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EXPLORING THE ANTI-INFLAMMATORY POTENTIAL OF ANTIEPILEPTIC DRUGS: MOLECULAR DOCKING INSIGHT AGAINST TNF-A AND IL-6

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ABSTRACT

Background: Epilepsy is a chronic neurological disorder that affects millions of people in the globe and is characterized by recurrent seizures and associated with neuroinflammation. Recent findings indicate that inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) also have important role in epileptogenesis and seizures propagation. **Objective**: The aim of the study was to evaluate the binding affinity of commonly prescribed antiepileptic drugs (AEDs) against key inflammatory targets (TNF-α and IL-6) through molecular docking studies. **Methods**: Molecular docking was performed using Schrodinger suite 2021-2 for six antiepileptic drugs (Valproic acid, carbamazepine, phenytoin, levetiracetam, lamotrigine, and topiramate). **Ibuprofen** takes as standard anti-inflammatory drug. Three-dimensional structures of target proteins were retrieved from the Protein Data Bank (PDB). **Results**: The Molecular docking studies disclosed variable binding affinities of AEDs with inflammatory targets (IL-6 and TNF-α). Lamotrigine demonstrated the strongest binding affinity to IL-6 (-4.909 kcal/mol), while Levetiracetam showed binding affinity with TNF-α (-3.561 kcal/mol) and Ibuprofen showed binding affinity with IL-6 (-3.867) and binding affinity with TNF- α was (-2.106). **Conclusion**: The proposed in silico study indicates possible anti-inflammatory actions of some antiepileptic drugs that might also play a role in their medicinal effectiveness in their non-traditional sodium blockage and GABAergic activities. More in-vitro and in-vivo studies are need to validate these computational results.

KEYWORDS: Antiepileptic drugs, Molecular docking, TNF-α, IL-6, Neuroinflammation.

INTRODUCTION

Epilepsy and Neuroinflammation

Epilepsy is one of the most prevalent neurological disorders, impacting almost 50 million people worldwide. It is characterized by recurrent, unprovoked seizures resulting from abnormal and excessive electrical activity in the brain.[1] The conventional understanding of epilepsy has focused on the imbalance in the excitatory and inhibitory neurotransmission.[2] New evidence point out the significant role of neuroinflammation in both the triggering and progression of epileptic conditions.[3] Cytokines, chemokines, and transcription factors are some of the **inflammatory mediators** that are increasingly being seen as important key players in epileptogenesis.[4] Tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) are among them and have specifically been considered to participate in seizure activity and brain damage associated with epilepsy.[5, 6]

Inflammatory Targets in Epilepsy

Tumor Necrosis Factor-alpha **(TNF-α)** is a pro-inflammatory cytokine that regulates neuronal excitability and synaptic transmission.[7, 8] High amounts of TNF-a have been found in patients of clinical epilepsy and experimental models of seizures. It is capable of raising neuronal excitability by promoting the glutamate synaptic transmission and inhibiting GABAergic synapses.[9,10] Interleukin-6 **(IL-6)** is a pleiotropic cytokine that taking part in immune regulation and neural plasticity.[11] The IL-6 levels are highly increased

in the epileptic brain and correlate with the severity of the seizure. IL-6 can modulate neuronal excitability and cause disruption of blood brain barrier.[12, 13]

Antiepileptic Drugs: Other than Traditional Mechanisms

Antiepileptic drugs (AEDs) represent the main mode of treatment for epilepsy management. Although their mechanisms are conventionally ascribed to the modulation of ion channels (sodium, calcium, potassium) and neurotransmitter systems (GABA, glutamate), multiple evidences propose that several AEDs may possess anti-inflammatory properties.[14,15] Understanding the possible synergies between AEDs and inflammatory targets may offer insights into new therapeutic effects of existing AEDs, Drug repurposing potential, Development of new anti-epileptic drugs with dual action and individualized therapy of inflammatory patterns.[16, 17]

In Silico Drug Discovery

Molecular docking is an in-silico computational approach that predicts the binding orientation and affinity of small molecules and biological targets (protein).[18] In-silico methods allow an early and detailed evaluation of potential drug molecule, helping prioritize promising candidates before committing to expensive laboratory and experimental studies.[19]

Study Rationale

This study employs computational methods to investigate the potential anti-inflammatory properties of commonly prescribed antiepileptic drugs by performing molecular docking studies to evaluate binding interactions between selected AEDs and inflammatory targets (**TNF-α and IL-6**) and Analyzing binding affinities.

