Repurposing of Drugs Using Network Pharmacology: An Exemplar Step in Drug Discovery

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Abstract: WHO Global Oral Health Status Report (2022) gives a statement Repurposing of medicines – the underrated champion of sustainable innovation. Network pharmacology approaches can also be used to map the unexplored target space and therapeutic potential of natural products, providing a systematic means by which to extend the druggable space of proteins implicated in complex diseases and rare diseases. Network pharmacology is an approach to drug design that encompasses systems biology, network analysis, connectivity and redundancy. Network-based intervention has been a trend of curing systemic diseases, but it relies on regimen optimization and valid multi-target actions of the drugs. The complex multi-component nature of medicinal herbs may serve as valuable resources for network-based multi-target drug discovery due to its potential treatment effects by synergy. With the aid of this novel process one can convert the orthodox concept of 1 drug, 1 target, 1 disease into 1 drug, multiple targets and multiple diseases. For complex diseases, most drugs are highly ineffective, and the success rate of drug discovery is in constant decline, while low quality, reproducibility issues, and translational irrelevance of most basic and preclinical research have contributed to this. Precise and effective therapeutic intervention is achieved by synergistic multi company network pharmacology and drug repurposing, obviating the need for drug discovery and speeding up clinical translation.

Keywords: Network pharmacology, Exemplar shift, Drug discovery, Repurposing, Nephrolithiasis

1. INTRODUCTION

A new discipline called network pharmacology (NP) has emerged which attempts to understand drug actions and interactions with multiple targets (1). Network pharmacological analysis presents an immense scope for exploring traditional knowledge to find solutions for the current problems challenging the drug discovery industry. NP can also play a key role in new drug discovery, drug repurposing, and rational formulation discovery (2). In systems biology and network pharmacology, network-based approaches are frequently used to visualize, analyze, and understand complex biological systems using different types of biologically relevant interaction data (3). Drug discovery investigations need to incorporate network pharmacology concepts while navigating the complex landscape of drug-target and target-target interactions. This task requires solutions that integrate high-quality biomedical data, combined with analytic and predictive workflows as well as efficient visualization (4). Low drug productivity has been a significant problem of the pharmaceutical industry for several decades even though numerous novel technologies were introduced during this period. Currently pharmacologic dogma, "single drug, single target, single disease", is at the root of the lack of drug productivity (5).
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Figure 1.1. Tree diagram of Drug therapy model in network pharmacology (6)

Current diseases are defined by a phenotype rather than by a disease mechanism. Thus, we hardly understand any disease mechanistically and treat symptoms chronically with low precision. When a mechanism is described, it often involves single targets (e.g., rare, typically monogenic diseases). In the case of complex diseases, the current ‘one disease–one target–one drug’ dogma will hardly yield any result when in fact, their causes are small signaling networks. (7) Network pharmacology exploits this concept by simultaneously targeting several components of a disease module, combining mechanistically related and therefore synergistic drugs. This

(i) Allows to reduce the dose of each drug,
(ii) Thereby decreases potential side-effects, and
(iii) Through synergy enhances the full therapeutic effect (8).

For example, more than 68.70% (1196/1741) of the FDA-approved drugs collected in the Latest Drug Bank (version 4.1) had been found to bind off-targets after they entered the market (9). Moreover, failed drugs, due to low efficacy, may also be revived and effectively utilized. An obvious advantage would be that any newly identified functions can be quickly evaluated in phase II clinical trials (10). NT provides a framework which may be used to overcome limitations of other methods for drug exploration such as those based on phenotypic effects or those based only on chemical structure; it serves as a tool to integrate knowledge from the pharmacological and genomic spaces (11). Therefore, we now propose an in silico-based multitarget approach based on human disease genes linked to further identify mechanistically related potential targets which could be then pharmacologically modulated following a network pharmacology therapeutic approach. (12) Various structural (topological) network measures have thereby contributed to uncovering unintuitive functional relationships and repositioning candidates in drug-disease and other networks. This review gives a broad overview of the topic, and offers perspectives on the application of topological measures for network analysis. (13). Drug Repo is a computational pipeline to repurpose drugs for new indications. The repurposing pipeline has various steps including: compound-target data analysis, structural analysis, gene-disease relationships and pathway analysis. The pipeline is able to repurpose ~0.8 million compounds across 606 diseases (including various cancers, cardiovascular and kidney diseases) (14).

