World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

Emerging computational and pharmacological study of topiramate: A brief review

Asiya Parveen [1], Nadeem Siddiqui [1,*], M. Shahar Yar [1], Shaiza Siddiqui [2], Vivek Kumar [3] and Shagufi Nazar [1]

[1] *Department of Pharmaceutical Chemistry, School of Pharmaceutical Education and Research, Jamia Hamdard, Hamdard Nagar, New Delhi – 110062, India.*
[2] *Department of Computer Engineering, Aligarh Muslim University, Aligarh, Uttar Pradesh, India.*
[3] *Department of Cardiology, Fortis Heart Institute, New Delhi -110025, India.*

World Journal of Advanced Research and Reviews, 2024, 21(01), 624–633

Publication history: Received on 25 November 2023; revised on 02 January 2024; accepted on 05 January 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.21.1.0023

Abstract

Topiramate, a second-generation antiepileptic drug used to manage and treat epileptic seizures was approved by the FDA in 1996 as a solo or supplementary for the therapy of epilepsy. The frequency, severity, quality of life, and adverse events that topiramate has on epilepsy patients, including children and adolescents, are summarized in this review. The medication has a generally favorable safety profile and is well accepted, although monitoring the patient's medication, preventing its abuse, and improving patient outcomes all require knowledge. Despite the numerous scientific theories that surround the drug, more research into the uniqueness of medicine is required. This review will highlight the drug profile, synthesis, pharmacology, ADME properties, and computational study of topiramate.

Keywords: Topiramate; Anticonvulsants; Synthesis; Molecular docking; Spectral information; HPLC.

1. Introduction

Epilepsy is one of the most common neurological diseases and the administration of anti-epileptic drugs is the first line treatment [1]. AEDs are mainly used for neurologic and psychiatric purposes and the primary use of this family of drug is treating seizures disorders.

Topiramate is the drug which belongs to broad- spectrum second generation anti-epileptic drugs with multiple mechanism of action [2]. Topiramate received FDA approval for the treatment of epilepsy as monotherapy or adjunctive therapy in 1996[3]. It can be combined with other drugs like valproic acid in the treatment of epilepsy. Similarly, it can also be used as a prophylactic in the treatment of migraine particularly in adults [4,6]. Basically, this drug is FDA approved for the following benefits (Figure1):

* Corresponding author: Nadeem Siddiqui

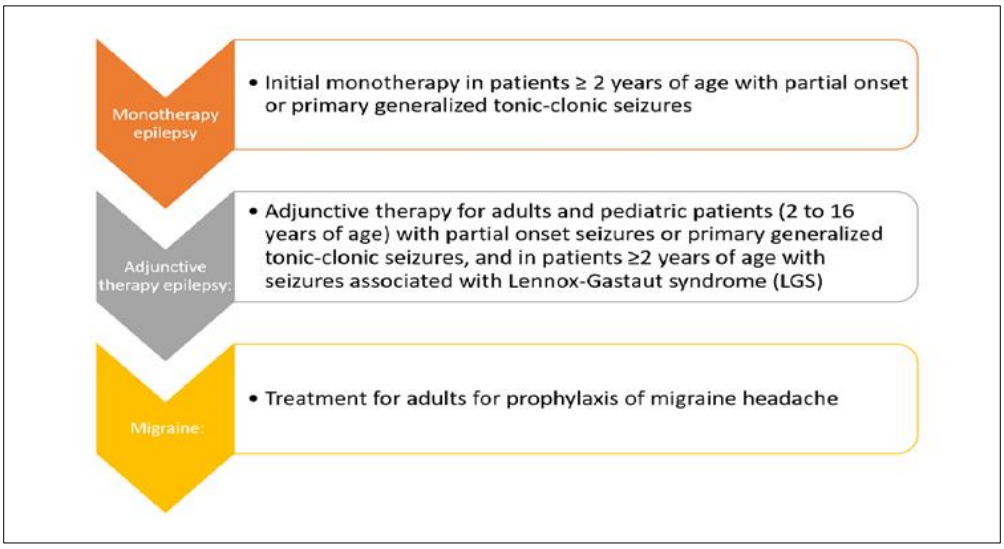


Figure 1 Therapeutic benefits of topiramate

In all these condition topiramate can be used as a monotherapy otherwise it can be combined with other anti-epileptic agents.This drug can be used both in the adults as well as pediatric patients but when it is used in children then the age should be greater than 2 years.

The absorption of topiramate after oral administration is rapid with a bioavailability of about 80% and 2-4 h is the time to peak plasma drug concentration. The role of therapeutic drug monitoring in management of patients is still being determined and the exact relationship between blood concentration of topiramate and its toxicity is not yet established [5].