MATERIALS AND METHODS

Selection of Drugs

Six commonly prescribed antiepileptic drugs and one anti-inflammatory (standard) drug were selected for this study based on their widespread clinical use and distinct chemical structures. **(Figure 1).**

Ligand Preparation

The structures of the drugs (Valproic acid, carbamazepine, phenytoin, levetiracetam, lamotrigine, topiramate and Ibuprofen) were retrieved from the NCBI PubChem database (https:// pubchem.ncbi.nlm.nih.gov/) (**Figure 1**). These drugs were then prepared prior to docking using the LigPrep application in Schrödinger Maestro Suite 2021-2 (LigPrep, version 12.8.117). LigPrep performs optimization of ligand structures viz. conversion of structures from 2 dimensional to 3 dimensional, correction of improper bond distances, bond orders, generation of ionization states, followed by energy minimization. The ligand structures prepared by LigPrep were then used for Molecular Docking.

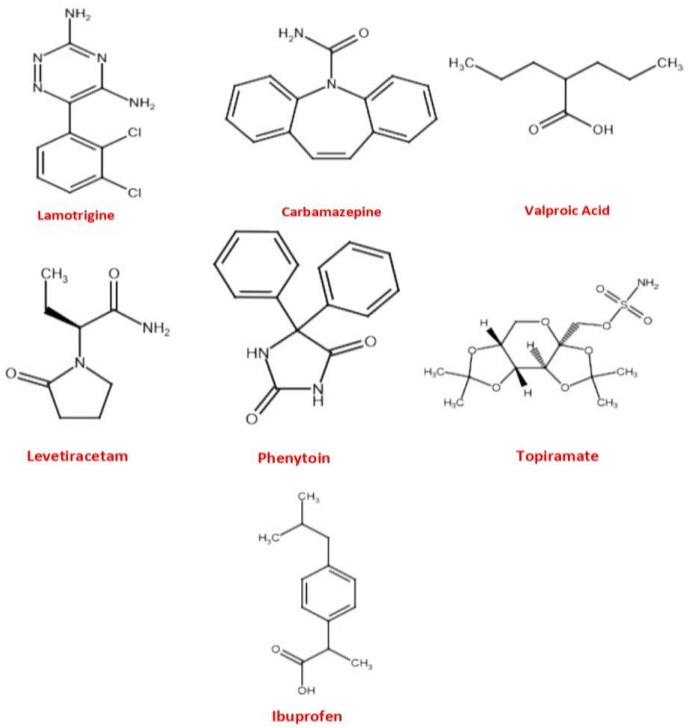


Figure 1: Structures of Docked Compounds

Target Protein Preparation

Three-dimensional crystal structures of target proteins **Tumor Necrosis Factor alpha (TNF-α)** (PDB ID: 3IT8, Resolution: 2.80 Å) and **Interleukin-6 (IL-6) (**PDB ID: 1P9M, Resolution: 3.65 Å) were obtained from the RCSB Protein Data Bank (https://www.rcsb.org/) in PDB format.

