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REPURPOSING IOPHENDYLATE: EXPLORING THE POTENTIAL OF A CONTRAST AGENT IN HYPERCHOLESTEROLEMIA THERAPY

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Keywords:

Ligand-based virtual screening, bempedoic acid, hyperlipidemia, ischemic heart disease, drug repurposing, molecular docking, bioactive compounds, pharmacokinetics, structural diversity, cardiovascular care

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ABSTRACT

The ligand-based virtual screening (LBVS) is regarded as a very convenient drug discovery platform for the identification of novel therapeutic leads, especially when the three-dimensional structure of the target protein is unknown. Here, the study investigates the application of LBVS to discover new agents for the treatment of hyperlipidemia, in this case, ischemic heart disease (IHD) and other alternatives or complementary agents to bempedoic acid. Using a set of databases (PubChem, ChEMBL, ZINC) and literature, a set of bioactive compounds including bempedoic acid analogs was screened. Compounds were filtered on the basis of chemical diversity, pharmacokinetics, biological relevance, and availability. A ligand-based virtual screening protocol grounded on similarity measures, including Tanimoto coefficients and molecular docking, was applied to rank compounds by structural similarity to bempedoic acid. A set of possible candidates was discovered, from which some showed better building affinities to target binding sites on chain A of respect to bempedoic acid; all compounds displayed docking scores better than that of bempedoic acid. Docking run analysis showed structural diversity of binding sites with the potential for optimization of drug repurposing strategies. The study provides candidate compounds which require better investigation as therapeutics for hyperlipidemia and IHD; LBVS is regarded as a powerful test that enabled the discovery of a novel class of lipid-lowering agents with encourages fewer side effects.

INTRODUCTION

LBVS is used in drug discovery, and it is based on the interactions of small molecules-ligand-protein [1]. Therefore, this makes it easy to compare known ligands with bioactive compounds for a chance to get new candidates to be made[2,3].LBVS is particularly useful for cases where the three-dimensional structure of the target protein is not known [4, 5, 6] which mostly occurs as a condition more often than not during the preliminary drug discovery research [7]. This work will attempt ligand-based virtual screening to discover and identify new therapeutic agents as substitutes or adjuncts in place of bempedoic acid for the management of hyperlipidemia [8, 9].

This study, with the help of well-curated databases of known bioactive compounds, has been designed in order to unveil the novel ligands that would have much more favorable pharmacological profiles and are likely to improve lipid-lowering efficacy [10]. To fulfill the previous objective, this study intends to verify the hypothesis that some structural features of known ligands may be used [11,12] in predicting the efficiency of new compounds for cholesterol-level regulation [13]. We hope to find new agents with higher potency or fewer side effects and offer more treatment options for patients suffering from dyslipidemia [14]. And focusing on this key aspect, the study would in general contribute to the understanding of lipid-lowering therapies more in detail and continue supporting demands for innovation in cardiovascular care [15]. Some of the multi-fold advantages it provides over traditional approaches like high throughput screening, including drastic cuts in investments of time and resources by focusing on those compounds which have a higher probability of efficacy according to their structural similarity [16]. It is also indicated that LBVS enables the screening of bulk chemical libraries in a manner so that new ligands, if not identified by experimentations, are searched and identified [17]. This agent can foresee the likely interaction and affinity, thereby a computational potential attached to this agent, which has made LBVS a very valuable tool in modern drug discovery [18]. Bempedoic acid is a novel therapeutic agent that is mainly used for the treatment of hyperlipidemia, especially in patients in whom satisfactorily low cholesterol levels cannot be achieved with statins alone [19]. It is an ATP-citrate lyase inhibitor that is, a reduction of cholesterol and triglycerides in the liver [20, 21, 22]. Bempedoic acid represents an important new drug for lipid management, especially those patients with atherosclerotic cardiovascular disease or at high risk [23,24]. Its mechanism of action is supplementary to the existing lipid-lowering therapies thereby underlining the need to invest more research into new, innovative agents that could benefit the patient [25,26]. As the science and medicine of cardiovascular disease change, so will the emphasis on identification of new therapeutic candidates become paramount [27,28].

