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"NETWORK PHARMACOLOGY IN DRAVYAGUNA RESEARCH: A CRITICAL APPRAISAL OF METHODS, REPORTING AND VALIDATION, WITH A PROPOSED MINIMUM STANDARD"

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ABSTRACT
Network pharmacology studies how a drug acts on networks of biological targets rather than on a single target, and it has been welcomed as a way to explain the multi-component, multi-target action of Ayurvedic drugs and formulations. Free databases and web tools now allow a complete study to be performed in silico within weeks, and publications applying a near-identical pipeline to Ayurvedic plants have multiplied. This review critically appraises each step of that pipeline as it is commonly applied in Dravyaguna research: compiling constituents, filtering them by predicted absorption and drug-likeness, predicting targets, building protein interaction networks, performing enrichment analysis and molecular docking, and validating predictions. At each step we identify recurrent problems. Compound lists describe what a plant has ever been reported to contain rather than what a classical preparation delivers; absorption filters rely on predicted values and arbitrary thresholds; promiscuous compounds such as curcumin and well-studied proteins dominate networks irrespective of the disease studied; enrichment results are often generic; docking scores are treated as evidence of activity; and experimental validation is frequently absent or uses irrelevant doses. We summarise the recommendations of the 2021 international evaluation guidance and of best-practice standards for phytopharmacological research, and propose a 12-item minimum standard for network pharmacology studies of Ayurvedic drugs. Used with chemically characterised classical preparations, transparent reporting and experimental or clinical validation, network pharmacology can test Dravyaguna hypotheses rather than merely decorate them.

KEYWORDS: Network pharmacology, Ayurveda, Dravyaguna, systems pharmacology, molecular docking, reproducibility, research methodology

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INTRODUCTION

Conventional drug discovery long assumed that one drug should act on one target. Network pharmacology replaced this with the view that drugs act on networks of proteins and that many effective drugs, and many diseases, are better described at the level of networks than of single targets.[1] The idea was quickly adopted in traditional Chinese medicine research, where it was presented as a bridge between holistic theory and molecular biology,[2] and the number of network pharmacology publications on traditional medicines has since grown very rapidly.[3]

The approach has obvious appeal for Dravyaguna. Ayurvedic drugs contain many constituents, are mostly prescribed in multi-ingredient formulations, and are described in classical texts by system-level properties such as rasa, guna, virya, vipaka and prabhava rather than by single mechanisms.[4] An early network analysis of Triphala mapped its constituents to molecular targets and diseases with special reference to cancer,[5] and curated databases of Indian medicinal plants now list 17,967 phytochemicals from 4,010 plants,[6] so a complete in silico study can be carried out with free tools in a few weeks.

This ease has a cost. Editors of a research topic devoted to setting standards for network pharmacology in traditional medicine noted that active-ingredient screening has become homogeneous, that the clinical effectiveness of the formulations studied is often ignored, and that network predictions frequently lack experimental verification.[7] The World Federation of Chinese Medicine Societies issued the first international evaluation guidance for network pharmacology in 2021 to address these concerns.[8,9] This review appraises each step of the pipeline as it is commonly applied to Ayurvedic drugs, relates the problems to the published guidance and to best-practice standards for phytopharmacology,[10,11] and proposes a minimum standard for future Dravyaguna studies.

METHODS

This is a critical methodological review. We examined methodological guidance, editorials and best-practice statements on network pharmacology and phytopharmacology, the documentation of the databases and tools most often used in published studies, and illustrative network pharmacology studies of Ayurvedic drugs. The appraisal is organised by the steps of the typical pipeline.

