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Drug Repurposing for Inflammatory Bowel Disease Based On Relations Among Drugs, Diseases and Genes

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1. Abstract

Drug repurposing, which treats new and other diseases utilizing existing drugs, has turned into a much-valuable strategy. It can also be referred to as re-examination of existing drugs that have failed to indicate utility for new diseases. In this work, we mainly focused on finding inflammatory bowel disease (IBD) associated drugs based on disease-disease relation and bi- clustering the drug-target interactions aided by known IBD risk genes. First a comprehensive bipartite network was constructed involving the drugs and their corresponding target genes based on data collected from BioSNAP database. A bi-clustering algorithm BiClusO was then applied to the bipartite network for finding high density clusters. The presence of IBD risks genes in the clusters were examined and statistically significant clusters were determined which were later utilized for IBD drug repurposing. Also, another set of potential IBD drugs were selected by examining disease-disease relations utilizing disease gene associations from BioSNAP database. Then a method was proposed to rank the common drugs acquired by the aforementioned two different approaches. Justifications for the 10 top ranked drugs were provided by searching relevant literatures.

2. Introduction

IBD (inflammatory bowel disease) is an inflammatory process confined to the colon and rectum in all conditions. It has clinical symptoms such as muscle spasms of the pelvis region, fatigue and weight loss, rectal bleeding, diarrhea and abdominal pain. Crohn's disease and Ulcerative colitis exhibit two main types of IBD [1]. Crohn's disease was first described by and named after the US physician Burril B Crohn and Ulcerative colitis was first explained by the British Physician Sir Samuel Wilks [1]. Ulcerative colitis asserts that primary dysregulation of mucosal immune system causes excessive immunologic responses to normal microflora [2]. Crohn's disease demonstrates the changes in the composition of stomach microflora and/or deranged epithelial barrier function generates pathological responses from the normal mucosal immune system [2].

IBD diseases initially may not affect the patients, but their condition will worsen with time. Consequently, they will start suffering from severe dyspnea (shortness of breath), while performing simple tasks like walking. On the other hand, medicines are capable of reducing inflammation and extending the length of remission periods, but they cannot cure the disease. The concept of polypharmacology involves the design or use of pharmaceutical agents that act on more than one targets. One application of polypharmacology is drug repurposing (sometimes referred to as drug repositioning or therapeutic switching). Since the conventional discovery and development of medical substances is a costly and tedious process, drug repurposing appears as an alternative solution to develop personalized treatments for chronic diseases (by identifying potential drug targets and their drugs).

Drug repurposing (also called drug reprofiling or re- tasking) is a procedure for identifying new practices for authorized or exploratory

drugs that are outside the scope of original medical manifestation [3]. Despite the dire need, the production of medicinal materials is not only expensive but also time-consuming. According to the estimation by a workshop held in 2014, bringing a new drug into the market successfully could take approximately 10 years and cost up to $1 billion [4]. In biopharmaceutical industry, companies have been relentlessly making efforts over the years to increase productivity by accompanying new drug discovery methods– one of them is drug repurposing. Drug repurposing pledges to be a beneficial tactic as it can re-examine current drugs to indicate utility for new diseases. Besides, it can save invaluable time and finances as well as determine the effectiveness of available medications.

Drug-gene interaction (DGI) is an association between a drug and a genetic variant that may affect a patient's response to drug treatment. The relationship between drug concentration and effect−pharmacodynamics (PD)−under genetic behavior, as drug receptors are the products of genes that reveal polymorphisms. The consequence of genetics on pharmacokinetics (PK) can introduce variability among individuals that may be the cause of treatment failure or toxicity [5]. Scientists have developed DGI databases based on various proven scientific methods that can be used to examine the functional modules of specific drug sets and their target interactions.