With an increasing number of patients incurring dyslipidemia, there is a need for well-tolerated and effective treatments [29, 30, 31]. In addition, the prevalence of statin intolerance and side effects of the current treatments pose the need to search for alternatives that may better the management of cholesterol without compromising the safety of patients [32, 33, 34].

MATERIALS AND METHODS

Data Collection: Sources of Bempedoic Acid Analogs

We started with compounds from a few reliable databases: PubChem, very large and comprehensive, harboring all chemical information available, including a wide array of bempedoic acid derivatives, ChEMBL for molecules with drug-like properties and established biological activities, and the ZINC Database, a free source of commercially available compounds that provides a large

collection of bempedoic acid analogs. Besides, we carried out a review of published articles and patents to collect even more derivatives of bempedoic acid, other than those mentioned in the above databases [35].

Ligand – Based virtual screening protocol.

In ligand-based virtual screening, compounds were selected on multiple criteria to highlight potential drug candidates. Chemical diversity was ensured through the assessment of structural variety with Tanimoto similarity coefficients [36,37,38]; ADMET properties were assessed to rank compounds according to favorable pharmacokinetic profiles for oral bioavailability; biological relevance was taken into account by considering compounds with reported activity against the target of interest; molecular weight between 300-500 Da and lipophilicity within LogP values 2-5 as optimized for pharmacological properties, and availability that allowed ease of experimentalvalidation [39, 40]. Candidates for drug repurposing were tested on Ligand-based Screen by using ligand-based virtual screening [41]. The approach made use of a known active ligand of an exemplified target as a template compound, and it was used as a template for screening by different similarity measures [42,43] like LigMate, FitDock-align, Morgan Fingerprint, LSalign, FP2, and FP4, to rank compounds based on their similarity scores and then to pick the top-ranked compounds for further studies in drug repurposing [44].

Docking studies

In one previous drug repurposing project, I attempted to generate a compound library from databases like ZINC and ChEMBL. Subsequently, I constructed a pharmacophore model using the active ligand in order to carry out virtual screening using molecular docking and pharmacophore-based methods. After post-docking analysis was done for evaluation of binding modes and interactions, I prioritized high-scoring compounds further for evaluation [45].

RESULT AND DISCUSSION

Result of ligand-based drug repurposing

Table 1: justification for selecting bempedoic acid as the primary ligand for designing new agents targeting ischemic heart disease.

Criteria	Justification
Mechanistic Relevance	Inhibits ATP-citrate lyase, reducing fatty acid and cholesterol synthesis, addressing key pathways in IHD.
Established Efficacy	Proven to effectively lower LDL cholesterol levels, a critical target in reducing cardiovascular risk.
Favorable Safety Profile	Demonstrates mild side effects compared to traditional therapies, enhancing its attractiveness for use.
Potential for Combination Therapy	Can be combined with other lipid-lowering agents for synergistic effects, beneficial for patients with comorbidities.
Research and Development Support	Extensive existing research on pharmacokinetics and molecular interactions facilitates further development.
Bioavailability and Pharmacokinetics	Good oral bioavailability and suitable pharmacokinetic properties support chronic disease management.
Regulatory Approval	Already approved for clinical use, providing a pathway for new formulations or derivatives in IHD treatment.

Table (1) gives the justification for selecting bempedoic acid as the primary ligand for designing new agents targeting ischemic heart disease.

