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Review Article

Multi-component Chinese medicine formulas for drug discovery: State of the art and future perspectives

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ABSTRACT

For hundreds of years, the drug discovery and development industry has aimed at identifying single components with a clear mechanism of action as desirable candidates for potential drugs. However, this conventional strategy of drug discovery and development has faced challenges including a low success rate and high development costs. Herein, we critically review state-of-the-art drug discovery and development based on multi-component Chinese medicine formulas. We review the policies and application status of new drugs based on multi-component Chinese medicines in the US, China, and the European Union. Moreover, we illustrate several excellent cases of ongoing applications. Biomedical technologies that may facilitate drug discovery and development based on multi-component Chinese medicine formulas are discussed, including network pharmacology, integrative omics, CRISPR gene editing, and chemometrics. Finally, we discuss potential problems and solutions in pre-clinical and clinical research in drug discovery and development based on multi-component Chinese medicine formulas. We hope that this review will promote discussion of the roles of multi-component Chinese medicine formulas in the discovery and development of new drugs for the treatment of human diseases.

Keywords: multi-component Chinese Medicine formula, drug discovery and development, case study, new technologies

1. INTRODUCTION

On the basis of historical evidence, humans have been using drugs since prehistoric times [1]. Empirical methods have dominated human drug discovery efforts for millennia, and the history of modern drug discovery can be traced back to the nineteenth century [2]. With the establishment and development of the organic synthesis industry, some compounds with medicinal value were serendipitously discovered by scientists. Examples include the anesthetic chloral hydrate and the phenothiazine derivatives used for disinfection [3]. From the 20th century, the development of synthetic chemistry and biology has led to advances in drug discovery [4]. This era led to the development of essential drugs such as antibiotics and vaccines [5]. Synthetic chemistry played a dominant role in drug discovery based on spectrometers and separation techniques, and capitalizing on the computer revolution [6, 7]. These novel technologies have allowed scientists to identify and isolate the active ingredients of natural medicines. The discovery of new drugs no longer relies on a random search for active natural products; instead, computer-aided drug design is applied to design new drugs rationally [8]. With rapid technological developments, scientists currently have access to more powerful computing tools, advanced recombinant DNA technology, and new technologies such as omics [9]. However, determining how to optimally integrate these technologies has been a hurdle in drug discovery.

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Chinese medicine, a form of traditional medicine in Asia, has drawn worldwide interest in the life sciences [10, 11]. Chinese medicine is also used as a supplementary alternative treatment in Western countries, and it provides a wealth of natural resources for medicinal substances. In addition, Chinese medicine is widely recognized as efficacious and safe for use in drug development [12]. However, owing to the complexity of the medicinal substances and their multi-target effects, a holistic understanding of the mechanisms of herbal medicines remains lacking. The discovery of bioactive compounds in herbs or herbal formulas used to treat specific diseases crucial for the development of medications based on Chinese medicine. Advanced pharmacology techniques are necessary to discover bioactive chemicals and their associated targets and molecular mechanisms. Cutting-edge drug discovery approaches include primarily network pharmacology, integrative omics, clustered regularly interspaced short palindromic repeats (CRISPR) gene editing, and chemometrics [13-15]. Network pharmacology is used to establish biological networks through analysis of the molecular relationships between Chinese medicines and their molecular targets, which may offer novel perspectives for studying complicated systems in Chinese herbal medicines and formulas used for treating diseases [16]. Integrative omics, a term recognized in multiple areas of biology, including genomics, transcriptomics, and proteomics, is an information-rich approach to finding a series of molecular and biological features. In Chinese medicine, multiple targets for treating diseases may be discovered by this high-throughput technology [17]. CRISPR gene editing can be directly used to modify genes [18]. This technology is useful in validating Chinese medicine targets for precise disease treatment. Chemometrics is a branch of chemistry that applies mathematics and statistics to identify the most effective assessment methods and experiments for mining bioactive compounds [19]. Through clinical and animal experiments, chemometrics can provide relevant chemical information for the treatment of specific diseases. In addition to biological validation, policies and cases of approval of Chinese medicine as new drugs in several countries are reviewed in detail herein. These successful cases and ongoing applications may guide effective and appropriate Chinese medicine drug development in accordance with policies. Overall, the understanding of how traditional Chinese medicine can successfully treat a wide range of diseases may be gained through current highly advanced biotechnology and artificial intelligence. These insights should aid in the creation of Chinese-medicine-associated precision medicines. Additionally, an in-depth understating of policies may promote the successful development of new medications and their licensing. All these crucial factors are expected to contribute to the precise and systematic modernization of Chinese medicine.