THE TYPICAL PIPELINE

Most published studies follow the same sequence. Constituents of the plant or formulation are retrieved from databases such as IMPPAT[6] or TCMSP.[12] They are filtered by predicted oral bioavailability and drug-likeness; the TCMSP authors, for example, screened licorice constituents at an oral bioavailability of at least 40% and a drug-likeness of at least 0.18,[12] and many later studies adopt similar fixed cut-offs. Targets of the retained compounds are predicted by structural similarity tools such as SwissTargetPrediction,[13] intersected with disease-associated genes from public databases, and assembled into a protein–protein interaction network using STRING.[14] Hub proteins are ranked by network centrality, the target set is subjected to Gene Ontology and pathway enrichment, and selected compound–target pairs are examined by molecular docking. Some studies end there; others add a limited in vitro or animal experiment.

Each step is defensible in principle, but each introduces assumptions that are rarely stated or tested. Table 1 summarises the main problems and the corresponding recommendations.

CRITICAL APPRAISAL BY STEP

What is being modelled?

The most fundamental problem is a mismatch between the substance studied in silico and the substance used in practice. A database entry for a plant aggregates constituents reported in any study, from any plant part, extraction solvent or geographical source, and gives no quantities. A classical Ayurvedic drug, however, is a specific part prepared in a specific way: an aqueous decoction (kvatha) extracts different constituents from a powder (churna) taken with honey or ghee, and an alcohol-based asava or arishta differs again. A network built from the database entry therefore models a hypothetical plant rather than the medicine the patient takes. The ConPhyMP guidelines require that the chemical composition of any extract used in pharmacological research be characterised and reported,[11] and the same requirement should apply to the material on which a network model is based.

Table 1. Common problems at each step of network pharmacology studies of Ayurvedic drugs.

Step	Common problem	Recommended practice
Compound selection	Database lists include constituents reported from any part, extract or chemotype of the plant, without quantities	Use constituents identified and, where possible, quantified in the actual preparation studied[11]
ADME filtering	Predicted values and fixed thresholds exclude glycosides, polyphenols and other constituents that may act after gut or microbial metabolism	Justify thresholds, report sensitivity to them, and consider metabolites[8]
Target prediction	Similarity-based predictions are unvalidated; promiscuous and assay-interfering compounds generate many targets[15,16]	Prefer experimentally supported interactions; flag known interference compounds; report prediction scores
Disease genes	Broad gene lists for complex diseases overlap with almost any target set	Use curated, disease-specific and preferably tissue- or stage-specific gene sets
Network construction	Well-studied proteins dominate interaction databases and become hubs in every network	Report confidence thresholds and database versions; compare against random or control compound sets
Enrichment	Generic pathways such as cancer and inflammatory signalling appear regardless of the question	Report background sets and multiple-testing correction; interpret with caution
Molecular docking	Docking scores treated as evidence of binding or activity	Use as hypothesis generation only; include known ligands as controls; confirm experimentally
Validation	Absent, or using isolated compounds at concentrations unattainable in vivo	Test the whole preparation first at therapeutically relevant doses, then mechanisms[7,10]

Filtering by predicted absorption

Filtering by oral bioavailability and drug-likeness is intended to remove constituents that cannot reach their targets. The values are themselves predictions from chemometric models, and the thresholds were proposed for screening rather than as biological cut-offs.[12] Many constituents of Ayurvedic drugs are glycosides, tannins or polyphenols with low predicted bioavailability that are transformed by gut microbes into absorbable metabolites, or that act locally in the gut. Removing them on the basis of a fixed threshold may discard the constituents responsible for the classical action. Studies should justify their thresholds, report how results change when thresholds are varied, and consider known metabolites.[8]

Promiscuous compounds and study bias

Some natural products interfere with many biological assays through aggregation, redox cycling, metal chelation or covalent reactivity. Such pan-assay interference compounds generate apparent activity against many unrelated targets.[15] Curcumin is the best-known example: it has been classified both as an assay-interference compound and as an invalid metabolic panacea, it is chemically unstable and poorly bioavailable, and none of its double-blind, placebo-controlled trials had succeeded at the time of a detailed review.[16] Because target-prediction tools and literature-derived databases reflect the number of published reports, such compounds acquire many predicted targets and appear as central nodes. A similar bias affects proteins: those studied most intensively have the most recorded interactions and tend to emerge as hubs whatever the disease or plant. Without control analyses using random or unrelated compound sets, a network that places familiar inflammatory and growth-signalling proteins at its centre may simply reflect the structure of the databases.

