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Research Article

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Network construction for hepatitis C towards systemic drug design strategies

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ABSTRACT

In drug discovery, the role of multiple receptors based therapeutics is found to be a highly critical approach in producing high efficacy with reduced side effects drug molecules. Hepatitis-C is found to be a threatful chronic disease, even ending up in death in many cases. In the present study, we have selected a few drugs which are found highly potent against Hepatitis-c and have studied their side effects. Understanding the source and hidden mechanisms of drug side effects is found to be challenging in the drug development process. Here comes the significance of system biology approaches for inter connecting different scales of drug actions like drug-protein interactions , drug side effects towards side effect prediction for uncharacterized drugs. The emphasis of the study is to extend the systems approaches towards drug discovery for Hepatitis-C by using network analysis. We performed an extensive analysis to retrieve the network of targeted proteins and side effects on the basis of co-occurrence of drugs in protein-binding profiles and side effect profiles. The analysis of 12 drugs with 18 proteins and 14 side effects resulted in the extraction of many correlated sets. This led to a biologically relevant assessment regarding the relationship between drug– targeted proteins and side effects. The identified side effects can be considered as possible phenotypic outcomes by drugs targeting the proteins that appear in the same correlated set. This study is found to be useful in predicting potential side effects of drug candidate compounds based on their protein-binding profiles.

Keywords: Protein-Drug - side effect interaction, Cytoscape, Blood Brain Barrier, Network analysis

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INTRODUCTION

Drug interactions usually cause side effects which has critical role in development of new drugs. Such interactions will either add or reduce the effects of drug and thus more often leads to adverse reactions. Hepatitis-c is an infectious disease affecting initially the liver, which is caused by the virus named hepatitis c virus (HCV), its infection is often without symptoms, but severe infection can also lead to cirrhosis, and might even develop into liver failure [1]. As of the year 2011, almost 100 medications are in the stage of development reported for hepatitis C [2]. Tremendous research is going on presently in the field of medicine and drug discovery towards Hepatitis-c but we focus on an approach to identify and understand Gene-drug-side effect interaction.

Systems biology focuses mainly on different interactions that happen in biological systems, precisely about the study of interactions between components of biological systems, and how these interactions give rise to the function and behavior of that system [3]. In 2013 Elumalai Balamurugan et al., [4] stated that Network-level analysis can reveal detailed insight on metabolic regulation and drug resistance. Taking this into consideration, we have selected a few Hepatitis C drugs which are in the phase of development and have their side effects explored. Hence, the

emphasis of the study is to provide an insilico strategy for understanding the interactive patterns of these drugs and the causal proteins for side effects.

A cell responds to environmental and physiological changes through reorganization of genomic expression. This kind of regulation is realized by transcriptional regulatory networks (TRNs), which are mainly controlled by transcription factors (TFs). Therefore, identifying the sophisticated architecture of TRNs would reveal the fundamental aspects of the mechanisms involved in the maintenance of life and adaptation to new environments [5,6,7,8 and 9].

To have a systems-level understanding of disease at the molecular level, proper knowledge about relevant physiological function is essential. Physiological process comprises of signaling network of chemical compounds, hormones, protein receptors, ligands, enzymes, transcription factors, ions or DNA/RNA that modulate biochemical reactions, electrical signals, mRNA transcription and protein translation [10]. These reactions occur with different kinetics, and simultaneously at different time points, as well as at varying levels of magnitude. Hence each physiological function or phenotype is controlled by a complicated network of signals. Each physiological component of the network .Thus, in a disease system, the signaling networks underlying physiological symptoms are most likely perturbed at more than one point (node or edge).

EXPERIMENTAL SECTION

2.1 Dataset

Dataset for network analysis was obtained from U.S. Department of Health and Human Services; National Institutes of Health- HCV Drugs in Development, from where 12 drugs in development phase were selected and their properties like Drug likeness, BBB, structure were calculated using different software's namely, mol inspiration, BBB software, etc. The dataset thus formed is presented in Table 1.