2. LITERATURE REVIEW

The major problem statement for this review article is to

- To find out new alternatives and substitutes for treating kidney stones
- To find out a new activity of an existing drug in pharmacological use.
- To assess different pharmacological moieties for their repurposing in other diseases
As a Chinese medicinal herb, Desmodium styracifolium (Osb.) Merr (DS) has been applied clinically to alleviate crystal-induced kidney injuries, but its effective components and their specific mechanisms still need further exploration and this research first combined the methods of network pharmacology and proteomics to explore the therapeutic protein targets of DS on oxalate crystal-induced kidney injuries to provide a reference for relevant clinical use.[15]

**Advantages of Drug Repurposing:**

1. Significantly lower costs for research and development (R&D).
2. Shortens the time it takes to develop new drugs because many existing substances have been shown to be safe in people and do not need to undergo Phase 1 clinical trials.
3. Possibility of reuse despite signs of negative effects and ineffectiveness in some cases.

Antiepileptic drugs repurposing for Nephrolithiasis activity using Network pharmacology

**Potential candidates**

- Valproic acid
- Carbamazepine
- Rufinamide
- Zonisamide
- Phensuximide
- Brivaracetam
- Ganaxolone

Neuroinflammation is an integral part of epilepsy pathogenesis and other convulsive conditions [16]. Both primary enzymes COX-1 and COX-2, which catalyze the synthesis of inflammatory prostanoids are main targets for NSAIDs, have been reported as potential neurotherapeutic targets for epilepsy correction and management [16]. Repurposing is defined as a planned strategic comprehensive technique of finding out new indications for an existing drug. The category of drugs chosen belong to Anti-Epileptic class (AED). The 2 major targets for docking are TNF- and IL-6. Age-standardized prevalence rate (ASPR) of kidney stones was estimated at 21.11%. Also, the ASPR was estimated 24.13% (95% CI 23.7–24.6) in men and 18.7% (95% CI 18.5–18.9) in women [17].

Valproic Acid (VPA) significantly inhibited LPS-induced production of TNF-alpha and IL-6 by THP-1 cells, whereas other AEDs did not. The findings are consistent with the idea that VPA suppresses TNF-alpha and IL-6 production via inhibition of NF-kappa B activation [18].

**Gap Analysis and Outlook:** There is a missing link between variable and potential use of many therapeutic moieties in different diseases. Repurposing and Network Pharmacology can fill in this missing link.

3. **MATERIALS AND METHODS**

![Figure 1.2. Cascade of Network Pharmacology](image-url)
A network pharmacology approach to explore active compounds and pharmacological mechanisms of epimedium for treatment of premature ovarian insufficiency (19).

Through database analysis, Jianpi Qingchang Huashi Recipe (JPQCHSR) contains 181 actives ingredients and 205 related therapeutic targets, and key compounds include kaempferol, quercetin, and luteolin, these scholars found that JPQCHSR acts on TNF, IL-17, and other signaling pathways, and ultimately play an important role in repairing intestinal immune damage and reducing the expression of inflammatory factors (20).

Single medicine treatment of ulcerative colitis: One study found that 12 active ingredients in Curcuma, including 148 target genes, were screened out by searching the database, and 54 potential targets for the treatment of ulcerative colitis were screened out by using molecular docking technology. A total of 24 core proteins were screened out by molecular docking technology. These targeted proteins effectively treat and relieve ulcerative colitis through the PI3K-Akt signaling pathway, JAK-STAT signaling pathway, and MAPK signaling pathway, to achieve the purpose of treating the disease (21).