Molecular Docking Protocol

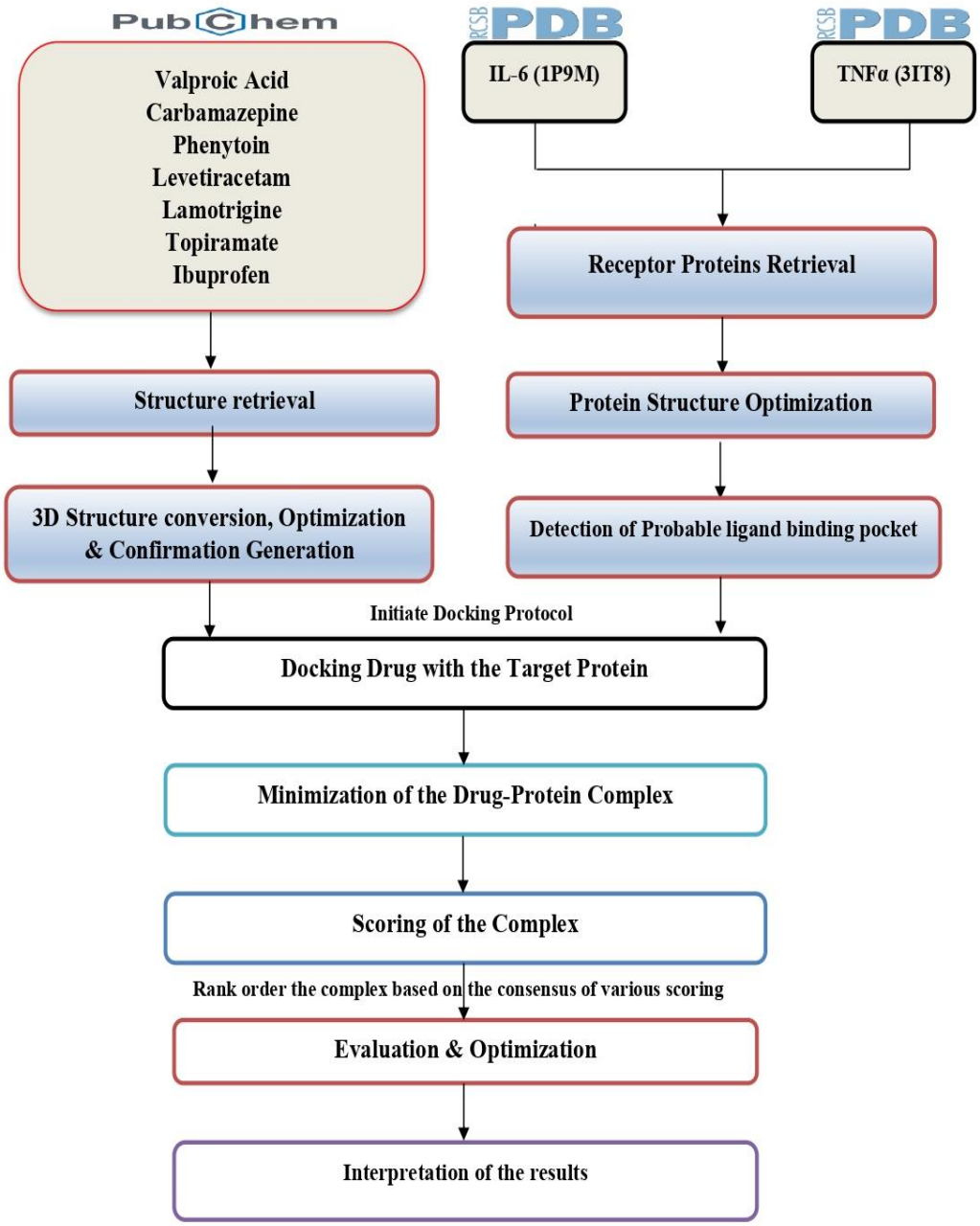


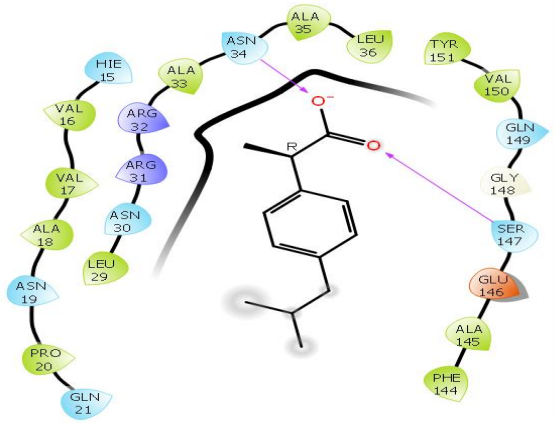
Figure 2: Workflow of molecular docking studies of selected drugs against inflammatory targets (IL-6 and TNF-α).