2. CHINESE MEDICINE FORMULA PRODUCTS IN DRUG DISCOVERY AND DEVELOPMENT: STATE OF THE ART

2.1 Food and drug administration

The US Food and Drug Administration (FDA) is an influential agency worldwide [20]. Generally, the FDA is responsible for protecting and advancing public health by monitoring and regulating drugs, biological products, medical devices, foods, cosmetics, tobacco products, and products emitting radiation. Over the years, the FDA has shown a paradigm shift in the application of regulatory policies to botanical drugs that have been commonly used worldwide, given that they differ in nature from nonbotanical drugs, such as synthetic, semi-synthetic, highly purified, or chemically modified drugs. The FDA provided draft guidance for botanical drugs in August 1996, released the draft "Guidance for Industry on Botanical Drug Products" in August 2000, issued the final version (with the same title) in June 2004, and then issued the first modified version ("Botanical Drug Development: Guidance for Industry") in December of 2016 [21-23].

The changes in the title indicate the shift in monitoring of botanical drugs from an end-product-based mode to a drug-development-based mode, and the supervision of the entire process from research and development to marketing and post-marketing. In addition, to better address late-phase development and filing of new drug applications (NDAs) for botanical medications, several suggestions have been amended. A series of sections have been written to introduce the details of experiences from NDAs and investigational new drug applications (INDs) for botanical drugs.

In detail, the new guidance specifically states that the term "botanical" includes plant materials, algae, macroscopic fungi, and their combinations, and therefore does not include drugs of animal origin, minerals, or materials derived from botanical species that are genetically modified to produce a single molecular entity; products produced by fermentation of yeast, bacteria, plant cells, or other microscopic organisms; or highly purified substances. Specific regulations for botanical drugs have been categorized as the marketing of botanical drugs (over-the-counter nonprescription drugs) under drug monographs; marketing of botanical drugs under NDAs; botanical drug development under INDs; clinical phase I, II, and III trials of botanical trials under INDs; and NDAs for botanical drug products [24].

The FDA received more than 800 INDs and pre-IND meeting requests associated with botanical drugs in the years preceding 2018; however, the approval rate has been extremely low. To date, only two NDAs for botanical drugs have been approved by the FDA: Veregen in 2006 and Fulyzaq in 2012 [22]. Nevertheless, some herbal medicines, such as *Andrographis*, *Cinnamomum cassia* twigs, and *Ganoderma Lucidum* fruiting bodies, have been included in the United States Pharmacopeia (USP 44-NF 39-2021) after approval by the FDA.

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Nonetheless, many botanical drug candidates based on Chinese medicine formulas, such as Kanglaite injection, Fuzheng Huayu tablet, compound Danshen dripping pill (CDDP; T89), Guizhi Fuling capsules (KYG0395), Xuezhikang capsules, and Lianhua Qingwen capsules have been approved by the FDA for clinical trials in America [25-29]. Owing to the multiple abundant bioactive components in Chinese medicine formulas, products based on these formulas and other botanical products are expected to serve as promising candidates for new drug discovery and development. Digoxin, paclitaxel, and artemisinin-based drugs are good examples of well-known drugs developed from naturally occurring molecules or derivatives in botanical materials [22].

The new guidance will substantially affect the development and applications of botanical drugs and related products, and lead to critical thinking about drug discovery and development based on traditional Chinese medicines and related products. Most of all, the therapeutic consistency of botanical drugs should be supported by a "totality of evidence". It includes well-controlled botanical raw materials, robust chemical, manufacturing, and controls, clinically relevant bioassay tests, and multiple-dose and batch clinical data [22, 30, 31]. Moreover, the use of Chinese medicine formulae and medicinal herbs has been based on cumulative human experience, yet standardization of data collection techniques and criteria is essential to use this wealth of information to support regulatory approval [24].

