

Editorial

Special Issue on Network Pharmacology Modeling for Drug Discovery

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During the process of drug discovery, many compounds have exhibited polypharmacological interactions with various biological entities [1–4]. This complexity poses a significant challenge in developing therapies to enhance efficacy with less toxicity, particularly for treating complex diseases such as cancer [5,6]. Meanwhile, the determination of bioactive compounds from natural products remains a tedious process with a low success rate, primarily due to the poor understanding of compound–activity relationships [7–9]. In response to this challenge, network pharmacology modeling has emerged as a promising paradigm for the next generation of drug discovery [10–12]. With the growing abundance of molecular data derived from both pharmacological and biological entities, the field of network pharmacology modeling has witnessed increasingly exciting applications [13–16]. This Special Issue, titled “Network Pharmacology Modelling for Drug Discovery”, which is available online at https://www.mdpi.com/journal/processes/special_issues/Network_Pharmacology_Modelling, aims to highlight the recent advances in this endeavor, with a specific focus on understanding the mechanisms of action of herb medicine. In what follows, we will provide a brief overview of the studies that were selected for the Special Issue, highlighting the database resources and computational tools that may be references for future studies.

1. Galangal against gastric cancer

Galangal, the rhizome of the ginger plant, has been reported to relieve stomach diseases. However, its potential treatment effects on gastric cancer remain largely unexplored. In [17], the authors determined a total of 13 active compounds of galangal, as well as their potential target genes from the TCMSP database [18]. Through a protein–protein network analysis and gene ontology enrichment analysis, they found that several known gastric cancer genes indeed interact with the key targets of galangal. Furthermore, they were able to validate several ligand–receptor bindings through computational simulations, suggesting the potential of galangal in treating gastric cancer.

2. Zhi Bai Di Huang Pill against Systemic Lupus Erythematosus (SLE)

SLE is an autoimmune disease where the body’s immune system mistakenly attacks its own organs, causing widespread inflammation and tissue damage. In [19], the authors explored the potential of a traditional Chinese medicine called Zhi Bai Di Huang Pill (ZBDHP) for the treatment of SLE. The TCMSP database was utilized to retrieve the active ingredients of ZBDHP, while their targets were predicted by the SwissTargetPrediction tool [20]. On the other hand, the SLE-associated genes were retrieved from the GeneCards [21], OMIM [22], and DisGeNET [23] databases. Further gene set enrichment analyses showed that ZBDHP may affect the PI3K, AKT, and mTOR signaling pathways. Similar databases and computational tools have also been used to study the following herb plants: Qianghuo Shengshi decoction (QHSSD) against ankylosing spondylitis [24] and Ocimum Sanctum against tuberculosis [25].



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3. *Glycyrrhiza Uralensis* against alcoholic liver injury

In [26], the authors explored the mechanisms of action of *Glycyrrhiza uralensis*, also known as Chinese liquorice, in treating alcoholic liver injury. Notably, multiple molecular docking tools were used, including AutoDock [27], PYMOL, and Discovery Studio. Using similar network pharmacology modeling approaches to those of [19], the authors provided initial evidence of *Glycyrrhiza uralensis* that may warrant future experimental validation using in vitro or in vivo studies.

4. Glutinol against multiple diseases

Glutinol is a triterpenoid compound that has been reported to have a range of antidiabetic, anti-inflammatory, and anticancer effects. In [28], the authors studied the mechanisms of action as well as the ADMET properties of glutinol. Confirming first that glutinol has drug-likeness properties through using the pkCSM tool [29], the authors determined target genes from the BindingDB database [30] and their interacting proteins from the STRING database [31]. A gene ontology enrichment analysis was performed using the DAVID tool [32]. Molecular docking with MOE has further revealed top binding targets of glutinol, such as CYP19A1.

5. Ginseng against COVID-19

Network pharmacology modeling has also been applied for treating the recent COVID-19 pandemic. In [33], the authors studied the low-molecular-weight compounds (LMWCs) from *Panax Ginseng C.A. Meyer* (PGCAM). Using SwissTargetPrediction and SEA [34] analyses, multiple target genes were predicted for COVID-19 and further validated using molecular docking simulations. Another antiviral study concerns quercetin against the influenza A virus (IAV), where a compound–target–pathway network has been established [35].

6. Sochehwan against metabolic syndrome

Sochehwan is a herbal formula of traditional Korean medicine with limited knowledge on its mechanisms of action. In [36], the authors studied its effect on metabolic syndrome. Using the TCMID database [37], active compounds of Sochehwan were retrieved and screened in the STRING database for their protein targets. Notably, the authors validated the efficacy of Sochehwan in a mouse macrophage cell line, mainly through the suppression of lipopolysaccharide-induced NF- κ B and MAPK inflammatory responses.

7. *Pueraria lobata* against diabetes

In [38], the authors determined the active ingredients of the roots of *Pueraria lobata* using mass spectrometry experiments, and then retrieved their targets from TCSMP and Drugbank [39]. A related study is on obesity, where the authors used similar mass spectrometry techniques to determine the metabolites of *Ilex cornuta* and identified the NOD-like receptor (NLR) signaling pathway as the key target when treating obesity [40].

8. Summary

Network pharmacology modeling is increasingly being recognized as a crucial tool for prioritizing potential drug candidates in in silico drug discovery processes, particularly for herbal medicine, which inherently contains multiple active ingredients. As we showcased the applications of network pharmacology modeling, it is also imperative to discuss their limitations. Firstly, as most of the studies have acknowledged, there is a lack of experimental validation concerning these potential drug targets. Moreover, while these studies focus on the elucidation of drug targets, they often leave unanswered how these interactions contribute to the synergistic or antagonistic effects in disease contexts. Understanding these network dynamics could significantly enhance our capacity to develop more targeted and effective treatment [41]. We anticipate that the Special Issue may bring more attention from a systems medicine perspective of drug discovery. With growing datasets about drug targets as well as their effects in multiple disease contexts, we look forward to further

advances in the mechanistic modeling of network pharmacology. These developments, we believe, could improve the efficiency of drug screening and ultimately improve clinical translation as well as precision medicine [42].

Conflicts of Interest: The author declares no conflict of interest.

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