Review Article

Indian Journal of Diabetes and Endocrinology
Volume 2 Number 2, July - December 2020

A Short Introduction on Network Pharmacology: Overview on Bioactives-Targets-Pathways Interaction

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How to cite this article:

Pukar Khanal / A Short Introduction on Network Pharmacology: Overview on Bioactives-Targets-Pathways Interaction. Indian Journal of Diabetes and Endocrinology. 2020;2(2):79-81

Abstract

Presently, network pharmacology is being popular in investigating the probable interaction of secondary metabolites from herbal medicines with multiple proteins involved in the various disease pathogenesis and understanding the probable molecular mechanism. The concept is based on the multi compound-multi protein interaction and somewhat different from a lock and key concept of drug discovery. In this context, this mini-review highlights the major aspects of network pharmacology during the conceptualization of herb-disease interaction.

Keywords: Geneontology; Network pharmacology; System biology.

Introduction

Basic concept and background

During the drug development process, it has been considered that a drug molecule acts via the lock and key concept in which a single key unlocks a specific lock; but what about the master key which is used to unlock the multiple locks? Further, it has been understood that a compound can up-or down-regulated multiple proteins which are well demonstrated by one of the cheminformatic tools i.e. DIGEP-Pred (http://www.way2drug.com/ge/). It means the concept of drug discovery or identifying the action of drug molecule may get varied as it is predicted to counteract over the multiple proteins. Further, the regulated proteins can interact with each other to modulate multiple pathways which can be interpreted using multiple open source databases like KEGG (https://www.genome.jp/kegg/) or Reactome (https://reactome.org/). So, the next question arises, what about the herbal products as it is composed of multiple secondary metabolites and they may have an affinity to act over multiple proteins and regulate numerous pathways. In this case, understanding the lock and key concept of each bioactive over individual protein is very difficult and is a time-consuming process. However, in 2007, Hopkins built a new concept of network pharmacology (Hopkins 2007) to explain the action of drug molecules in multiple targets rather than a single; implemented by us to investigate the to understand the herb-disease interaction in herbal medicines in multiple pathogeneses (Khanal et al., 2020 a,b; Duyu et al 2020a,b; Patil et al 2021; Khanal and Patil 2020). The generalized backbone of network pharmacology is presented in Figure 1.

Understanding the network pharmacology

The concept of network pharmacology relating to herbal medicines can be implemented via the four main steps i.e. identification of the bioactives or secondary metabolites from medicinal plant/agent, target prediction of secondary metabolites, enrichment prediction, and network analysis.

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Further, in silico molecular docking (Mandar et al. 2021) can also help to identify the lead hit within the constructed network via the prediction of binding affinity and number of hydrogen bond interactions.

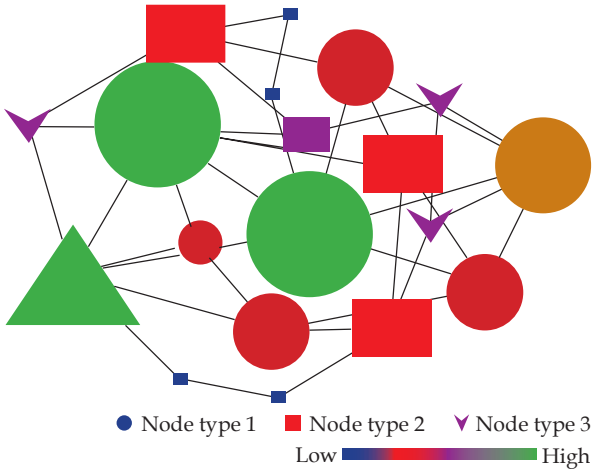

Fig. 1: General skeletal of network pharmacology.

Identification of the bioactives or secondary metabolites from an herbal product

For the identification of the bioactives from herbal medicines, three approaches can be made. First, retrieve the bioactive information from the published literature which can include the research or review articles, medicinal books, or official pharmacopeias. The second approach could be the retrieval of the bioactives information from the database. Some of the open-source databases like ChEBI (https://www.ebi.ac.uk/chebi/), PhytoChemical Interactions DB (https://www.genome.jp/db/pcidb/), TCM Database@Taiwan (http://tcm.cmu.edu.tw/) or Dr. Duke's Phytochemical and Ethnobotanical Databases (https://phytochem.nal.usda.gov/phytochem/search) database can be implemented in mining the bioactives from herbal medicines. Third, the combination of both of the above databases can be implemented.

Further, the identified bioactives can be queried in the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) or ChemSpider (http://www.chemspider.com/) to retrieve the bioactives information which is related to their phytochemistry, molecular weight, molecular formula, SMILES, and 3D or 2D structure. Further, the relevant literature associated with the bioactives can also be retrieved.

Identification of the targets of bioactives

The targets of the bioactives can be retrieved from the multiple cheminformatics tools like SwissTarget Prediction (http://www.swisstargetprediction.ch/), BindingDB (https://www.bindingdb.org/bind/index.jsp), and DIGEP-Pred (http://www.way2drug.com/ge/). Further, bioactives related to biological spectrum can also be retrieved from the online server PASS online (http://www.pharmaexpert.ru/passonline/) which predicts the probable biological spectra of the bioactives by querying their SMILES.

Gene enrichment and Network construction and network analysis

After the identification of regulated proteins, the list of gene codes of targets (can be retrieved from the NCBI gene (https://www.ncbi.nlm.nih.gov/gene/) or Uniprot (https://www.uniprot.org/) database. The list of targets can be queried in STRING (https://string-db.org/) database and identify the probably regulated pathways. Multiple pathways can be identified associated with multiple diseases concerning KEGG (https://www.genome.jp/kegg/) or Reactome (https://reactome.org/) database based on their false discovery rate, strength, and regulated proteins. Further, the gene ontology data can be identified to reflect the probably regulated proteins in various cellular compartments, molecular function, and biological spectrum. Further, a bioactive-target-pathway network can be constructed using a java based platform, Cytoscape (Shannon et al 2003). Cytoscape is not limited to construct the network, but it is also linked to the analysis of the network. A network can be treated either as directed or undirected and the whole network can be analyzed for average short path length, betweenness centralities, closeness centralities, clustering coefficient, eccentricity, edge count, in degree, neighborhood connectivity, outdegree, partner of multiedge node pairs, and self layout for node layout and edge betweenness for edge map.

Conclusion

Although network pharmacology can help in identifying the interactions of bioactives, targets, and pathways interactions, it is to be understood that it is a completely knowledge-based study. A single false hit of the bioactive or improper inclusion of any edge can interpret the whole network wrongly. Further, the outcome of the result may vary based on the source utilized in the mining of the bioactives and their targets. Another aspect that may influence the correlation of the network and experimental pharmacology is drug absorptivity and ADMET profile. So, one should think "are the

bioactives chosen for the network pharmacology, do they get absorbed from the gastrointestinal tract if supplemented orally?" Secondly, what about the prodrugs and the metabolites of phytoconstituents? Do they get completely excreted or again they act on other proteins to generate the secondary effects?

Conflict of interest

The author of this draft has no conflict of interest in any financial and non-financial means.

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