

New Drugs from Old Sources

Network Pharmacology as it Relates to Traditional Chinese Medicine and Other Natural Products

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Summary

The production of new drugs has slowed down in recent years until the discovery of network pharmacology. Network pharmacology is fast becoming the preferred method of new drug discovery. This method allows researchers the ability to conduct their studies through a much more efficient process. Taking this process and applying it to traditional Chinese medicine allow pharmacological researchers the ability to produce drugs from natural products. Natural products have been used throughout history to aid with various pathologies in different methods. Expanding the application of network pharmacology can help researchers produce more effective drugs with less time and resources used during the research and development.

Network pharmacology is a drug discovery method that involves mapping potential drug targets over known biological maps. This method aims to improve the drug development process by aiding in target identification, lead discovery and optimization, identifying mechanisms of actions, and preclinical safety and efficacy assessments. (Zhang et al., 2012) This allows for researchers to determine what interactions are possible with a new drug. The ability to predict these targets saves researchers many valuable researchers.

The network pharmacological approach to drug discovery has allowed for researchers to conduct extensive research with existing treatment methods, one such treatment methods is traditional Chinese medicine (TCM). TCM has been used for thousands of years and has gone through countless changes over this time. TCM consists of various mind and body practices, and herbal remedies. The efficacy of these herbal remedies has been difficult to determine because of the vast number of areas of the body that can be effected by a single herbal compound. Network pharmacology focuses on mapping the targets of these herbal remedies to properly define the mechanisms of action (MoA). MoAs are the specific biochemical interaction through which a drug produces an effect on the body. TCM has been known to have viable therapeutic effects, but because of the lack of understanding of the MoAs, these treatment options have not been widely recommended in western medicine. Now that researchers have begun to document the MoAs of TCM, the active compounds of these herbal remedies can be isolated to help develop effective drug treatment methods.

Background

Network pharmacology is a new and exciting concept in drug discovery. The basis of this concept is forming data bases of existing drugs and the protein in which they interact. When drugs enter the body, they interact with several targets beyond the intended target. This happens despite traditional drug research

focuses on a one-target one-drug method. This method leads to researchers needing to discover possible side effects during the testing phase of the potential drug. Having side effects go unnoticed until testing causes wasted time and money, slowing the creation of new drugs. Network pharmacology has the potential to help researchers move past the traditional drug discovery methods.

State of the Sciences

One aspect of drug research that is improved with the use of network pharmacology is the prediction of molecular targets. According to research presented in the article “Predicting New Molecular Targets for Rhein Using Network Pharmacology”, the efficient identification of drug targets is aided by the computational integration of various knowledge sources. Information on transcription factors, proteins, genes, biological compounds, and other regulatory molecules provide the structure to help form the biological networks that are used in network pharmacology. (Zhang et al., 2012) The researchers in this article developed their own biological networks by obtaining data from 15 different sources before beginning to construct the target network for rhein (a highly bioactive component of rhubarb that is known to contribute in the cell death of human cancer cells). Once both networks are completed the researchers created visual representations of the proteins and genes effect by the pathology and the rhein molecules and use this information to develop a treatment method.