2.2 National medicinal products administration

Over the past few years, China has focused on expanding the traditional Chinese medicine sector. To accelerate the development of Chinese medicines, the National Medical Products Administration (NMPA) has established a series of policies, regulations, and official information based on regulatory science (RS). RS is a novel discipline to evaluate the benefits and risks of decisions, which is used by drug regulatory authorities to formulate strategies regarding medicinal products. For instance, The US FDA, the European Medicines Agency (EMA), and the Pharmaceuticals and Medical Devices Agency in Japan have emphasized the value of RS as a foundation of high-quality assessment in strategic plans [32]. In China, the NMPA created the Chemistry, Manufacturing, and Controls (CMC) Guidance System for Chinese medicine and launched the Regulatory Science Action Plan, the first official initiative to keep pace with global RS development trends, in May 2019 [33]. Several critical areas are emphasized in the development of Chinese-medicine-associated RS.

NMPA's main responsibility is supervising Chinese medicines' safety, efficacy, quality, and approval for marketing. To achieve these goals, strengthening regulatory systems through RS development is considered a critical step. Unlike chemically synthesized drugs, Chinese medicines are complex multi-component systems whose quality depends on the chemical composition of many structurally diverse compounds. Setting quality standards for most herbal materials and final processed products is extremely challenging. Moreover, the "single component, single target" research mode in modern medicine poses challenges in clarifying the characteristics of synergistic responses among different components, action pathways, and effect targets [34]. Therefore, an efficient scientific evaluation approach must be implemented for Chinese medicine quality control. Fundamental experimental and clinical studies have made substantial advances in Chinese medicine. Biological testing, for example, has been advocated to identify Chinese medicine sources [35]. Additionally, evaluation of biological responses, biological activity, and quality markers has been suggested in quality evaluation. Moreover, during RS development, new techniques and methods such as chemometrics and mass spectroscopy are used to advance quality standards [33].

Second, drug discovery should meet the clinical needs of various therapeutic areas. Since the "Requirements for Registration Classification and Application Materials of Chinese Medicines" was issued by the NMPA, the research and development of new drugs has advanced. As of 2021, 54 applications of innovative Chinese medicine formulas had been accepted, 11 of which have been approved. Among them, Qingfei Paidu granules, Huashi Baidu granules, and Xuanfei Baidu granules are the most effective anti-coronavirus prescriptions used by many academicians and experts in Wuhan since the outbreak of COVID-19. They are derived from ancient recipes, and are also the first variety medicines reviewed under the updated NMPA requirements. From 2010 to 2020, the NMPA approved 58 innovative drugs [36]. Although innovative drugs are distributed across various fields, greater attention should be paid to the discovery of Chinese medicine drugs.

2.3 European medicines agency

The Committee on Herbal Medicinal Products (HMPC) in the European Union is known as the EMA, which is responsible for collecting and obtaining scientific data on herbal medicinal products, herbal substances, and herbal preparations, to facilitate harmonization of the products on the European market. The mission of the EMA is to monitor and oversee the safety and efficacy of (traditional) herbal medicines by enforcing regulations, directives, and scientific guidelines [37]. Under the EMA, development of herbal medicinal products in the European Union is systematically conducted, with an emphasis on legal safeguards and thorough ethical consideration [38]. A simplified registration procedure for (traditional) herbal medicines has been introduced in the EU to encourage benefits that outweigh risks. This procedure using rigorous scientific standards is convenient for assessing medicines worldwide, and providing partners and stakeholders with independent, science-based information on herbal medicinal products [39]. Moreover, the EMA confronts issues

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associated with herbal medicinal products previously marketed outside the EU as well as a growing number of combination products in member states. Therefore, the EMA periodically revises its scientific guidelines on herbal medicinal products, to help drug developers prepare marketing-authorization applications on medicinal products for human and veterinary use. The most recent version of the EMA guidelines on the quality of (traditional) herbal medicinal products (EMA/HMPC/CHMP/CVMP/201116/20051 Rev. 3) was published on May 12, 2022. Currently, excellent molecular pharmacology research is conducted by Chinese medicine practitioners and researchers on isolated, well-characterized small molecules and substances. The primary objectives are to expedite the deciphering of biological processes, and the development and deployment of computationally demanding methods for innovative therapeutic applications. A more inclusive resource that represents drug diversity more accurately will be critical in the future, to better serve humanity in the modernization of traditional herbal medicines in the EU.