A drug-gene module (DGM) is a subset of DGIs, where groups of drugs participate cooperatively by regulating a bunch of genes to control different biological processes [6]. The DGIs can be represented as a bipartite graph. A bipartite graph is a network of two disjoint sets of nodes, where each edge connects a node from one set to a node of the other set while no edge is allowed within any single set. A bi-cluster is a high density (in terms of connected edges) subgraph of a bipartite graph. Bi-clustering has numerous applications in different fields of study. For example, in biology, gene expressions under certain conditions form a bipartite network which helps identify cellular response, disease diagnosis and pathway analysis. Biological network analysis of the pairwise combinations of protein, drug, metabolite, conserved functional subsequences and factor binding sites can predict or understand different cellular mechanisms.

In this research, we mainly focused on DGM detection from DGIs by a new bi-clustering approach developed recently in our lab [7, 8]. We explored IBD related genes in DGMs detected within DGI networks. DGIs are defined as interactivities between drug compounds and target proteins that play important part in genomic drug discovery [9]. Then, we examined the presence of IBD risk genes in the clusters and determined statistically significant clusters. We utilized those clusters for IBD drug repurposing. Finally, we ranked different drugs contingent on the dataset size and connectivity of IBD associated genes in the drug regulatory modules from bi-clusters. We computed modules enrichment with known IBD genes by Fisher's exact test and employed statistically significant modules to predict IBD drugs.

We also calculated similarity score for each disease with IBD using their associated genes. Diseases with high similarity scores were distinguished first and after that, their corresponding drugs were identified using the DGI dataset.

3. Materials and Method

3.1. Data Collection and Pre-Processing

3.1.1. Drug-Gene Interaction Data

Drugs affect only the rate at which existing biological functions proceed. Drugs do not change the basic nature of these functions or create new functions. There are databases that have accumulated information of interactions between drugs and their target genes. These databases are called DGI database. DGI is an association between a drug and a genetic variant that may affect a patient's response to drug treatment. The DGI network contains information like which genes are targeted by which drugs. Drug targets are molecules that play a critical role in the transport. Drug target information is widely used to facilitate computational drug target discovery, drug design, drug docking or screening, drug metabolism prediction, druginteraction prediction, and general pharmaceutical research [10].

We downloaded DGI data consisting 15,138 DGIs among 5017 unique drugs and 2324 unique genes from BioSNAP database [10]. In this dataset, the maximum degree of a drug is 147, minimum degree is 1 and average degree is 3.017. Only one drug is connected with 147 genes and 2986 drugs are connected to only 1 gene. For example: Lepirudin is connected with only 1 gene and NADH is connected with 147genes.

3.1.2. IBD Risk Genes Data

We downloaded well curated and well-studied IBD genes from three databases: The Comparative Toxicogenomics Database (CTD) [11], DisGeNET [12] and GWAS [13]. The number of genes collected from CTD, DisGeNET and GWAS databases are 900, 1100 and 386, respectively. By combining all data, we created a set of 2087 IBD related genes. The Venn diagram of the reported IBD genes in these three databases is shown in (Table 1) (Figure 1).

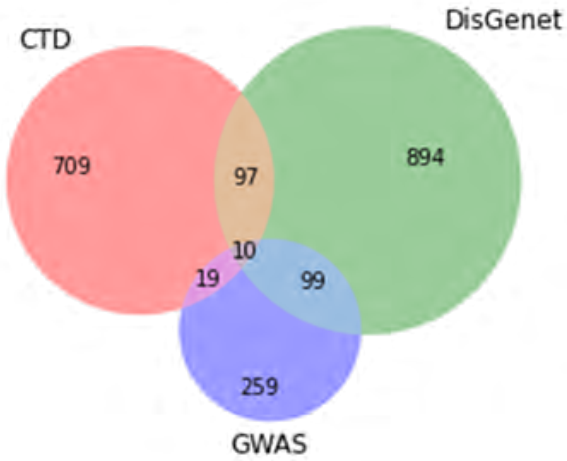

Figure 1: Venn diagram is showing overlapping between IBD genescollected from three different sources