For the support of clinical studies, a reliable and simple method of analysis is needed. As the molecule has no UV, Visible or fluorescence absorption due to which the analysis of topiramate in blood is complicated and cannot be quantified by the technique such as HPLC with spectrophotometer or fluorescence detector. However, the analysis of topiramate can be done by using HPLC with refractive index detector [5].

Over the last three decades, AED search has come a long way and is considered as the modern era of anticonvulsants. Since 1993, there has been development of clinically efficient drugs for symptomatic relief of epilepsy along with topiramate, several new AED's have been validated worldwide. (Table.1).

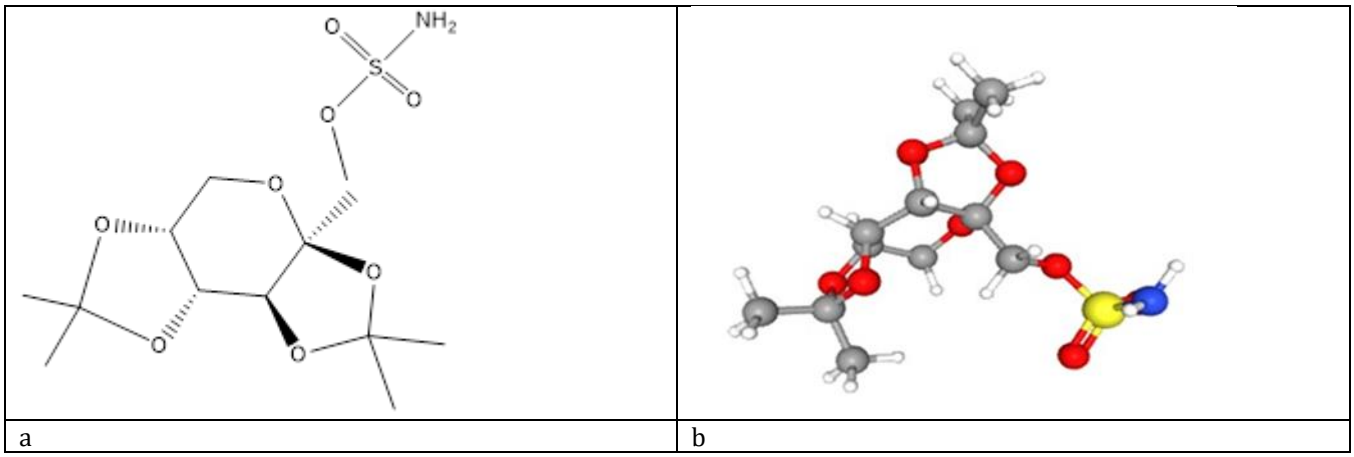
Table 1 Chronological development of AEDs

Year	**Name of AEDs**
1993	Felbamate
1993	Gabapentin
1994	Lamotrigine
1996	Fosphenytoin
1996	Topiramate
1997	Tiagabine
1999	Levetiracetam
2000	Zonisamide
2000	Oxcarbazepine
2004	Pregabalin

2. Drug Profile

Topiramate, having anticonvulsant property, is structurally distinct from other known AEDs as it is a sulfamate substituted and a derivative of the naturally occurring monosaccharide D-fructose [6].

The molecular structures and brand names (manufacturers) are shown in (Figure 2,3) and computed and physio-chemical properties are listed in (Table 2,3).



a b

Figure 2: a) 2D structure; b) 3D structure[7]

IUPAC Name: 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate.

