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RESEARCH LETTER

Network pharmacology and in silico pharmacokinetic prediction of Ozanimod in the management of ulcerative colitis: A computational study

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1 | INTRODUCTION

Inflammatory bowel disorders are non-infectious chronic inflammation of the esophageal tract (IBD). IBD is divided into two types: ulcerative colitis (UC) and Crohn's disease. The highest incidence and prevalence rates of ulcerative colitis are seen in North America and northern Europe, with incidence rates ranging from 9 to 20 cases per 100 000 person-years and prevalence rates ranging from 156 to 291 cases per 100 000 persons.[1] OZM is contraindicated in patients with previous history of cardiovascular complications. The dose and dosage of OZM is 0.23 mg by oral route (qDay) for 1 to 4 days followed by 5 to 7:0.46 mg and on eighth day titrated to 0.92 mg PO (qDay). OZM is not highly recommended in pregnant and lactating women since existing animal studies not reported with enough evidence. The in silico analysis of Ozanimod (OZM) is not yet been fully characterized. The current study was designed to investigate the pharmacokinetic profile of the OZM and its interaction potential with UC target protein.

2 | DRUG OVERVIEW

OZM is a sphingosine-1-phosphate (S1P) receptor modulator approved by FDA in March 2020 for UC. The molecular weight of OZM is 404.47, with 07 rotatable bonds and acceptable bonds. The water solubility rate was −3.154 (log mol/L), the intestinal absorption rate is 91.053% in humans, OZM is a substrate of P-glycoprotein, and CYP3A4 followed by an inhibitor of P-glycoprotein I and II, clearance 0.69 (log ml/min/kg), Minnow toxicity −0.231(log mM).[2,3]

3 | METHOD

The pharmacokinetic profile of OZM was observed from the PKCSM online server. Pass online tool is used to predict the biological activity profile of the compound. OSIRIS Property Explorer program is used to estimate the toxicity profile. Target genes associated with the OZM (accepted by Lipinski's rule) were obtained via Swiss Target Prediction (STP) (http://www.swisstargetprediction.ch/) with "Homo Sapiens" setting. The Autoimmune disease & Ulcerative colitis (AID & UC) targeted genes were generated from DisGeNET (https://www.disgenet.org/search). The overlapping genes between AID, UC & OZM genes were visualized on the Venn diagram by InteractiVenn (http://www.interactivenn.net/). The gene(s)–gene (s) network is constructed by STRING (https://string-db.org/) analysis.

4 | DRUG ACTIVITY DATA FROM PASS ONLINE PROGRAM

The estimated activity of a substance is predicted as probable activity (Pa) and probable inactivity (Pi). The substances revealing Pa higher than Pi are the only components thought about as feasible for a specific medical activity. The Pa value and Pi value for Autoimmune disorders treatment shows 0.645 and 0.009, respectively. The Pa value and Pi value for systemic lupus erythematosus treatment shows 0.572 and 0.004. followed by 0.514 and 0.009 for multiple sclerosis treatment.[4] Toxicity is accountable for the withdrawal and failure of new chemical entities. The toxicity profile of selected drugs was analyzed