2.4 Common features among FDA, NMPA, and EMA

Several characteristics are shared by the FDA, NMPA, and EMA policies:

- Safety and efficacy: for a product to be approved for use, all three organizations require evidence that it is both safe and effective.
- Good manufacturing practices: to ensure quality and consistency, the agencies require that items be produced in compliance with GMPs.
- Post-marketing surveillance: all three organizations must keep track of a product's safety after it enters the market.
- Regulatory authority: the FDA, NMPA, and EMA all have the power to enact laws and take action against goods that do not meet regulatory standards.
- Transparency: although the agencies' levels of transparency vary, all mandate some level of information sharing to the public.

Overall, these shared characteristics highlight the need to ensure that products are reliable and safe for use by the general public, supported by regulatory monitoring. The use and regulation of Chinese medicine products differ among the US, China, and the EU. The details are described below.

3. DISCOVERY AND DEVELOPMENT OF MULTI-COMPONENT CHINESE MEDICINE FORMULAS FOR DISEASE INTERVENTIONS: A CASE STUDY

Drug discovery based on multi-component Chinese medicine formulas is an important area of research for disease intervention. This case study focuses on three Chinese medicines: PHY906, Realgar-Indigo formula (RIF), and CDDPs. These three drugs were selected as representative Chinese medicines with well-known therapeutic effects. PHY906 is a Chinese medicine that has been used for centuries. PHY906 has been shown to decrease the toxicity and enhance the efficacy of chemotherapy in animal models and clinical trials. RIF is a Chinese medicine formula used for the treatment of acute promyelocytic leukemia (APL). RIF has been shown to induce differentiation and apoptosis of leukemia cells, and has been used as an adjunct therapy for APL in China. CDDPs are a widely used Chinese medicine formula approved in China for treating cardiovascular disease.

3.1 PHY906

PHY906 is a decoction from Huang Qin Tang herbal mixture including four main herbs: *Scutellaria baicalensis* Geori (scute), *Glycyrrhiza uralensis* Fisch (licorice), *Paeonia lactiflora* Pall (peony), and *Ziziphus jujuba* Mill (Chinese date). The main ingredients are baicalin, baicalein, glycyrrhizic acid, and wogonin [40]. This medicine was first documented more than 1800 years ago for treating gastrointestinal disorders such as diarrhea, nausea, and vomiting [41]. Each of the four herbs has various biological properties including anticancer, hepatoprotective, and immune-regulatory activities. Teams led by Professor Yung-Chi Cheng at Yale University have developed PHY906 as an adjuvant agent in cancer treatment. Preclinical and clinical studies have indicated that PHY906 not only potentiates the anticancer activity of drugs and therapies, but also diminishes the toxicity and resistance induced by anticancer drugs and chemo-, radio-, or targeted therapies [42-45]. Current preparations of PHY906 are consistent and available on the market, as demonstrated by Phytomics QC with standardized chemical and biological fingerprints. PHY906 differs from the Huang Qin Tang mixture and exhibits strong enhancement activity toward anticancer agents, whereas the Huang Qin Tang mixture does not [41].

In colon cancer treatment, PHY906 enhances the anticancer activity of irinotecan (CPT11) toward HCT116 cells and decreases gastrointestinal toxicity [40]. A metabolomics study has demonstrated that PHY906 ameliorates CPT11-induced gastrointestinal toxicity, mainly by regulating glycine, serine, and threonine pathways [46, 47]. The potential mechanisms of action include intestinal epithelial protection; decreased neutrophil or macrophage infiltration; decreased tumor necrosis factor-alpha expression in the intestines; and decreased pro-inflammatory factors, such as nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX2), and inducible nitric oxide synthase (iNOS). PHY906 inhibits the growth and proliferation of colorectal cancer cells by inducing apoptosis, and increases the cytotoxicity of 5-fluorouracil against resistant cells and colorectal cancer cells, possibly through inhibition of thymidylate synthase

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expression [48]. PHY906, in contrast, may protect the epithelial barrier against colon cancer cell invasion and control cancer cell death via the response to steroid hormone stimuli; moreover, the genes E2f1, Hsfy2, and Nfyb may be possible therapeutic targets [49].