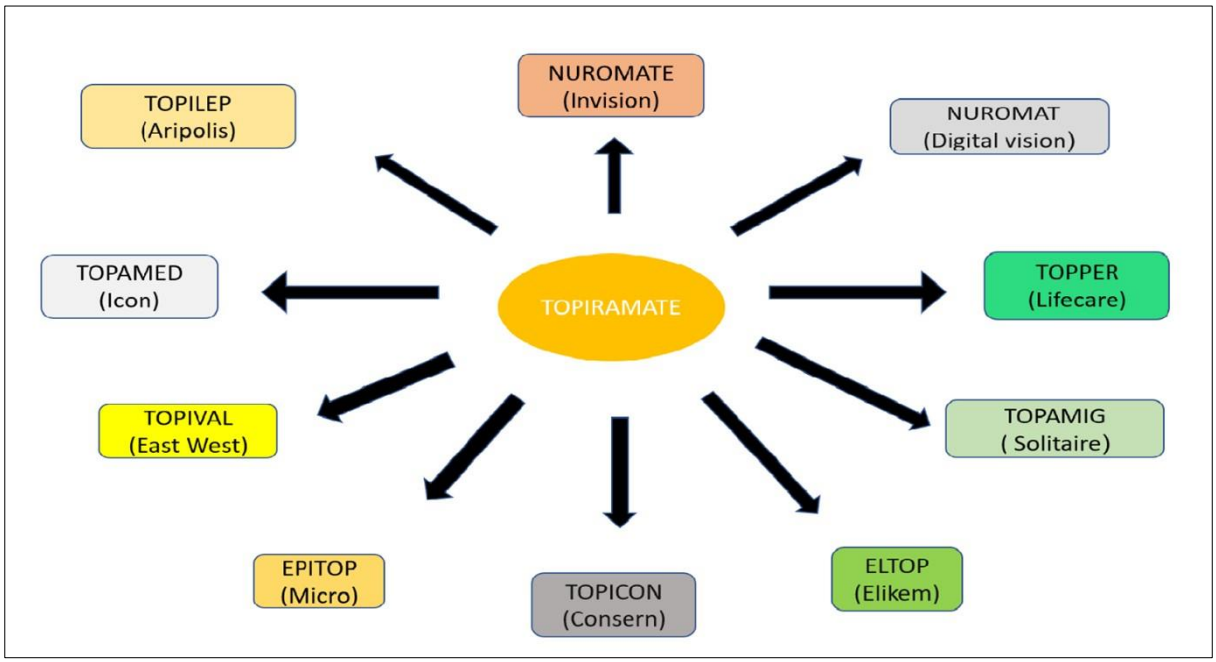


Figure 3 Brand Names (Manufacturers)

2.1. Synthesis

Synthesis: It can be synthesized by two routes (Figure4):

Route 1: Involves the reaction of D-fructose (A) with acetone in the presence of sulphuric acid to produce bisacetonide (B). The required topiramate (C) is then created by condensing bisacetonide(B) chemical with sulfamoyl chloride in the presence of sodium hydride.

Route 2: In order to create the azido derivative (E), the intermediate (B) must first undergo a reaction with sulfuryl chloride to create sulfochloridate (D). To create topiramate (C), the azido derivative (E) was either reduced by copper powder in methanol or catalytic hydrogenation with palladium on carbon.

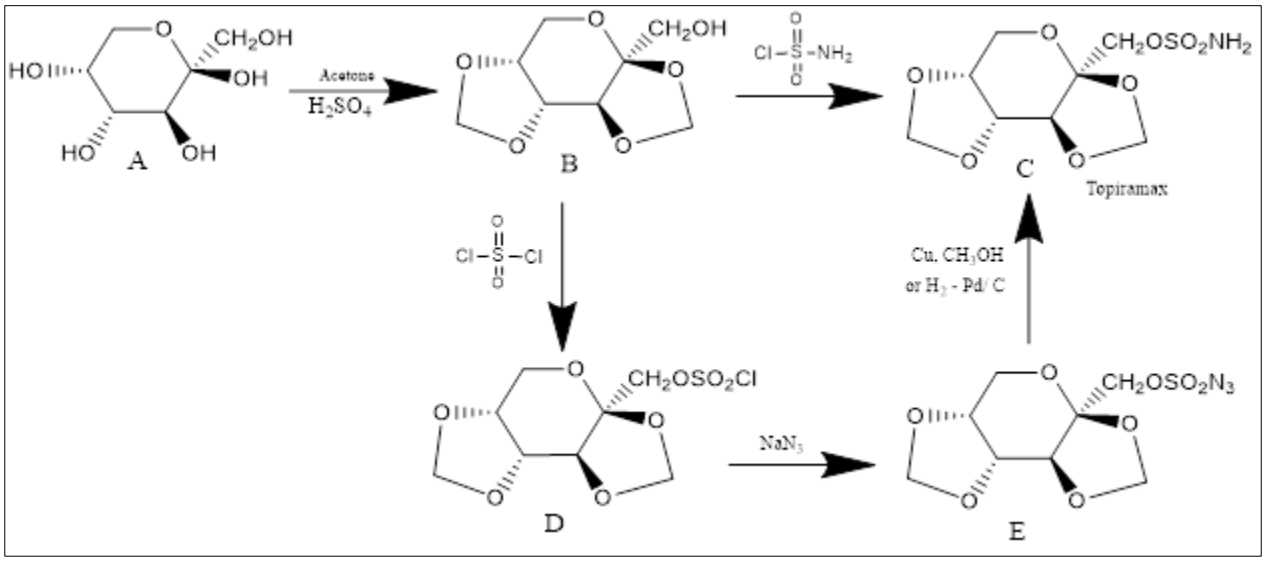


Figure 4 Synthetic route for Topiramate

2.2. Mechanism of action

Topiramate's exact mode of action is unknown, however there is sufficient data to explain why the medicine has an anticonvulsant effect having multiple mechanisms of action that include blockade of voltage-sensitive sodium channels, potentiation of GABA(A)-evoked chloride flux, blockade of kainite/AMPA type of glutamate receptors. It also inhibits carbonic anhydrase [8].