RESULTS

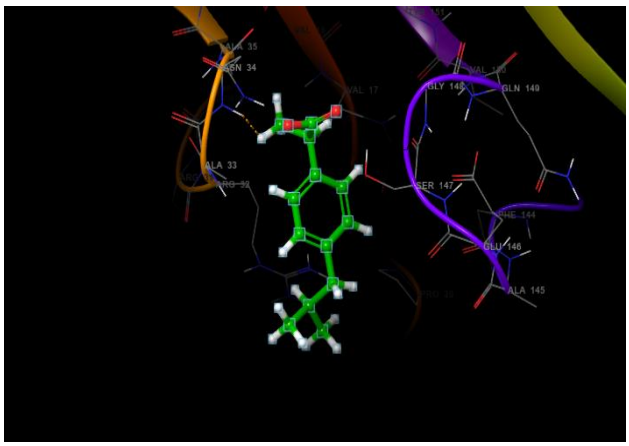
The results of our docking analysis, pertaining to each drug are presented below. The docking scores and binding affinities are presented in **(Table 1)**.

Table 1: Comparative Extra Precision Glide Scores of Antiepileptic Drugs against IL-6 and TNF-α.

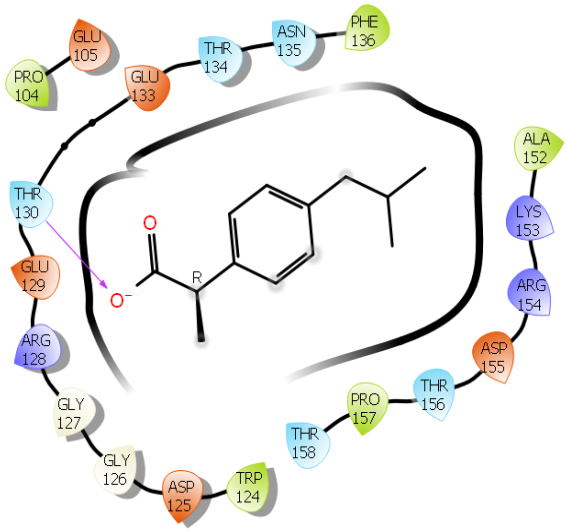
Tumor Necrosis Factor alpha (TNF-α)		
S. No.	**Drug**	**XP GScore(kcal/mol)**
1	Lamotrigine	-1.817
2	Carbamazepine	-1.822
3	Valproic Acid	-2.187
4	Levetiracetam	-3.561
5	Phenytoin	-2.009
6	Topiramate	-2.571
7	**Ibuprofen (std)**	-2.106
Interleukin-6(IL-6)		
S. No.	**Drug**	**XP GScore(kcal/mol)**
1	Lamotrigine	-4.909
2	Carbamazepine	-4.597
3	Valproic Acid	-2.396
4	Levetiracetam	-3.844
5	Phenytoin	-4.017
6	Topiramate	-3.104
7	**Ibuprofen (std)**	-3.867



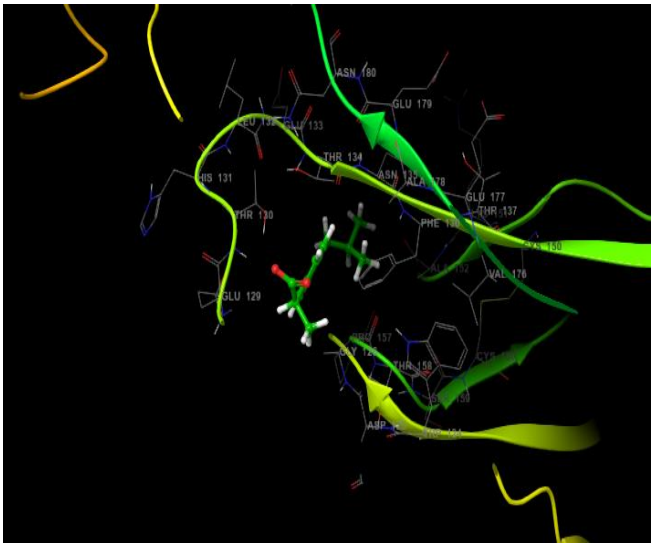
(a)