Docking and enrichment

Molecular docking estimates whether a compound can be fitted into a protein binding site, and its score

is not a measure of affinity or of biological effect. Docking is useful for generating hypotheses but should include known ligands as positive controls and should not be presented as confirmation of a network prediction. Enrichment analysis of target sets that are biased towards well-studied proteins will return the pathways in which those proteins are annotated; the appearance of broad cancer, inflammatory or metabolic pathways is therefore weak evidence of a specific mechanism unless the background set and correction for multiple testing are reported.

Reproducibility

Databases are updated continuously, and interaction resources such as STRING change their content and scoring between versions.[14] Studies that do not report database versions, access dates, confidence thresholds and software settings cannot be reproduced. The 2021 evaluation guidance emphasises reliability, standardisation and verifiability as the core criteria for network pharmacology studies.[8,9]

Validation

Network predictions are hypotheses. The research-topic editors recommended that the overall effect of an extract or formulation be tested first, followed by investigation of specific mechanisms, using therapeutically relevant doses, credible models and stated chemical composition, with clinical trials as the most rigorous verification.[7] Best-practice guidance for phytopharmacological research makes the same points about dose relevance, controls and characterisation.[10] Experiments that test an isolated constituent in cell culture at concentrations far above those achievable after oral use of the classical preparation do not validate a network model of that preparation.

A DRAVYAGUNA PERSPECTIVE

Network pharmacology is attractive to Ayurveda researchers because it seems to speak the language of holism. There is a risk, however, that it is used to translate classical concepts into lists of genes after the fact, which adds little to either. Rasa, guna, virya, vipaka and prabhava are system-level descriptions of how a substance affects the body;[4] mapping a single plant to hundreds of predicted targets does not by itself explain why it is bitter, hot in potency or indicated in a particular condition.

A more productive use is to test hypotheses that arise from Dravyaguna itself. Do drugs that share a rasa or virya share target or pathway profiles more than chance would predict? Does a classical combination act on a network in a way its individual ingredients do not, as the logic of formulation implies? Does the choice of dosage form or vehicle (kalpana and anupana) change the predicted and measured network effect? Such questions can be answered only if the model is built on characterised preparations and if predictions are tested experimentally. Framed in this way, network pharmacology becomes a tool for examining classical claims rather than for decorating them.

A PROPOSED MINIMUM STANDARD

Table 2 sets out a 12-item minimum standard for network pharmacology studies of Ayurvedic drugs, derived from the 2021 evaluation guidance,[8] the ConPhyMP guidelines,[11] best-practice recommendations for phytopharmacology[10] and the problems identified above. Journals publishing Ayurveda research could ask authors to complete it on submission.

LIMITATIONS

This review is a methodological appraisal rather than a systematic survey of published studies, and it does not quantify how often each problem occurs in the Ayurveda literature. The problems described are drawn from guidance documents, database documentation and well-known methodological critiques, and some well-conducted studies already meet most of the proposed standard.

CONCLUSION

Network pharmacology has real potential for Dravyaguna research, but as commonly practised it models what a plant might contain rather than what a classical medicine delivers, relies on predicted values and arbitrary thresholds, is vulnerable to promiscuous compounds and database bias, and is often left unvalidated. Building models on chemically characterised preparations, reporting methods transparently, including control analyses, and testing predictions with the whole preparation at relevant doses would make such studies credible. Researchers should use the method to test hypotheses that arise from Dravyaguna itself rather than to translate classical concepts into gene lists after the fact.

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