** | **The use of piracetam was useful in controlling spasticity in eight of sixteen patients with cerebral palsy with minimal side-effects** | **The effect of piracetam on regional cerebral blood flow was studied in 18 patients with acute cerebral ischemia by the intra-arterial 133Xenon clearance method using a 10-detector-equipment. The use of piracetam was associated with a statistically significant (P is less than 0.005) increase of cerebral blood flow in grey matter which was attributed to activation of central nervous system metabolism** |
| **An experimental study on rats showed that piracetam has anxiolytic properties** | **A study showed that in the social interaction test of anxiety, piracetam (100 mg/kg) had an anxiolytic effect very similar to that observed after five days of chlordiazepoxide 5 mg/kg/ day and piracetam (50-300 mg/kg) had a non-sedative anxiolytic effect** | **A double-blind study with a cross-over technique found that piracetam significantly increased verbal learning of dyslexics by 15.0% and volunteer students by 8.6% over and above their placebo increase** |
| **A study reported that treatment of chronic schizophrenic patients with piracetam was associated with cognitive improvement but with no improvements in symptom rating, social behavior rating or the disease state** | **An experimental study showed that piracetam can be useful in the treatment of post-hypoxic edema of the brain by improving the microcirculatory changes and reducing the manifestations of posthypoxic edema of the brain** | **A study reported that the use of piracetam (10 g i.v./hour) in 26 in normal course of delivery at term was associated with a stabilization of cerebral** |
| **In an experimental study on the brain of cats, piracetam (100 mg/kg i.v) was associated with an increased local cortical cerebral blood flow in 84% of the experiments on cats without hypoxia and in 40% of the experiments with slight hypoxia** | **In a double-blind trial, comparing the effects of piracetam and a placebo in 22 patients, the use of piracetam was associated with a significant reduction of symptoms associated with vertigo of central origin. The effect of piracetam was attributed to an enhanced control of the cerebral cortex on the subordinated vestibular centers.** | **Experimental studies on mice showed that piracetam can significantly improve learning capacity of young mice and performance in old mice suggesting that it is effective in improving the function of the aging brain** |
| **A clinical study showed that piracetam 6 g daily given by drip infusions for 10 days was associated with improvement in the acute and chronic syndrome of consciousness disturbances caused by clinical syndromes of cerebrovascular disease and dementia** | **An experimental study showed that piracetam had protective effects in various types of hypoxia in mice, cats and rats except hemic hypoxia induced by injection of sodium nitrite** | **A study compared the effects of piracetam with placebo in a double-blind cross-over study of 30 learning disabled boys. Piracetam caused a decrease in the amount of delta activity and an increase in the average EEG frequency. This effect of piracetam was attributed to increased alertness and/or decreased fatigue** |
| **An experimental study showed that piracetam/choline combination (100 mg/kg of each) was associated with memory enhancement several times better than rats received piracetam alone** | **The use of piracetam in the management of neuroleptic side effects has been reported and a clinical study showed that piracetam in a dose of 40 g given intravenously was effective in reducing the extra-pyramidal side effects induced by neuroleptic drugs** | **A double-blind cross-over controlled trial with a placebo showed that piracetam was effective in tardive dyskinesia** |

## Protection Against Aggressions of the Brain

Piracetam has been demonstrated to protect some brain functions, as measured by EEG, from a variety of 'aggressions' or brain traumas generated by hypoxic or toxic assaults in experimental animals. Both cerebral hypoxia and drug intoxication are

examples of these injuries. When rats were retested after being trained in a passive avoidance test and then exposed to hypoxia, they behaved like untrained animals, whereas those given 100 mg/kg piracetam during the acquisition training or immediately before the retention test showed good retention and acted as if they hadn't been exposed to the amnesic effects of hypoxia.

Piracetam's antihypoxic action was demonstrated in various other animal models, including anoxic, haemic, and ischemic hypoxias, by Nikolova *et al*. (1984), demonstrating that piracetam has a broad range of antihypoxic properties. Similarly, after piracetam treatment, brain recovery time, or the time it took for hypoxic rabbits' EEGs to return to normal, was significantly shortened. The antihypoxic effect of piracetam has also been shown to be enhanced by the simultaneous administration of epoprostenol (prostacyclin; prostaglandin 12), through an unknown mechanism, while piracetam and dihydroergocristine produced similar synergistic effects in animal models of cerebral hypoxia and ischaemia **[5]**.

