Ind. J. Pharm. Edu. Res., 2026; 60(2s):s627-s637.
https://www.ijper.org

Original Article

Synthesis and Evaluation of Mutual Prodrug of Mefenamic Acid and Etodolac with Sesamol for the Treatment of Alzheimer's Disease

Prayaga Rajappan Krishnendu[1], Shebina Pareed Rasheed[1,*], Vibina Kaippollil[1], Arun Rasheed[1], Jibin Joy[1], Pattilthodika Suhail[2,*]

[1]Department of Pharmaceutical Chemistry, Al Shifa College of Pharmacy, Perinthalmanna, Malappuram, Kerala, INDIA.
[2]Department of Pharmacology, Al Shifa College of Pharmacy, Perinthalmanna, Malappuram, Kerala, INDIA.

ABSTRACT

Background: Epidemiological and clinical trial data suggest that NSAIDs can be used for managing Alzheimer's disease. This research area began with the observation of reduced incidence and progression of Alzheimer's disease in arthritic patients who are on NSAID medication. **Objectives:** This study focuses on the mutual prodrug of Mefenamic acid and Etodolac with Sesamol for treating Alzheimer's disease. **Materials and Methods:** The mutual prodrugs of NSAIDs with Sesamol were synthesized using the Steglich esterification method. These hybrids were characterized through various spectrometric and physicochemical methods, followed by pharmacological evaluation. **Results:** The hybrids demonstrated improved aqueous and organic solubility along with enhanced lipophilicity. In antioxidant activity tests, the Mefenamic acid prodrug had an IC_{50} value of 101.80, comparable to Ascorbic acid (IC_{50} of 102.90), while the Etodolac prodrug had an IC_{50} value of 97.62, indicating higher activity than the benchmark. The increasing Log p-value (Mefenamic acid prodrug- 3.63 and Etodolac prodrug- 3.72) shows that the synthesized Prodrugs are more lipophilic hence can permeate the BBB easily. Behavioral studies on Albino mice showed cognitive improvements in Alzheimer's disease-induced brains. Microscopic examination of the treated mice brain tissue revealed normal histology compared to the control group. **Conclusion:** These findings suggest that the prodrug strategy may enhance BBB transport characteristics and provide a neuroprotective effect on the brain, offering a promising treatment for Alzheimer's disease in arthritic patients.

Keywords: Alzheimer's disease, Antioxidants, Mutual prodrug, Mefenamic acid, Etodolac, Sesamol, Neurodegenerative disorder.

Correspondence:
Dr. Shebina Pareed Rasheed
Department of Pharmaceutical Chemistry, Al Shifa College of Pharmacy, Perinthalmanna, Malappuram-679325, Kerala, INDIA.
Email: shebinaniz@gmail.com

Mr. Pattilthodika Suhail
Department of Pharmacology, Al Shifa College of Pharmacy, Perinthalmanna, Malappuram-679325, Kerala, INDIA.
Email: ptsuhl@gmail.com

Received: 05-11-2025;
Revised: 29-12-2025;
Accepted: 16-02-2026.

INTRODUCTION

Neurons are the building block of the nervous system which includes the brain and spinal cord.[1] There are 100 billion neurons in a healthy adult responsible for the conduction of signals creating the cellular basis of sensations, emotions, movements, skills, thoughts, and memories,[2] and are normally not replaced themselves if it gets damaged. So, the treatment for Neurodegenerative Disorders (NDs) like Alzheimer's, Parkinson's disease, Huntington disease, Amyotrophic lateral sclerosis, and Prion disease is still a question in the world of Research.[3-9] In our study, we concentrated on the most prevalent, destructive, and incurable disorder among the NDs called Alzheimer's Disease (AD). AD is a cumulative destructive disorder with two major pathologies, hyperphosphorylated tau protein found in neurofibrillary tangles and beta-amyloid plaques.[10-14] The accumulation of plaques may cause neuronal death while the tau tangles will block the entry of nutrients and essential molecules.[15] Only very few FDA-approved drugs (rivastigmine, galantamine, donepezil, memantine, and memantine combined with donepezil) are available for the treatment of AD and are dealing with the symptoms rather than the major cause of the disease.[16-18]

For the past 30 years of research in the field of AD suggested the influence of NSAIDs.[19-24] The characteristic features of AD comprise microglial accumulation, activation of the complement cascade, and cytokine-mediated acute phase response.[23,25] NSAIDs can influence the inflammatory responses by inhibiting the cyclooxygenase enzymes (both COX-1 and COX-2) and also by upregulating Peroxisome Proliferator-Activated Receptor gamma (PPARγ).[26-29] PPARγ, a ligand-activated transcription factor coming under the category of nuclear receptor family which can regulate anti-inflammatory response, mitochondrial

DOI: 10.5530/ijper.20261831

activation in response to various intracellular and extracellular stimuli, and Aβ degradation.[26,30] Although PPARγ is a well-known receptor, its role in the treatment of AD is recently focused on. Besides the influence on PPARγ, NSAIDs are identified as γ-Secretase Modulators (GSMs). GSMs can influence APP and thereby controls the Aβ1-42 population.[21,22,31,32]

Even though we have enough evidence to connect both NSAIDs and AD and the clinical application is still uncertain. The reason behind this uncertainty is thought to be the low lipophilic profile of NSAIDs to cross the Blood-Brain Barrier (BBB).[33,34] 90% of the therapeutic agent aimed to target CNS fails to enter on account of the occurrence of the Blood-Brain Barrier (BBB).[35] As the substrate swing in between the CNS and systemic circulation is regulated by the blood-brain barrier,[36] design a molecule having high permeability for the management of AD is crucial.

Sesamol, a naturally occurring phenolic compound found in sesame oil and seeds, has antioxidant and anti-inflammatory properties. It may have neuroprotective effects, potentially aiding in treating AD by preserving neuronal function and preventing damage.[37] It also initiates caspase cascades and induces apoptosis in cancer cells via pathways controlled by receptors and mitochondria.[38] However, research on its specific effects on Alzheimer's is still in its early stages. More comprehensive studies, including clinical trials, are needed to determine its efficacy, optimal dosage, and safety for human use. Sesamol has been well investigated for its potential as a therapeutic agent, with substantial evidence indicating its role as a metabolic regulator beneficial for the prevention of cancer, inflammation, hepatotoxicity, and oxidative stress from free radicals.[39]

A prodrug concept is an optimistic approach in the field of research in AD as this technique will help to enhance the lipophilicity of moiety.[40] By conjugating an antioxidant to the NSAID, the whole moiety will act as a Mutual prodrug. To enhance the brain availability of NSAIDs and to take the advantage of neuroprotective effect of Sesamol to reduce the oxidative stress, and neuroinflammation associated with AD, mutual prodrug of NSAIDs with antioxidant has been designed.

MATERIALS AND METHODS

Materials and Instruments

Mefenamic acid and Etodolac were purchased from TCI Chennai, Sesamol, Sigma Aldrich USA, N,N'-Dicyclohexylcarbodiimide (DCC) and (4-washed Dimethylaminopyridine) DMAP were from Loba Chemie, anhydrous Dichloromethane (DCM) was from Nice Chemicals, Kochi. The IR spectrophotometer (Shimadzu 8201 PC) at Al Shifa College of Pharmacy in Perinthalmanna, Kerala, was used to record the infrared spectra. NMR spectrophotometer (Bruker Advance II 400 spectrometer) at SAIF Punjab University Chandigarh was used to record ^{1}H and ^{13}C NMR spectra. The samples were prepared in $CDCl_3$ with Tetra Methyl Silane (TMS) as an internal standard, and the results are in parts per million (ppm). IIT Ropar, Chandigarh, used a mass spectrophotometer (Q-Tof Micro Waters) to record mass spectra.[41-44]

Experimental

General method

To the stirred mixture of 10 mmoL of carboxylic acid (mefenamic acid/Etodolac) in 10 mL of anhydrous Dichloromethane (DCM), 110 mg of 4-dimethylaminopyridine (DMAP) and 10 mmol of sesamol were added. The temperature was maintained at 0-8°C, N,N'-Dicyclohexylcarbodiimide (DCC) was added to the above reaction mixture, which was mixed for 5 min at the same temperature and subsequently for 3 hr at 20-25°C. Thereafter, the precipitated urea was removed by filtration, washed with ethanol, and the filtrate was subjected to evaporation. The filtrate was dissolved in DCM and then extracted with saturated $NaHCO_3$ solution and then dried over $MgSO_4$. Evaporation removes the solvent, and recrystallisation isolates the ester. Before recrystallisation, the excess amount of sesamol present in the product was washed off with alcohol.[45,46] The compound was characterized by TLC (Hexane: Ethyl acetate (2:1)), melting point, solubility, Infrared spectroscopy (IR), Proton (^{1}H) NMR, Carbon 13 (^{13}C) NMR, and mass spectrometry (Figures 1 and 2).