(b)

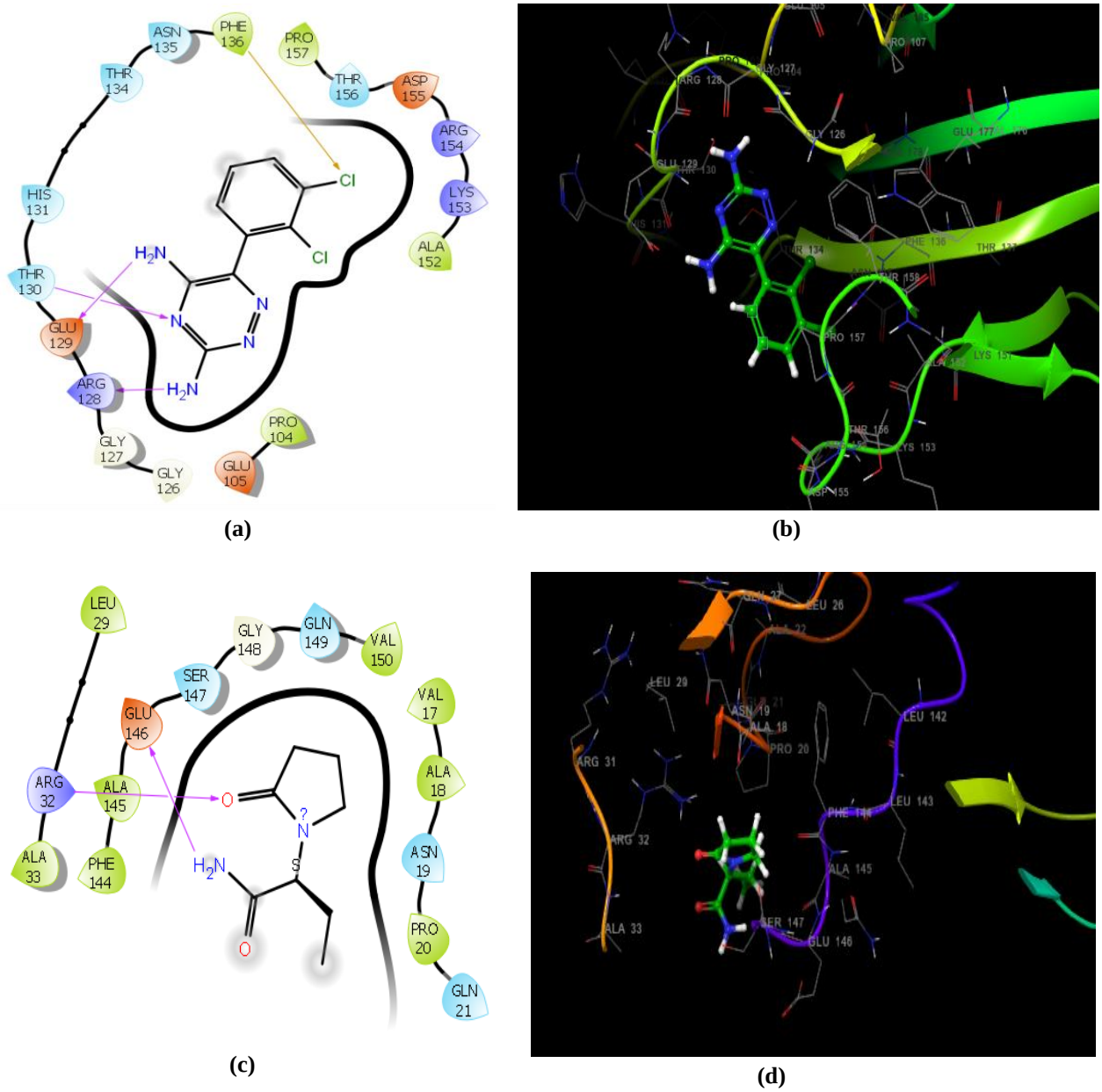


(c)