Dimov *et al*. (1983) used topically applied chemicals known to have a depressive effect on neuronal function to study the effect of piracetam on local depression of cortical activity in cats. Piracetam reduced cortical activity depression caused by potassium chloride, decreased the duration of depression caused by adenosine monophosphate, and provided practically complete protection against depression caused by phenobarbital. In rabbits given an overdose of barbiturates, the effects of piracetam were examined. Piracetam, when given orally or intravenously before a lethal dosage of secobarbital (quinalbarbitone), provided superior protection against death compared to control rats. Piracetam also protected against the EEG correlates of barbiturate intoxication, in addition to mortality **[6]**.

**Piracetam Pharmacokinetics in Focal Cerebral Ischemic Rats**.

Except for brain penetration, all pharmacokinetic parameters of piracetam were found to be similar in the ischemic stroke condition, including area under curve (AUC), maximum plasma concentration (C max), time to reach the maximum plasma concentration (t max), elimination half-life (t 1/2), volume of distribution (V z), total body clearance, mean residence time, and bioavailability. In ischemic stroke rats, piracetam exposure (AUC) in the brain and CSF was found to be 2.4 and 3.1 times higher, respectively, than in control rats. The infarct volume generated by blockage of the middle cerebral artery was reduced by 35.77 percent when piracetam was utilized **[7]**.

**By correcting physiological changes in the cortex and hippocampus, piracetam and risperidone co-treatment corrected extinction impairments in experimental paradigms of post-traumatic stress disorder.**

In the present study investigate was done to observe the effect of piracetam, risperidone, and their combinations in experimentally created PTSD-like phenotype in rats with the goal of improving exposure therapy outcomes by targeting the extinction window with pharmacological drugs in PTSD. A single extended stress model (SPS) was used to induce PTSD-like behavioural alterations in male SD rats. Piracetam, risperidone, and combinations of the two were employed as therapeutic treatments, while sertraline was used as a conventional treatment for 14 days, coupled with extinction training. The SPS paradigm effectively caused PTSD-like behaviour in rats, according to the findings. Risperidone and piracetam were found to be successful in restoring the extinction deficit, behavioural abnormalities, altered cortical and hippocampal BDNF, IL-6, TNF-, caspase-3, oxidative stress indicators, and neurotransmitter levels when used together at high doses. In the combination-treated groups, plasma corticosterone and nitrite levels were also observed to be reversed. In rats, piracetam, risperidone, and their combination restored the physiological cascades in the cortex and hippocampus, as well as successfully suppressing fear memory and a symptom cluster of PTSD-like phenotype, according to early findings. As a result, they could be utilised as an effective complement to exposure therapy for the treatment of PTSD **[8]**.

**Experimental substantiation of the expediency of the combined use of piracetam and metformin for pharmacological cognitive disorders in prolonged hyperglycemia conditions.**

Chronic hyperglycemia, insulin resistance, endothelial dysfunction, and disruption of the blood-brain barrier's integrity are all thought to have a role in the development of cognitive abnormalities in diabetic encephalopathy. Taking this into consideration, one of the most recent trends in the treatment of cognitive impairments caused by persistent hyperglycemia is the co-administration of antihyperglycemic and nootropic drugs, particularly metformin and piracetam. Piracetam has been proven to have insufficient nootropic capacity to eliminate cognitive impairments in experimental alloxan-induced hyperglycemia.

In alloxan-induced hyperglycemia, the combination of metformin and piracetam enhances the level of constitutive NO-synthase of nitric oxide in platelets, which may indicate a favourable effect of the

combination on blood rheological qualities to some extent. The intracellular pool of NADPH, which is required as a cofactor of endothelial NO synthase is effected by piracetam and hence lowers NO production and endothelium-dependent vasodilation, is known to be reduced by prolonged hyperglycemia caused by sustained activation of NADPH oxidase **[9]**.