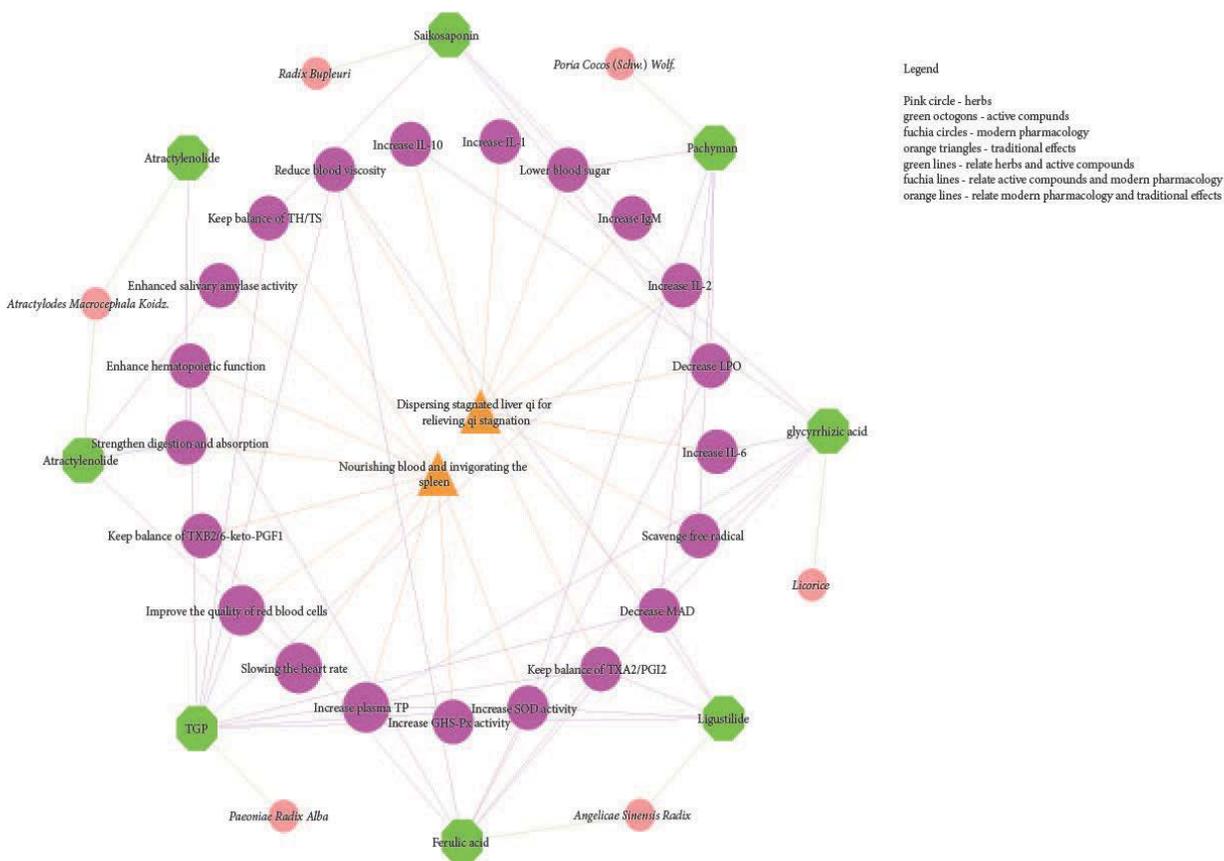


Figure 1: Relationship between modern pharmacology and traditional efficacies of Xiaoyao Powder

TCM has been proven to be effective at treating certain pathologies, but it is not recommended very often in western medical communities due to the lack of scientific explanation of the MoAs of the compounds. Network pharmacology is now being used to help define the MoAs of compounds found in TCM. According to a study conducted by Liu et al. “TCM has been widely utilized in the treating of infertility for centuries and has been proven efficient in the regulating of endocrine and promoting ovulation.” The study later states that “Application of TCM has been blocked by the absence of scientific comprehension regarding its mechanism. Therefore, it is important to explore and reveal the TCM mechanism.” These mechanisms are revealed by using networks of known modern pharmacological methods and relating those networks to ones developed for the TCM remedy that is being studied. The TCM remedy and the modern method should target the same pathology, an example of a combined map of such networks can be seen in figure 1. There are multiple articles that discuss the discovery of the MoAs of TCM remedies as they relate to specific pathologies. One such article is “Insight into the Molecular Mechanism of an Herbal Injection by Integrating Network Pharmacology and In Vitro” (Ma et al., 2015) The article “Network Pharmacology-Based Antioxidant Effect Study of Zhi-Zi-Da-Huang Decoction for Alcoholic Liver Disease” provides another example of a centuries old

treatment method (Zhi-ZiDa-Huang), that is now more likely to gain traction in western medical communities due to the discovery of the MoAs.

The remedies used in TCM are widely known to exert their effects in a variety of methods. The article “Network Pharmacology-based Prediction of the Active Ingredients and Potential Targets of Mahuang Fuzi Xixin Decoction for Application to Allergic Rhinitis”, It is undeniable that herbal medicines found in TCM exert their therapeutic effects through synergistic effects of multiple compounds on multiple targets. (Tang et al., 2015) This can be a very effective treatment method due to the synergistic nature of biological functions that are found in the body.