Determination of Partition Coefficient

The partition coefficient of drug and Prodrug between n-octanol saturated with phosphate buffer of pH 7.4 was determined using the shake flask technique. A measured quantity of 100 mg of sample was added to 20 mL of n-octanol. To the above solution, 20 mL of phosphate buffer was added. In a separating funnel, the materials were firmly shaken at room temperature. To separate the organic and aqueous layers, set aside for 20 min. The aqueous layer is removed. Each drug and Prodrug's resulting solution was examined, and the absorbance of the solutions was determined by UV spectroscopic method.[47,48]

Protein Binding Studies

The protein binding of drug and Prodrug was investigated in this work using the equilibrium dialysis technique in Phosphate-Buffered Saline (PBS) of pH 7.4. A beaker was filled with 100 mL of a solution of synthesized Prodrugs (10 g/mL) in phosphate buffer. The dialysis tube's opening end was tied with an egg membrane, in which egg albumin (6%) was taken up and dipped into the solution taken in the beaker. The entire system was mounted on a magnetic stirrer and rotated at a slow rate. The temperature was kept at 37±0.5°C. 1 mL of the PBS comprising medication solution was exchanged with 1 ml of fresh PBS every 1 hour. The concentration of the withdrawn samples was determined using a UV spectrophotometer after they were diluted further with 1 mL phosphate buffer.[49,50]

Blood Brain Barrier Permeability Assay (PAMPA)

The Parallel Artificial Membrane Permeation Assay (PAMPA) technique was used in early drug research to predict the passive, transcellular permeation of drugs through the blood-brain barrier. Stock solutions of drug samples in DMSO were prepared at a concentration of 10 mM and stored at 0°C until needed. In order to achieve a final sample concentration of 0.01-0.1 mM and restrict the DMSO concentration to 1% (v/v), the buffer at pH 7.4 was used to dilute the stock solution before it was added to a 96-well filter plate. The final dilutions were added to the donor wells in 270 µL, and 200 µL of pH 7.4 buffer was added to the acceptor well. The donor plate, which has an aqueous donor with an analyte on the bottom, an aqueous receiver on top, and a synthetic lipid membrane in the centre, was placed correctly on top of the acceptofilterer plate to form a sandwich. The test material diffuses from the donor well and enters the acceptor well through the lipid membrane. The sandwich was allegedly intact when it was penetrated. To determine the drug concentration in the donor, receiver, and reference wells, UV spectrometry was used.[51,52]

Stability in different buffer solutions

Prodrugs were tested hydrolytically in both Simulated Gastric Fluid (SGF) at pH 1.2 and Simulated Intestinal Fluid (SIF) at pH 7.4 at 37±0.5°C to evaluate the stability in different conditions. The semipermeable membrane was secured to a glass cylinder with open ends on both sides. Each compound (100 mg) was weighed and placed in a glass cylinder that had been dipped into the various buffer solutions at room temperature for one inch. At half-hour intervals, the sample from the beaker was withdrawn, and the same quantity of buffer solution from the batch solution was transferred to the beaker. UV Spectrometer was used to determine concentration. The procedure was repeated for a total of eight hr.[49,52,53]

Antioxidant Assay (DPPH scavenging assay)

The Kato technique was used to measure hydrogen donating activity in the presence of a stable DPPH radical. 0.05 mL of the test sample (10 mM) dissolved in methanol was added to a methanolic solution of DPPH (100 M, 2.95 mL). After shaking the reaction mixture, the absorbance was evaluated at 517 nm. As a control, ascorbic acid was utilized. The amount of discoloration shows how effective the test chemicals are in scavenging free radicals.[54,55] The following formulae were used to calculate the ability to scavenge the DPPH radical:

$$\% \text{ Antiradical activity} = \frac{\text{Control Absorbance} - \text{Sample Absorbance}}{\text{Control Absorbance}} \times 100$$

Pharmacological evaluation

Experimental Animals

Six groups of albino mice were randomly assigned, each with five mice, consisting of a control and a standard group. The mice were kept in acrylic cages at standard climatic environments of 25°C, comparative humidity of 45-55%, in a fully-ventilated room with a 12:12 hr light: dark cycle, and nurtured ad libitum with standard rat food and water. Before the trial, all animals were given a week of acclimatization. All investigations with animals were held as per the rules of Institutional Animal Ethics Committee (IAEC), Department of Pharmacology, Al Shifa College of Pharmacy, Perinthalmanna, Kerala.

Grouping and induction of neurotoxicity

The aluminum-induced model resulted in neurotoxicity. The oral dose of aluminium chloride (100 mg/kg/day) for three months caused neurodegeneration.[51] All animals were distributed into six groups, each with five animals. The first group receives CMC and acts as a control group. Only Aluminum chloride was given to the second group. Mefenamic acid (50 mg/kg), Etodolac (2 mg/kg), Mefenamic acid prodrug (3 mg/kg), and Etodolac prodrug (0.174 mg/kg) were given orally to the third, fourth, fifth, and sixth groups, respectively.

Behavioral study

Behavioral investigations can assess movement, exploration, and anxiety all at the same time. The open-field test and the marble burying test are the two behavioral tests that are employed.

Open field test

The mice were exposed to an open field apparatus twice (40 cm×50 cm×60 cm), separated by 24 hr. To investigate probable mobility qualities, the equipment's linoleum floor was split into 12 equal squares by chalk lines. In both sessions, the animals were placed in the back left square and allowed to walk around freely for 5 min before being counted for head dips, line crossings, and rearing.[56-59]

Marble burying test

In this experiment, mice were kept in separate plastic cages (21×38×14 cm) with 5 cm thick sawdust bedding. 30 clean glass marbles with a diameter of 10 mm were equally distributed on the bedding. After 30 min of exposure to the marbles, the mice were removed and the marbles that had not been buried were counted. If sawdust-covered two-thirds of a marble's surface area, it was considered buried. As a locomotion index, the total number of marbles buried was considered.[60,61]

Statistical analysis

In a statistical investigation, the pharmacological activity of the produced Prodrugs on animals was evaluated using a one-way

Analysis of Variance (ANOVA). The significance was determined using the Dunnet's-test, and the experimental results were reported as mean SEM.

Histopathological studies

The mice were sacrificed by cervical dislocation after being anesthetized with Ketamine IV infusion. After opening the skull and dissecting the forebrain, the brains were extracted without causing any damage. The materials were fixed in formalin for 48 hr after being rinsed with normal saline and treated separately for histological examinations. Paraffin slices of 5 m thickness were obtained and treated in an alcohol-xylene series before being stained with hematoxylin and eosin dye. Microscopically, the slices were evaluated for histological abnormalities, particularly in the cortex.[62,63]

Evaluation of Physicochemical Properties

The physicochemical properties (logP, TPSA, number of hydrogen bond donors and acceptors, BBB) of new molecules were evaluated with the help of the online software SwissADME.[64-67]

RESULTS

The synthesis of mutual Prodrugs of Mefenamic acid and Etodolac was carried out successfully according to the synthetic protocol. The structures of synthesized compounds were displayed in Figure 1. The anticipated structures were confirmed with the help of various spectral data such as IR, NMR, and Mass.

Chemistry

The synthetic route of prodrugs (both mefenamic acid Etodolac) was shown in scheme 1 and scheme 2. Figure 3 depicts the mechanism through which the ester prodrug is synthesized. Synthesis involves steglish esterification method, formation of an ester group between carboxylic acid of drug and hydroxyl group of an antioxidant. The coupling reaction was carried out in presence of Dicyclohexylcarbodiimide (DCC) and 4-Dimethyl Aminopyridine (DMAP). The intermediate O-acylisourea formed as a result of the reaction between NSAID and DCC converted to active amide in the presence of DMAP. The active amide thus reacted with an alcohol to give ester.