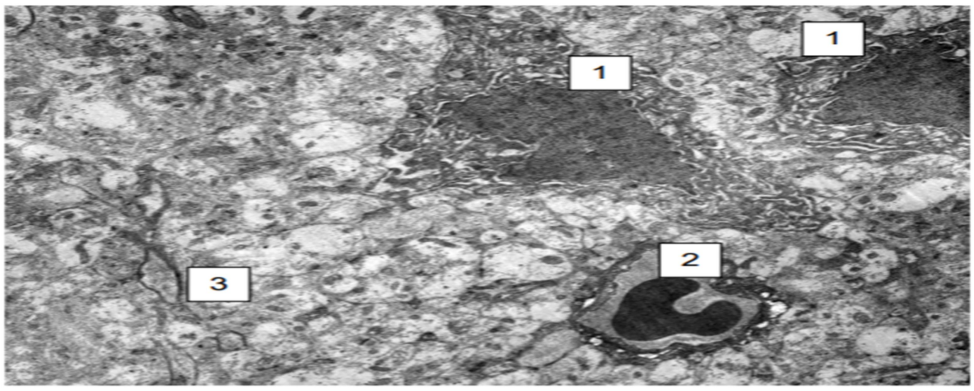


**Figure 1: Hippocampus of alloxan-diabetic rats. 400/500 mg/kg piracetam + metformin Pyramidal neurons with modest ultrastructural abnormalities (1). Arteriole precapillary (2). Tissue oedema is mild and widespread (3). 5000 Electronogram**

**Piracetam a metabolic enhancer, has a new therapeutic effect in the treatment of neurological disease**

Various death signalling systems have been implicated in neurodegenerative illnesses over the last two decades, but no disease-status changing medication is currently available. Because the modern era has seen a number of failures in generating novel pharmacological entities, repurposing clinically utilised medications is a wise approach. Piracetam has been used in clinical trials for a long time, but its mechanism of action is still unknown. Recent research, on the other hand, have revealed new therapeutic activity including interruption in signalling networks. Recent studies have shown that it can reduce ethanol-induced memory loss and neuroinflammation via the mTOR/Akt pathway.