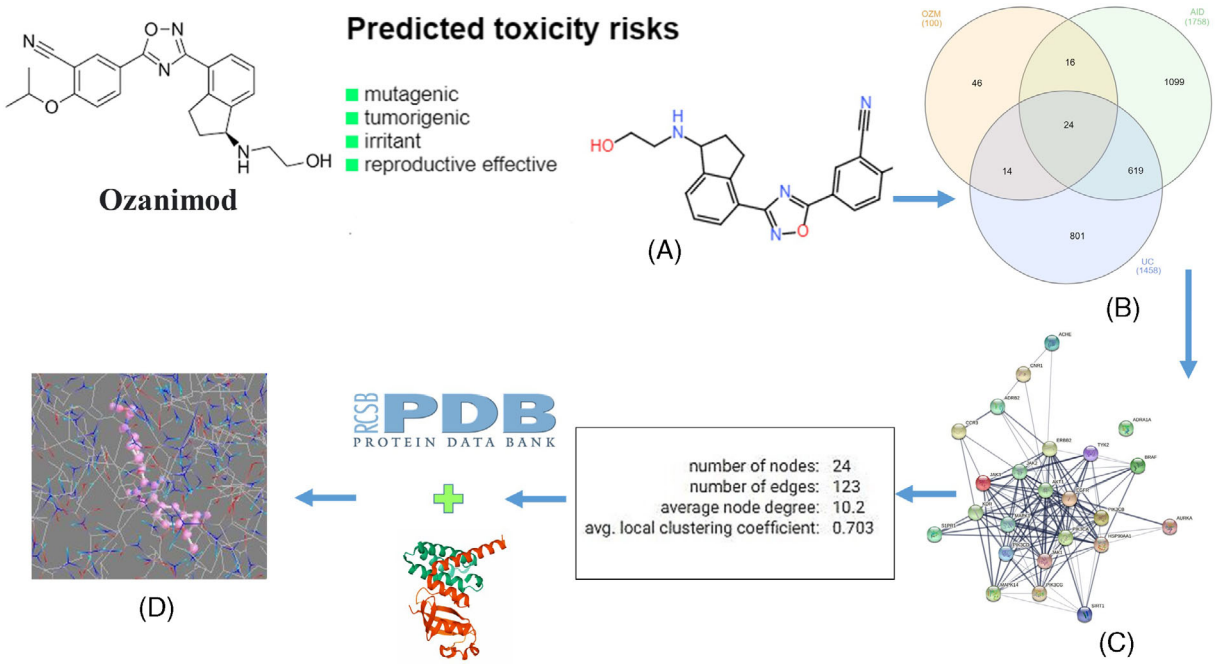

FIGURE 1 (A) Toxicity profile of OZM; (B) overlapped protein for OZM vs auto immune disease and ulcerative colitis; (C) network analysis from STRING database; (D) molecular docking analysis of OZM

through the OSIRIS Property Explorer program by a color scale. OZM passes all the factors Tumorigenicity, mutagenicity, irritant, reproductive effect with green color representation[5] (Figure 1A). Overlapping Target Proteins between AID, UC, and OZM showed that 24 target proteins were overlapping between the two public databases[6] (Figure 1B). Protein-protein interaction from 24 overlapping target proteins from STRING analysis shows that 24 nodes, 123 edges, and PPI enrichment *P*-value was <1.0e-16. The *P*-value indicates that there was a significant connection between the protein and biological activity of the drug. In protein-protein interaction (PPI), the MAPK1 target exhibited the highest degree and is considered as a hub target protein[7] (Figure 1C).

5 | MOLECULAR DOCKING ANALYSIS OF OZM WITH MAPK1

In determining binding affinities and interactions of OZM with MAPK1 in pyRx virtual screening tool,[8] Avogadro V.1.2.0 and molegro molecular viewer is used for geometry optimization. The crystal structure of the selected protein was downloaded from the protein data bank. The localized charge on the iron was chosen as Fe2+. At pH 7.0, hydrogens were added to all protein structures to produce ionization and tautomeric modes for all hetero groups. The total protein was then minimized to a maximum root mean square deviation (RMSD) value of 0.3°A to avoid the steric clashes of added hydrogen atoms.[9] In silico molecular docking is a powerful technique to discover novel ligands for receptors of existing structures and it plays a key role in the structure-based drug design. Molecular docking plays a crucial role in the field of computer-aided drug designing, which screens for a small molecule and gives a targeted binding site of a protein. The molecular docking studies were performed for OZM G against the MAPK1 target. The structures were designed, and the binding interaction energies were calculated using score techniques. A more negative range indicates the effective confirmation of bounding ligand-target. OZM showed a stronger binding affinity. The docking score for OZM G against MAPK1 was −7.7 kcal/mol. The docked compound is illustrated in Figure 1D. Due to the good binding affinity, this analysis indicated that our predicted compound might be more effective in the management of UC. The increased mortality rate is observed in geriatrics with existing complications like infection, shock, anemia, and those who require repeated surgical interventions. Clinical trials reported 01 mg of OZM is administered in both trials with placebo as a control group, there was a significant change between the control group and treatment group (Table 1). However, headache and back pain are the majorly reported adverse drug reactions. The in silico evolution has demonstrated and it has directly visualized the drug profile and its effects in the treatment of UC.

