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ORIGINAL ARTICLE

Neuroprotective Role of Acamprosate and Rasagiline in Epilepsy: *In Silico* and *in Vivo* Study

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Abstract

Background/Aim: Current treatments for epilepsy have only indicative relief without smashing the pathological trademarks of the disease. The unmet need is to find new therapeutic active drug candidates for effective management of epilepsy and associated neurological disorders. The present study aimed to examine the antiepileptic agonistic potential of rasagiline and acamprosate in epileptic mice model.

Methods: Docking studies were performed to predict the binding interaction of rasagiline and acamprosate towards N-methyl-D-aspartate (NMDA) glutamate receptors (PDB: 3QEL). The *in vivo* study was employed in Swiss albino mice. Acute epilepsy was induced by pentylenetetrazole (PTZ) and various behavioural and biochemical parameters were evaluated inconsistently with the pathophysiology of epilepsy.

Results: All the behavioural and biochemical parameters were found to be improved with an increase in rasagiline dosage. The maximum dose of the rasagiline (4 mg/kg, po) produces the maximal anti-epileptic effects. When rasagiline at dose 4 mg/kg was co-administrated with acamprosate 400 mg/kg, the anti-epileptic potential was observed significantly higher than only rasagiline. Both compounds have good docking results with 3QEL in comparison with the PDB-binded ligand. Docking studies of rasagiline and acamprosate highlighted that these drugs have potential in the inhibition of NMDA receptor subunit GluN1 and GluN2B and *in vivo* studies showed their agonistic potential against epilepsy.

Conclusion: The anti-epileptic potential of these drugs could be further explored using more specific anti-epileptic parameters. Further studies still required to be performed so as to explore its potential in clinical trials.

Key words: Acamprosate; Rasagiline; Epilepsy; Pentylenetetrazole; N-methylaspartate.

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Introduction

The uncontrollable and irregular electrical impulses by a group of neurons in the central nervous system (CN)S, induced the condition of epilepsy.[1] As a consequence; the routine of the brain neurotransmission alters some sensual and behavioural functions.[2] Symptoms include loss of awareness, tongue biting, tremors, falling down, twitching motions, urinary incontinence and scleroderma and atherosclerosis. According to the WHO report on epilepsy in 2024, approximately 50 million people in the world have epilepsy.[3] Furthermore; many persons with epilepsy

in developing countries do not receive the necessary healthcare support.[4]

The cellular damage and disease development in the CNS are largely regulated by free radical production. Oxidative stress is a condition where the pro-oxidant balance shifts in the direction of pro-inflammatory radicals, which could cause organic damage. Initially, the concept of oxidative stress was conceptualised as an inequality of reactive oxygen species elimination and generation of new ones. This concept was initially believed to be detrimental to cells.[5] Brain is the most aerobically active and highly susceptible to oxidative-induced damages. Previous studies suggested that oxidative injuries induced by the over production of free radicals have a major contribution to the beginning and development of epilepsy.[6]

Glutamate act as an important excitatory neurotransmitter and glutamate receptors are located in the spinal cord and brain. The N-methyl-D-aspartate (NMDA) response depends upon the exclusive mixtures of subunits. The movement of ions through NMDA receptor coupled ion channels is affected by the contribution of both the NR1 and NR2 subunits.[7] The driving force for Na^+ is reduced by disruption of energy metabolism and neurotoxic abuses. Intercellular movement of cations (ie Na^+) is required for the depolarisation of neurons. Neuronal excitotoxicity is produced by the entry of extra Ca^{2+}, which causes even cell death.[8] Excitation of neurons occurs in the CNS because of NMDA receptors. Additionally, to glutamatergic impulses transmitted from the entorhinal cortex in epilepsy pathology, glutamate-mediated excitability may participate in epilepsy pathology. Furthermore, seizures may trigger selective excitotoxicity cell death by activating NMDA receptors.[9]

Studies showed that rasagiline as a selective MAO-B inhibitor and were approved by USFDA in 2006 for the management of mechanical symptoms in Parkinson disease treatment. Along with MAO-B inhibitory activity, rasagiline indirectly raises the level of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, in the brain.[10] Furthermore, rasagiline was also found to decrease glutamate excite-toxicity in neurons, by antagonizing NMDA and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) glutamate receptors.[11, 12] Rasagiline has also shown antioxidant potential along with neuroprotective and neuro-restorative potential.[13]