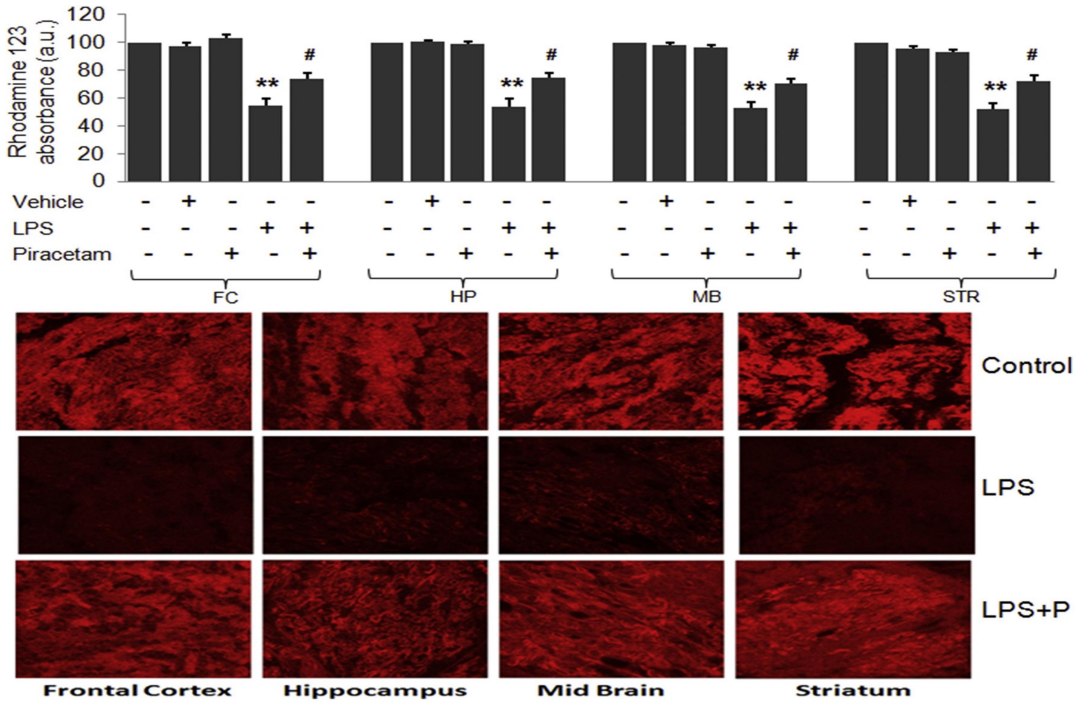


**Figure 2: a- Bar diagram illustrating the (i) reduced activity of glutathione reductase (GRd) enzyme (ii) decreased level of glutathione (GSH) and (iii) increased lipid peroxidation (MDA level) after LPS treatment in frontal cortex (FC), hippocampus (HP), mid brain (MB) and striatum (STR) regions of rat brain. Piracetam treatment inhibited the LPS induced alterations in all rat brain regions. Data are expressed (in % of control) as mean ± SEM, analysed by ANOVA post hoc test Dunnet's and Newman keul's test. * = p < 0.05, ** = p < 0.01 control vs. LPS. # = p < 0.05, ## = p < 0.01 LPS vs. LPS+ piracetam. $$ = p < 0.01 control vs. piracetam per se.**

**b- Western blot images showing the reduced level of glutathione reductase (GRd) and glutathione (GSH) with increased level of malonaldihyde (MDA) after LPS treatment in frontal cortex (FC), hippocampus (HP), mid brain (MB) and striatum (STR) regions of rat brain. Piracetam treatment inhibited the LPS induced alterations in all rat brain regions**

Because it is administered orally, a pharmacokinetic investigation revealed that parameters influencing its brain penetration had no effect on its brain-related therapeutic action. It could also be used in conjunction with metformin to treat dementia in patients with T2DM-induced encephalopathy. Piracetam may also protect rats from ischemia/reperfusion injury caused by testicular torsion/detorsion . The goal of this study was to see how piracetam worked under neuroinflammatory conditions, which are a common occurrence in most brain diseases. The researchers wanted to see if piracetam could help with caspase-independent death, inflammatory reactions, oxidative stress, DNA fragmentation, and apoptosis. Because oxidative stress-mediated neurodegeneration is present in both AD and PD, the researchers first looked at the effect of piracetam on LPS-induced oxidative stress. The researchers discovered that LPS decreased levels of GSH and GRd activity in all of the rat brain regions tested, which were restored with piracetam therapy, demonstrating piracetam's antioxidative properties.