The drugs which were initially screened for selection were namely, HCV-796, VALOPICITABINE, ALINIA, CLEMIZOLE, TARIBAVIRIN, GOLOTIMOD and SCY-635. The datasets were formed from these drugs by calculating its properties. The Blood Brain Barrier (BBB) property of the drugs was calculated from its structure based on its hydrogen bonds and free radicals using the online software for BBB calculation. Secondly, the Drug Likeness of the drugs was calculated from the online software named Molinspiration.

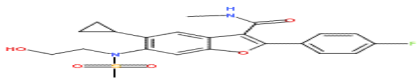
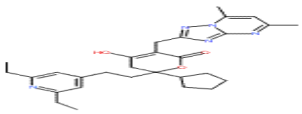
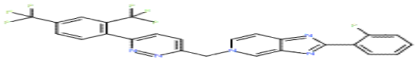
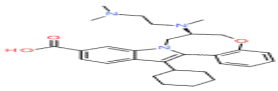
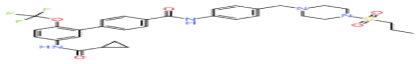
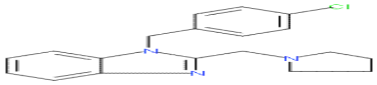
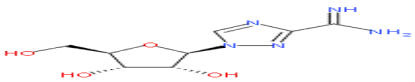
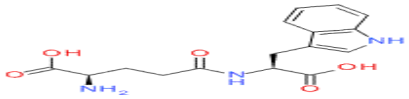
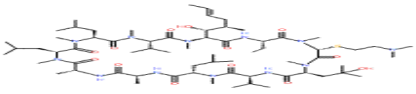
2.2 Drugs, targets and Side effects

Side effects were extracted from the SIDER 2 database [11] which includes information of drugs and their respective side effects. The drug–target information were retrieved from the STITCH 3 database [12], which is based on Drug Bank [13], GLIDA [14], Matador ([15], PDSP BindingDB , ChEMBLdb etc. Using a STITCH confidence cutoff of 0.5, we found drug targets for 12 of the drugs with 14 side-effect information.

2.3 Drug Interaction Network

Cytoscape is an open source bioinformatics software platform for visualizing molecular interaction. Additional features are available as plug-ins. Plug-in is available for network analysis [16]. Once the dataset was formed it was then used as input for creating the network. To visualize and to analyze the network Cytoscape was being used. In this study, Cytoscape version 3.0.2 has been used for analysis of network. The data extracted for network construction.

Table 1: Dataset

Sl. No.	Drug name	DL	BBB	DS
1.	HCV-796	4.25	0.032	
2.	FILIBUVIR	0.7	0.089	
3.	VALOPICITABINE	-18.68	-0.071	
4.	TEGOBUVIR	-4.59	0.138	
5.	MK-3281	-4.26	-0.026	
6.	ALINIA	-3.57	-0.009	
7.	AZD-7295	-6.75	0.075	
8.	DACLATASVIR	-11.82	-0.034	
9.	CLEMIZOLE	4.35	0.057	
10.	TARIBAVIRIN	-0.87	-0.044	
11.	GOLOTIMOD	-24.9	0.064	
12.	SCY-635	3.28	-0.060	

DL - Drug Likeness; BBB - Blood brain barrier; DS - Drug structure.

RESULTS AND DISCUSSION

The network was created from the datasets formed from the drugs presented in the dataset using Cytoscape (Fig 1). This network was created by incorporating all the required information starting from the name of the drug and its protein interactions till its side effects. The mother network which was created by Cytoscape version 3.0.2 was then analyzed for interactions.