Acamprosate is characterised as antagonism of NMDA receptors. It exerts its action by binding on acamprosate binding site.[14] Moreover; acamprosate antagonizes potassium-induced increase in intracellular calcium in mice cultured mesencephalic neurons is directly concentration-dependent.[15] It improves transmission of the GABAergic system by acting as its agonist.[16] It shows anti-inflammatory action by decreasing the release of tumour necrosis factor-α (TNF-α).[17]

A docking score is a value that measures how likely a molecule is to bind to a target. Glide Score is a scoring function that predicts how tightly a ligand binds to a protein. Glide energy is a scoring function used in the Glide docking program to evaluate the binding affinity of a ligand to a protein receptor. Dock Score, Glide Score and Glide energy helps in the identification of target sites of the ligand and the receptor molecule. Docking studies were performed to check the interaction of rasagiline and acamprosate towards NMDA glutamate receptors. On the basis of literature PDB 3QEL (NMDA receptor with subunit GluN1 and GluN2B in complex with ifenprodil) was selected for the docking studies. Docking score, glide score and glide energy in comparison with PDB ligand were used for the study.[18] The current study was planned to assess the antiepileptic potential of rasagiline and acamprosate in mice.

Methods

Chemicals

The rasagiline and acamprosate were bought from *Belco Pharma*, Bahadurgarh, India and pentylenetetrazole (PTZ) was purchased from SRL chemical suppliers. All other chemical used in the study were purchased from *Sigma Aldrich* (*Merk*, NJ, USA).

Animals

Swiss albino mice having weight range 25-30 g, of both sexes were approved by the IAEC of MD University, Rohtak, India and were purchased from Animal House, Luvas University, Hisar, Haryana, India as per the guidelines prescribed by Committee for Control and Supervision of Experiments on Animals (CCSEA), New Delhi, India. CCSEA guidelines were used for all the experimentations on animals with all safety measurement. They were kept in groups of five with water *ad libitum* under

natural day and night cycles. Cervical dislocation method was used for euthanasia described by Aguwa et al.[19]

Experimental model

PTZ-induced acute epilepsy

PTZ (60 mg/kg, intraperitoneally (ip)) was used for the induction of seizures. Animals were observed during the first thirty minutes for behavioural convulsion parameters, ie, latency, duration of convulsions and total number of convulsions. An increase in latency, decrease in duration of convulsions and the number of convulsions was considered as a measure of anti-epileptic potential.[20]

Treatment schedule

Animals were randomly separated into different six groups. Group 1 designed as control group. Epileptic seizures were induced in the remaining five groups with the administration of PTZ (60 mg/kg, oral). Group 2 served as the vehicle. In groups 3, 4 and 5 rasagiline was administered at dose level of 1, 2 and 4 mg/kg respectively.[21] Group 6 administered with acamprosate (400 mg/kg, oral) and co-administered with rasagiline (4 mg/kg, oral).[22]

Behavioural parameters

Following the thirty minutes of test drug(s) administration, seizures were induced by PTZ (60 mg/kg, ip). The animals were detected during the first thirty minutes for behavioural parameters, ie (a) latency, (b) duration of convulsions (c) a total number of convulsions.

Biochemical parameters

Tissue preparation. The mice's brains were extracted following cervical dislocation and rapidly homogenised in ten times their body weight in phosphate buffer (pH 7.4, cold). Brains of animals were submerged in cold normal saline. For fifteen minutes, the homogenates were centrifuged at 3000 rpm. After being separated and placed in an aliquot, cell pellets and supernatants were deep frozen at -20 °C till biochemical analysis.