Mefenamic acid-Sesamol prodrug: Pale yellow colour product with yield-76% mp-103-105°C, Rf-0.93, UV Absorbance λ_{max} (nm): 246 (SGF), 260 (SIF), 249 (PBS) IR (KBr, cm^{-1}): 3323 cm^{-1} (NH Stretching), 3076 cm^{-1} (Aromatic CH), 2914 cm^{-1} (Aliphatic CH), 1697 cm^{-1} (Ester C=O). ^1H NMR (400 MHz, $CDCl_3$): δ=2.15, 2.31 (s, 6H) CH_3, 6.008 (s, 2H) O- CH_2-O, 6.64-8.16 (d, 10H Ar.H), 7.32 (t, H Ar.H), 9.16 (s, H) NH ^{13}C NMR (500 MHz, $CDCl_3$): δ=13.99-20.58 (2 CH_3), 104.17-148.15 (18C, Ar C), 101.74 (O-C-O), 167.68 (C=O) Mass (m/z): 362 (M^+).

Etodolac-Sesamol prodrug: White colour product with yield-71% mp-117-120°C, Rf-0.81, UV Absorbance λ_{max} (nm): 253 (SGF), 265 (SIF), 260 (PBS) IR (KBr, cm^{-1}): 3374 cm^{-1} (NH Stretching), 3056 cm^{-1} (Aromatic CH), 2962 cm^{-1}, 2903 cm^{-1} (Aliphatic CH), 1731 cm^{-1} (Ester C=O) ^1H NMR (400 MHz, $CDCl_3$): δ=0.91, 1.29 (t,6H) CH_3, 2.83, 2.89 (m,4H) CH_2, 2.16 (m, 2H) ring CH_2, 3.15

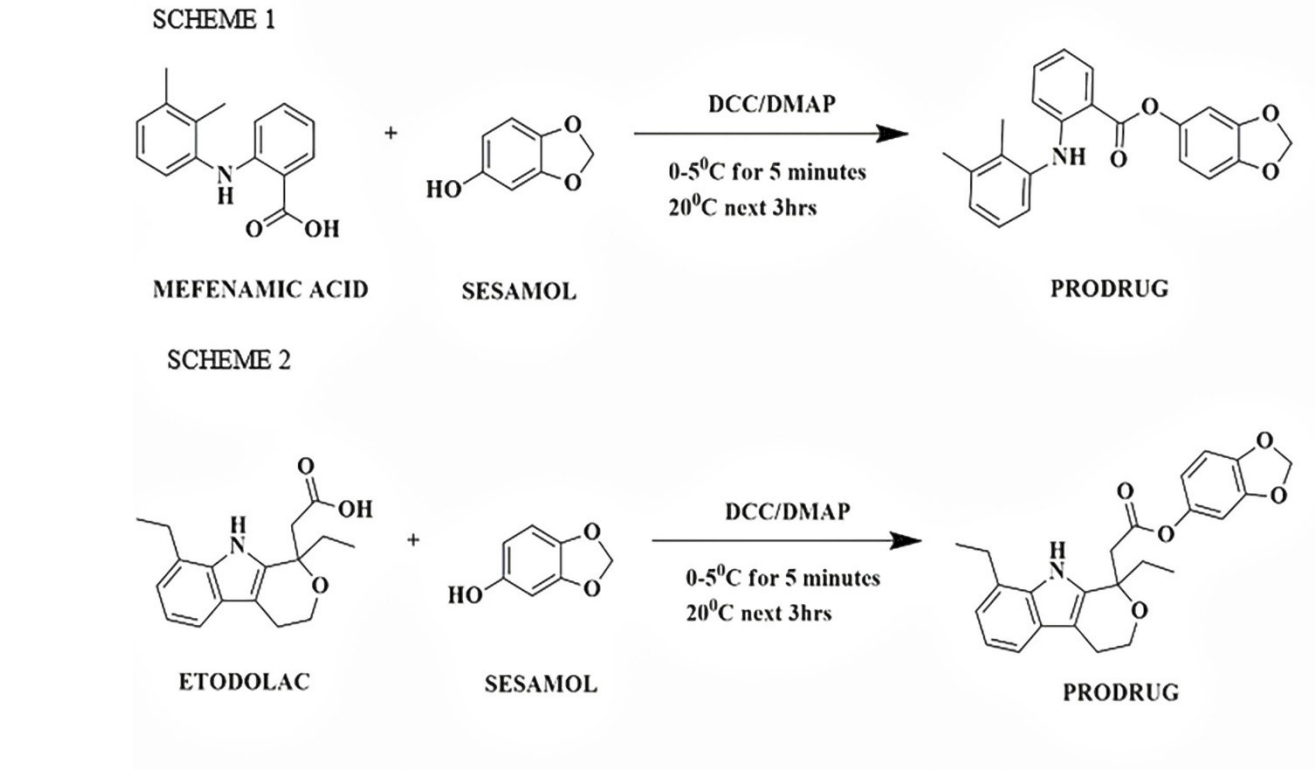

Figure 1: Synthesis scheme of prodrug.

(d, 2H) ring CH_2, 4.01 (m, 2H) CH_2-CO, 5.99 (s, 2H) O- CH_2-O, 6.45, 6.78, 7.01, 7.38 (d, 6H Ar.H), 6.53 (s, H Ar.H), 8.78 (s, H) NH ^{13}C NMR (500 MHz, $CDCl_3$): δ =13.74-7.66 (2 RCH_3) 24.45, 30.79 (2 RCH_2) 148.15-103.58 (12ArH), 22.4-74.75 (3C Cyclo hexanone ring), 43.13 (1C, CH_2-C=O), 171.80 (1C, C=O), 101.83 (1C, O-CH_2-O) Mass (m/z): 408.17 (M+).

Solubility study

The synthesized prodrugs showed low solubility in water, 0.1 M HCl, and 0.1 M NaOH. Acidic medicines like mefenamic acid and etodolac have solubility in 0.1 M HCl. According to the data, prodrugs have higher organic solubility than parent drugs. The solubility of prodrugs in organic solvents including ether, ethanol, and acetone ranges from modest to high, implying increased lipophilic behavior.

Evaluation of Partition Coefficient

The Log P values of Prodrugs were shown to be higher in comparison with parent drugs. According to the findings, the majority of the Prodrugs were partitioned into the organic phase. When compared to the original medication, the synthesized Prodrug has a higher partition coefficient, indicating that the molecule is more lipophilic. This might play a role in the compound's increased absorption through the lipoidal cell membrane of BBB. The Mefenamic acid prodrug has a log P value of 1.35 which is more than the parent drug (0.33) while the prodrug of Etodolac has a value of 1.43 which is also more than that of the parent drug (0.56).

Protein binding study

When compared to parent medicines, the Prodrugs demonstrated much-reduced protein binding (Table 1). This might be advantageous in terms of Prodrug availability for hydrolysis in various body fluids.

Parallel Artificial Membrane Permeability Assay (PAMPA)

The prodrugs' Blood-Brain Barrier (BBB) penetration is assessed using the PAMPA assay. The PAMPA demonstrated that the prodrugs exhibited a noteworthy permeability and CNS bioavailability, with a Pe value exceeding 6.0×10^{-6} cm/s. For CNS medication delivery to be effective, brain penetration is essential. The PAMPA-BBB test was utilised in this investigation to evaluate the brain penetration of Prodrugs. The compound's effective permeability (Log Pe) and the equation were used to calculate the permeation rate. Compounds with a Pe value greater than 4.0×10^{-6} cm/s were classified as potentially permeable (CNS+), while molecules with a Pe value less than 2.0×10^{-6} cm/s were classified as possibly non-BBB permeable (CNS-).

Stability in different buffer solutions

The hydrolysis tests were done in simulated gastric fluid with a pH of 1.2 to represent the state of the stomach, and simulated intestinal fluid with a pH of 7.4 to represent the state of the intestine. Figure 3 shows the results of a comparative study of the Prodrugs in simulated fluids. The quantity of Mefenamic acid regenerated on hydrolysis of the corresponding prodrug in SIF was 76 %, while the extent of Etodolac regenerated was 84 %, according to the findings. The lowest reversal was found at stomach pH (SGF, pH 1.2), suggesting that produced Prodrugs are stable in gastric pH, both fasting and fed. At higher pH values, i.e., in SIF representing the intestine, the percentage reversion was significantly greater, making the free medication accessible for absorption in the intestine. Slow hydrolytic release of both prodrugs in higher pH suggests the slow and sustained release of parent drugs from corresponding prodrugs.