Topiramate mainly works by blocking voltage-gated sodium channels, which mainly results of uninterrupted depolarizations during seizures and blockage of high-voltage-activated calcium channels is also done. Additionally, it alters voltage-gated K+ channels, which stabilise neuronal membranes and inhibit the propagation of action potentials as well as chronic membrane depolarization and neuropeptide release by lowering excitability [9].

Topiramate antagonizes the AMPA/Kiante subtype of the glutamate receptor, the blocking of Kiante leads to elicit potentials which reduces neuronal [10]. Topiramate enhances the activity of neurotransmitter gamma-aminobutyrate at some subtypes of the GABA (A) receptor, which enhances inhibitory effects excitability and could contribute to the drug's antiepileptic action.

Topiramate being a fragile inhibitor of carbonic anhydrase enzyme particularly isoenzyme II and IV causing acidosis in the brain which results in protecting against seizures by down regulating NMDA receptor activity (Figure 5).

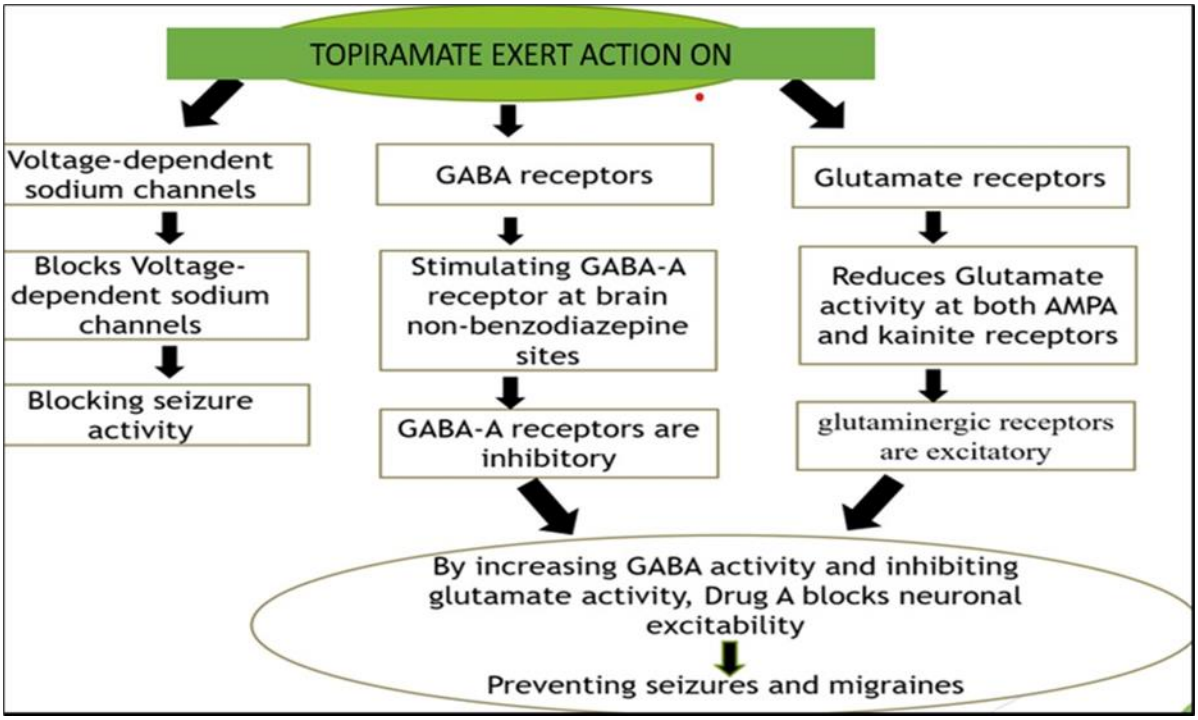


Figure 5 Mechanism of action of topiramate

An aberrant and uncontrolled electrical discharge in the brain that results in a seizure. As a result, there is a brief disruption in brain activity that is characterized by:

- Decreased alertness,
- Strange sensations
- Focused involuntary movement or convulsions.

2.3. Pharmacokinetics

2.3.1. Absorption

The absorption of topiramate is effectively from GI tract showing peak plasma levels 2-3 hours. More than 80% of the drug is bioavailable [11]. The peak plasma concentration slows down as a result of intake of food, but the degree of absorption is unaffected. The absorption of the drug is slowed in presence of food however, there is no significant outcome [12]. As a result, topiramate can be given independently of mealtime. Topiramate's pharmacokinetics are linear and predictable over the prescribed dosing range (15-400 mg/day) [13].

