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REVIEW

Application of network pharmacology in synergistic action of Chinese herbal compounds

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Abstract

Herbal medicines are frequently blended in the form of multi-drug combinations primarily based on the precept of medicinal compatibility, to achieve the purpose of treating diseases. However, due to the lack of appropriate techniques and the multi-component and multi-target nature of Chinese medicine compounding, it is tough to explain how the drugs interact with each other. As a rising discipline, cyber pharmacology has formed a new approach characterized by using holistic and systematic "network targets" via the cross-fertilization of computer technology, bioinformatics, and different multidisciplinary disciplines. It can broadly screen the active ingredients of traditional Chinese medicine, enhance the effective utilization of drugs, and elucidate the mechanism of drug action. We will overview the principles of Chinese medicine compounding and dispensing, the research methods of network pharmacology, and the software of network pharmacology in the lookup of compounded Chinese medicines, aiming to supply thoughts for the better application of network pharmacology in the research of Chinese medicines.

Keywords Network pharmacology · Traditional Chinese medicine compound · Synergistic effect

Introduction

Clinically, doctors have a long history of using Chinese medicines to treat patients in China and have gathered a wealth of experience in making Chinese medicines and how to select them. TCM has attracted worldwide attention because of its remarkable therapeutic efficacy, relatively low toxicity, and costs (Lei et al. 2024). The human body is a self-sustaining chemical system capable of Darwinian evolution, and TCM is also a complex system with "multi-components, multi-targets, and multi-pathways" (Li et al. 2024a). When herbal medicines enter the body, the interactions that occur with the organism are system–system interactions (Hu et al. 2021). Chinese medicines are compounded according to the rules of the monarch, minister, adjuvant, and guiding medicine (Jun, Chen, Zuo, and Shi) (He et al. 2022a). Among these rules, the monarch medicine is the one that has the main therapeutic effect on the disease in the prescription; the minister medicine can assist the monarch medicine, which can effectively strengthen the therapeutic effect of the monarch medicine; the adjuvant medicine can eliminate or slow down the toxicity of the monarch medicine and the minister medicine; and the assistant medicine enabler can mainly reconcile all the medicines to play a synergistic effect. As Chinese medicine compound prescriptions are composed of two or more medicines with many complex ingredients, it is very tough to completely elucidate the mechanism of action of TCM in the cure of diseases. Network pharmacology is the interactions between components from the perspective of chemical composition, from "point" to "line", and then from "line" to "surface". It analyzes the interactions among components from the perspectives of interrelationships, structural properties, action targets, and other attributes, which provides ideas for interpreting the material basis of the efficacy of traditional Chinese medicines.

Network pharmacology is a new discipline based on the theory of systems biology, which can be used to design multi-target drug molecules by selecting particular signaling

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nodes (Tang et al. 2021), which mainly includes network construction (Wang et al. 2022a), data mining (Pan et al. 2022), and network analysis and experimental validation (Huang et al. 2021). Firstly, using database search, combined with visualization tools to construct the network; then, at the cellular, molecular, and overall biological levels, to conduct multi-level analysis of specific signal nodes in the network, to identify the key nodes, and from the perspective of the overall balance of the biological network, to discover the pharmacological active ingredients, mechanisms of action and prescription rules of drug prevention and treatment (Duan et al. 2024; Li et al. 2022; Zhou et al. 2022). The theory of "network targets" breaks through the limitations of the "single target" research model, focusing on the comprehensive effects of disease biological networks, describing the overall regulatory mechanism of TCM formulas, and conducting research according to the standards of network pharmacology (Shao 2021). Due to the complex mechanism of action of TCM and the scarcity of relevant data, Li Shao's group established DrugAI by combining network pharmacology and artificial intelligence methods to predict the "activation/inhibition" mechanism of action between drugs and targets (Zhang et al. 2023). The research model of TCM primarily based on network targets promotes the progressive improvement of TCM network pharmacology in combination with clinical experiments, computer applications, and artificial intelligence. In this article, we will review the two directions of Chinese medicine compounding and compounding principles and network pharmacology, aiming to provide ideas on how to study Chinese medicine efficiently.