The drug hydrolysis profiles of the Prodrugs were fitted to zero-order and first-order kinetic models as stated in the method, and the results suggest that the first-order kinetic model has a good correlation. As a result, the first-order release rate constant K and associated $t_{1/2}$ values for the Prodrugs were obtained and are shown in Figure 3. The kinetic studies revealed that all of the Prodrugs showed first-order kinetics, with the Prodrugs' $t_{1/2}$ being higher than that of the parent drug.

DPPH Scavenging assay

The antioxidant capabilities of the newly synthesized compounds were assessed using the 2,2-Diphenyl-1-Picrylhydrazyle (DPPH) radical scavenging test, as well as the antioxidant properties of a standard antioxidant, Ascorbic acid, in comparison research with the synthesized compounds. A solution of the purple-colored DPPH radical was combined with the test chemical for the DPPH assay, and the reduction in absorbance was measured spectrophotometrically.

Table 1: Protein binding of Parent drugs and Prodrugs.

Drug	Initial amount of the drug(mg)	Amount of drug bound (mg)	Amount of drug unbound (mg)	Percentage (%)
Mefenamic acid	10	8.91	1.09	89.1
Etodolac	10	9.84	0.16	98.4
Mefenamic acid prodrug	10	6.213	3.78	62.13
Etodolac prodrug	10	7.57	2.43	75.7

This technique is predicated on the DPPH radical being scavenged from the antioxidant, resulting in a reduction in absorbance at 517 nm. The percent inhibition value was calculated using the absorbance obtained which is tabulated in Table 2. Calibration curves were produced using percent inhibition values which were used to calculate the IC_{50} value for Prodrugs and the standard, Ascorbic acid. Mefenamic acid prodrug has an IC_{50} of 101.80, which is equivalent to Ascorbic acid (102.90), while ES has an IC_{50} of 97.62, which indicates that it has greater activity than the benchmark.

Evaluation of Physicochemical Properties

Cheminformatics was used to predict the physicochemical properties of newly synthesized molecules. SwissADME an online software was used to determine the Topological Polar Surface Area (TPSA) and other characteristics. Table 3 lists the characteristics of both parent drugs and prodrugs. A TPSA value of 50-80 Aº indicates better BBB penetration. All of the synthesized compounds had better penetration than the parent compound, according to the findings. The synthesized compounds have a higher log p (octanol/water system) value than the original medication. The increasing Log *p*-value shows that the synthesized Prodrugs are more lipophilic hence can permeate the BBB easily.

The SwissADME data also revealed the number of atoms, volume, number of hydrogen bond acceptors number of hydrogen bond donors, and number of rotatable bonds. The number of hydrogen bond acceptors is less than 10 number of hydrogen bonds is fewer than 5, and the number of rotatable bonds is less than 10. The produced molecules follow all of these approaches.

The BOILED-Egg model represented in Figure 4, predicts the GI absorption and BBB permeability of new compounds. The white portion of the Boiled Egg model reflects the high likelihood of GI tract passive absorption, while the yellow region (yolk) indicates the strong chance of BBB permeability. Both molecules have better polarity as well as lipophilicity, hence better absorption as well permeability.

Pharmacological evaluation

Behavioral Study

The Open field test and the Marble burying test were used to track behavioral characteristics. Tables 4 and 5 show the monitored data and head dipping, rearing, and line crossing were used to measure cognitive function in exploratory behavioral investigations. When compared to CMC-treated mice, oral treatment of aluminium chloride substantially increased neurotoxicity (control group). The neuroprotective activity of the parent drug-treated mice did not improve significantly. However, when compared to the parent drug, all of the Prodrugs exhibited an improvement in habituation memory. The Etodolac-Sesamol Prodrug outperformed the Mefenamic acid-Sesamol Prodrugs in terms of activity.

The marble-burying test provides behavioral data that may be used to evaluate locomotion. When compared to the control group, the aluminium chloride-induced group had reduced motility. However, the synthesized antioxidant mutual Prodrugs

Table 2: Percentage Antiradical activity of prodrugs.

Concentration	% Antiradical activity		
(µg/mL)	Mefenamic acid prodrug	Etodolac prodrug	Ascorbic Acid
15	18.88	15.69	22.23
30	31.91	27.92	30.67
60	44.22	42.48	40.34
120	67.36	59.43	56.98
240	89.89	90.69	86.17

Table 3: Properties of the compounds from SwissADME.

Properties	Mefenamic acid	Etodolac	Mefenamic acid prodrug	Etodolac prodrug
TPSA	49.33 Aº	62.32 Aº	56.79 Aº	69.78 Aº
LogP	2.27	2.23	3.63	3.72
Heavy atom	18	21	27	30
Rotatable bonds	3	4	5	6
Violations	0	0	0	0
H bond Acceptors	2	3	4	5
H bond Donors	2	2	1	1
Aromatic Heavy atom	12	9	18	15

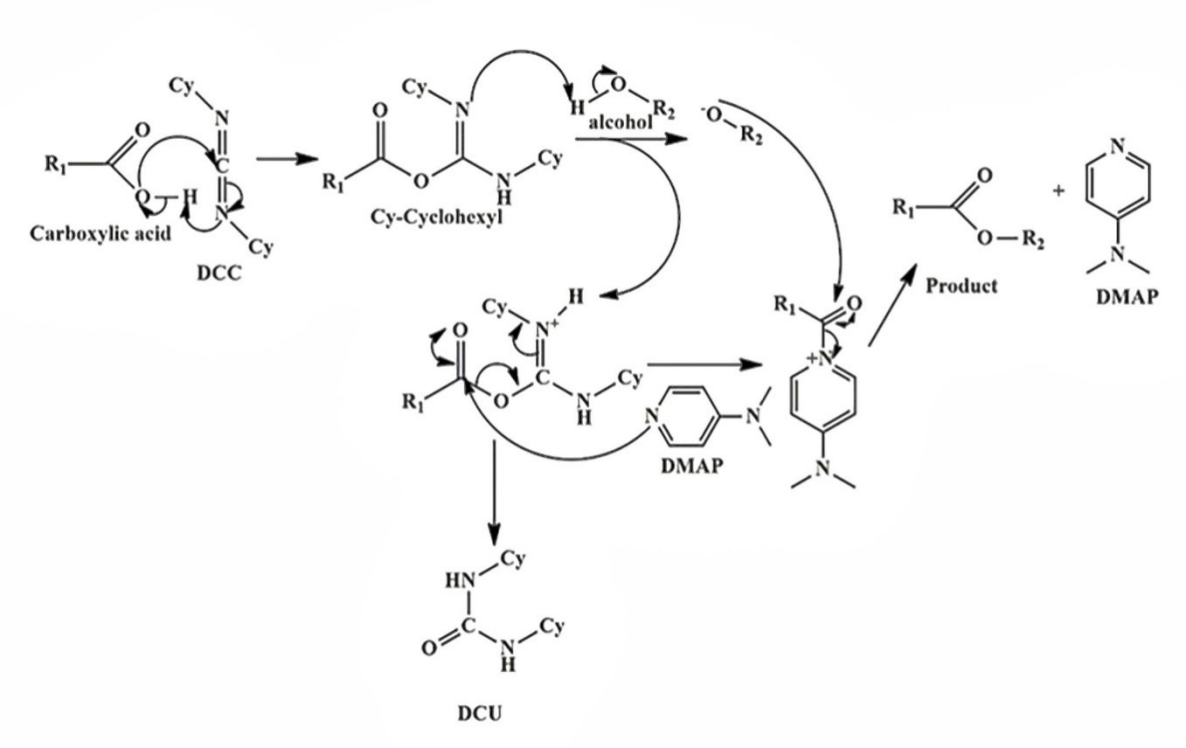

Figure 2: Mechanism of esterification mediated by Dicyclohexylcarbodiimide.

Table 4: Effect of synthesized Prodrugs on Open Field Exploration.