6 | CONCLUSION

This computer-aided study suggests that OZM would be a suitable option for the management of UC. The ultimate aim of this research is to understand the in silico pharmacokinetic profile of OZM for UC. More in vitro, in vivo, and clinical studies needed to be addressed to enhance the evidence.

TABLE 1 Major adverse events reported in two clinical trials[10,11]

	Study 1 Clinical trial 1 (NCT01647516)		Study 2 Clinical trial 2 (NCT02435992)	
Adverse events	**Ozanimod (1 mg)**	**Placebo**	**Ozanimod (1 mg)**	**Placebo**
Serious adverse events	2/67 (2.99%)	4/65 (6.15%)	17/429 (3.96%)	11/216 (5.09%)
Nonserious adverse events	8/67 (11.94%)	9/65 (13.85%)	15/429 (3.50%)	13/216 (6.02%)
Headache	2/67 (2.99%)	3/65 (4.62%)	1/429 (0.23%)	NR
Backpain	1/67 (1.49%)	1/65 (1.54%)	NR	NR

Abbreviation: NR, not reported.

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CONFLICTS OF INTEREST

No conflicts of interest have been identified or declared by any of the authors.

AUTHOR CONTRIBUTIONS

Conceptualization: Sarvesh Sabarathinam.

Formal analysis: Priya S.

Writing-original draft: Thangavel Mahalingam Vijayakumar.

All authors have read and approved the final version of the manuscript.

Corresponding author, Vijayakumar, had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author, Vijayakumar, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

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

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REFERENCES

1. Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet*. 2012;380(9853):1606-1619.
2. Ayati A, Falahati M, Irannejad H, Emami S. Synthesis, in vitro antifungal evaluation and in silico study of 3-azolyl-4-chromanone phenylhydrazones. *Daru*. 2012;20(1):46.
3. Rashid M. Design, synthesis and ADMET prediction of bis-benzimidazole as anticancer agent. *Bioorg Chem*. 2020;2020(96):103576.
4. Prasanth DSNBK, Murahari M, Chandramohan V, Panda SP, Atmakuri LR, Guntupalli C. In silico identification of potential inhibitors from cinnamon against main protease and spike glycoprotein of SARS CoV-2. *J Biomol Struct Dyn*. 2021;39(13):4618-4632.
5. Preethi L, Ganamurali N, Dhanasekaran D, Sabarathinam S. Therapeutic use of Guggulsterone in COVID-19 induced obesity (COVIBESITY) and significant role in immunomodulatory effect. *Obesity Med*. 2021;24:100346.
6. Oh KK, Adnan M, Cho DH. A network pharmacology analysis on drug-like compounds from Ganoderma lucidum for alleviation of atherosclerosis. *J Food Biochem*. 2021;45(9):e13906.
7. Oh KK, Adnan M, Cho DH. Network pharmacology approach to decipher signaling pathways associated with target proteins of NSAIDs against COVID-19. *Sci Rep*. 2021;11(1):9606.
8. Bibi N, Farid A, Gul S, et al. Drug repositioning against COVID-19: a first line treatment. *J Biomol Struct Dyn*. 2021;1-15.
9. Duchowicz PR, Castro EA. QSPR studies on aqueous solubilities of drug-like compounds. *Int J Mol Sci*. 2009;10(6):2558-2577.
10. Efficacy and safety study of Ozanimod in ulcerative colitis. https://ClinicalTrials.gov/show/NCT01647516
11. Safety and efficacy trial of RPC1063 for moderate to severe ulcerative colitis. https://ClinicalTrials.gov/show/NCT02435992.

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