Result of Ligand-Based Screening using the Drug-Rep platform

Table 2: Matching scores and target interactions of various compounds

Rank	Compound	Name	Score	Rank	Compound	Name	Score
1	DB11936	Bempedoic acid	1.000	11	DB01187	Iophendylate	0.250
2	DB00548	Azelaic acid	0.324	12	DB14104	Linoleic acid	0.250
3	DB03017	Lauric acid	0.308	13	DB04224	Oleic Acid	0.250
4	DB00770	Alprostadil	0.307	14	DB06689	Ethanolamine oleate	0.250
5	DB12839	Pegvaliase	0.292	15	DB03193	Stearic acid	0.247
6	DB13966	Isopropyl myristate	0.275	16	DB01245	Decamethonium	0.247
7	DB11117	Undecylenic acid	0.269	17	DB01241	Gemfibrozil	0.247
8	DB00929	Misoprostol	0.269	18	DB01783	Pantothenic acid	0.242
9	DB03796	Palmitic Acid	0.267	19	DB11190	Pantethine	0.242
10	DB00410	Mupirocin	0.262	20	DB06826	Unoprostone	0.255

The table (2) summarizes the results of a ligand-based virtual screening analysis, which returns a list of compounds ranked according to a similarity score compared to an active ligand. The top-scoring compound was Bempedoic acid (DB11936), with a score of 1.000, and the lowest score was that of Azelaic acid (DB00548), with a score of 0.324. Compounds span the gamut from relatively simple fatty acids, Lauric acid (DB03017) and Palmitic acid (DB03796), through to pharmaceuticals like Mupirocin (DB00410) and Misoprostol (DB00929), scoring between 0.269 and 0.242 for the latter end members. A large number, including Iophendylate (DB01187) and Linoleic acid (DB14104), have score values near or below 0.250. The scores spread quite widely, thereby inducting a form of chemical diversity such that higher-scoring compounds are better drug repurposing candidates based on the similarity of structure.3.3 Docking studies and validation process results.

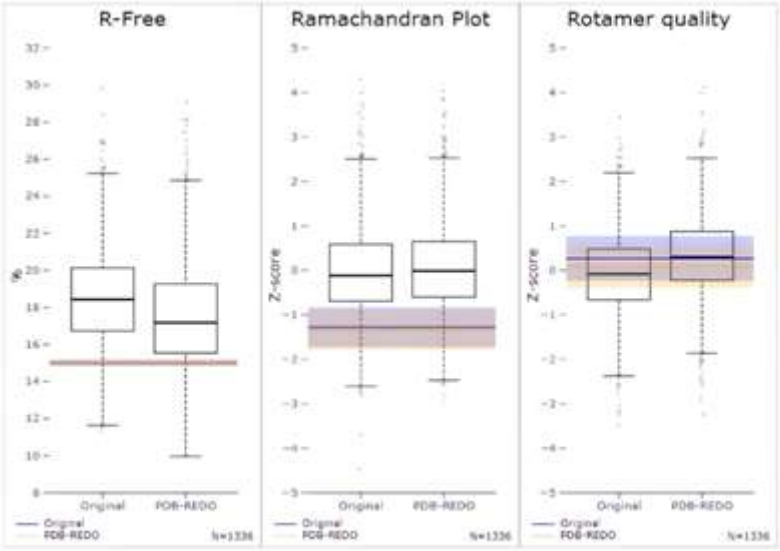
Table 3: Validation metrics from PDB-RED

Validation Metrics	Original	PDB-REDO
Crystallographic refinement		
R	0.1276	0.1272
R-free	0.1488	0.1498
Bond length RMS Z-score	0.146	0.946
Bond angle RMS Z-score	0.859	0.904
Model quality raw scores percentiles		
Ramachandran plot normality	47	46
Rotamer normality	93	91
Coarse packing	25	23
Fine packing	27	29
Bump severity	20	21
Hydrogen bond satisfaction	54	46

Refinement parameters and quality model scores between the original and PDB-REDO-refined structures are compared in the table (3). For refinement parameters, the results for both models are practically identical: especially R (0.1276 for the original and 0.1272 for PDB-REDO) and R-free (0.1488 for the original and 0.1498 for PDB-REDO) values are very close indicating a comparable fit to experimental data. However, the RMS Z-score of the bond length for the original model is significantly lower in comparison to the model produced by PDB-REDO (0.146 vs. 0.946), thus suggesting that the latter's bond length geometry is not optimal enough.PDB-REDO yields higher RMS Z-scores for bond angles as well, meaning there is a minor improvement in the geometry of bond angles (0.904 vs. 0.859). Model quality scores reflect very slight differences in packing and hydrogen bond satisfaction: the original model is marginally better at rotamer and coarse packing normality, while the PDB-REDO model appears to do marginally better at fine packing and bump severity. The **figure (1)** represents ComparativeAnalysis of Model Quality Metrics: Original vs. PDB-REDO Refinement

Overall, though, despite some similarity between the models, PDB-REDO refinement doesindeed appear to provide marginal gains in geometry and in packing, albeit at the cost of satisfaction of hydrogen bonds.Model quality compared to resolution neighbours.