Group		Open Field Exploration (counts/5 min)		
		Head dips	Rearing	Line crossing
Group 1	CMC	10±0.447	24±0.836	32±0.483
Group 2	$AlCl_3$	1±0.000[a]	6±0.316[a]	12±0.836[a]
Group 3	$AlCl_3$+Mefenamic acid	4±0.836[b]	15±0.800[b]	24±0.000[b]
Group 4	$AlCl_3$+Etodolac	3±0.707[c]	13±0.663[c]	20±0.225[c]
Group 5	$AlCl_3$+Mefenamic acid prodrug	7±0.547[d]	19±0.316[d]	28±0.707[d]
Group 6	$AlCl_3$+Etodolac prodrug	9±0.836[e]	22±0.707[e]	31±0.924[e]

The results are expressed as the mean SD of five animals. ANOVA statistical significance is shown by superscripts, followed by Dunnet's test. [a] $p<0.001$ denotes the importance of the difference between groups 2 and 1. [b] $p<0.05$ denotes the difference between groups 3 and 2. [c] The significant comparison of Group 4, 5, 6 with Group 3 is represented, $p<0.05$, [d] $p<0.01$, and [e] $p<0.001$.

treated groups outperformed the parent drug-treated group in terms of activity. Etodolac in combination with sesamol prodrugs had more action than Mefenamic acid in combination with antioxidant prodrugs. The following Table 5 depicts the outcome of marble burying. The values are expressed as the mean SD of six animals.

Histopathological studies

The results of histopathology of mouse brains from the CMC (Control), the negative control group, Mefenamic acid prodrug, the prodrug of Etodolac, Mefenamic acid, and Etodolac treatment groups were examined and which is depicted in Figure 5. In the cerebellum of control animals injected with CMC, the cell arrangement and architecture are normal. The astrocytes and glial cells are normal, and the cerebellum is normal. The architecture of cells in the brain exhibited some substantial change in the brain sections of parent drug-treated groups such as Etodolac and Mefenamic acid. The section shows abnormal astrocytes and glial cells. The brain architecture of the negative control group exhibited larger nuclei and deviations from normal and a few giant astrocytes are seen. There are diffuse and focal collections of lymphocytes and plasma cells. Some areas show necrosis. Similar changes are seen in the cerebellum also. The animals treated with prodrugs exhibited Normal astrocytes and glial cells. There are no signs of stromal edema and the cerebellum is found to be normal.

DISCUSSION

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are commonly used as neuroprotective agents in treating neurodegenerative disorders due to their role in inflammatory processes. However, their low brain accessibility hinders their therapeutic use. To improve their use, regular dosages and targeted drug

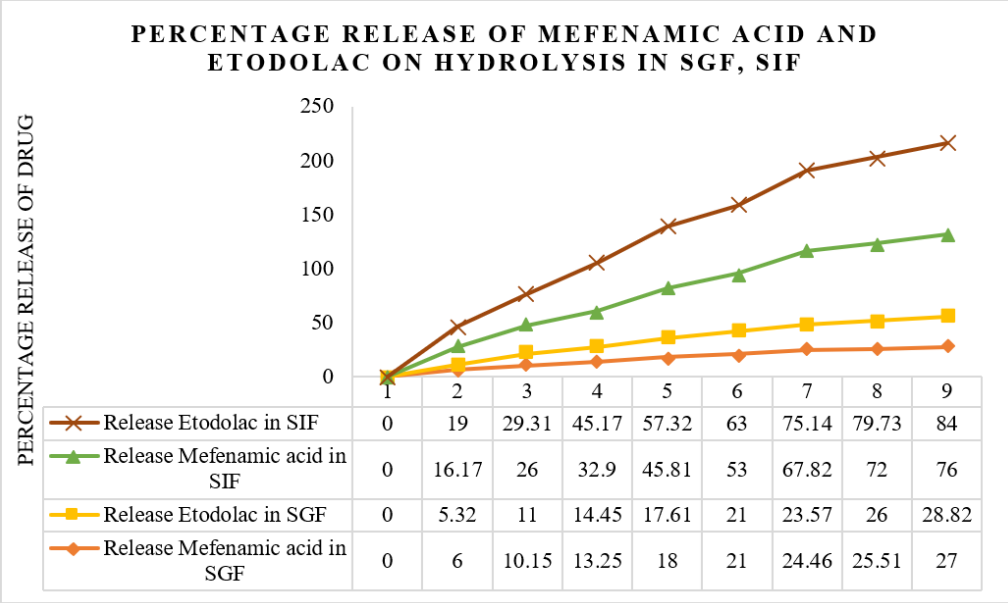

Figure 3: First-order kinetic plots of prodrugs in SGF and SIF.

delivery through prodrug-based drug design are crucial in the pharmaceutical industry.[19-25]

The study introduces Mutual Prodrugs, a method to improve brain accessibility by temporarily hiding the acidic group of NSAIDs like Mefenamic acid and Etodolac. These prodrugs were created by conjugating Mefenamic acid and Etodolac with Sesamol using Steglish esterification techniques. Thin-Layer Chromatography (TLC) confirmed the purity of both the synthesized prodrugs and their parent drugs, as indicated by a single spot on the chromatogram. Prodrugs, which have greater aqueous and organic solubility than parent drugs, are lipophilic and have increased lipophilicity, potentially contributing to increased drug absorption across the lipoidal cell membrane in the brain.

The prodrug formulated with sesamol exhibited increased anti-inflammatory action and demonstrated a sustained release profile using the carrageenan-induced paw oedema technique. Numerous investigations shown that carrageenan induces paw oedema. The oedema caused by carrageenan elicited an immediate and localised inflammatory response.[68]

Prodrugs are characterized to ensure they have the anticipated characteristics and are more readily available for hydrolysis in various bodily fluids.[37] *In vitro* hydrolysis tests were conducted in SGF (pH 1.2) and SIF (pH 7.4) to simulate the state of the stomach and duodenum. The lowest reversion was found at stomach pH (1.2), indicating that produced Prodrugs are stable in gastric pH, both fasting and fed. The kinetic experiments determined the rate of hydrolysis and the $t_{1/2}$ values, with both Prodrugs having first-order kinetics and a higher $t_{1/2}$ than the parent drug. The DPPH test and the percent antiradical activity of synthesized prodrugs were shown to be more active in the biochemical

Table 5: **Effect of synthesized Prodrugs on marble-burying test.**

	Group	Number of marbles buried (5 mi)
Group 1	CMC	25±0.924
Group 2	$AlCl_3$	8±0.582[f]
Group 3	$AlCl_3$+Mefenamic acid	16±0.550[g]
Group 4	$AlCl_3$+Etodolac	15±0.789[h]
Group 5	$AlCl_3$+Mefenamic acid prodrug	20±0.581[i]
Group 6	$AlCl_3$+Etodolac prodrug	22±0.581[j]

The statistical significance determined by ANOVA using Dunnet's test is shown by the superscript. The significance of the difference between the negative control and group 1 is represented by [f] $p<0.01$. [g] $p<0.05$ denotes the importance of the difference between groups 3 and 2. The importance of 4, 5, 6 in group 3 is represented by [h] $p<0.05$, [i] $p<0.01$, and [j] $p<0.001$.

investigation. Recent advancements in pharmaceutical sciences and biotechnology have greatly expanded the number of drugs under development for treating AD. However, the BBB remains a major functional and structural hurdle for drugs targeting specific brain areas. One potential method to enhance drug delivery for AD is the implementation of a prodrug strategy.[69,70] Therefore, utilizing prodrug designs that leverage endogenous transporters and enzymes within the BBB may offer improved treatment options for AD.[69,70]

The topological polar surface area, which was discovered through molinspiration, is an essential metric for predicting the transport characteristics of medicines. Synthesized Prodrugs have Topological Polar Surface Areas (TPSA) ranging from 50 to 80 A°. The TPSA value with the lowest measurement indicated the

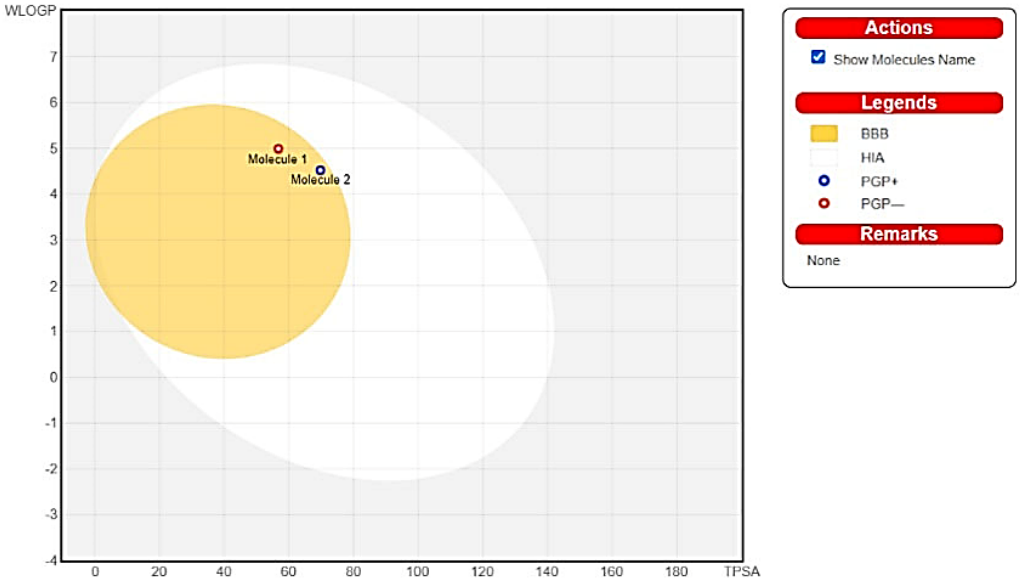

Figure 4: Boiled-egg prediction of GI absorption and brain penetration.