2.3.2. Distribution

The plasma protein-plasma protein binding of topiramate ranges from 13% to 17%. As blood concentration rises, the fraction of bound topiramate drops [14].

2.3.3. Metabolism

Topiramate is broken down through hydroxylation, hydrolysis, and glucuronidation [15].

2.3.4. Excretion

Topiramate is excreted by the kidneys in both its unmodified form and as metabolites. Topiramate clearance in adults ranges from 20 to 30 mL/min. The average plasma elimination half-life is about 21 hours. The elimination half-life varies with age and the administration of enzyme-inducing or inhibitor medications concurrently. Patients using enzyme-inducing medications such as phenytoin, barbiturates, and carbamazepine have higher clearance [16].

2.4. Side effects

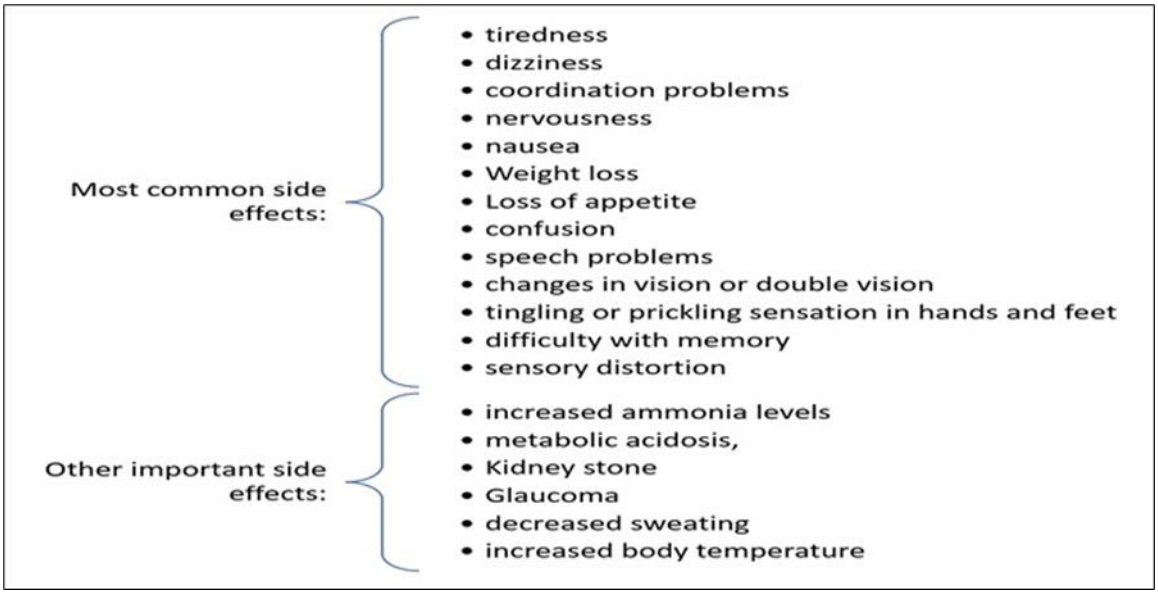


Figure 6 Side effects of topiramate.

Table 2 Computed Properties

S.No.	Properties*	Values*
1.	Molecular Formula	$C_{12}H_{21}NO_8S$
2.	Molecular weight	339.36
3.	X LogP3-AA	-0.8
4.	Hydrogen bond donor count	1
5.	Hydrogen bond acceptor count	9
6.	Rotatable Bond count	3
7.	Exact Mass	339.09878780
8.	Monoisotopic Mass	339.09878780
9.	Topological polar surface area	124 $Å^2$
10.	Heavy atom count	22
11.	Formal charge	0
12.	Complexity	556
13.	Isotope atom count	0
14.	Defined atom stereocenter count	4
15.	Undefined atom stereocenter count	0
16.	Defined bond stereocenter count	0
17.	Undefined bond stereocenter count	0
18.	Covalently bonded unit count	1
19.	Compound is canonicalized	yes

*Properties and values obtained from PubChem [7].

Table 3 Physio-chemical Properties.

S.No.	Properties*	Values*
1.	Physical state	Solid
2.	Color/ form	White crystalline powder
3.	Taste	Bitter
4.	Melting point	125-126 °C
5.	Solubility	Soluble in sodium hydroxide or sodium phosphate. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol.
6.	Vapor pressure	7.0X10-8 mm Hg at 25 °C
7.	Log P	0.13
8.	pKa	8.7
9.	Collision cross section	170.1 $Å^2$

*Properties and values obtained from PubChem [7].

2.5. Spectral Information

The hypothetical ^1H NMR and ^{13}C NMR spectrum was computed by ChemDraw Professional 16.0 (Figure 7,8).