Principles of Chinese medicine compounding and synergy

TCM is a treasured advent of the Chinese state and a treasure from ancient Chinese science, which performs a special and lasting function in the lengthy history of the Chinese nation's proliferation and inheritance of Chinese culture (Ren et al. 2024). The compounding of Chinese medicine refers to the selective combination of two or more drugs with different efficacies according to the different symptoms of different stages of diseases. Based on the "Treatise on typhoid and miscellaneous diseases" and the "Shennong's Classic of Materia Medica", Chinese doctors have further developed the theories of "harmony of the seven emotions", "harmony of odor and character", and "compatibility of each other" based on the summary of their clinical experience, to make scientific combinations of medicines, and to achieve the purpose of prescribing the right medicine for the right disease (Xie et al. 2021).

Extracts of herbs consist mainly of complex mixtures of their compounds, active ingredients, and other substances (Ming et al. 2021). Chinese medicines have a variety of chemical components and multiple monomers, which have certain synergistic effects in treating or reducing toxic side effects, and the study of the synergistic mechanism of Chinese medicines can help researchers discover new therapeutic targets and therapeutic efficacy. Take Astragalus as an example, in clinical practice, Astragalus is mostly used to replenish qi, stop sweating, and expel pus, and its pharmacologically active components mainly include astragalus saponins, astragalus polysaccharides, flavonoids, and amino acids (Liang et al. 2022). Among them, astragaloside has anti-inflammatory (Su et al. 2021), anticancer, antioxidant, and immunomodulatory effects (Luo et al. 2021), and astragaloside IV can promote neurogenesis and angiogenesis by enhancing PPARγ receptors and thus (Li et al. 2021); Astragalus polysaccharides have a variety of pharmacological effects such as anti-infection, metabolic regulation, and radiation resistance (Chen et al. 2021) and also enhance the immune function of macrophages (Xu et al. 2024). In ancient China, the ancients put a variety of Chinese medicines together and boiled them to make tonics, during the boiling process, the nature of the tonics would change and new compositional products might be produced. Chinese medicines themselves contain a variety of chemical components, and together with the compounding and synergistic effects between drugs, the target point for their efficacy is difficult to determine. Therefore, how to quickly find the effective targets of drugs becomes particularly important. The network pharmacological study of Chinese medicine compounds is more literature, its analysis method is similar, its analysis idea is from the chemical composition, seeking the chemical composition corresponding to the target gene, the key protein, and then, through the signal transduction of the protein to play the overall effect of the formula, the pharmacological study of Chinese medicine compound has a very important role in the interpretation of its different diseases with the same treatment, the same disease with the different treatment of the identification mechanism, but also for the exploration of the material basis of the efficacy of the compound of traditional Chinese medicine to provide the direction of the investigation.

Network pharmacology

Research methods in network pharmacology

Network pharmacology targets biological networks, develops drug targets and molecular targets, and screens the network for drug-disease targets to enhance drug efficacy through multiple modulations of signal transduction (See Fig. 1). The analysis process involves constructing a network model by retrieving information and analyzing the network.