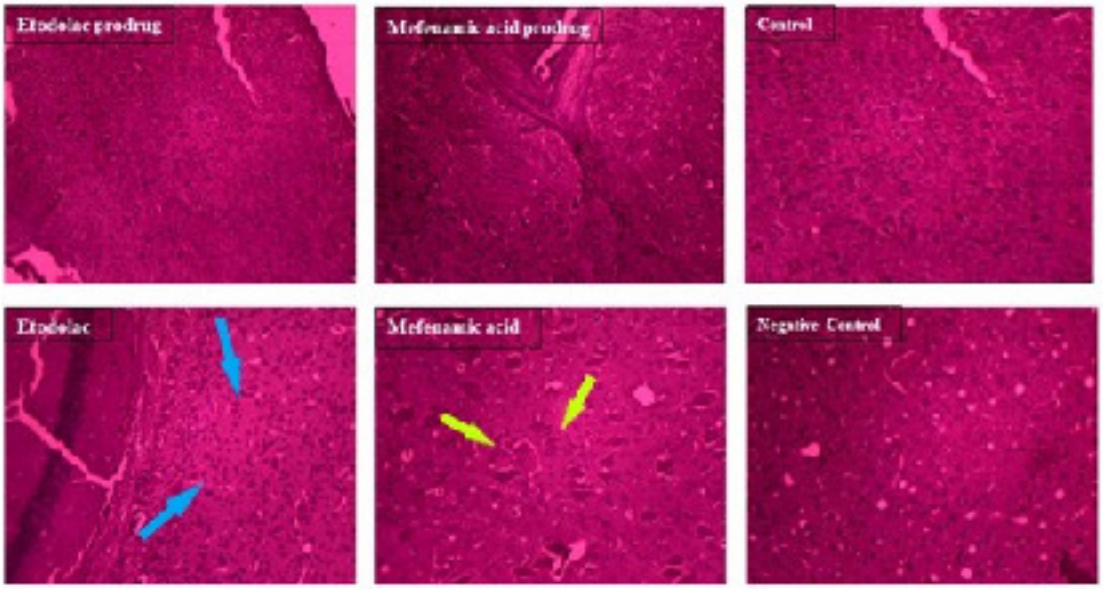

Figure 5: Histopathological studies of the cerebellum. Mefenamic acid prodrug treated group has shown sections that show normal astrocytes and glial cells, the stroma shows edema and inflammatory cell infiltrate and the cerebellum shows small foci of necrosis and inflammatory reaction than the Mefenamic acid treated group (yellow arrow). While the Etodolac prodrug treated group shows normal astrocytes and glial cells. Stroma shows edema and inflammatory cell infiltrate. Cerebellum also shows edema, a small area of necrosis, and a collection of inflammatory reactions than the Etodolac treated group (blue arrow).

highest transport efficiency through lipoidal membranes, such as the BBB.

A pharmacological study was conducted to validate the actions of synthesized Prodrugs by monitoring behavioral characteristics and brain histology. The study used the Marble burying test to track the behavioral characteristics of rats who showed cognitive impairment due to neurodegeneration after receiving aluminium chloride orally. The study demonstrated the efficacy of prodrugs against neurodegenerative diseases, with the synthesized prodrug-treated groups outperforming the parent drug-treated group in terms of activity. The study also found that both Prodrugs showed normal cortical cells in the cerebral cortex of control rats, indicating a protective effect. The neuroprotective effect was observed in all Prodrug-treated animals.

CONCLUSION

As a result, the novel prodrugs produced outperformed the original drug in terms of lipophilicity, brain targeting efficiency, drug targeting index, relative efficiency, and concentration efficiency. Based on the findings, it can be inferred that the

prodrug strategy might achieve the objective of enhancing BBB transport characteristics while also having a neuroprotective impact on the brain. With this background, it would be useful to focus future studies on the clinical features of antioxidant-based NSAID prodrugs to produce a powerful prodrug that is more stable, soluble, and bioavailable and has a greater neuroprotective impact. To confirm, we must carry out additional assessments. The positive results can be due to prodrugs due to a combination of antioxidant and anti-inflammatory actions of sesamol and NSAIDs, respectively. The combination of the anti-inflammatory and antioxidant properties of NSAIDs and sesamol may account for the favourable outcomes. Numerous literary works substantiate the notion that neuroinflammatory conditions and oxidative stress play a role in the progression of neurodegenerative diseases.

ACKNOWLEDGEMENT

All the authors thank the faculties of Al Shifa College of Pharmacy, SAIF, Punjab University Chandigarh, and IIT Ropar, as well as JEEVA Speciality Laboratory Thrissur, for providing the best of all possible facilities, which has made our venture easier.

ABBREVIATIONS

NDs: Neurodegenerative Disorders; **AD:** Alzheimer's disease; **PPARγ:** Peroxisome Proliferator-Activated Receptor Gamma; **GSMs:** γ-Secretase Modulators; **BBB:** Blood-Brain Barrier; **DCC:** Dicyclohexylcarbodiimide; **DMAP:** Dimethylaminopyridine; **DCM:** Dichloromethane; **TMS:** Tetra Methyl Silane; **PAMPA:** Parallel Artificial Membrane Permeation Assay; **SGF:** Simulated Gastric Fluid; **SIF:** Simulated Intestinal Fluid; **TPSA:** Topological Polar Surface Area.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL COMMITTEE APPROVAL

All investigations with animals were held as per the rules of Institutional Animal Ethics Committee (IAEC), Department of Pharmacology, Al Shifa College of Pharmacy, Perinthalmanna, Kerala (IAEC/082/22).

SUMMARY

The novel prodrugs outperformed the original drug in terms of lipophilicity, brain targeting efficiency, drug targeting index, relative efficiency, and concentration efficiency. This suggests that the prodrug strategy could enhance BBB transport characteristics and have a neuroprotective impact on the brain. Future studies should focus on antioxidant-based NSAID prodrugs for more stable, soluble, and bioavailable prodrugs with greater neuroprotective impact.