Additionally, PHY906 may be used in combination with the chemotherapeutic medication capecitabine to treat advanced hepatocellular cancer (HCC). A phase II clinical trial has found that PHY906 not only increases the anticancer effects of capecitabine but also decreases adverse effects, such as diarrhea, pain, fatigue, and liver injury [50]. PHY906 also modulates adaptive and innate immunity, and potentiates anticancer activity for immunotherapies in HCC treatment by decreasing immune tolerance and monocytic myeloid-derived suppressor cells; inducing an inflammatory microenvironment with elevated M1-like macrophages; and potentiating the action of interferon-gamma (IFN-γ) [51]. Furthermore, the anticancer activity of sorafenib is enhanced by PHY906 in liver cancer, through increases in the expression of monocyte chemoattractant protein-1 (MCP1), infiltration of macrophages, autophagy, and alterations in the cancer microenvironment [52].

Moreover, according to a phase I trial, patients receiving a combination of PHY906 and capecitabine for advanced pancreatic and other gastrointestinal cancers tolerate the drugs well; the highest tolerated dose is 1500 mg/m^2 for capecitabine and 800 mg/m^2 for PHY906 twice per day [53]. In addition, PHY906 might target IL-6 in the treatment of pancreatic cancer in patients [54]. In short, PHY906 is believed to be a promising supplementary medication for the treatment of cancer, because of its potential to increase anticancer effectiveness while decreasing adverse effects and alleviating post-operative discomfort. Consequently, the uses of PHY906 have raised awareness regarding the use of both Chinese and Western medicine in the treatment of cancer.

3.2 Realgar-Indigo formula

RIF is an arsenic treatment made up of several traditional Chinese medicines such as realgar, Indigo Naturalis, Salvia miltiorrhiza, and Radix psudostellariae. Realgar plays a critical role in this formula, whereas the other ingredients are adjuvant components. The main active elements are tetraarsenic tetrasulfide (As4S4), indirubin, and tanshinone IIA [55]. This formula was initially created in the 1980s and received medical approval in 2009 in China [56]. The effectiveness of RIF in treating APL has been demonstrated. A multi-center phase II clinical trial with consolidation phases has indicated that RIF (60 mg/kg daily) plus all-trans retinoic acid (ATRA) without chemotherapy is an effective first-line consolidation treatment for individuals with high-risk APL [57]. A non-inferiority, randomized phase 3 trial has reported that 97% (67 of 69) of patients treated with RIF-ATRA had event-free survival at 2 years, as compared with 94% (34 of 36) of patients treated with arsenic trioxide-ATRA [58]. No significant differences were observed between the effects of intravenous arsenic trioxide paired with ATRA and oral RIF administered with ATRA [59]. In addition to being effective in adult patients, RIF is effective and safe in pediatric APL. A randomized, multicenter noninferiority trial has demonstrated that oral RIF, which has the benefit of shortening hospital stays, is as efficient and safe as intravenous arsenic trioxide for treating pediatric APL [60]. According to pharmacokinetic analysis, children, compared with adults, experience a more favorable steady state with a RIF dosage of 60 mg/kg/d. This finding indicates that patients with pediatric APL who have just received a diagnosis can safely use the formula [61]. Mechanistically, the RIF combination has shown synergy with As4S4, indirubin, and tanshinone IIA in a murine model. This treatment increases G1/G0 arrest in APL cells, myeloid differentiation regulator reprogramming, and promyelocytic leukemia-retinoic acid receptor oncoprotein degradation. Furthermore, the "monarch, minister, assistant, and envoy" compatibility principle in traditional Chinese medicine has been reported [55].