Figure 1: Comparative Analysis of Model Quality Metrics: Original vs. PDB-REDO Refinement



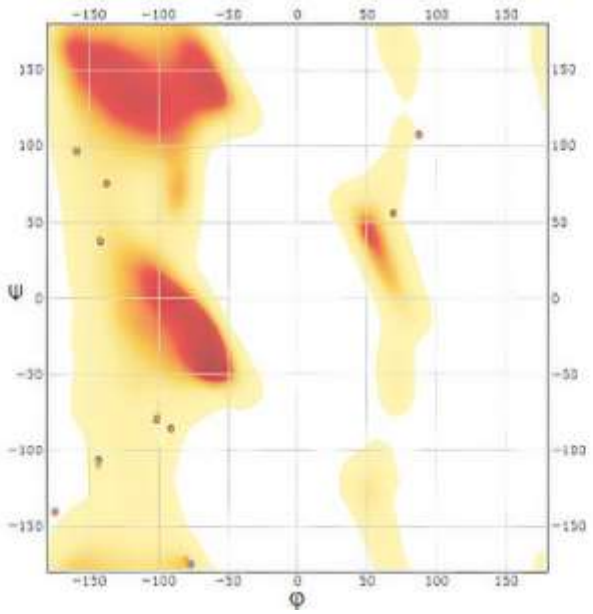


Figure 2: Kleywegt – like plot

The figure (2) represents a kleywegt-like plot, depicting the distribution of phi (Φ) and psi (Ψ) dihedral angles of amino acids in a protein structure, where the color gradient represents the density of conformational states, the red regions indicate favored conformations,while the scattered blue and orange dots highlight individual residues, providing insights into the stereochemical quality and structural integrity of the protein backbone.

Docking results:

Table 4: Binding Affinity Analysis of Drugbank compounds to target pockets: Identification of Potential drug candidates

DrugBank ID	Pocket	Score	Chain	DrugBank ID	Pocket	Score	Chain
DB11936	C3	-5.6	A	DB06826	C3	-5.2	A
DB00548	C3	-4.6	A	DB01187	C1	-6.7	A
DB03017	C3	-4.4	A	DB14104	C3	-5.0	A
DB00770	C3	-5.0	A	DB04224	C3	-5.2	A
DB12839	C1	-5.5	A	DB06689	C3	-4.9	A
DB13966	C3	-5.8	A	DB03193	C1	-4.6	A
DB11117	C1	-5.4	A	DB01245	C1	-5.3	A
DB00929	C4	-5.4	A	DB01241	C1	-7.1	A
DB03796	C1	-5.2	A	DB01783	C1	-5.2	A
DB00410	C3	-5.8	A	DB11190	C1	-6.2	A

The table (4) presents the docking scores of various compounds from the DrugBank database, showing their binding affinity to different pockets (C1, C3, C4) on chain A. The scores range from -7.1 (for DB01241 in pocket C1) to -4.4 (for DB03017 in pocket C3), with the more negative scores indicating stronger binding affinities. Notably, DB01241 (score: -7.1) and DB01187 (score: -6.7) exhibit the strongest binding in pocket C1, while compounds like DB11936 (score: -5.6) and DB00410 (score: -5.8) show moderate binding affinities in pocket C3. The distribution of docking scores across different pockets suggests a variety of binding preferences, with pocket C3 hosting a larger number of compounds, while pockets C1 and C4 also show promising binding interactions. Overall, the data highlights the potential of these compounds as candidates for further drug repurposing, with a focus on those binding more tightly to their respective pockets.