REFERENCES

1. Franze K, Janmey PA, Guck J. Mechanics in neuronal development and repair. Annual review of biomedical engineering. 2013;15(1):227-51. https://doi.org/10.1146/annurev-bioeng-071811-150045
2. Liu J, Hlávka J, Hillestad RJ, Mattke S. Alzheimer's disease facts and figures. Alzheimer's Dement. 2020; 16: 391-460.
3. Lopez JA, González HM, Léger GC. Alzheimer's disease. Handbook of Clinical Neurology. 2019;167:231-55. https://doi.org/10.1016/b978-0-12-804766-8.00013-3
4. Hayes MT. Parkinson's disease and Parkinsonism. The American journal of medicine. 2019;132(7):802-7. https://doi.org/10.1016/j.amjmed.2019.03.001
5. Kalia LV, Lang AE. Parkinson's disease. The Lancet. 2015; 386(9996): 896-912. https://doi.org/10.1016/s0140-6736(14)61393-3
6. Khanna K, Gambhir S, Gambhir M. Current challenges in Detection of parkinson's disease. Journal of Critical Reviews. 2020;7(18):1461-7.
7. Coupé C, Gordon PH. Amyotrophic lateral sclerosis-clinical features, Pathophysiology and Management. European Neurol Rev. 2013; 8: 38-44.
8. Roos RA. Huntington's disease: a clinical review. Orphanet journal of rare diseases. 2010;5:1-8. https://doi.org/10.1186/1750-1172-5-40
9. Liberski PP, Gajos A, Sikorska B, Lindenbaum S. Kuru, the first human prion disease. Viruses. 2019; 11(3): 232. https://doi.org/10.3390/v11030232
10. Brion JP, Couck AM, Passareiro E, Flament-Durand J. Neurofibrillary tangles of Alzheimer's disease: an immunohistochemical study. Journal of submicroscopic cytology. 1985;17(1):89-96.
11. Zhagn L, Li Z. Alzheimer and the discovery of Alzheimer's disease. Zhonghua yi shi za zhi (Beijing, China: 1980). 2014;44(5):288-90.
12. Cole GM, Teter B, Frautschy SA. Neuroprotective effects of curcumin. The molecular targets and therapeutic uses of curcumin in health and disease. 2007:197-212. https://doi.org/10.1007/978-0-387-46401-5_8
13. Peng C, Trojanowski JQ, Lee VM. Protein transmission in neurodegenerative disease. Nature Reviews Neurology. 2020; 16(4): 199-212. https://doi.org/10.1038/s41582-020-0333-7
14. Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. Nature medicine. 2004;10(Suppl 7):S10-7. https://doi.org/10.1038/nm1066
15. Hanseeuw BJ, Betensky RA, Jacobs HI, Schultz AP, Sepulcre J, Becker JA, Cosio DM, Farrell M, Quiroz YT, Mormino EC, Buckley RF. Association of amyloid and tau with cognition in preclinical Alzheimer disease: a longitudinal study. JAMA neurology. 2019; 76(8): 915-24. https://doi.org/10.1001/jamaneurol.2019.1424
16. Briggs R, Kennelly SP, O'Neill D. Drug treatments in Alzheimer's disease. Clinical medicine. 2016;16(3):247-53. https://doi.org/10.7861/clinmedicine.16-3-247
17. Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. F1000Research. 2018;7. https://doi.org/10.12688/f1000research.14506.1
18. Suhail P, Venkatachalam VV, Joseph S, Murali R, Renganathan AB. In vitro Anticancer Potential and Molecular Modelling Study of Flavanol Glucoside from Graviola (Annona muricata) Fruit: A Potential Inhibitor of Antiapoptotic Proteins. 2024;13(4): 167-77. https://doi.org/10.33263/LIANBS134.167
19. McGeer PL, Rogers J. Anti-inflammatory agents as a therapeutic approach to Alzheimer's disease. Neurology. 1992; 42(2): 447. https://doi.org/10.1212/wnl.42.2.447
20. Weggen S, Eriksen JL, Das P, Sagi SA, Wang R, Pietrzik CU, Findlay KA, Smith TE, Murphy MP, Bulter T, Kang DE. A subset of NSAIDs lower amyloidogenic Aβ42 independently of cyclooxygenase activity. Nature. 2001;414(6860):212-6. https://doi.org/10.1038/35102591
21. Prade E, Bittner HJ, Sarkar R, Del Amo JM, Althoff-Ospelt G, Multhaup G, Hildebrand PW, Reif B. Structural mechanism of the interaction of Alzheimer disease Aβ fibrils with the non-steroidal anti-inflammatory drug (NSAID) sulindac sulfide. Journal of Biological Chemistry. 2015; 290(48): 28737-45. https://doi.org/10.1074/jbc.m115.675215
22. Weggen S, Eriksen JL, Sagi SA, Pietrzik CU, Ozols V, Fauq A, Golde TE, Koo EH. Evidence that nonsteroidal anti-inflammatory drugs decrease amyloid β42 production by direct modulation of γ-secretase activity. Journal of Biological Chemistry. 2003;278(34):31831-7. https://doi.org/10.1074/jbc.m303592200
23. Aisen PS. Inflammation and Alzheimer's disease: mechanisms and therapeutic strategies. Gerontology. 1997; 43(1-2): 143-9. https://doi.org/10.1159/000213842
24. Stuve O, Weideman RA, McMahan DM, Jacob DA, Little BB. Diclofenac reduces the risk of Alzheimer's disease: A pilot analysis of NSAIDs in two US veteran populations. Therapeutic advances in neurological disorders. 2020;13:1756286420935676. https://doi.org/10.1177/1756286420935676
25. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikelenboom P, Emmerling M, Fiebich BL, Finch CE. Inflammation and Alzheimer's disease. Neurobiology of aging. 2000; 21(3): 383-421. https://doi.org/10.1016/s0197-4580(00)00124-x
26. Lehmann JM, Lenhard JM, Oliver BB, Ringold GM, Kliewer SA. Peroxisome proliferator-activated receptors α and γ are activated by indomethacin and other non-steroidal anti-inflammatory drugs. Journal of Biological Chemistry. 1997;272(6):3406-10. https://doi.org/10.1074/jbc.272.6.3406