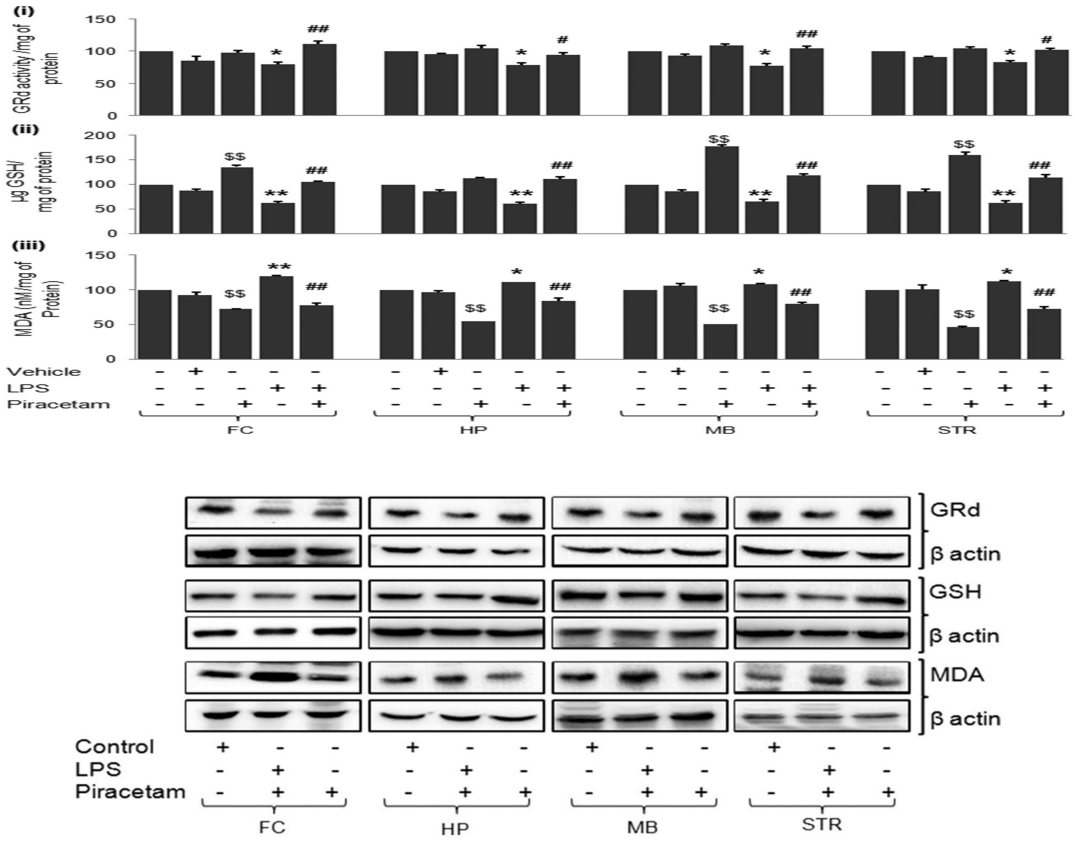


**Figure 3: a- Bar diagram illustrating the (i) reduced activity of glutathione reductase (GRd) enzyme (ii) decreased level of glutathione (GSH) and (iii) increased lipid peroxidation (MDA level) after LPS treatment in frontal cortex (FC), hippocampus (HP), mid brain (MB) and striatum (STR) regions of rat brain. Piracetam treatment inhibited the LPS induced alterations in all rat brain regions. Data are expressed (in % of control) as mean ± SEM, analysed by ANOVA post hoc test Dunnet's and Newman keul's test. * = p < 0.05, ** = p < 0.01 control vs. LPS. # = p < 0.05, ## = p < 0.01 LPS vs. LPS+ piracetam. $$ = p < 0.01 control vs. piracetam per se.**

**b- Western blot images showing the reduced level of glutathione reductase (GRd) and glutathione (GSH) with increased level of malonaldihyde (MDA) after LPS treatment in frontal cortex (FC), hippocampus (HP), mid brain (MB) and striatum (STR) regions of rat brain. Piracetam treatment inhibited the LPS induced alterations in all rat brain regions**

It was previously observed that LPS treatment generated oxidative stress and inhibited mitochondrial complex I activity in the rat brain. Other researchers have described the antioxidative properties of piracetam, which are consistent with present findings. Piracetam administration also resulted in considerable absorption in all of the rat brain regions tested, confirming piracetam's presence in all of them and suggesting a competitive role in such neuroprotective processes. Piracetam treatment to rats results in a large amount of piracetam in the blood plasma. The measured levels suggested that LPS, as well as the inflammatory circumstances caused by LPS treatment, may have a regulatory effect on p-glycoprotein-mediated piracetam absorption **[10]**.

**Effect on Breath-holding spells (BHS)**

In children, breath-holding episodes (BHS) are a common non-epileptic paroxysmal

occurrence. In this study examination of the efficacy of oral theophylline, piracetam, and iron therapies in children with uncomplicated BHS was done. This retrospective analysis included a total of 146 children with uncomplicated BHS (75 females and 71 boys). Nontreated (no anaemia and no treatment), oral theophylline (10 mg/kg/d as a single daily dosage), piracetam (40 mg/kg/d in two divided doses), and elemental iron (3 mg/kg/d as a single daily dose) therapies were given to the children. Only children with iron deficient anaemia received iron treatment.

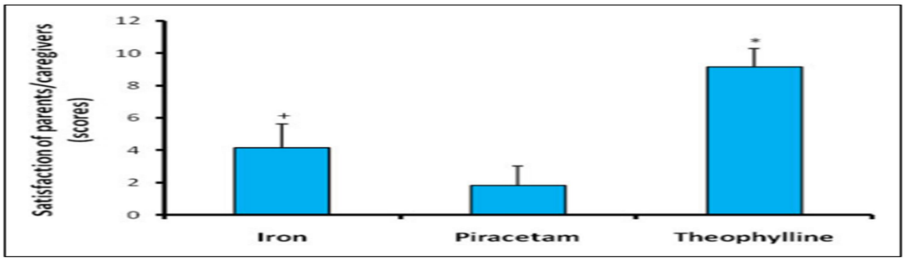


**Figure 4: Scores given by the parents/caregivers to identify satisfaction in the drug treatment groups. þP < .01 when compared to piracetam, *P < .001 when compared to other groups**

All of the youngsters were evaluated neurologically, cardiologically, and biochemically. The bulk of the patients were suffering from cyanotic episodes (83.6 percent). Treatments with iron (58.8%) and theophylline (82.9%) reduced the number of attacks per month significantly, but not with piracetam therapy (8.8%) or the nontreated group (4.7) percent. In the theophylline group, parent/caregiver satisfaction was found to be high (P.001). Theophylline was shown to be the most effective medication for reducing the frequency of simple BHS in children.