The networks that are constructed are useful and predicting the side effects of drugs before the even go into clinical trials. There is a large amount of biological data that contains information about what triggers unwanted effects in the human body. If a potential drug is ran thru a biological network and matches up with these know triggers then the components of that drug can be modified to reduce and possibly eliminate these effects. This concept is discussed in the article “Traditional Chinese Medicine Network Pharmacology: Theory, Methodology, and Application”. (Shao, 2013)

Network pharmacology also improves drug development by helping to produce drugs that are structurally more diverse than drugs that are already on the market. According to research conducted by Wang et al. “ PhIN (polypharmacology interactions network) introduces molecule-molecule functional similarity by defining that functional similarity of two molecules is determined by their interactive targets in common.” The article goes on to state that “Functional similarity might also help to develop more structurally diverse leads during drug development.” This is important because it gives researchers the ability to create new methods to treat a pathology. Figures 2-3 are from the 2012 article “Molecular Scaffold Analysis of Natural Products Databases in the Public Domain”. These figures show an example of how researches select the known information in treating a pathology and compare the chemical structures of these methods to help increase the diversity of treatments.

Database	Code	URL	Molecules (M)	Molecular similarity ^a Mean (SD)
Specs	SC	http://www.specs.net	562	0.54 (0.17)
Analyticon ^b	NP-ALY	http://www.ac-discovery.com	2472	0.48 (0.15)
TimTec	NDL	http://www.timtec.net	3040	0.38 (0.12)
Traditional Chinese Medicine	TCM	http://tcm.cmu.edu.tw	32 358	0.51 (0.15)
ZINC (natural products subset)	NP-ZINC	http://zinc.docking.org	89 425	0.39 (0.13)
Combinatorial library set	TPIMS	http://www.tpims.org	267	0.62 (0.15)
Commercial	Maybridge	http://www.maybridge.com	11 326	0.31 (0.11)

^aCalculated with Molecular ACCess System (MACCS) keys (166 bits) and the Tanimoto coefficient.

^bThe structures were retrieved from Clemons *et al.* [19].

Figure 2

Database	M	Frequency counts					CSR	Scaled Shannon entropy				
		<i>N</i>	<i>N/M</i>	<i>N_{sing}</i>	<i>N_{sing}/N</i>	<i>N_{sing}/M</i>	<i>F₅₀</i>	SSE ₅	SSE ₁₀	SSE ₂₀	SSE ₅₀	SSE ₁₀₀
SC	562	163	0.29	109	0.67	0.19	0.06	0.98	0.91	0.88	0.84	0.80
NP-ALY	2472	1206	0.49	841	0.70	0.34	0.14	0.98	0.94	0.92	0.92	0.92
NDL	3040	1433	0.47	1058	0.74	0.35	0.11	0.97	0.96	0.94	0.92	0.91
TCM	32 358	12 267	0.38	6814	0.56	0.21	0.13	0.83	0.81	0.84	0.88	0.90
NP-ZINC	89 425	15 968	0.18	6402	0.40	0.07	0.05	0.90	0.90	0.92	0.92	0.92
TPIMS	267	119	0.45	60	0.50	0.22	0.21	0.95	0.96	0.97	0.96	0.94
Maybridge	11 326	8085	0.71	7229	0.89	0.64	0.30	0.79	0.75	0.72	0.74	0.75

CSR, cumulative scaffold recovery; SSE, scaled SE; TCM, Traditional Chinese Medicine.

Figure 3

Network pharmacology can be used to develop drugs from a variety of natural sources. According to a study conducted by Gu *et al.*, 2013 “Natural products have vast chemical diversity, not only structural diversity but also various biological activity, so as to guarantee the opportunities to find different kinds of lead compounds for different diseases. We find that NPs and FDA approved drugs share a lot of space in chemical space. Moreover, NPs have a large quantity of lead-like molecules, which could be used as scaffolds to expand the chemical library”

Future Research

Researchers should devote time and effort in to the development of permanent network databases that can be accessed readily. One of the largest hold back in conducting studies using network pharmacology is the building of the actual networks. Researches must gather all of the relevant information from a large number of sources and then build the network. If these networks were stored in a location that allows for researchers to access the information as needed. The use of these pre-constructed networks will save valuable time and

other resources during the development of new drugs. The visual modals of the more complex networks are a source of concern for researchers. The source of these concerns can be seen in figure 4, where the network for multi target drug compound for infertility is combined with the network for the target human proteins. This issue can be corrected with the development and refinement of three dimensional modeling software. There are a few researches that have developed such programs but they have yet to become an industry standard. The refinement of these programs should aid in helping to advance the use of such programs.