27. T. Heneka M, Reyes-Irisarri E, Hull M, P. Kummer M. Impact and therapeutic potential of PPARs in Alzheimer's disease. Current neuropharmacology. 2011; 9(4): 643-50. https://doi.org/10.2174/157015911798376325
28. Zolezzi JM, Inestrosa NC. Peroxisome proliferator-activated receptors and Alzheimer's disease: hitting the blood-brain barrier. Molecular neurobiology. 2013;48(3): 438-51. https://doi.org/10.1007/s12035-013-8435-5
29. Bas A. In't veld, Annemieke Ruitenberg, Albert Hofman, Lenore J. Launer, Cornelia M. Van Duijn, Theo Stijnen, Monique M.B. Breteler BHCS (2001) Nonsteroidal anti-inflammatory drugs and the risk of Alzheimer's Disease. N Engl J Med 345: 1515-1521. https://doi.org/10.1056/nejmoa010178
30. Mandrekar-Colucci S, Landreth GE. Nuclear receptors as therapeutic targets for Alzheimer's disease. Expert opinion on therapeutic targets. 2011 Sep 1;15(9):1085-97. https://doi.org/10.1517/14728222.2011.594043
31. Eriksen JL, Sagi SA, Smith TE, Weggen S, Das P, McLendon DC, Ozols VV, Jessing KW, Zavitz KH, Koo EH, Golde TE. NSAIDs and enantiomers of flurbiprofen target γ-secretase and lower Aβ42 in vivo. The Journal of Clinical Investigation. 2003; 112(3): 440-9. https://doi.org/10.1172/jci18162
32. Wanngren J, Ottervald J, Parpal S, Portelius E, Strömberg K, Borgegård T, Klintenberg R, Juréus A, Blomqvist J, Blennow K, Zetterberg H. Second generation γ-secretase modulators exhibit different modulation of Notch β and Aβ production. Journal of Biological Chemistry. 2012;287(39):32640-50. https://doi.org/10.1074/jbc.m112.376541
33. Perioli L, Ambrogi V, Bernardini C, Grandolini G, Ricci M, Giovagnoli S, Rossi C. Potential prodrugs of non-steroidal anti-inflammatory agents for targeted drug delivery to the CNS. European journal of medicinal chemistry. 2004; 39(8): 715-27. https://doi.org/10.1016/j.ejmech.2004.05.006
34. Zhao Y, Qu B, Wu X, Li X, Liu Q, Jin X, Guo L, Hai L, Wu Y. Design, synthesis and biological evaluation of brain targeting l-ascorbic acid prodrugs of ibuprofen with "lock-in" function. European journal of medicinal chemistry. 2014;82:314-23. https://doi.org/10.1016/j.ejmech.2014.05.072
35. Zhang X, Liu X, Gong T, Sun X, Zhang ZR. In vitro and in vivo investigation of dexibuprofen derivatives for CNS delivery. Acta Pharmacologica Sinica. 2012; 33(2): 279-88. https://doi.org/10.1038/aps.2011.144
36. Golden PL, Pollack GM. Blood-brain barrier efflux transport. Journal of Pharmaceutical Sciences. 2003;92(9):1739-53. https://doi.org/10.1002/jps.10424
37. Nair AB, Dalal P, Kadian V, Kumar S, Garg M, Rao R, Almuqbil RM, Alnaim AS, Aldhubiab B, Alqattan F. Formulation Strategies for Enhancing Pharmaceutical and Nutraceutical Potential of Sesamol: A Natural Phenolic Bioactive. Plants. 2023; 12(5): 1168. https://doi.org/10.3390/plants12051168
38. Wei P, Zhao F, Wang Z, Wang Q, Chai X, Hou G, Meng Q. Sesame (Sesamum indicum L.): A comprehensive review of nutritional value, phytochemical composition, health benefits, development of food, and industrial applications. Nutrients. 2022;14(19):4079. https://doi.org/10.3390/nu14194079
39. Singh N, Vishwas S, Kaur A, Kaur H, Kakoty V, Khursheed R, Chaitanya MV, Babu MR, Awasthi A, Harish V, Yanadaiah P. Harnessing role of sesamol and its nanoformulations against neurodegenerative diseases. Biomedicine & Pharmacotherapy. 2023; 167: 115512. https://doi.org/10.1016/j.biopha.2023.115512
40. Najjar A, Karaman R. The prodrug approach in the era of drug design. Expert opinion on drug delivery. 2019;16(1):1-5. https://doi.org/10.1080/17425247.2019.1553954
41. Hossain M, Hossain M. The Mass Spectrometer and Its Components. Selected Reaction Monitoring Mass Spectrometry (SRM-MS) in Proteomics: A Comprehensive View. 2020:17-52.
42. Richards SA, Hollerton JC. Essential practical NMR for organic chemistry. John Wiley & Sons; 2023 Apr 3.
43. Yadav LD. Organic spectroscopy. Springer Science & Business Media; 2004 Dec 9.
44. Allred RA. The structures and reactivities of Group 12 metal complexes coordinated by tripodal nitrogen/sulfur ligands possessing internal hydrogen bond donors. Utah State University; 2003.
45. Neises B, Steglich W. Simple method for the esterification of carboxylic acids. Angewandte Chemie International Edition in English. 1978;17(7):522-4.
46. Shah K, Shrivastava SK, Mishra P. Evaluation of mefenamic acid mutual prodrugs. Medicinal Chemistry Research. 2013; 22: 70-7.
47. Leo A, Hansch C, Elkins D. Partition coefficients and their uses. Chemical reviews. 1971;71(6):525-616.
48. Paschke A, Neitzel PL, Walther W, Schüürmann G. Octanol/water partition coefficient of selected herbicides: Determination using shake-flask method and reversed-phase high-performance liquid chromatography. Journal of Chemical & Engineering Data. 2004; 49(6): 1639-42.
49. Rasheed A, Kumar CA, Mishra A. Synthesis, hydrolysis studies and pharmacodynamic profiles of amide prodrugs of dexibuprofen with amino acids. Journal of Enzyme Inhibition and Medicinal Chemistry. 2011;26(5):688-95. https://doi.org/10.3109/14756366.2010.548327
50. Suhail P, Joseph S, Ajeesh V, Sreelakshmi S, Anil K. Antiestrogenic and toxicological evaluation of methanolic extract of Saraca asoca and Cynometra travancorica. Journal of Research in Pharmacy. 2022; 26(5). http://dx.doi.org/10.29228/jrp.218
51. Javed MA, Jan MS, Shbeer AM, Al-Ghorbani M, Rauf A, Wilairatana P, Mannan A, Sadiq A, Farooq U, Rashid U. Evaluation of pyrimidine/pyrrolidine-sertraline based hybrids as multitarget anti-Alzheimer agents: In-vitro, in-vivo, and computational studies. Biomedicine & Pharmacotherapy. 2023; 159:114239. https://doi.org/10.1016/j.biopha.2023.114239
52. Gupta D, Gupta SV, Lee KD, Amidon GL. Chemical and enzymatic stability of amino acid prodrugs containing methoxy, ethoxy and propylene glycol linkers. Molecular pharmaceutics. 2009;6(5): 1604-11. https://doi.org/10.1021/mp900084v
53. Suhail PT, Balasubramanian T, Roshini KV, Anil K. A Comparative Evaluation Study of Anti-inflammatory Activity of Saraca asoca and its Commonly used Substitute Plants. Asian Journal of Pharmaceutical and Health Sciences. 2019; 9(4).
54. Smitha Rani, Suhail PT, Hannaha KA, Jinsha P, Mohammed Naseef, Habil Ashraf et.al. Quality parameters of polyherbal formulation of three different marketed brands of vilwadi gutika: a comparative evaluation study. International Journal of Research and Review. 2023;10(12):366-71.
55. Dholkawala F, Voshavar C, Dutta AK. Synthesis and characterization of brain penetrant prodrug of neuroprotective D-264: Potential therapeutic application in the treatment of Parkinson's disease. European Journal of Pharmaceutics and Biopharmaceutics. 2016; 103: 62-70. https://doi.org/10.1016/j.ejpb.2016.03.017
56. Suhail PT. Comparative evaluation of antioxidant activity of methanolic extract of Saraca asoca and its commonly used substitute plants. Int. J. Res. Rev. 2019;6:37-43.
57. Taïr K, Kharoubi O, Taïr OA, Hellal N, Benyettou I, Aoues A. Aluminium-induced acute neurotoxicity in rats: Treatment with aqueous extract of Arthrophytum (Hammada scoparia). Journal of Acute Disease. 2016; 5(6): 470-82.
58. Balkaya M, Kröber JM, Rex A, Endres M. Assessing post-stroke behavior in mouse models of focal ischemia. Journal of Cerebral Blood Flow & Metabolism. 2013;33(3):330-8. https://doi.org/10.1038/jcbfm.2012.185
59. Aoyama K, Wang F, Matsumura N, Kiyonari H, Shioi G, Tanaka K, Kinoshita C, Kikuchi-Utsumi K, Watabe M, Nakaki T. Increased neuronal glutathione and neuroprotection in GTRAP3-18-deficient mice. Neurobiology of disease. 2012 Mar 1; 45(3): 973-82. https://doi.org/10.1016/j.nbd.2011.12.016
60. Angoa-Pérez M, Kane MJ, Briggs DI, Francescutti DM, Kuhn DM. Marble burying and nestlet shredding as tests of repetitive, compulsive-like behaviors in mice. JoVE (Journal of Visualized Experiments). 2013;24(82):e50978. https://doi.org/10.3791/50978
61. Wolmarans DW, Stein DJ, Harvey BH. Of mice and marbles: novel perspectives on burying behavior as a screening test for psychiatric illness. Cognitive, Affective, & Behavioral Neuroscience. 2016; 16: 551-60. https://doi.org/10.3758/s13415-016-0413-8
62. Garman RH. Histology of the central nervous system. Toxicologic pathology. 2011;39(1):22-35. https://doi.org/10.1177/0192623310389621
63. Abidfaheem T, Joy J, Rahaman AR, Nagappan K, Anbiah SV, Rani S, Suhail P. Pharmacological Activities of Polyherbal Formulations of Saraca asoca and Its Substitute Plants: A Comparative Evaluation Study. Journal of Pharmacology and Pharmacotherapeutics. 2025: 0976500X241309438.
64. Daina A, Zoete V. A boiled egg to predict gastrointestinal absorption and brain penetration of small molecules. ChemMedChem. 2016;11(11):1117-21. https://doi.org/10.1002/cmdc.201600182
65. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific reports. 2017; 7(1): 42717. https://doi.org/10.1038/srep42717
66. Daina A, Michielin O, Zoete V. iLOGP: a simple, robust, and efficient description of n-octanol/water partition coefficient for drug design using the GB/SA approach. Journal of chemical information and modeling. 2014;54(12):3284-301. https://doi.org/10.1021/ci500467k
67. Nair AS, Oh JM, Koyiparambath VP, Kumar S, Sudevan ST, Soremekun O, Soliman ME, Khames A, Abdelgawad MA, Pappachen LK, Mathew B. Development of halogenated pyrazolines as selective monoamine oxidase-B Inhibitors: Deciphering via molecular dynamics approach. Molecules. 2021; 26(11): 3264. https://doi.org/10.3390/molecules26113264
68. Nija B, Rasheed A, Kottaimuthu A. Development, characterization, and pharmacological investigation of sesamol and thymol conjugates of mefenamic acid. J. Evol. Med. Dent. Sci. 2020;9:3909-16.
69. Bhilare NV, Marulkar VS, Kumar D, Chatap VK, Patil KS, Shirote PJ. An insight into prodrug strategy for the treatment of Alzheimer's disease. Medicinal Chemistry Research. 2022; 31(3): 383-99.
70. Travers--Lesage V, Mignani SM, Dallemagne P, Rochais C. Advances in prodrug design for Alzheimer's disease: the state of the art. Expert Opinion on Drug Discovery. 2022;17(4):325-41. https://doi.org/10.1080/17460441.2022.2031972

Cite this article: Krishnendu PR, Rasheed SP, Kaippollil V, Rasheed A, Joy J, Suhail P. Synthesis and Evaluation of Mutual Prodrug of Mefenamic Acid and Etodolac with Sesamol for the Treatment of Alzheimer's Disease. Indian J of Pharmaceutical Education and Research. 2026;60(2s):s627-s637.