Superoxide dismutase (SOD) estimation. Using this approach, 0.15 mL of hydroxylamine hydrochloride to the mixture, which already included 0.1 mL of supernatant, 1.9 mL of distilled water, 0.15 mL of Triton-X100 and 75 µL of Nitro blue tetrazolium chloride (NBT). The mixture's absorbance at 560 nm was then used to quantify the amount of superoxide dismutase (SOD) present in the supernatant that inhibited the reduction of NBT.[23, 24]

Catalase estimation. The reaction mixture had 1mL of 0.01 M (7.0 pH) phosphate buffer, brain homogenate 0.1 mL, and 0.4 mL of 2M hydrogen peroxide. By adding 2 mL of the dichromate acetic acid reagent, the process was stopped. Catalase assayed through calorimeter at 620 NM. This procedure involved mixing 0.1 mL of brain homogenate with 0.4 mL of distilled water and 0.1 mL of phosphate buffer 0.01 M, which had a pH of 7.4. Half a mL of 2M H_2O_2 solution was added to initiate the reaction. After cooling (becoming green), the mixture was measured at 570 nm against a blank. Without the addition of H_2O_2 (2–10 mol/mL), the internal blank solution set was operated under the same circumstances. The concentration of catalase was articulated in moles of catalase/mg protein.[25]

Measurement of reduced glutathione (GSH). The treated sample was combined with an equivalent volume of 10 % trichloroacetic acid in order to separate the proteins. The sample is centrifuged at 2000 rpm for 10 minutes at 4 °C. Four mL of water, half a mL of 5-nitrobenzoic acid, two mL of buffer (pH 8.4) and 0.1 mL of the supernatant were added. The absorbance was measured at 412 nm after 15 minutes.[26]

Malondialdehyde (MDA) estimation. A 0.2 mL of sodium lauryl sulphate (8.1 %), 1.5 mL of thiobarbituric acid (0.8 %) and 1.5 mL of ethanoic acid (20 %) with pH 3.5 were combined with 0.1 mL of the treated tissue sample. The mixture was heated to 100 °C for 60 minutes and then cooled under running water. Five mL of n-butanol-pyridine (15:1 v/v) and one mL of distilled water were then added. After centrifuging it at 4,000 rpm and shaking it hard for 10 minutes, a pink organic layer formed. The absorbance at 532 nm was measured using a Shimadzu UV-1800 double beam spectrophotometer in comparison to a blank solution that comprised a reaction mixture free of brain homogenate supernatant. Tetra-methoxy-propane was used to create a standard curve for the purpose of calculating the MDA concentration. The results were expressed as nmol/mg protein.[27]

In silico studies

Schrodinger suite 2022-1 was used for *in silico* studies. Glide module was used to illustrate the

interaction between rasagiline, acamprosate and NMDA-related core proteins. On the basis of mechanism of NMDR antagonist PDB: 3QEL. The target proteins were prepared *via* protein preparation wizard in Schrodinger. Water molecules were deleted along with addition of hydrogen atoms and energy minimisation was achieved using the OPLS_2005 force field. The grid box was generated at centre of the active site of target protein. The rasagiline and acamprosate were docked into the catalytic domain of protein having PDB id 3QEL by using *Grid-based Ligand Docking*. The Dock score, Glide Score, Glide emodel and Glide energy were recorded for additional studies.[28-31]

Statistical analysis

After analysing the data using One-way ANOVA, the Bonferroni multiple comparison post-hoc test was run. The results were presented as mean ± SEM, and the statistical significance was denoted by * or ** for $p < 0.01$ and 0.001, respectively. When comparing p values to the vehicle, $p < 0.05$ was denoted by a '#'.

Results

Effect of rasagiline and acamprosate on latency, duration and number of convulsions

Latency of convulsion was found least in the vehicle-treated group. However, in drug-treated groups, a dose-dependent increase in latency for convulsion was observed, as illustrated in Figure 1(a). Co-administration of drugs revealed a more significant rise in latency for convulsion when compared to the vehicle-treated group.

The effect of rasagiline and acamprosate on the duration of convulsions is demonstrated in Figure 1(b). Different doses of rasagiline exhibited a noteworthy decrease in the duration of convulsions. But the co-administration with acamprosate showed a more noteworthy reduction in the duration of convulsions as compared to vehicle-treated group.

The number of convulsions in different groups is shown in Figure 1(c). In drug-treated groups, a dose-dependent decrease in the number of convulsions was observed. But co-administration of drugs displayed a more significant reduction in numbers of convulsions in contrast to the vehicle-treated group.