Network pharmacology consisting of natural products is seen as a viable therapeutic method for Diabetes mellitus and. employing network pharmacology-based approach to explore the active ingredients of Astragaloside IV as a best treatment option against type 2 diabetes mellitus (T2DM) (22).

In the light of network pharmacology, elaborated on the active compounds of Ginkgo biloba leaves, their potential target, and associated pathways for treating CCVD, hence providing a theoretical basis for additional experimental research. Their findings revealed that Ginkgo biloba leaves exhibit a protective effect on CCVDs, most likely by regulating various processes and attacking multiple targets linked to a variety of biological pathways. Their study provides an important reference for understanding the efficacy of Ginkgo biloba leaves in the treatment of CCVDs and a fresh technique for discovering new medicines from plants (23).

Tamsulosin, an alpha-1-adrenoceptor blocking agent, is thought to induce spontaneous stone passage by relaxing ureteral smooth muscle tone. However, tamsulosin has not been proven effective for increasing ureteral stone passage and is not approved by the Food and Drug Administration for this indication [24].Litholytico-bacteriostatic agents such as ethylenediaminetetraacetic acid (EDTA) can be used for direct dissolution of calcium and magnesium containing urinary stones.[25]. Explanatory analyses of randomised controlled trials with sodium/glucose cotransporter isoform 2 inhibitors indicated a 30%-50% reduced rate of stone events in patients with diabetes. Underlying mechanisms remain unclear. We aim to determine the effect of empagliflozin on urinary supersaturations in non-diabetic kidney stone formers to evaluate their therapeutic potential for recurrence prevention. We will provide first clinical trial evidence on whether urinary supersaturations are affected by empagliflozin in kidney stone formers [26].

Pasbanbheda is a drug mentioned in the Ayurvedic system of medicine for various ailments but mainly as a diuretic and lithotriptic.[27]. Formulating a nanoparticle carrier can aid in providing a decent efficacy in kidney stones [28]. There is accumulating evidence that epileptic activity is accompanied by inflammatory processes. In the present study, we evaluated the effect of levetiracetam (Keppra), an anticonvulsant drug with decisive antiepileptic features, with regard to its putative anti-inflammatory potential [29]. The aim of this study was to investigate the effects of the new generation ASM brivaracetam (BRV) in an astrocyte-microglia co-culture model of inflammation. The results obtained were favourable for designing certain derivatives for the same in order to bring nephro protective activity.[30]

4. CONCLUSION

In recent years, many pharmaceutical companies are developing new drugs with the discovery of novel biological targets by applying the drug repositioning strategy in drug discovery and development program. This strategy is highly efficient, time saving, low-cost and minimum risk of failure. It maximizes the therapeutic value of a drug and consequently increases the success rate.
Thus, drug repositioning is an effective alternative approach to traditional drug discovery process. Moreover, attempts can be made to determine the efficacy of natural, botanical, herbal moieties in different diseases. The contents in this article, combined with the theoretical analysis and software’s of network pharmacology in other chapters, can provide researchers or students with relevant software tools and practical operation methods that can be used for reference, as well as provide rapid and convenient software tool selection and practical guidance for actual research on network pharmacology. Different dynamic networks and quantitative networks may be another tendency, and more and more employment of network pharmacology technology will make the expenditure much less in the future. This review laysthe groundwork for further research on the protective mechanisms of medicinal plants in diseasetreatments and the applications of network pharmacology in drug discovery.

5. ETHICS STATEMENT

We will abide by the laws, rules, and regulations of my community, work, and country. We will openly take responsibility for my actions, and only make agreements, which we intend to keep.

REFERENCES

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Citation: Mr Payaam Vohra & Mr Gaurav Pandey. “Repurposing of Drugs Using Network Pharmacology: An Exemplar Step in Drug Discovery " ARC Journal of Pharmaceutical Sciences (AJPS), vol 8, no. 1, 2023, pp. 01-6, doi: https://doi.org/10.20431/2455-1538.0801001.

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