(d)

Figure 3: (a) 2D structure of Ibuprofen complex with TNF-α, (b) 3D structure of Ibuprofen complex with TNF-α (c) 2D structure of Ibuprofen complex with IL-6, (d) 3D structure of Ibuprofen complex with IL-6.



(a) **(b)**

(c) **(d)**

Figure 4: (a) 2D structure of Lamotrigine complex with TNF-α, (b) 3D structure of Lamotrigine complex with TNF-α, (c) 2D structure of Levetiracetam complex with IL-6, (d) 3D structure of Levetiracetam complex with IL-6.

DISCUSSION

The current in silico research demonstrates the possible role of commonly used antiepileptic drugs (AEDs) in anti-inflammatory activity by interacting with the main pro-inflammatory agonists, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). The outcome of molecular docking indicates that all the antiepileptic drugs under consideration have had quantifiable binding affinities with XP GScore -1.817 to -4.909 kcal/mol, that supporting the hypothesis of complementation between anti-inflammatory actions and classical antiepileptic actions. Drugs having aromatic rings and multiple hydrogen-bonds showed superior binding, suggesting that structural rigidity and aromaticity enhance interactions with inflammatory targets, whereas more flexible, less aromatic molecules displayed weaker interactions. These findings are consistent and showing evidence that epilepsy is not just a neuronal hyper excitability disorder but also involves significant neuro-inflammatory pathways.[20] The Elevated TNF-α levels in the epileptic patients and experimental seizure models stimulate glutamatergic transmission and inhibit GABAergic transmitter, thus promoting the seizure propagation.[21] IL-6 overexpression in epileptic brains correlates with seizure severity and contributes to blood–brain barrier disruption and modifies neuronal excitability.[22] The dual action of inhibiting neuronal excitability and suppressing brain's inflammatory response by certain AEDs may therefore underlie part of their clinical efficacy and neuroprotective potential.

Exploiting this dual mechanism could be particularly beneficial in treatment-resistant epilepsy associated with prominent neuroinflammation, supporting the development of therapeutic strategies that would address target electrical and inflammatory components of epileptogenesis at the same time.[23,24]

CONCLUSION

This in silico study evaluated the possible anti-inflammatory efficacy of six frequently prescribed antiepileptic drugs through molecular docking with TNF-α and IL-6. All of the AEDs showed interaction with inflammatory targets and the XP GScore was between **-1.817 to -4.909 Kcal/mol**. Aromatic system drugs with multiple hydrogen bonding groups exhibited superior binding whereas flexible structure with reduced aromatic nature were observed to have lower interactions. Such results indicate that anti-inflammatory effects could be a significant, but not adequately recognized, side effect of the antiepileptic therapy of some antiepileptic drugs. The dual action neuronal excitability and inflammatory mechanism could contribute to their clinical efficacy and neuroprotective effects. This study contributes to the growing recognition that epilepsy is not merely a disorder of neuronal excitability but also involves significant inflammatory components. Therapeutic strategies targeting both aspects may offer superior outcomes for patients with epilepsy, particularly those with treatment-resistant forms associated with prominent neuroinflammation.

Contribution

MA and SK contributed in conception and design of manuscript. MS and AY compiled the literature and wrote the manuscript. MA, H, T and NSK reviewed the manuscript.

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Declarations

All authors contributed equally to this work and share first authorship.

Ethical approval and consent to participate

Not Applicable.

Consent of publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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