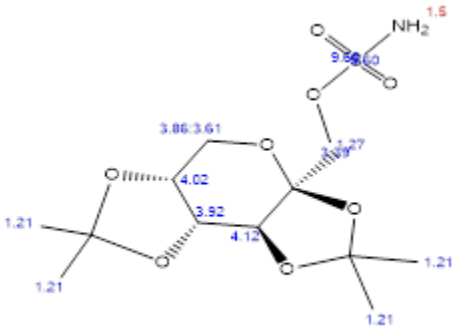


Figure 7 ChemNMR^1H Estimation

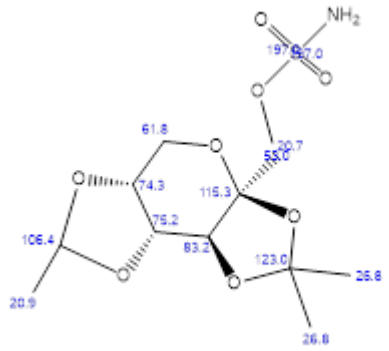


Figure 8 ChemNMR^{13}C Estimation

3. HPLC method of analysis

The absence of chromophore moieties in topiramate makes it challenging in presence of its main degradation product to be analyzed. A new method development for its estimation is needed, however much work has not been reported. A brief survey on its estimation is delineated. A new simple, precise, reliable, rapid and reproducible RP-HPLC method for validation of topiramate was developed to estimate topiramate in pharmaceutical dosage[17].Topiramate in pharmaceutical has been determined by a new sensitive and easy HPLC technique which is found to be more selective and linear[17].A HPLC method was developed and found suitable in determination of coating integrity of topiramate sprinkle formulation[18].Quantitative and dissolution of topiramate in tablet dosage forms have been determined by a HPLC method which was developed and validated[19].An isocratic HPLC method was applied for estimation of topiramate in sprinkle formulation. Recently a HPLC method has been developed for determination of topiramate using RI detector. The method was found to be simple, accurate, sensitive and selective and can be easily and conveniently adopted for quantitative analysis of topiramate [20]. A HPLC method for determination of topiramate using RI detector was developed [21]. The method was found to be simple, accurate, sensitive and selective. The developed method can easily and conveniently be adopted for quantitative analysis of topiramate [21].

4. Computational Study

4.1. Molecular Docking

The molecular docking analysis was carried out utilizing the Molecular Operating Environment 2015.10 (MOE) Windows 10 Version 22H2 for x64 to evaluate their interaction and binding modalities with target receptors. Molecular Operating Environment 2015.10 (MOE) was used to create the 2D structures for synthesized molecules and then convert those 2D structures to their corresponding 3D structures [22]. From Protein Data Bank, the X-ray crystal structure of 4COF (PDB id) was downloaded and solved at a resolution of 2.97. By allocating H-bonds, performing minimization, and preparing the protein according to the MOE Quick Prep technique, the protein was optimized. The primary steps in molecular docking research include choosing and getting ready the right protein, grid creation, and getting ready the ligand, then docking and its analysis. Their binding affinities and the correct positioning of these chemicals in the receptor's active site was determined by using the docking score, hydrogen bonds, and pi-pi interactions generated with the enclosed amino acids. After being minimized, the ligand was saved in.mdb format. binding poses for the compound were analyzed by examining their free energy scores.

5. Results and Discussion

Molecular docking studies were used to evaluate topiramate's affinity for the GABA(A) R-BETA 3 homo-pentamer, the human gamma-aminobutyric acid receptor. The docking score was found to be -5.0730 Kcal/mol. Figure 9 displays the 2D ligand interaction diagram for topiramate. Topiramate conforms well to the GABA(A) R-BETA 3 structure and establishes a single hydrogen bond with the most important active site residues.