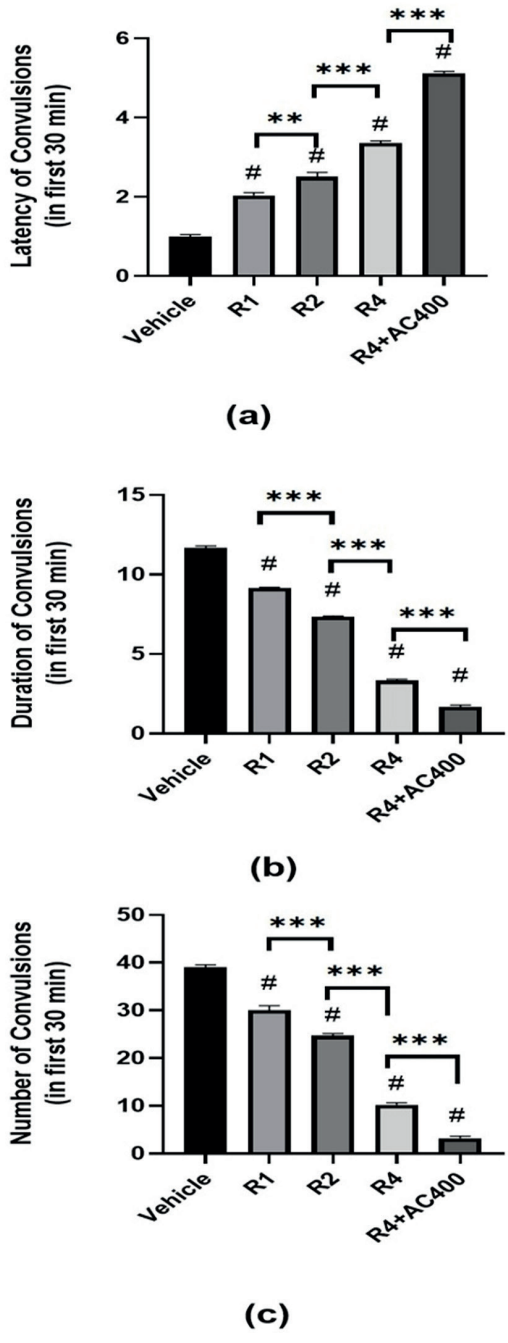

Figure 1: Effect of rasagiline and acamprosate on: (a) Latency of convulsions, (b) Duration of convulsions, (c) Numbers of convulsions (in first 30 min) in mice

R1, R2, and R4 represent rasagiline when administered 1, 2 and 4 mg/kg, po, respectively. AC400 represent acamprosate 400 mg/kg, po.

Effect of rasagiline and acamprosate on SOD level

In Figure 2(a), the SOD levels in the various treatment groups are displayed. Comparing the group treated with the vehicle to the one treated with various medication dose concentrations, the level of SOD improved dramatically. However, the combination demonstrated a higher degree of SOD amplification.

Effect of rasagiline and acamprosate on catalase level

It was discovered that the vehicle group's catalase level was significantly lesser than the control groups. In comparison to other treatment groups, the co-administration of both rasagiline and acamprosate resulted in a significantly higher increase in the catalase level, as seen in Figure 2(b). However, the amount of catalase enzyme increased in a concentration-dependent way with treatment of rasagiline.

Effect of rasagiline and acamprosate on MDA level

Figure 2(c) illustrates the impact of rasagiline and its combination on the MDA level. The group treated with the vehicle had a significant increase in MDA levels, however there was a concentration-dependent decrease in rasagiline. Nonetheless, compared to those receiving a vehicle treatment, co-administration of rasagiline (4 mg/kg) with acamprosate (400 mg/kg) resulted in a more notable decrease in the MDA level.

Effect of rasagiline and acamprosate on GSH level

The GSH levels in the various treatment groups are displayed in Figure 2(d). When compared to the control, the GSH level in the car dropped dramatically. Rasagiline, on the other hand, enhanced the amount of GSH concentration in a dependent manner; nevertheless, the combination showed a greater improvement in GSH levels than the group that received vehicle treatment.