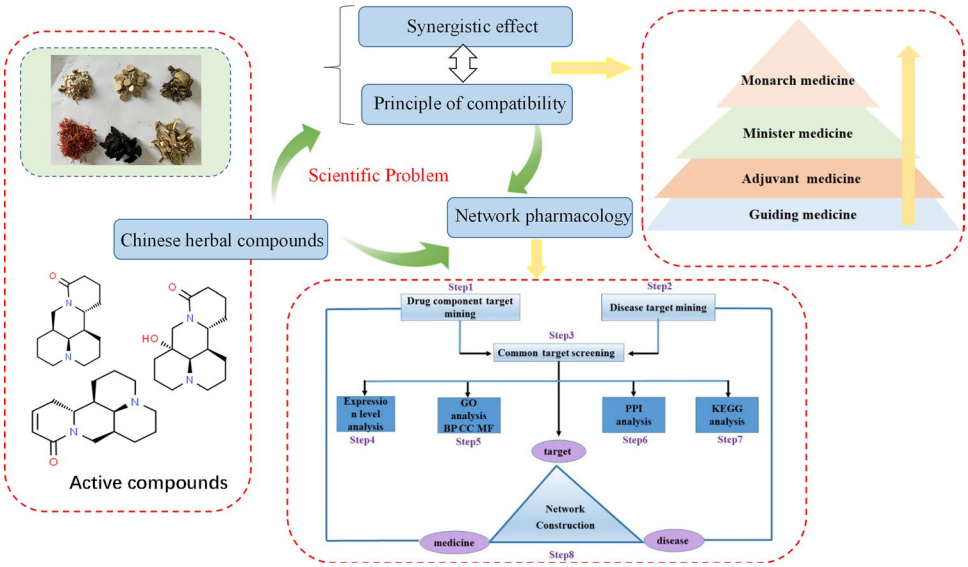

Fig. 1 Network pharmacology and Chinese herbal compound

Drugs, targets, genes, and diseases can form complex biological networks with a large number of nodes and connections, and network visualization software allows for a more intuitive representation of the network, as well as network analysis to obtain information on node topology, including nodes, edges, and extent (Niu et al. 2022). Where nodes can represent genes, proteins, herbal medicines disease phenotypes, etc., and nodes connected to nodes represent interactions between targets and targets (Yin et al. 2023). Network building for TCM research requires the screening of bioactive compounds first, and there are two main screening methods: one is to screen through experimental data, such as obtaining bioactive compounds from serum pharmacology experiments, and the other is to screen through databases. Commonly used databases for drugs are TCMSP, TCMID, TCMdatabase@Taiwan, DrugBank, etc. (Jiang et al. 2022; Lu et al. 2022; Wu et al. 2024). For example, Zhao et al. (2022) investigated the pharmacological mechanism of andrographolide in the treatment of vascular cognitive impairment by searching Genecards, OMIM, and other databases to visualize compound targets and drug targets by obtaining different biological networks such as compound-target networks, disease-gene network, and PPI network through visualization techniques. He et al.(2022b) explored the common mechanism of action of Huanglian classified formulation on type 2 diabetic zebrafish by using network pharmacology with untargeted metabolomics to predict the key targets to find the common mechanism of action by visualizing the compounds and drug targets.

After identifying the compound, another key node in the biological network is the target, which is collected through the available databases (Table 1). For example, Zhou et al. (2022), investigated the mechanism of Moluodan for the therapy of chronic atrophic gastritis retrieve drugs and disease targets through a database of TCM network pharmacology analysis platform. Li et al. (2024b), explored the mechanism of Coptidis Rhizome in the treatment of periodontitis by searching the database to obtain the potential active components, targets of action of Coptidis Rhizome, and disease targets.

The third step of network building for TCM research is network visualization. The presentation of the relationship between drugs and diseases depends on network visualization tools. Most of the visualization in network pharmacology research can be realized by professional software tools such as Cytoscape, GUESS, and Pajek. There are three network analysis methods in total, including network structure analysis, network function analysis, and network analogy analysis. Wang et al. (2023) used bioinformatics to screen the main chemical components and potential target genes of Daqinjiao Decoction (DQJD), identified the key targets of Cerebral small vessel disease (CSVD) based on the network module, and performed GO and KEGG pathway enrichment analysis. Results revealed that DQJD might play a role by targeting the key targets including Caspse3 and P53 and regulating the P53 signaling pathway. Deng et al. (2021) used network pharmacology to explore the pharmacodynamic basis and mechanism of the anti-inflammatory and antiviral effects of Isatis indigotica, using UPLC-Q-TOF–MS for chemical analysis, SwissADME for screening of active ingredients through gastrointestinal absorption prediction and drug similarity analysis. SwissADME was used to screen the active ingredients by gastrointestinal absorption prediction and drug similarity analysis, and the "active ingredient-anti-inflammatory" and "active ingredient-antiviral" networks were constructed, and the relevant targets were identified by network analogy analysis and cell validation experiments were carried out. In addition, network analogies were used to analyze the various stages