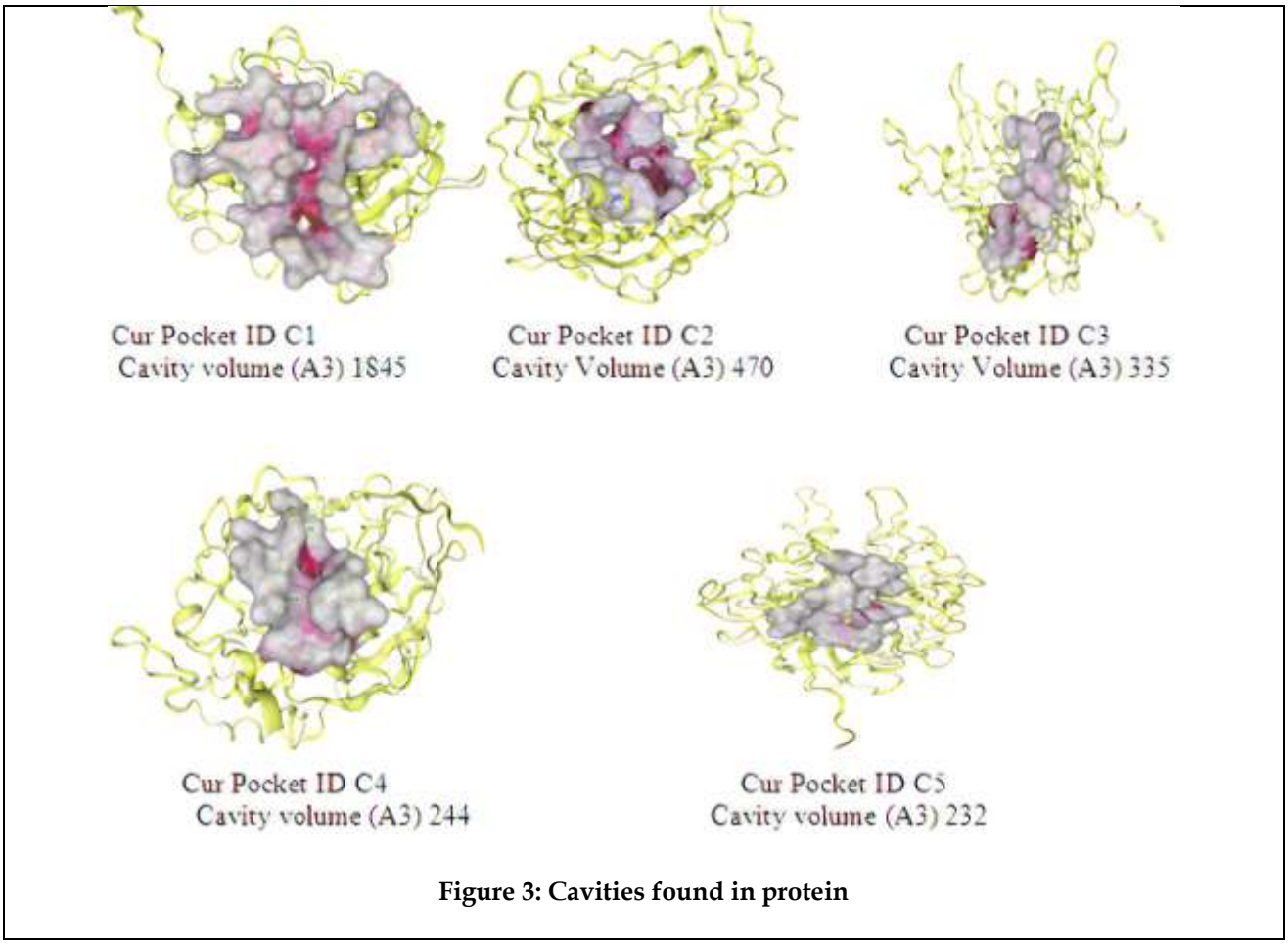


Figure 3: Cavities found in protein

Figure (3) illustrates five distinct CurPocket binding sites with varying cavity volumes, ranging from 1845 A3 to 232 A3 showcasing the structural diversity of potential ligand – binding pockets on the target protein; this highlights crucial docking sites for exploring the binding efficacy of bempedoic acid and its analogs, aiding in the optimization of their repurposing for ischemic heart disease through enhanced drug target interactions.