RIF has been in use for approximately 30 years, and the efficacy and safety of regimens based on RIF have been well demonstrated. Arsenic, a naturally occurring substance, has the potential to be the first oral arsenic formulation used in APL. The combination of oral arsenic and ATRA, in the long term, is expected to make treatment safer, less expensive, and more readily available to patients.

3.3 Compound Danshen dripping pills

CDDPs are well-recognized Chinese medicine formulas, which have been approved for treating cardiovascular diseases in China since 1994. CDDPs are composed primarily of three naturally derived ingredients: Salvia miltiorrhiza, Panax notoginseng, and Borneol. Twenty-eight years' clinical application and experience has demonstrated that CDDP is effective in improving circulation, removing stasis, and alleviating pains, thus achieving substantial efficacy in treating cardiovascular diseases [62]. As a multi-component Chinese medicine formula, CDDPs include complex active pharmacodynamic molecules, such as borneol, phenolic acids (salvianolic acids U, T, tanshinol, protocatechualdehyde, rosmarinic acid, etc.), and saponins (notoginsenoside R, ginsenosides Rb1, Rg1, and Re, etc.). The pharmacokinetic characteristics of CDDPs have been systemically evaluated in rats and healthy human volunteers. The TMAX for the main ingredients of CDDPs is below 1 hour, thus indicating that CDDPs are rapidly absorbed after oral administration [63]. CDDPs have multiple pharmacological effects, owing to their multi-component nature. Salvia miltiorrhiza extracts are effective in inhibiting peroxidative damage and improving myocardial function by regulating energy metabolism [64, 65]. Notoginseng extracts inhibit platelet adhesion and aggregation, have anti-inflammatory activity, and inhibit lipid deposition [66]. Borneol not only serves as

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an adjuvant for drug formulations but also has coronary dilating and analgesic effects [67]. CDDP formulations can achieve complementary and synergistic therapeutic effects, according to Chinese medicine theories.

CDDPs are the first Chinese medicine formulations to complete phase II clinical trials under FDA supervision. In the phase II study, 125 participants with chronic stable angina pectoris were randomized into three groups: placebo, low dose, and high dose. The low-dose group was treated with 20 CDDP pills twice per day, whereas the high-dose group received 30 pills. The treatment lasted 8 weeks. After 4 weeks, the average improvement in total exercise duration was 20 seconds in the low-dose group (P = 0.18) and 43 seconds in the high-dose group (P = 0.005), with respect to the placebo group. No adverse drug effects were observed during the clinical trial, thus suggesting that CDDPs effectively ameliorates coronary heart disease with minimal toxic effects [63].

Advances in biomedicine technology have provided researchers with a versatile toolbox to evaluate the pharmacological effects of CDDPs more clearly. In a recent investigation, Hu et al., through network pharmacology, discovered the critical pharmacological actions of CDDPs in treating coronary heart disorders, and found that CDDPs activate angiogenesis-associated signaling through the PI3K/AKT pathway. Subsequent in vivo experiments have corroborated that CDDPs promote angiogenesis in zebrafish [68]. In a different study, Guo et al. used a metabolomics platform to explore the mechanism of CDDPs in cardiac disease. Their observations have indicated that CDDPs decrease ischemia by driving a metabolic shift in the ischemic heart toward fatty acid metabolism [69].

4. NEW TECHNOLOGIES IN DRUG DISCOVERY FROM MULTI-COMPONENT CHINESE MEDICINE FORMULAS

4.1 Network pharmacology

Multi-component Chinese medicine formulas are commonly considered to have multi-component, multi-pathway, and multi-target effects [70-72]. Owing to the lack of quantitative and objective data supporting their efficacy and safety, clarifying the pharmacological action of multiple components in a single herb or Chinese medicine formula is difficult, thus hindering the international community's acceptance of multi-component Chinese medicine formulas [73]. With the rapid development of systems biology, multidirectional pharmacology, computational biology, and other disciplines, as well as the cross-talk of cutting-edge technologies, such as artificial intelligence and big-data analysis, the new systematic drug research discipline of network pharmacology has emerged in recent years [74-76].