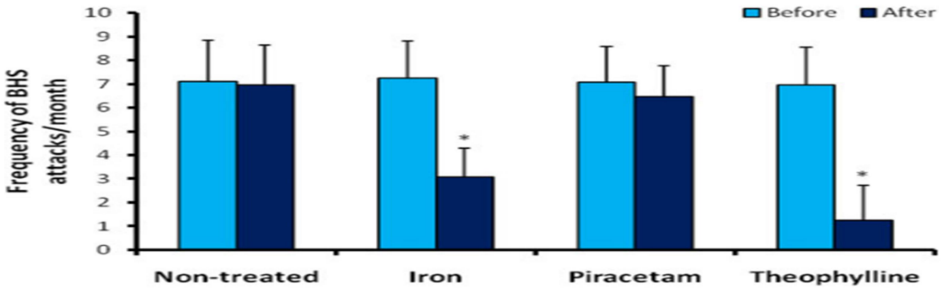


**Figure 5: Frequencies of BHS in study groups before and after treatments. *P < .0001 when compared to before treatment value**

The results of this trial suggest that oral theophylline was successful in treating BHS. Iron treatment can decrease BHS in children with iron deficient anaemia, according to our findings. In this trial, however, piracetam had no discernible

effect on BHS. In this study, 83.6 percent of breath-holding subjects had cyanotic spells, and 16.4 percent had pallid spells, according to the clinical classification. This research findings were in line with those of other investigations. Piracetam was found to be ineffective in the treatment of children with BHS in this research. In a study similar to present, Ashrafi *et al* found that piracetam had no therapeutic benefit when compared to placebo. The use of piracetam in children with BHS has yielded beneficial outcomes in several studies. These studies suggest that piracetam medication reduces the number of assaults significantly. As a result, they come to the conclusion that piracetam is a safe and effective treatment for BHS in children. This research findings, however, contradict this view. One of the study's major flaws is that the data was collected retrospectively, which made it impossible to distribute patients in the treated and nontreated groups in a randomised manner **[11-14]**.

**Piracetam reduces the signs of binge eating disorder in rats**

Binge eating disorder (BED) is a stress-related condition characterised by episodes of binge eating. Other neuropharmacological effects of piracetam, a nootropic drug, have been reported. The current study looked at the influence of piracetam (200 mg/kg i.p.) on BED in female rats that were given free access to palatable cookies for 2 hours on alternate days. An increase in binge eating behaviour and weight gain proved BED. EPM (Elevated plus maze), OFT (open field test), and Y-maze studies show that BED causes anxiety, cognitive, and memory problems. Stress and excitotoxicity are indicated by elevated levels of plasma corticosterone (CORT), glutamate in the nucleus accumbens (NAC), hypothalamus (HYP), and prefrontal cortex (PFC). Furthermore, dopamine levels were found to be higher in NAC and PFC and lower in HYP, suggesting that dopamine is involved in motivating behaviour for palatable eating and cognitive impairments. Surprisingly, in BED, food behaviour controlling hormones such as leptin were raised while ghrelin levels were lowered. In addition, the level of acetylcholine, which controls cognitive behaviour, was reduced in BED. Piracetam reduced binge eating behaviour and associated body weight while also regulating the levels of neurotransmitters in the affected areas. In the fast-refed model, however, piracetam had no effect on regular feeding behaviour. Furthermore, piracetam reduced vascular endothelial growth factor expression in certain brain regions. Piracetam has anxiolytic properties and improved cognitive deficits in BED patients. As a result, preclinical research

suggests that piracetam could be used to treat BED **[15]**.

**In Alzheimer's illness, piracetam also helps to repair membrane alterations**

It was recently shown that the hippocampus membranes of Alzheimer's disease (AD) patients have lower fluidity, which could be attributable to membrane abnormalities that differ from the age-related changes previously observed. Surprisingly, piracetam therapy of AD membranes in vitro also normalised these abnormalities. Hippocampus membranes from age-matched non-demented controls had a weaker effect. Long-term piracetam medication appears to reduce the progression of several clinical aspects of Alzheimer's disease, according to new clinical research. It was believed that the membrane-modifying actions of piracetam are also responsible for this impact, resulting in positive effects on AD-specific signal transduction systems **[16]**.