Table 1: Statistics of datasets

Database	No. of IBD Genes
CTD	900
DisGeNET	1100
GWAS	386

3.1.3. Disease-Gene Relational Data

Disease-gene association (DGA) network contains information on disease-associated genes. The information about genes and variants involved in human diseases can be used for the investigation of molecular mechanisms of diseases and their comorbidities, the analysis of the properties of disease-gene relations, the generation of hypotheses on drug therapeutic action and drug adverse effects, the validation of computationally predicted disease-genes [10]. We downloaded DGA data which has 21,357 entries involving 519 unique diseases and 7294 unique genes from BioSNAP database [10]. In this dataset, the maximum degree of a disease is 485, minimum degree is 10 and average degree is 41.150. Only one disease is connected with 485 genes and 41 diseases are connected with 10 genes. For example: Adenomatous Polyposis Coli is connected with 10 genes and Prostatic Neoplasms is connected with 485 genes.

3.1.4. Clustering by BiClusO

At first, we clustered DGI bipartite data using BiClusO algorithm. Our lab recently developed a bi-clustering algorithm called BiClusO [7, 8]. This algorithm was mainly developed for identifying bi-clusters from a bipartite graph since a given drug can bind to different sets of genes, which implies a given drug can be found in different bi-clusters. Based on this algorithm, the bi-cluster set from a bipartite graph can be overlapped to a certain degree i.e., any node may

belong to more than one cluster.

The basic theory of BiClusO is to convert a two- dimensional problem to one dimensional one by data folding, solve it as a one-dimensional problem and unfold it again [7, 8]. Thus, BiClusO algorithm first converts the bipartite graph to a simple graph by taking any node set and measuring the association between those node pairs using relation number and Tanimoto coefficient, and then performs simple graph clustering using the polynomial-time heuristic algorithm DP-ClusO [14], also developed by our lab. Finally, the attachment of the nodes from the second set creates each bi- cluster.

4. Results and Discussion

4.1. Drug Selection by Bi-Clustering

We applied BiClusO algorithm to find bi-clusters in the DGI network using the following parameter values: `relation number=3, Tanimoto coefficient=0.33`, `cluster density=0.5, `attachment probability=0.5, and `cluster property=0.5`. Initially we acquired 339 clusters. A typical cluster consists of a bunch of drugs that are emphatically associated with a bunch of genes. Such densely connected clusters contain system level information on relations between drugs and genes. Out of these clusters, our target is to find the clusters that are statistically rich with IBD risk genes. We hypothesize that the drugs included in such clusters are IBD related drugs. To find such significant clusters we employed Fisher's exact test. An example cluster is shown in (Figure 2). In (Figure 2), the green nodes in the drug side are drugs that are connected to IBD genes. Red nodes indicate the drugs that are connected to non-IBD genes. The blue nodes attached by thin red edges are overlapping clusters.

In this cluster, there are 26 genes out of which 6 are IBD risk genes. With these values and total number of genes in the DGI network, we prepared a contingency table as shown in (Table 2) for this cluster and calculated the p-value of the cluster using equation (1). Similarly, to calculate P value for each cluster we determined the values of a, b, c and d as demonstrated in table 2 and we calculated the p-values for all the clusters.

$$P_{value} = \frac{(a+b)!(c+d)!(a+c)!(b+d)!}{a!b!c!d!n!} \quad (1)$$

After calculating p-value for each cluster, we selected potential drugs from those clusters with p-value ≤ 0.05. We found that out of 339 clusters, 254 clusters have a $P_{Value} \leq 0.05$. From these 254 clusters, we selected 876 drugs as potential drugs.

We assigned a score called S_{score} (significance score) to each drug as a measure of confidence of prediction based on the p-value of the cluster it belongs to. The formula of S_{score} is shown in equation (2). The greater the score, the higher is the significance.

$$S_{Score} = -\log(p_{value}) \quad (2)$$

As BiClusO produces overlapping clusters, a drug may belong to more than one cluster and, therefore, can have more than one S_{score}. We used the lowest Pvalue corresponding to a drug to calculate its S_{score}.