As shown in the figure (4) Molecular Docking of Bempedoic acid: key binding interactions for ischemic heart disease takes place.

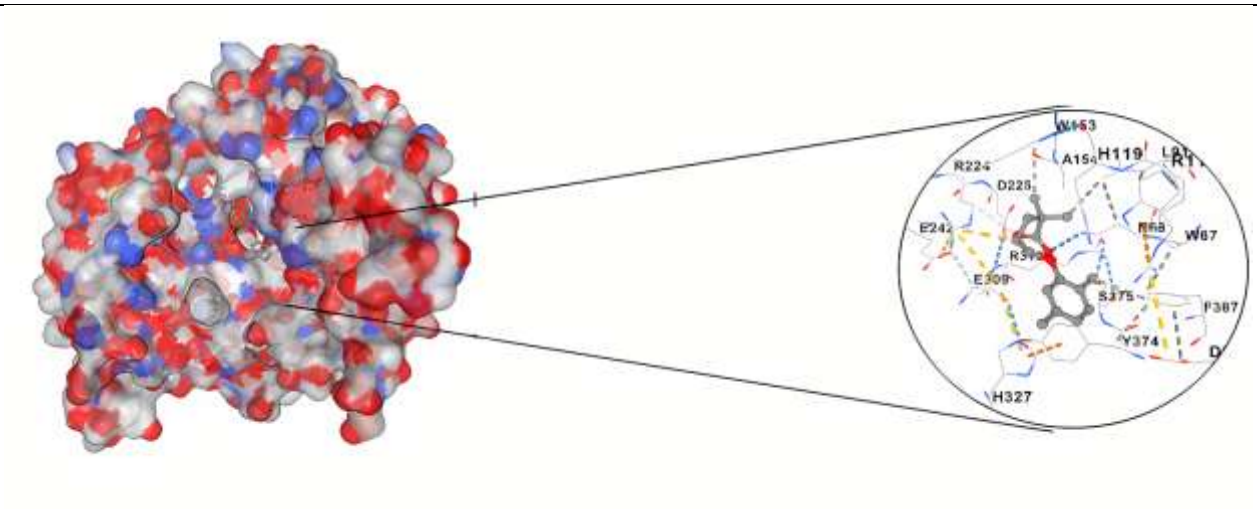


Figure 4: Molecular Docking of Bempedoic acid: key binding interactions for ischemic heart disease

4 CONCLUSION

Ligand-based drug repurposing analysis selected a compound, bempedoic acid, as being mechanistically relevant to IHD with established efficacy in lowering LDL cholesterol with a favorable safety profile, and it could be used concomitantly for additive effects.

The Drug-Rep binding scores revealed bempedoic acid, DB11936, at a score of 1.000 and being significantly above other compounds like azelaic acid, 0.324, and lauric acid, 0.308. The docking further supported the potential ability of gemfibrozil, DB01241, with a strong binding affinity to pocket C1 at -7.1 kcal/mol and iophendylate, DB01187, and pantethine, DB11190, showing the scores of -6.7 kcal/mol and -6.2 kcal/mol, respectively.

The validation metrics showed improvement in the quality of the produced models, especially for the PDB-REDO model, which reported a score of 0.1498 and also in the percentile's improvement in the Ramachandran plot and rotamer normality. Large volumes were found for the cavity structures. However, pocket C1 was large enough with a volume of 1845 A^3 to host an appropriate interaction of the ligand. These results together advance the therapeutic potential of bempedoic acid and analogues as IHD therapy by mandating further research into their maximized efficacy.

5 CONFLICT OF INTEREST:

The author declares no conflict of interest, financial or otherwise.

6 ACKNOWLEDGEMENTS:

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