Table 1 Database about Chinese medicine, target, and disease

	Database	URL	Full Name/function
Chinese medicine database	TCMSP	https://tcmspw.com/tcmsp.php	Traditional Chinese medicine systems pharmacology database and analysis platform
	TCMID	http://www.megabionet.org/tcmid/	Traditional Chinese medicines integrated database
	TCMdatabase@Taiwan	http://tcm.cmu.edu.tw/	Traditional Chinese medicine database
	Pubchem	https://pubchem.ncbi.nlm.nih.gov/	Quickly find chemical information from authoritative sources
	DrugBank	https://go.drugbank.com/	Power bigger research and better decisions with the world's most robust drug knowledge
	ChEMBL	https://www.ebi.ac.uk/chembl/g/	ChEMBL brings together chemical, bioactivity, and genomic data to aid the translation of genomic information into effective new drugs
Target database	PDB	http://www1.rcsb.org/	Protein data bank
	Uniprot	https://www.uniprot.org/	Protein sequences and related detailed annotations of the database
	STRING	https://www.string-db.org/	Predict the gene expression relationship of the same functional protein
Disease database	OMIM	https://omim.org/	Online mendelian inheritance in man
	GEO	http://www.geosc.com/	Gene expression omnibus
	GAD	http://geneticassociationdb.nih.gov	Genetic association database

of the disease, and the mechanism of interference was investigated by establishing various disease networks for each stage and important biomarkers obtained through high-throughput techniques.

As herbs are affected by different environments, different regions, the same herb, the efficacy will be different, the drug enters the body, the efficacy of the drug will also change with individual differences, in a dynamic process, and the network analysis is static, so after using the network analysis, the results should be verified. In recent years, several scholars have carried out studies on network validation, for example, Sun et al. (2022a) found that the mechanism of action of Huo Luo Xiao Ling Dan for the treatment of atherosclerosis may be the MAPK signaling pathway using molecular docking and molecular dynamics simulations after first predicting the target of Huo Luo Xiao Ling Dan for the treatment of atherosclerosis using network pharmacology and subsequently validating the mechanism of action using a mouse monocyte macrophage leukemia cell line. In terms of the type of literature, review articles were the least, accounting for about 1.34%; research papers accounted for about 96.7%, suggesting that this type of research is currently in the stage of theoretical application, and most researchers are trying to adopt the method for theoretical validation of subsequent studies.

Application of network pharmacology

The application of network pharmacology in the optimization of TCM formulas

Network pharmacology is a drug research methodology primarily based on network analysis and systems biology, which can be used to optimize the composition and dosing patterns of herbal formulas. By constructing compound-target networks, compound-compound networks, and target-pathway networks in TCM formulas, the composition, mechanism of action, and optimization direction of TCM formulas can be studied in depth, to enhance the efficacy and security of TCM formulas (Cao et al. 2023). The interactions and synergies between the various compounds in Chinese herbal formulas are important factors in determining the efficacy of Chinese herbal formulas (Zhou et al. 2021). Interactions and synergistic effects between different components in Chinese herbal formulas can be predicted by establishing compound–compound networks and compound-target networks in Chinese herbal formulas. For the TCM formula "ZhuyuPill", network pharmacological studies have found that compounds such as berberine,

coptisine, and evodiamine can exert their underlying protective role on Atherosclerosis primarily via MAPK and NF-κB pathways (Pan et al. 2023).

In addition, it is also possible to predict the potential active ingredients in herbal formulas using network pharmacology to further optimize the composition of herbal formulas (Ren et al. 2023). The dosing pattern of Chinese herbal formulas includes dosage, frequency, and duration of treatment (Lv et al. 2024). Network pharmacology explores the dose–response relationship between different compounds and their targets by creating various networks to find better dosing patterns, improve therapeutic efficacy, and reduce side effects (Xiang et al. 2023). For example, Shenkangning is usually used clinically for the remedy of chronic glomerulonephritis, Wei et al. (2022) explored the molecular targets and signaling pathways of the disease or the drug at multiple degrees and views through establishing a chronic nephritis targeting network and searching for the interactions between the compounds in Shenkangning and the targets associated to chronic nephritis. Qingfeiyin is mainly composed of herbs such as Ephedra, Glycyrrhiza glabra, and Almonds Pueraria Mirifica. Wang et al. (2022b) provided a new strategy for the research of the mechanism of action of Qingfeiyin in the therapy of acute lung injuries by setting up a network to discover the workable active components of Qingfeiyin.