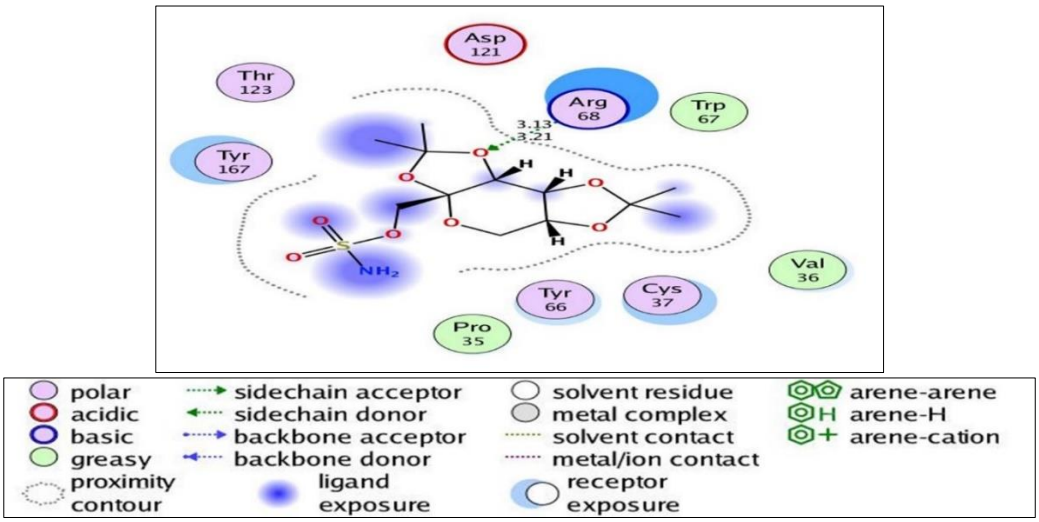


Figure 9 2D Ligand interaction of topiramate

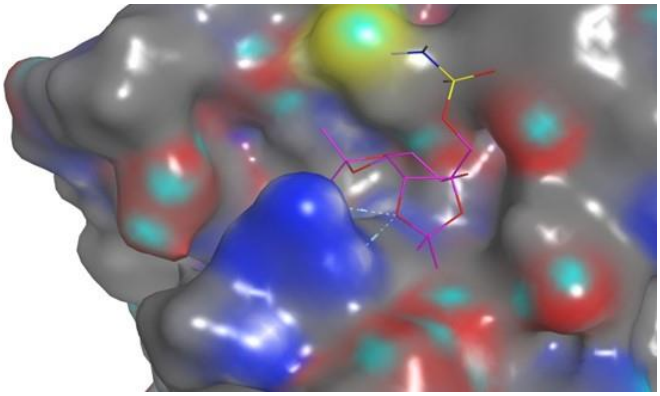


Figure 10 The receptor surface view of topiramate

The hydrogen bonding with the Arg68 amino acid residue was seen in the docking investigation. The receptor surface view of topiramate was represented in Figure 10.

The 3D ligand interaction diagram of topiramate is represented in Figure 11.

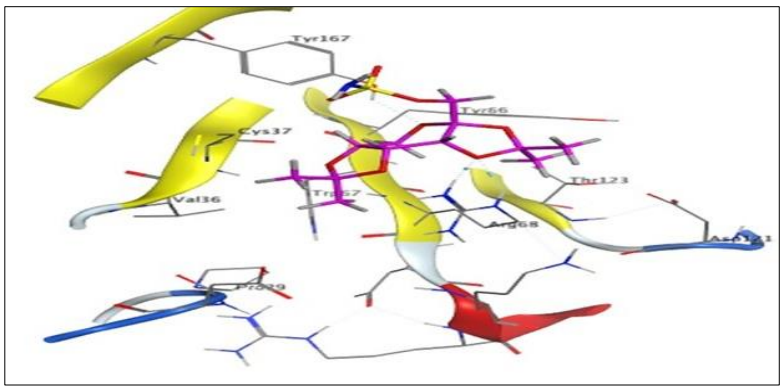


Figure 11 3D Ligand interaction of topiramate

6. Conclusion

This review presents an impetuous summation of pharmacological and computational study on topiramate (TPM). The drug constitutes a promising addition to the marketed anti-epileptic drugs. TPM has favorable pharmacokinetic and bioavailability and could be a valuable choice for considering it to be a third line treatment for patients suffering from refractory status epilepticus, however furthermore explanations are demanded.

Compliance with ethical standards

Acknowledgements

The contribution of all the authors is gratefully acknowledged.

Disclosure of conflict of interest

The authors declare no conflict of interest.

References

[1] Hanaya, R., & Arita, K. The new antiepileptic drugs: Their neuropharmacology and clinical indications. Neurologia medico-chirurgica. Japan neurosurgical society. 2016; 56(5):205–220.

[2] Goswami, D., Kumar, A., Khuroo, A. H., Monif, T., & Rab, S. Bioanalytical LC-MS/MS method validation for plasma determination of topiramate in healthy Indian volunteers. Biomedical chromatography. 2009; 23(11): 1227–1241.

[3] Hu, C., Zhang, Y., & Tan, G. Advances in topiramate as prophylactic treatment for migraine.Brain and Behavior, John Wiley and Sons Ltd. 2021;11(10): 01-09.

[4] La Marca, G., Malvagia, S., Filippi, L., Fiorini, P., Innocenti, M., Luceri, F., Pieraccini, G.,Moneti, G., Francese, S., Dani, F. R., & Guerrini, R. Rapid assay of topiramate in dried bloodspots by a new liquid chromatography-tandem mass spectrometric method. Journal of pharmaceutical and biomedical analysis. 2008; 48(5): 1392–1396.