Table 2: Contingency table for Fisher's exact test

	IBD Genes	**Non-IBD Genes**	
In cluster	a	b	a + b
Not in cluster	c	d	c + d
	a + c	b + d	n

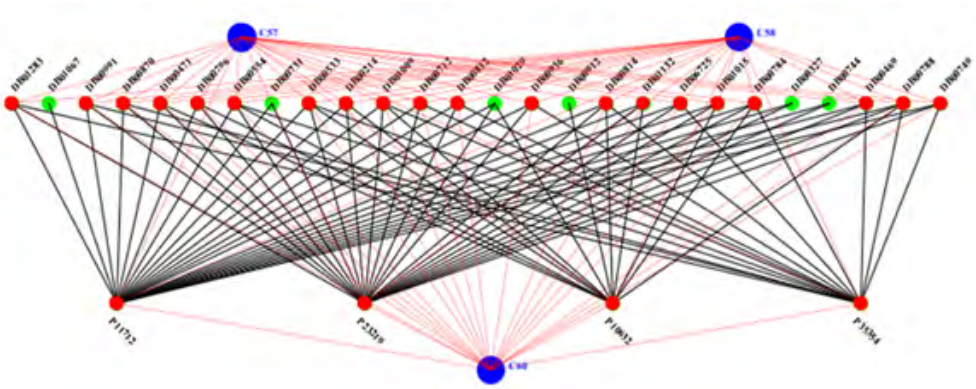

Figure 2: An example of a cluster

4.2. Drug Selection Based on Disease-Disease Relation

Analyzing disease-disease relationships plays an important role for understanding disease mechanisms and finding alternative uses for a drug [15]. The similarity between two diseases can be computed as a function of the associated genes or, alternately, the biological processes related with them [16]. In this method, we calculated the similarity between two diseases based on their target genes. The flow of this method is shown in (Figure 3).

At first, we collected the list of diseases and their associated genes from the BioSNAP database. In this case, there are 21,357 entries involving 519 diseases such as Salivary Gland Neoplasms, Psychoses, Substance-Induced, Nephrotic Syndrome, Chron's disease, Acute Promyelocytic Leukemia, Precursor B-Cell Lymphoblastic Leukemia-Lymphoma, Parkinson's disease, Sepsis etc. Then we clustered genes associated with each disease and prepared 519 lists of genes. The union of all these 519 lists consists of 7294 genes.

Afterwards, we calculated the similarity scores for 519 diseases with IBD. The similarity scores for each disease were calculated by comparing the genes associated with IBD to the genes associated with each of the other diseases. For this,`DOSE` package of R was used and by employing `clusterSim` function, the disease similarity was calculated.

The matching score ranges between 0 and 1 where 1 indicates the maximum similarity. (Figure 4) shows the similarity between IBD disease and some other selected diseases.

Additionally, we merged DGI dataset and the DGA dataset and created a new network named disease-drug association (DDA). After that, based on varying similarity scores (by keeping varying number of nodes in the DDA network), we determined how many drugs were associated with the diseases in the DDA. The relation between associated drugs and disease similarity is shown in (Figure 6). From this figure, we empirically selected 0.95 as a threshold disease similarity value for this study. Corresponding to 0.95 similarity score, there are 4107 drugs and 114 diseases. Some of these diseases are Lupus Erythematosus, Crohn's disease, Arthritis, Albuminuria, Edema, Rheumatoid Arthritis, etc. We then ranked these 4107 drugs based on the number of diseases they are connected to out of those aforementioned 114 diseases in the disease-gene-drug network represented in (Figure 5). We call this number Dscore, which is a measure of the strength of the association of the corresponding drug with IBD disease. For example, the drug Etanercept is connected to 100 diseases similar to IBD. So, the Dscore of Etanercept drug is 100.