Network pharmacology-assisted screening and design of novel Chinese medicine molecules

Network pharmacology can predict the mechanism of action and interactions of novel TCM molecules through the establishment of TCM molecule–target networks and TCM molecule–compound networks to optimize molecular design (Zhang et al. 2022a). Chinese medicine molecule–target network analyzes the mechanism of action and effects of Chinese medicine molecules by establishing links between them and known drug targets (Shao et al. 2023). The TCM molecule–compound network analyzes the interactions and synergies between TCM molecules and compounds by establishing links between TCM molecules and known compounds. This approach designs more effective herbal molecules by predicting interactions and synergies between novel herbal molecules and known compounds (Wilson et al. 2022).

A study reported that 142 primary targets for the cure of diabetic nephropathy have been recognized by screening Astragalus membranaceous—Angelica sinensis compound in the TCM database via network pharmacology and molecular docking techniques (Dong et al. 2021). Using data mining and network pharmacology methods to explore the molecular biology mechanism of TCM in treating gastric precancerous lesions, a total of 482 compound formulas, including 603 types of TCM, were studied to obtain compounds and targets for TCM in treating gastric cancer. In the end, six high-frequency TCMs were found to be involved in the treatment of gastric precancerous lesions. The mechanism of their treatment for gastric precancerous lesions is mainly related to the following pathways: tumor pathway, PI3K-AKT pathway, immunity, inflammation, etc. (Zhang et al. 2022b). In summary, network pharmacology performs an essential position in the research of TCM and has extensive applications in the screening and design of novel Chinese medicine molecules. By establishing various networks, predicting drug action mechanisms and interactions, and optimizing TCM molecular screening, the effectivity and success rate of TCM molecular improvement can be considerably improved, presenting better assistance for the clinical application of TCM.

Network pharmacology in natural medicinal chemistry

Natural medicinal chemistry research refers to the study of the composition, structure, and chemical properties of natural medicines to explore their pharmacodynamic components and mechanisms of efficacy and to further optimize and develop medicines with improved efficacy and safety (Hanna et al. 2024). Network pharmacology can be used to analyze the mechanism of action and interactions of compounds in natural medicines, providing important support and guidance for the research and improvement of natural medicines. Natural medicines contain many different compounds, which can interact with multiple targets in the human body to produce different effects. The use of network pharmacology to construct "compound-target networks" can analyze the relationship between different compounds and targets, providing important ideas for drug optimization and development (Wu et al. 2023a). For example, through the establishment of compound–target networks, the interactions between compounds in different natural medicines and tumor cells can be analyzed, natural medicine compounds with anti-tumor activity can be identified, and their structures and efficacies can be further optimized so that more effective anti-tumor drugs can be developed (Kumari and Kumar 2023).

Compounds in natural medicines can interact and synergize with each other to produce more potent medicinal effects (Mishra et al. 2021). Pharmacodynamic pathways are the biological pathways through which drugs produce their effects, and pathway fingerprinting of drugs has the potential for drug similarity assessment, which can provide new insights into the mechanism of action of natural products by characterizing the similarity of pathway fingerprints through the heterogeneous network of "drug-target-pathway" (Guo et al. 2021). Compound networks can analyze

the interactions between different compounds, optimize the compounding of drugs, and improve drug efficacy.

The use of network pharmacology in the development of new drugs

New drug discovery is the first and most crucial step in drug development. First of all, traditional new drug discovery methods often require a large number of experiments and data analyses, which are time-consuming and costly in terms of human resources (Su et al. 2024). Network pharmacology performs a vital role in different stages of new drug discovery by using different databases of TCM information resources, combined with systems biology, to construct different networks to screen compounds with potential pharmacological effects (Han et al. 2024). Wu et al. (2023b) successfully identified the active phytochemicals and molecular pathways of Gleditsiae Spina for the treatment of Colorectal cancer (CRC), which provides a basis for further development of anti-CRC drugs based on the active components of Gleditsiae Spina in the future.