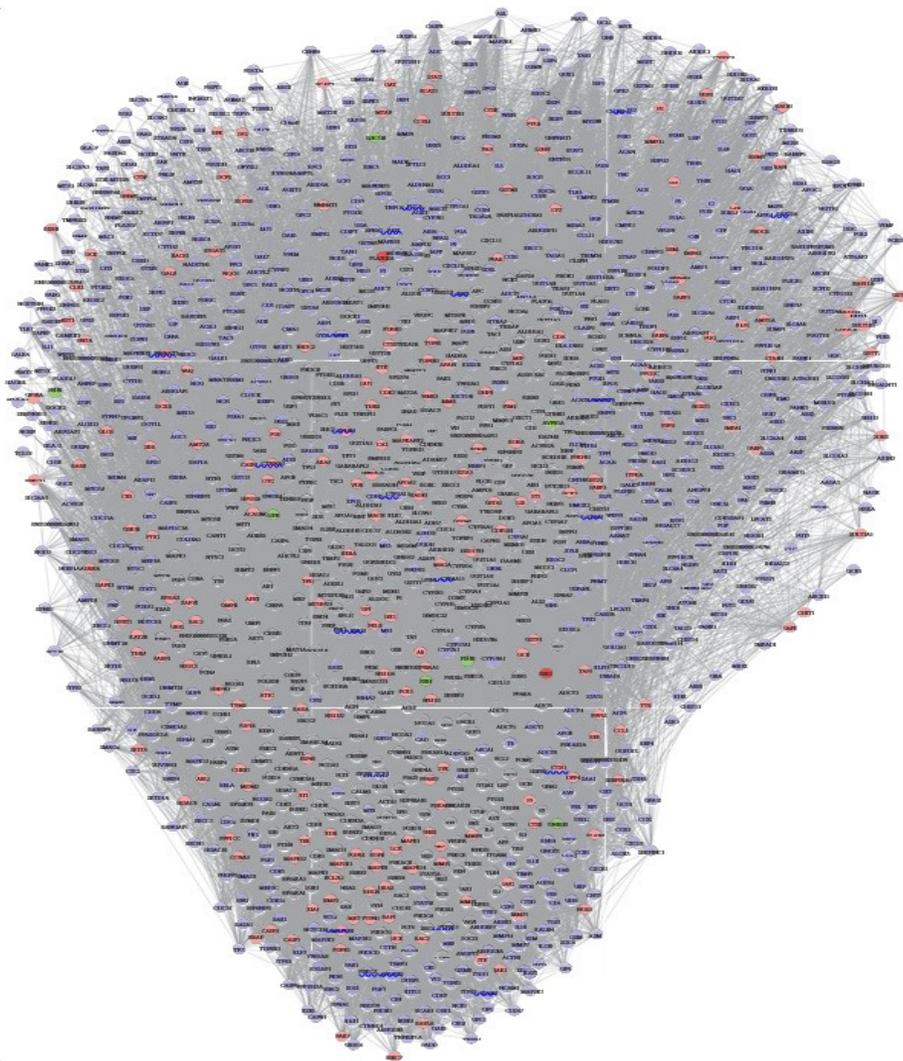


Figure 4 Active compound target-infertility target-other human proteins' PPI network (blue circle, pink circle, green circle, and red circle stand for another human protein, compound targets, compound-infertility targets, and infertility targets, resp.).

Future research involving network pharmacology should also expand its uses to other natural remedies.

Throughout human history civilizations have developed methods for treating illnesses that we may have disregarded for the use of more modern treatment methods. The network pharmacological research that has been presented in the area of TCM shows that some centuries old methods can be highly effective. The efficacy of these treatments can only be further refined once the MoAs of these treatments are discovered.

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