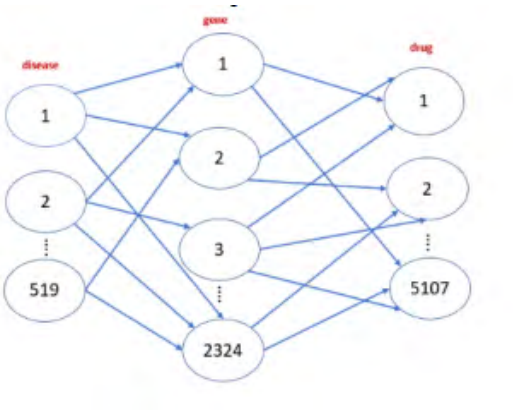

Figure 3: Flow of the disease-disease relation approach

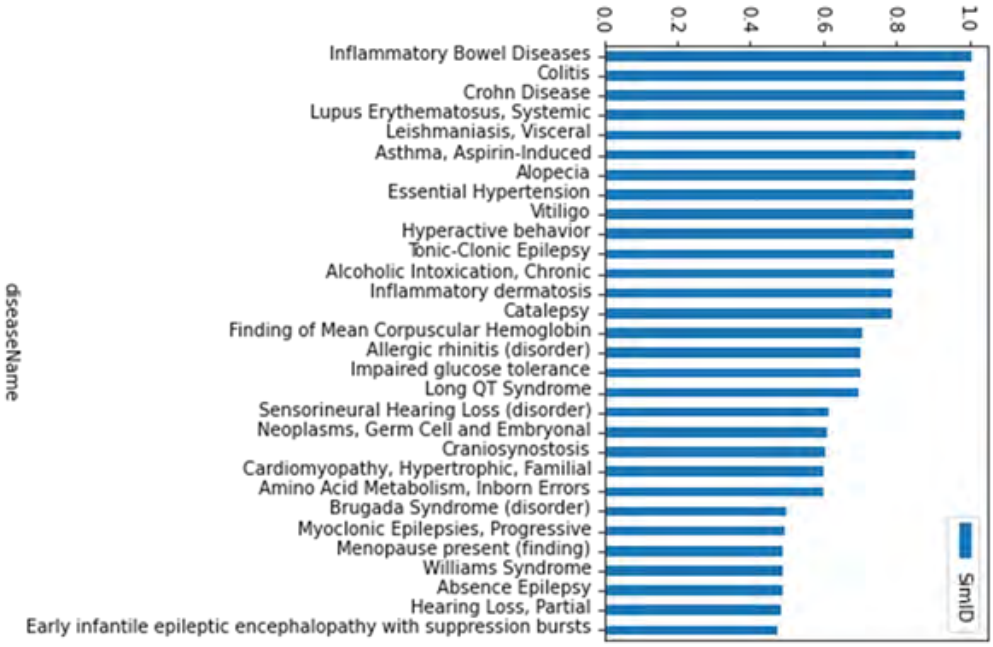

Figure 4: Disease similarity between IBD and other diseases

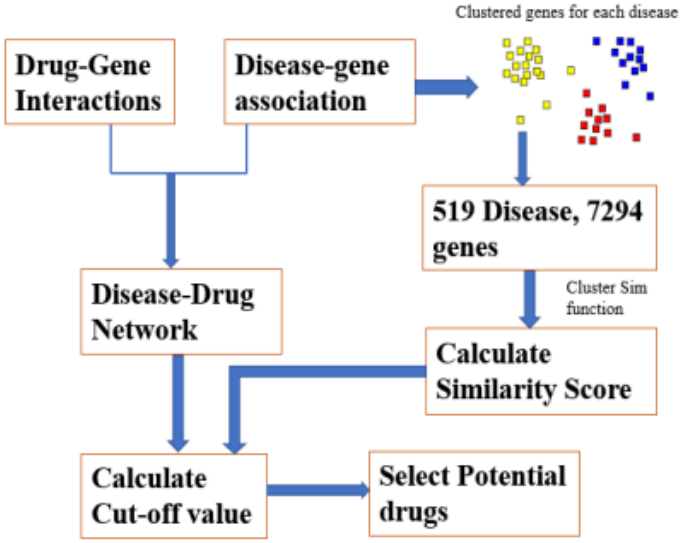

Figure 5: An example of disease-gene-drug network

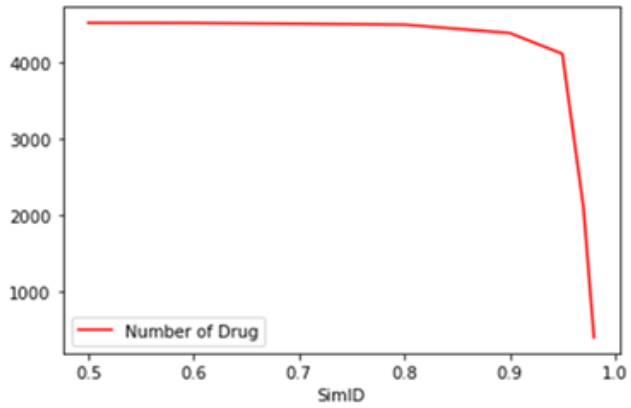

Figure 6: Calculation procedure of minimum cut-off value

4.3. Drug Selection Based on Disease-Disease Relation

Based on bi-clustering and disease-disease relation method, we found 876 and 4107 drugs, respectively. After that, we selected common drugs that are obtained from these two methods. We learned that there are 874 common drugs. (Figure 7) shows the selection process of common drugs. As shown in (Figure 7), most of the drugs obtained from the bi-clustering method are present in the drugs obtained from the disease- disease relation method. We then ranked these 874 drugs according to their $Drug_{value}$. The formula of $Drug_{value}$ is shown in equation (3), which is based on S_{score} and D_{score} of a drug. In sub-sections (1) and (2) of this section, we discussed how to calculate S_{score} and D_{score} of a drug. According to our hypothesis, the higher $Drug_{value}$ of a drug indicates that it is more likely to be useful for IBD.

$$Drug_{value} = S_{score} \times D_{score} \text{----------(3)}$$

After calculating Drugvalue for each drug, we sorted the drugs in descending order based on their $Drug_{value}$. Here, we selected the top 10 drugs useful for IBD empirically.

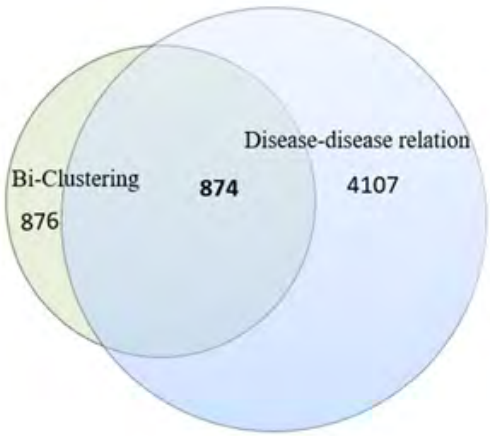

Figure 7: Selection process of common drugs

4.4. Validation by Literature Search

We carried out a manual literature search for validating our top 10 repurposed drug candidates for IBD that have been shown above in (Table 3). Cisplatin is applied within veins and usually the preferred chemotherapy treatment for patients diagnosed with various types of malignancies (e.g., leukemia, lymphomas, breast, testicular, ovarian, head and neck, cervical