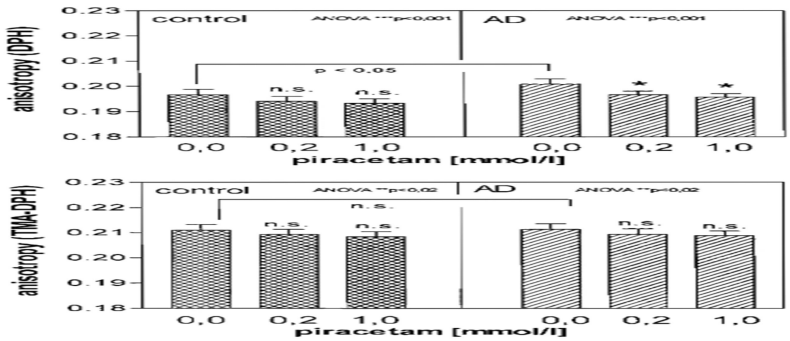


**Figure 6: Effect of in vitro treatment with piracetam (0,2 and l.0mmol/l) on the fluidity of hippocampal brain membranes of AD patients and controls labeled with DPH at 37$^{o}$C**

**Effects on the fluidity of the membranes of human blood cells**

Modification of circulating blood rheological properties through modifying platelet aggrega- tion and adhesion, as well as the deformability of erythrocytes, could be a significant feature of the pharmacological activities of nootropics like piracetam. Although the methods by which piracetam affects both types of blood cells are unknown, at least some of these effects could be related to piracetam's effects at the cellular membrane level. In this research lower hydrocarbon core fluidity in membrane preparations of lymphocytes, platelets, erythrocytes, and neutrophils from old human probands, similar to what we found in the brain was discovered. In vitro treatment with piracetam increased platelet membrane fluidity exclusively in the elderly (but not in the young). Piracetam had no effect on the membranes of the other blood cells in juvenile probands **[17]**.

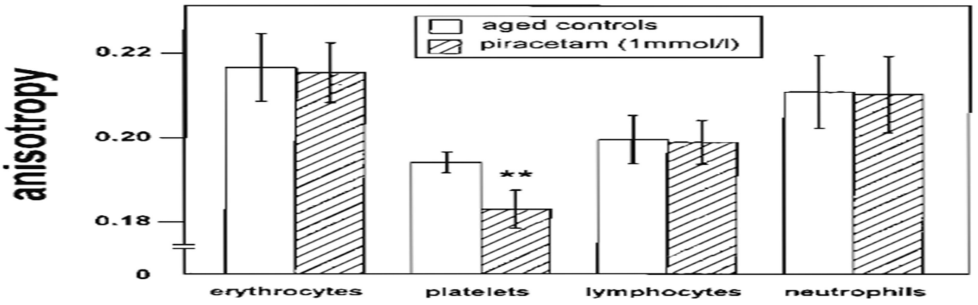


**Figure 7: Effect of in vitro treatment with piracetam (1.0 mmol/l) on the anisotropy of DPH in blood cell membranes from aged but non-demented subjects**

## CONCLUSION

Piracetam has emerged as a important moiety because of its various established pharmacological activities. As a result of it a huge research potential is yet to be explored in the development of its related drugs.

### Conflict of interest

Authors have no conflict of interest.

## REFERENCES

**[1]** B. Winblad, "Piracetam: A Review of Pharmacological Properties and Clinical Uses," 2005.

**[2]** A. Al Mosawi, "Recent Uses of Piracetam in Pediatric Neurology. SunKrist Neurology, Neurosurgery and Stroke Journal Medical leadership View project An accreditded TOT course for physicians View project," Accessed: Feb. 04, 2022. [Online]. Available: https://www.researchgate.net/publication/341189692.

**[3]** M. W. Vernon and E. M. Sorkin, "Piracetam: An Overview of its Pharmacological Properties and a Review of its Therapeutic Use in Senile Cognitive Disorders," *Drugs Aging*, vol. 1, no. 1, pp. 17–35, 1991, doi: 10.2165/00002512-199101010-00004.