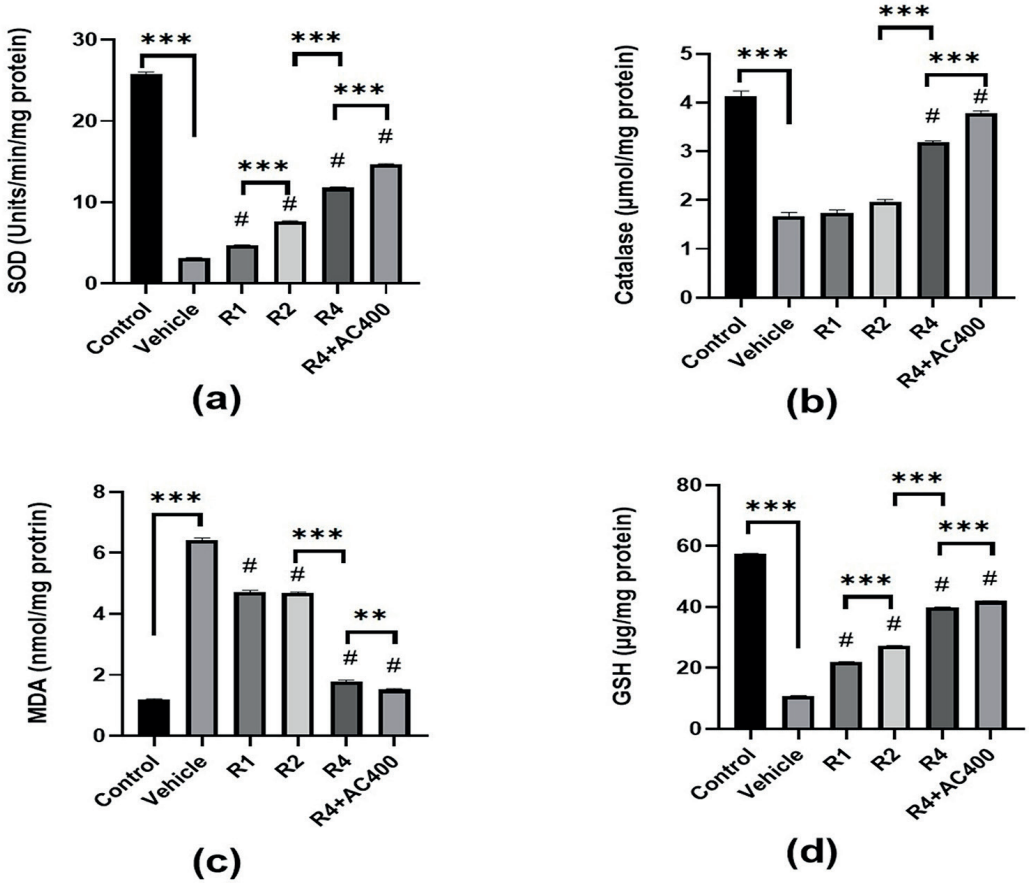

Figure 2: Effect of rasagiline and acamprosate on: (a) Superoxide dismutase (SOD), (b) Catalase, (c) Malondialdehyde (MDA), (d) Reduced glutathione (GSH) level in mice brain

R1, R2, and R4 represent rasagiline when administered 1, 2 and 4 mg/kg, po, respectively. AC400 represent acamprosate 400 mg/kg, po.

Docking results

Docking results have been shown in Table 1. The binding pattern of rasagiline with 3QEL, showed interaction with PRO 78, PHE 114, ILE 111, GLN 110, ALA 107, GLU 106, THR 233 and PHE 176. GLU 106 forms hydrogen bond with the electronegative atom of rasagiline shown in Figure 3. While the binding pattern of acamprosate with 3QEL wrapped by GLU 106, ALA 107, GLN 110, THR 174, TYR 175, PHE 176, PRO 177, MET 207, THR 233 and GLU 236. GLN 110 and GLU 236 forms hydrogen bond with the electronegative atom of acamprosate shown in Figure 4.