Table 2 : Data extracted for Network construction

Drug Name	Target Proteins	Side Effects of Drugs
HCV – 796	Top - 1	Head ache, Myalgia, Fever, Stomach pain, Anthralgia, Rashes.
Valopicitabine	DYNLRB1,LDB3,IL1RN,UCK2,UCK1	Gastrointestinal effects
Alinia	TPO	Head ache, Fever, Stomach pain, Nausea, Itching, Diarrhea, Vomiting
Clemizole	HRH4	Synergistic effects
Tariba Virin	ADA,HDAC1,LDB3,CYGB,CYP7B1,RLN2	Anemia, Vomiting, Hypotension
Golotimod	ggt	Nil
Scy – 635	PPIA,CD151,HMMR	Nil

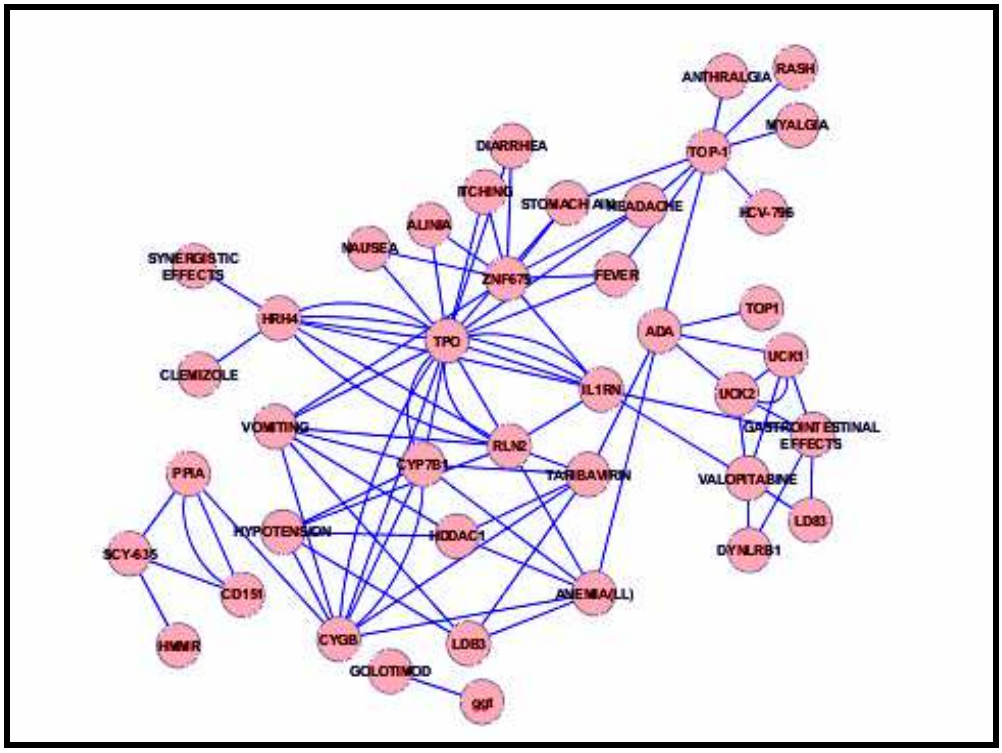


Fig 1: Network showing Drug-Target protein - Side Effects Interaction

From the network we understand that the drug initially interacts with the receptor protein which in turn shows some causal side effects. The drug interaction with the protein and corresponding side effects is coincidently connected with the side effect and the receptor protein of the other drug and thus the network goes on. So initially, a network was formed between the drug and the respective receptor protein and there was another network created between the drug and its causal side effects. Finally these two networks were united together to get the final network. For example, the drug HCV-796 interacts with its receptor protein TOP-1 and the drug had causal side effects like headache, myalgia, fever, stomach pain, anthralgia and rash. Taribavirin is another drug which interacts with ADA, LDB3 and HDDAC1 its receptor proteins and has causal side effects like vomiting, anemia and hypotension. The receptor protein ADA of Taribavirin interacts with the receptor protein and side effects of the drug HCV-796. The network thus created is analyzed and explained in detail (Table 3). The protein–side effect relations thus predicted can be further used to describe the drug–side effects as well as to quantify the contributions of proteins towards the cause of origination of side effects. For many drugs, there is a target that is thought to mediate the therapeutic effect of the drug.