[5] Bahrami, G., Mirzaeei, S., & Kiani, A. Sensitive analytical method for Topiramate in humanserum by HPLC with pre-column fluorescent derivatization and its application in humanpharmacokinetic studies. Journal of chromatography B: Analytical technologies in thebiomedical and life sciences. 2004; 813(1–2):175–180.

[6] Arnone, D. Review of the use of topiramate for treatment of psychiatric disorders. Annals ofgeneral psychiatry. 2005; 4(1): 01-14.

[7] National Center for Biotechnology Information (2023). PubChem Compound Summary forCID 5284627, Topiramate. Retrieved November 1, 2023from https://pubchem.ncbi.nlm.nih.gov/compound/Topiramate.

[8] Guerrini, R., Carpay, J., Grošelj, J., van Oene, J., Schreiner, A., Lahaye, M., Schwalen, S.,Lagae, L., Sadzot, B., Van Bogaert, P., van Rijckevorsel, K., Willems, C., Alexiev, A., Bojinov,S., Chavdarov, D., Ganeva, G., Minchev, D., Hajnsek-Propadalo, S., Lusic, I., Svendsen, T. Topiramate monotherapy as broad-spectrum antiepileptic drug in a naturalistic clinical setting.Seizure.2005; 14(6): 371–380.

[9] Harte, R., McKay, G., and Llano, A. Topiramate. In Practial Diabetes. John Wiley and SonsLtd. 2020;37(1): 34-35a.

[10] Ängehagen, M., Ben-Menachem, E., Rönnbäck, L., & Hansson, E. Novel Mechanisms ofAction of Three Antiepileptic Drugs, Vigabatrin, Tiagabine, and Topiramate. Neurochemicalresearch.2003; 28(2): 333-340.

[11] Sehneiderman, J. H. Topiramate: Pharmacokinetics and pharmacodynamics. Canadian Journalof neurological sciences.1998; 25(3): S3-S5.

[12] Thummar, K., Navin, S., Jethva, D., & Sheth, N. Quantitative Analysis of Topiramate inHuman Plasma using LC-MS/MS and its Application to Pharmacokinetics study. WorldJournal of pharmacy and pharmaceutical sciences. 2018; 7(5): 1016-1032.

[13] Guerrini, R., & Parmeggiani, L. Topiramate and its clinical applications in epilepsy. Expertopinion on pharmacotherapy.2006; 7(6): 811–823.

[14] Langtry, H. D., Gillis, J. C., Davis, R., Ben-Menachem, E., Davidson, D. L. W., Michelucci,R, Patsalos,; P N, Privitera, M., & Richens,; A. (n.d.). Topiramate A Review of itsPharmacodynamic and Pharmacokinetic Properties and Clinical Efficacy in the Managementof Epilepsy. Springer; 54 (5):752-773.

[15] Mozayani, A., Carter, J., & Nix, R. Distribution of Topiramate in a Medical Examiner's Case. Journal of analytical toxicology.1999; 23: 556-558.

[16] Kshirsagar MB, Mahajan MP, Sawant SD. Method development and validation by RP- HPLCfor estimation of topiramate in bulk and pharmaceutical dosage form. International Journal ofchemistry technology research. 2017; 10(7): 843-849.

[17] Majnooni MB, Jalili R; Mohammadi B,Miraghace SS, Bahrami MJ, Fakhri S,Bahrami.Development and validation of a new method for determination of topiramate inbulk and pharmaceutical formulation using high performance liquid chromatography- UVdetection after pre-column derivatization. Journal of reports in pharmaceutical sciences.2014; 3(2):179-183.

[18] Dumg HT, Guh HY, KOCY, Micheel AP, Thakur MS. A HPLC assay for coating integrity oftopiramate sprinkle formulation. Journal of pharmaceutical and biomedical analysis. 2012;29(1-2): 69-74.

[19] Ali MNR, Ansari M, Walker R. Development of a stability-indicating high-performance liquidchromatographic method for analysis of topiramate and dissolution rate testing in topiramatetablets. Asian Journal of chemistry. 2010; 22(5):3856-3866.

[20] Biro A, Pergel E, Arvai I, Hisz I, Szepesi G, Peter A, Lukacs F. High-Performance liquidchromatographic study of topiramate and its impurities. Chromatographia.2006; 63: 5137-5141

[21] Parveen A, Siddiqui N, Yar MS, Kumar D. Analytical method development and validation forassay of an antiepileptic drug -A by HPLC. [M.Pharm. Thesis]. New Delhi: JamiaHamdard;2023.

[22] Cakmak, E.N., Gur, M., and Kiran, B. Investigation of Structure-Activity Relationships WithMolecular Docking for Some Antiepileptic Drugs And Voltage-Gated Calcium (CaV) Channels. Journal of engineering and sciences. 2022; 8(1): 28-53.