Table 1: Docking results of rasagiline and acamprosate against PDB: 3QEL

PDB	Ligand	Docking score	Glide score	Glide emodel	Glide energy
3QEL	3QEL Ligand	-8.685	-8.685	-69.397	-61.725
	Rasagiline	-8.370	-8.370	-62.786	-58.657
	Acamprosate	-7.577	-7.577	-59.109	-57.496

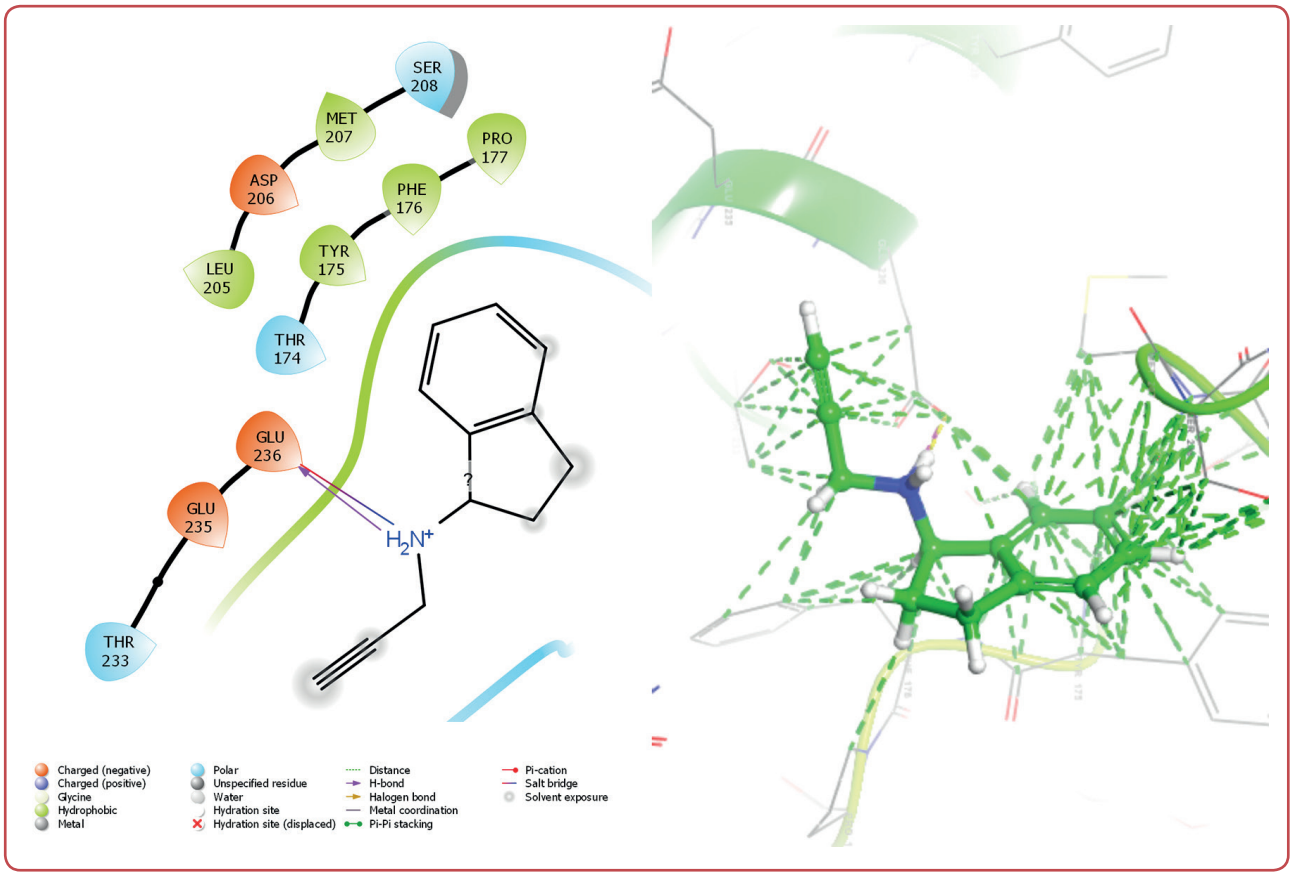

Figure 3: The binding pattern of rasagiline with 3QEL

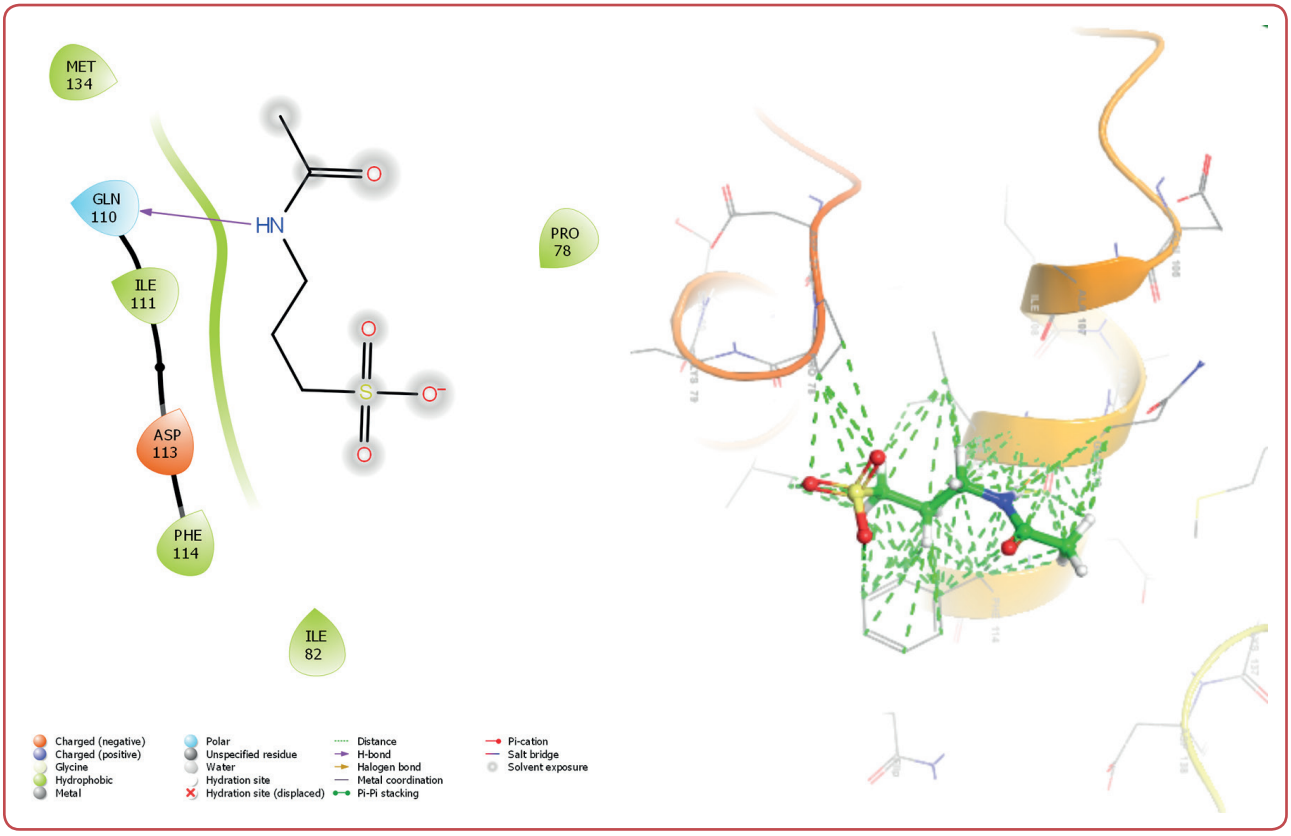

Figure 4: The binding pattern of acamprosate with 3QEL

Discussions

According to the data published by WHO in the year 2024, epilepsy has a prevalence of approximately 50 million people worldwide. Due to the increased prevalence and inability of anticonvulsant drugs to respond appropriately, highlighted attention is required in the development of new generation anticonvulsant drugs.[32]

Dopamine is metabolised by the MAO enzyme (especially MAO-B). It affects the redox status of neuronal and glial cells, which contributes to oxidative stress. The neuroprotective properties of MAO inhibitors and the distinct function of MAO have been demonstrated. MAO-B converts MPTP to MPP+ by oxidation; blocking MAO-B stops MPTP oxidation and hence, MPP+ neurotoxicity. These findings point to a link between MAO-B and neuronal death in neurodegenerative diseases. These inhibitors reduce the oxidation of substrates and oxygen-free radicals, mediate the cell death signal pathway in mitochondria and promote endurance by inhibiting apoptotic Bcl-2 and neurotrophic factors.