Table 3: Network analysis Output

DRUG	PROTEIN	SIDE EFFECTS	Causal PROTEIN
HCV-796	TOP-1	Headache	ADA
HCV-796	TOP-1	Myalgia	Not Found
HCV-796	TOP-1	Fever	Not Found
HCV-796	TOP-1	Stomach pain	Not Found
HCV-796	TOP-1	Anthralgia	Not Found
HCV-796	TOP-1	Rash	Not Found
Valopitabine	DYNLRB1	Gastrointestinal effects	Not Found
Valopitabine	LD83	Gastrointestinal effects	Not Found
Valopitabine	IL1RN	Gastrointestinal effects	Not Found
Valopitabine	UCK2	Gastrointestinal effects	UCK1
Valopitabine	UCK1	Gastrointestinal effects	UCK2
Alinia	TPO	Headache	CYGB
Alinia	TPO	Fever	CYP7B1
Alinia	TPO	Stomach pain	HRH4
Alinia	TPO	Nausea	IL1RN
Alinia	TPO	Itching	RLN2
Alinia	TPO	Diarrhea	Not Found
Alinia	TPO	Vomiting	Not Found
Clemizole	HRH4	Synergistic effects	RLN2
Taribavirin	ADA	Anemia	Not Found
Taribavirin	HDDAC1	Vomiting	Not Found
Taribavirin	LDB3	Hypotension	Not Found
Golotimod	ggt	Not Found	Not Found
SCY-635	PPIA	Not Found	CD151
SCY-635	CD151	Not Found	PPIA
SCY-635	HMMR	Not Found	Not Found
Alinia	ZNF675	Headache	Not Found
Alinia	ZNF675	Fever	Not Found
Alinia	ZNF675	Stomach ain	Not Found
Alinia	ZNF675	Nausea	Not Found
Alinia	ZNF675	Itching	Not Found
Alinia	ZNF675	Diarrhea	Not Found
Alinia	ZNF675	Vomiting	Not Found
Taribavirin	HDDAC1	Anemia	Not Found
Taribavirin	HDDAC1	Vomiting	Not Found
Taribavirin	HDDAC1	Hypotension	Not Found
Taribavirin	LDB3	Anemia	Not Found
Taribavirin	LDB3	Vomiting	Not Found
Taribavirin	LDB3	Hypotension	Not Found
Taribavirin	CYGB	Anemia	TPO
Taribavirin	CYGB	Vomiting	CYP7B1
Taribavirin	CYGB	Hypotension	PPIA
Taribavirin	CYP7B1	Anemia	CYGB
TARIBAVIRIN	CYP7B1	Vomiting	TPO
Taribavirin	CYP7B1	Hypotension	Not Found
Taribavirin	RLN2	Anemia	HRH4
Taribavirin	RLN2	Vomiting	TPO
Taribavirin	RLN2	Hypotension	Not Found
	IL1RN	Not Found	ZNF675
	IL1RN	Not Found	HRH4
	IL1RN	Not Found	RLN2
	IL1RN	Not Found	TPO
	ADA	Not Found	TOP1
	ADA	Not Found	UCK2
	ADA	Not Found	UCK1
	HRH4	Not Found	IL1RN
	HRH4	Not Found	TPO

CONCLUSION

A biological network has been constructed to understand that the interactions of a few drugs which inhibit Hepatitis C activity, their receptor proteins and the side effects caused due to these proteins. The protein–side effect relations

and drug target relations thus deduced can be further subjected to quantify the contributions of proteins towards the cause of origination of side effects. Thus the study strengthens the thought that target molecules plays critical role in mediating the therapeutic effect of the drug.

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