Secondly, pharmacodynamic evaluation is also one of the important aspects of drug development, and its role is to assess the biological effects and therapeutic effectiveness of drugs. Traditional methods of pharmacodynamic evaluation often require a large number of animal experiments and clinical trials, which are time-consuming and costly. Network pharmacology, on the other hand, can predict the mechanism of action and therapeutic effects of drugs by analyzing their targets and pathways, thus saving time and financial costs. For example, network pharmacology can be used to assess the selectivity and affinity of a drug for multiple targets, as well as its therapeutic efficacy for allopathic treatment (Su et al. 2022). In addition to being able to assess the effectiveness of drugs, network pharmacology can also assess the toxicity of drugs and predict their side effects and toxicity. For example, Luo et al. (2023) used a network pharmacology approach to predict candidate targets associated with Triptolide (TPL) toxicity and performed in-depth RNA-seq analyses and found that c-Jun is a potential target of TPL and Per1 related circadian rhythm signaling is involved in TPL induced renal toxicity.

Joint application of network pharmacology and bioinformatics

With the continuous development of modern science and technology, the modernization of TCM has come to be an important development direction. The development of modernized Chinese medicine requires the combination of traditional experience and modern science and technology. Network pharmacology and bioinformatics, as two emerging interdisciplinary disciplines, are becoming important tools in the development of modernized Chinese medicine (Zhang et al. 2022c). Problems such as the exact mechanism of the efficacy of TCM and their effective constituent have always been the bottleneck in the modernization of TCM, and the cross-fertilization of network pharmacology and bioinformatics can provide technological support for the solution of these problems (Han et al. 2022). Network pharmacology and bioinformatics are two interrelated and interdependent emerging disciplines with the following characteristics: (1) High-throughput data analysis capability: Network pharmacology and bioinformatics can handle a large amount of molecular data and genetic data, and excavate the correlation and law of Tai et al. (2022). (2) Multi-level and multi-scale research capability: Network pharmacology and bioinformatics can study biological systems from different perspectives and levels, including molecules, cells, tissues, organs, and other different levels of research (Wu et al. 2021). (3) Systematic and comprehensive: Network pharmacology and bioinformatics can provide comprehensive support and guidance for the modernization of TCM through integrated analysis and evaluation of the entire biological system (Shen et al. 2023).

The characteristics of TCM multi-component and multi-target make the screening and optimization of active substances for an important part of TCM modernization research (Chen et al. 2023). Bioinformatics is integrated with network pharmacology to predict and screen potentially effective substances by drawing on biological data such as genomes, transcriptomes, proteomes, and metabolomes (Gu et al. 2023). For example, Sun et al. (2022b) explored the mechanism of action of Danggui Buxue Decoction for the cure of type 2 diabetic nephropathy with the aid of combining lipidomics, transcriptomics, and network pharmacology, Firstly, the lipid metabolism profiles of renal samples had been analyzed by way of using UPLC-Q Exactive MS technology, and after screening and identifying the biomarkers, transcriptomics analyses had been carried out via using RNAseq, and finally, network pharmacology methods have been used to expose the possible molecular mechanisms.

Conclusion

Synergy is an important feature of life's activities and the quest for modern pharmacotherapeutics. The essence of the principle and practice of Chinese medicine lies in the remedy thinking of "disease-person" integration. Through network pharmacology technology and metabolomics, we can quickly and efficiently elucidate the treatment concept of "disease–person" integration. This article focuses on the synergistic effects of TCM, network pharmacology research methods, and the adhibition of network pharmacology in TCM compounding to provide ideas for improving the

effective utilization of drugs and elucidating the mechanism of drug action.

Network pharmacology performs a vital function in the study of the material basis and mechanism of the efficacy of TCM, the understanding of the law of compounding and compounding, the study of new drugs, and the quality control of TCM. Although network pharmacology is promising, there are still some limitations. Firstly, the database is not comprehensive; compared to conventional Chinese medicine, there is less information on the chemical composition of ethnic and regional medicines in the database, which is not widely recognized, and the database needs to be further improved. Secondly, network pharmacology can qualitatively analyze the compounding pattern of Chinese herbal medicines via the establishment of a "component–target–disease" network. However, it is not possible to determine the content of Chinese herbal medicines before and after metabolism in the body for different ratios in the formula pairs, and the differences in the types of ingredients, which leads to the changes in the content of single herbs being neglected, and therefore, it is particularly important to calculate the changes in the content of the ingredients involved in the experiments. In conclusion, network pharmacology has been developing at an extremely fast pace in the last decade, and it is believed that this model will allow TCM to take a new step forward in the global pharmaceutical industry.

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Declarations

Conflict of interest The authors declare no competing interests.

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