cancers, sarcomas and so on) [17]. Since 1990s, Cisplatin remained one of the most stable and popular drugs for clinical use. Etanercept is a human dimeric fusion protein, which has been revealed to possess a very low rate (< 2%) of immunogenicity for patients with psoriasis, psoriatic arthritis, rheumatoid arthritis, and congestive heart failure [18]. Etanercept is a competitor inhibitor of TNF-α and treatment with TNF-α inhibitors has been a significant advance in the medicaments of IBD [18, 19]. Colorectal cancer is one of the most recurring cases of cancer mortality throughout the world and Oxaliplatin, a third- generation platinum compound, has demonstrated a definite role in the management of colorectal cancer [20]. VX-702 is one of a series of second-generation, orally active p38 MAP kinase inhibitors, which has the potential for treating inflammation, rheumatoid arthritis and cardiovascular diseases [21]. Carboplatin is considered the ultimate chemotherapy procedure and it has successfully replaced Cisplatin for the initial treatment of ovarian cancer following primary debulking surgery [22]. Adalimumab is a monoclonal antibody that is used to treat rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis, uveitis etc. [23]. AV411 (Ibudilast) is approved for treating asthma and stroke due to its anti-inflammatory potential [24]. CRx-119 is a novel orally available syncretic drug candidate in clinical development for immune inflammatory diseases. It inhibits certain pro-inflammatory biomarkers, such as TNF-α, IL-6 & CRP and increases the anti-inflammatory cytokine IL-10 [25]. SCIO- 469 is presently in development as a potential therapy for inflammatory disorders and depicts a first-generation oral p38 MAP kinase inhibitor. SCIO-469 acts as an indirect TNF-α inhibitor, but also has potential anti-inflammatory activity since it blocks the production of IL-1β and COX-2 [26]. Chloroquine has been used worldwide since 1930s for the treatment of malaria (and other parasitic infections) and it is a cheap drug