**[4]** A. Al Mosawi, "A Novel Therapeutic Approach for the Treatment of Brain Atrophy."

**[5]** M. Nikolova, R. Nikolov, R. Tsikalova, and D. Popivanov, "Piracetam effect on the visual evoked potentials in cats," *Drugs Exp. Clin. Res.*, 1980.

**[6]** S. Dimov, R. Nikolov, M. Nikolova, and S. Moyanova, "Effect of piracetam in some models of general and local depression of the cortical bioelectrical activity in cats," *Arch. Int. Pharmacodyn. Ther.*, 1983.

**[7]** P. Paliwal, D. Dash, and S. Krishnamurthy, "Pharmacokinetic Study of Piracetam in Focal

Cerebral Ischemic Rats," *Eur. J. Drug Metab. Pharmacokinet. 2017 432*, vol. 43, no. 2, pp. 205–213, Sep. 2017, doi: 10.1007/S13318-017-0435-9.

**[8]** A. Uniyal, R. Singh, A. Akhtar, Y. Bansal, A. Kuhad, and S. P. Sah, "Co-treatment of piracetam with risperidone rescued extinction deficits in experimental paradigms of post-traumatic stress disorder by restoring the physiological alterations in cortex and hippocampus," *Pharmacol. Biochem. Behav.*, vol. 185, no. July, p. 172763, 2019, doi: 10.1016/j.pbb.2019.172763.

**[9]** A. E. Lievykh, N. S. Bondarenko, S. N. Dronov, V. I. Mamchur, I. V. Tverdokhlib, and V. I. Zhyliuk, "Experimental substantiation of the expediency of the combined use of piracetam and metformin for pharmacological correction of cognitive disorders in conditions of prolonged hyperglycemia," *Medicni Perspekt.*, vol. 25, no. 3, pp. 30–39, Oct. 2020, doi: 10.26641/2307-0404.2020.3.214647.

**[10]** D. K. Verma *et al* ., "New therapeutic activity of metabolic enhancer piracetam in treatment of neurodegenerative disease: Participation of caspase independent death factors, oxidative stress, inflammatory responses and apoptosis," *Biochim. Biophys. Acta - Mol. Basis Dis.*, vol. 1864, no. 6, pp. 2078–2096, Jun. 2018, doi: 10.1016/J.BBADIS.2018.03.014.

**[11]** A. I. Dai and A. T. Demiryürek, "Effectiveness Oral Theophylline, Piracetam, and Iron Treatments in Children With Simple Breath-Holding Spells," *J. Child Neurol.*, vol. 35, no. 1, pp. 25–30, 2020, doi: 10.1177/0883073819871854.

**[12]** A. Abbaskhanian, S. Ehteshami, S. Sajjadi, and M. S. Rezai, "Effects of Piracetam on Pediatric Breath Holding Spells: A Randomized Double Blind Controlled Trial," *Iran. J. Child Neurol.*, vol. 6, no. 4, p. 9, 2012, doi: 10.22037/ijcn.v6i4.3915.

**[13]** H. Sawires and O. Botrous, "Double-blind, placebo-controlled trial on the effect of piracetam on breath-holding spells," *Eur. J. Pediatr.*, 2012, doi: 10.1007/s00431-012-1680-1.

**[14]** M. M. Donma, "Clinical efficacy of piracetam in treatment of breath-holding spells," *Pediatr. Neurol.*, 1998, doi: 10.1016/S0887-8994(97)00153-7.

**[15]** Y. Hussain and S. Krishnamurthy,

"Piracetam attenuates binge eating disorder related symptoms in rats," *Pharmacol. Biochem. Behav.*, vol. 169, pp. 35–47, Jun. 2018, doi: 10.1016/J.PBB.2018.04.003.

**[16]** B. Croisile, M. Trillet, J. Fondarai, B. Laurent, F. Mauguire, and M. Billardon, "Long-term and high-dose piracetam treatment of Alzheimer's disease," *Neurology*, vol. 43, no. 2, pp. 301–305, 1993, doi: 10.1212/WNL.43.2.301.

**[17]** M. Moriau, L. Crasborn, E. Lavenne-Pardonge, R. Von Frenckell, and C. Col-Debeys, "Platelet anti-aggregant and rheological properties of piracetam. A pharmacodynamic study in normal subjects," *Arzneimittel-Forschung/Drug Research*, 1993. https://pubmed.ncbi.nlm.nih.gov/8457235/ (accessed Apr. 09, 2021).