When compared to control, rasagiline and acamprosate both showed antioxidant effects in PTZ-induced seizure model. ROS are highly reactive oxidising molecules. Their inequalities cause the activation of cellular defence mechanisms. Due to this, oxidative stress gets increases which damage the biomolecules and lead to cells dis-functioning. Increased ROS also causes deregulation of redox-sensitive signalling pathways and the death of neuronal cells.[33] ROS-induced changes in GABA neurotransmission were revealed in ground breaking research examining the worldwide. The impact of increased oxidative stress leads to damage in neurons. It also affects the transmission of neurons to synapses and the excitability of neurons.

The administration of MAO–B inhibitor and GABA agonist to PTZ-treated mice minimises oxidative stress and reduced the severity of brain and oxidative damage. Inference may be drawn that MAO–B inhibitors and GABA agonists could be a useful adjunct to reduce the risk of brain oxidative damage in epileptic mice.

The epileptic episodes also disturb some sensual anal behavioural functions.[34] Co-administration of rasagiline and acamprosate considerably shortens the length of convulsion; nevertheless, treatment of rasagiline and acamprosate to PTZ produced epileptic mice to enhanced latency of convulsion in a dose-dependent way. Noteworthy, ROS and matrix metalloproteinases (MMPs) are considered as main contributors to the pathogenesis of epilepsy which leads to apoptosis and necrosis of neuronal cells. The ROS generated after the mechanical facilitated injury induces lipid peroxidation. Although both, rasagiline and acamprosate play a significant role in the avoidance in contradiction of ROS mediated brain tissue irregularities. Previous studies reported that acamprosate has strong free radical scavenging properties to reduce lipid peroxidation.[35] In the current study when compared with the vehicle-treated group, rasagiline in different dosages and in co-administration with acamprosate remarkably reduces the level of MDA. The ROS augmented oxidative stress in epilepsy also causes the depletion in enzymatic activity of various antioxidant enzymes. Catalase breaks the hydrogen peroxides into water and oxygen and protects the cell from oxidative damage; is an important antioxidant enzyme present in the body and elevates during the epileptic condition. GSH is also an important antioxidant found in all animal cells, protecting the cells from hydroxyl and superoxide radical damage.[36] Results affirm that rasagiline either alone or in co-administration with acamprosate significantly increases the level of SOD, catalase and GSH in mice brain, when compared with the vehicle-treated group, indicating the potential pharmacological potential of co-administration of rasagiline with acamprosate in diminishing the ROS induced oxidative stress.

In silico study results of rasagiline and acamprosate towards glutamate NMDA-related core proteins justified their mechanism of action. Dock Score, Glide Score, Glide energy and binding affinities of rasagiline and acamprosate towards proteins such as NMDA resulting in antiepileptic activity. Presented study indicates the potential of rasagiline and acamprosate towards epilepsy management and can be utilised together for more effective outcomes.

Conclusion

Many epileptic patients do not receive proper treatment because of not knowing about anti-epileptic drugs, deficiency of educational beliefs, humiliation and poor health organisation. Anti-epileptic potential of rasagiline was observed in a dose-dependent manner amongst the evaluated three doses of rasagiline (1, 2, and 4 mg/kg). All the parameters (latency of convulsion, duration of convulsion, total numbers of convulsions and biochemical) evaluated in the study showed a noteworthy restoration with the enhancement in the dose of rasagiline. The highest dose of rasagiline (4 mg/kg) has shown maximum anti-epileptic potential as compared to other doses used in the study. When this best effective R4 was administered in co-administration with acamprosate (400 mg/kg), the anti-epileptic potential was found to be increased many folds as compared to the rasagiline per se. The mechanism of action of rasagiline and acamprosate towards glutamate NMDA-related core proteins defensible by using docking studies on Schrodinger software and their result showed interaction. Docking and *in vivo* studies suggest anti-epileptic potential of rasagiline and acamprosate. The anti-epileptic potential of these drugs can be explored using more specific anti-epileptic parameters. Also, these drugs may be evaluated in other models of epilepsy.

Ethics

The study was approved by the IAEC of MD University, Rohtak, India with an approval letter No: 360-73, dated 5 May 2016.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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