belonging to the World Health Organization (WHO) list of essential drugs [27].

We selected the aforementioned drugs as prospective candidates for drug repurposing based on two criteria. First, known IBD drugs; we, checked whether a drug has already been used for treatment against IBD or if it has been investigated as a therapy for IBD. This process allowed us to analyze whether a drug was used in the treatment of IBD, investigated in IBD or if it causes colitis-like side-effects. Second, efficacy in other inflammatory diseases; in this case, we explored whether a drug has been investigated or is being used for treatment in other inflammatory disorders.

Table 3: Top ten novel repurposed drugs for IBD

Drug Name	S_{score}	D_{score}	$Drug_{value}$
Cisplatin	9.48999	82	778.1792
Etanercept	6.326641	100	632.6641
Oxaliplatin	9.48999	65	616.8493
VX-702	5.257939	108	567.8574
Carboplatin	9.48999	59	559.9094
Adalimumab	6.326641	88	556.7444
AV411	4.9441	111	548.7951
CRx-139	4.9441	109	538.9069
SCIO-469	5.257939	89	467.9566
Chloroquine	4.367598	88	384.3486

5. Conclusion

IBD is a chronic inflammatory gastrointestinal tract (GIT) disorder for which very few safe and effective therapies are available for long-term treatment and disease maintenance [28]. In this work, we presented a method for predicting IBD related repurposed drugs by integrating the results of two different novel proposed approaches.

One method is to predict IBD related drugs by bi-clustering DGIs and set of known IBD risk genes from DisGeNET, CTD and GWAS databases. We utilized BiClusO algorithm for bi- clustering the DGI network. We determined clusters enrichment with known IBD risk genes by Fisher's exact test and used those statistically significant clusters to predict novel IBD drugs.

Another method is to predict IBD related drugs by calculating the similarity between two diseases. We have exploited similarity measures between diseases based on known disease-gene associations information effectively, and performed drug repurposing. Based on the calculated similarity, DGI network is connected with disease-gene network via common gene to construct a disease-drug network. Finally, D_{score} is measured to prioritize candidate drugs for each disease. We used a DGI network, IBD risk genes and DGA network in order to perform our experiments. Finally, we carried out a comprehensive literature review to validate our proposed method's performance. Moreover, 10 potential drugs were repurposed for IBD disease. By literature survey we observed that most of these drugs are substantially related to IBD. Our approach is expected to be useful for finding new effective IBD drugs. Future works of this study include experiments and clinical trials with our prioritized lists of candidate drugs. These approaches will confirm whether our candidate drugs have the potential to treat IBD disease. It is noteworthy that the results obtained in this work are outcome of an academic research. Therefore, drugs predicted by this work cannot be utilized for treating IBD patients unless they are confirmed by further research, trials on animal models and other necessary procedures for drug development.

6. Acknowledgment

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7. Conflict of Interest

There is no conflict of interest among the authors.

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