Dual Activation of TMEM16A and TRPV4 by Eact : A Novel Therapeutic Strategy for Cystic Fibrosis

Razan Orfali[1], Ali Alfaiz[1], Madhawi Alanazi[2], Rahaf Alabdulsalam[1], Reem Saud[3]

[1] Research Centre, King Fahad Medical City, Riyadh Second Health Cluster, 12231, Saudi Arabia.
[2] Pharmacy Administration, AlYmamah Hospital, Riyadh Second Health Cluster, 14222, Saudi Arabia.
[3] Dar AlHekmah University, Jeddah, 22246, Saudi Arabia

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Introduction

Cystic fibrosis (CF) is a chronic, progressive, and often fatal genetic disease primarily affecting the respiratory systems of children. The loss of CFTR function in CF results in airway surface dehydration and impaired mucociliary clearance. While no cure exists for CF, several treatments can alleviate symptoms and slow disease progression. Based on recent findings[1], Eact can offer a novel dual-target therapeutic approach by activating both TMEM16A and TRPV4 channels, thereby improving respiratory function in CF patients.

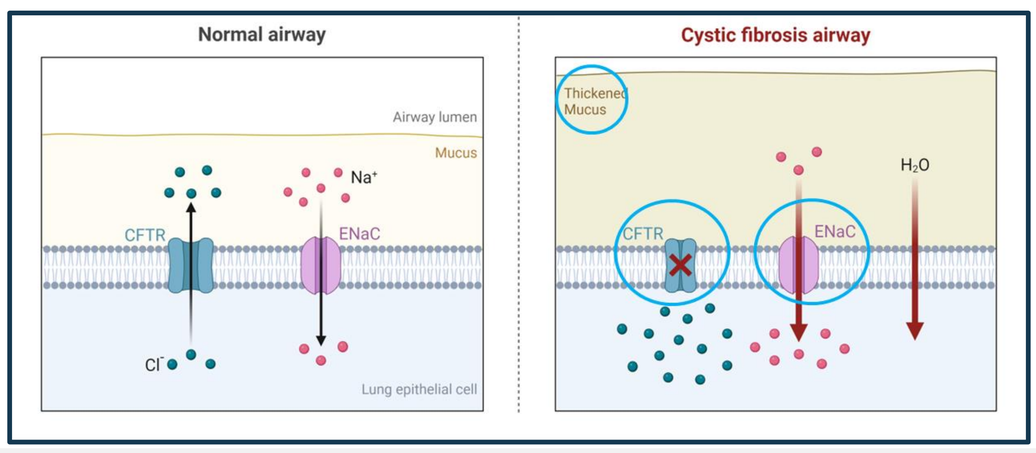

Figure 1 **Genetic mutations in the CFTR cause cystic fibrosis (CF).** Blue circles indicate various strategies to address CF: (1) Targeting CFTR to restore its function, (2) Targeting the epithelial sodium channel (ENaC) to prevent mucus dehydration, and (3) Directly modifying mucus to reduce its viscosity.

TMEM16A: (ANO1), a calcium-activated chloride channel (CaCC)
TRPV4: Vanilloid transient receptor potential channel

Aim

To determine the binding interactions of Eact with TRPV4 and TMEM16A channels using molecular docking simulations and evaluate their potential as dual-acting therapeutic compounds for enhancing mucociliary clearance and improving pulmonary manifestations in cystic fibrosis.

Methods

Docking of Eact with TRPV4 (PDB: 8FC8) and TMEM16A (PDB: 5OYB) Using AutoDock Vina and Schrödinger's Glide.

- **Protein Preparation:**

TRPV4 (PDB ID: 8FC8) and TMEM16A (PDB ID: 5OYB) structures were prepared using AutoDock MGL tool and Schrödinger's Maestro.

- **Ligand Preparation:**

Eact and Resveratrol structures were obtained from PubChem and prepared using AutoDock MGL tool and Schrödinger's LigPrep.

- **Docking Simulations:**

AutoDock Vina: Structures were converted to PDBQT format. Docking grids were generated, and each ligand was docked to both proteins, producing 100 poses initially and then filtering down to the top 10 for further analysis.

Schrödinger's Glide: Docking grids were prepared, and each ligand was docked to both proteins, producing 100 poses per ligand.

- **Analysis:**

Mean binding energy, lowest binding energy, and cluster sizes were extracted and compared.

Results

Binding Interactions of Eact with TRPV4 and TMEM16A.

Table 1 **Eact with TRPV4:**

	AutoDock Vina	Schrödinger's Glide
Mean Binding Energy (kcal/mol)	-6.9	-7.0
Lowest Binding Energy (kcal/mol)	-7.9	-8.0
Cluster Size	10	10

Table 2 **Resveratrol* with TRPV4:**

	AutoDock Vina	Schrödinger's Glide
Mean Binding Energy (kcal/mol)	-7.5	-7.6
Lowest Binding Energy (kcal/mol)	-8.6	-8.4
Cluster Size	9	14

Table 3 **Eact with TMEM16A:**

	AutoDock Vina	Schrödinger's Glide
Mean Binding Energy (kcal/mol)	-6.8	-7.1
Lowest Binding Energy (kcal/mol)	-7.8	-8.1
Cluster Size	10	10

Table 4 **Resveratrol with TMEM16A:**

	AutoDock Vina	Schrödinger's Glide
Mean Binding Energy (kcal/mol)	-7.1	-7.7
Lowest Binding Energy (kcal/mol)	-8.3	-8.6
Cluster Size	7	10

Resveratrol*
A natural polyphenol activates TMEM16A and is currently in clinical trials for CF treatment.

Eact with TRPV4:

Eact with TMEM16A:

Conclusion

The molecular docking simulations of Eact with TRPV4 and TMEM16A reveal its potential as a dual-acting therapeutic for cystic fibrosis. Eact showed significant binding interactions, making it a promising CF treatment candidate. Future *in vitro* studies should validate these results.

Acknowledgment

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References

1- Genovese M, Borrelli A, Venturini A, et al. TRPV4 and purinergic receptor signalling pathways are separately linked in airway epithelia to CFTR and TMEM16A chloride channels. J Physiol. 2019;597.