Hopkins developed the concept of network pharmacology in 2007 [77]. This method highlights the system-level and biological-network investigation of molecular connections between medications and treatments. Its research philosophy is in line with the holistic concept of traditional Chinese medicine. Consequently, network pharmacology has been widely used in the discovery of active compounds of drugs and traditional Chinese medicine, investigation of overall mechanisms of action, analysis of drug combinations, and prescription compatibility laws, thereby providing new ideas for studying complex systems in traditional Chinese medicine and revealing new scientific insights [78, 79]. The "network-target" theory first proposed in the field of traditional Chinese medicine has become the core theory of network pharmacology, and the development of network pharmacology itself has also indicated that traditional Chinese medicine research can be at the forefront of methods in related fields internationally [77].

Databases such as TCMSP, TCMID, and UniProt are used to retrieve the active components, target proteins, and genes of related drugs. Simultaneously, databases such as GeneCards are used to retrieve disease targets [80]. After the intersection of drug targets and disease targets, a "drug-intersection target gene-disease" network is constructed. The interactions between drugs and diseases are explored through visualization tools and algorithms to reveal the potential mechanisms of drug treatments for diseases [81, 82].

The functional characteristics of the multiple components of Chinese medicine formulas, and the research advantages provided by network pharmacology have promoted research and development in Chinese medicine compounds and new drugs [83]. Studies have confirmed that the effective substances and mechanisms of multi-component Chinese medicine formulas play important roles in revealing drug-related compatibility mechanisms and achieving the modernization of Chinese medicine [84-86].

Owing to the diversity and complexity of network pharmacology research, as well as the limitations in current research and conditions, many problems remain to be solved. Network pharmacology research in the future must further standardize data, develop new algorithms and improve their precision, combine experimental and clinical data, perform sufficient scientific investigation, conduct in-depth mining of the overall characteristics and principles of traditional Chinese medicine, and provide more in-depth information for innovation across medical life science disciplines.

4.2 Integrative omics

In multidiscipline biology, omics methods (whose name is based on the suffix -omics)—such as genomics, transcriptomics, proteomics, epigenomics, metabolomics, lipidomics, and microbiomics—are defined as high-throughput, information-rich assays to obtain a set of molecular measurements within cells or tissues [87-89]. Advances in systems biology and personalized medicine in clinical settings have driven a paradigm shift from single target specificity to holistic views of biological

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systems with dynamic complexity; consequently, omics technologies have been rapidly applied in almost all biomedical fields, including Chinese medicine [90]. In light of the broad recognition of the role of Chinese medicine in modern medicine, the advent of multi-omics platforms could help Chinese medicine meet the requirements for precision medicine proposed in Western medicine and gain new insights into Chinese medicine.

We identified more than 10,000 articles in a PubMed search using keywords of omics techniques together with Chinese medicine in the titles or abstracts, representing a tenfold increase from ten years ago. Omics approaches at different levels have helped Chinese medicine studies address concerns in modern society, including quality control, cellular targets, molecular mechanisms, pharmaco-toxicity, and clinical validation [91]. In Chinese herbal medicine, the use of phytocomplexes, mixtures of plant parts or their extracts, is very common and requires a critical analytical procedure for quality control to meet the requirements for reproducibility and standardization in herbal preparations. High-throughput multi-omics platforms enable rapid, cost-effective identification and quality control of Chinese herbal medicines. For example, metabolomic approaches using MALDI-TOF-MS and UPLC-Q/TPG/MS have facilitated the characterization of metabolites of Chinese medicines [92, 93], and phytochemomics and herbogenomics have enabled toxicity assessment of herbal remedies [94, 95]. In agreement with the holistic view of Chinese medicine, multi-component Chinese medicine formulas are active against certain syndromes or diseases that often simultaneously affect multiple cellular functions instead of a single target. However, conventional Chinese medicine research is incapable of investigating the systemic actions of bioactive components and the associated molecular mechanisms, because of the complexity of the chemical components [91, 96]. Through integrating omics data and robust analytic strategies (e.g., bioinformatics and computational tools), Chinese medicine studies have broadened the focus from a "one target, one drug" perspective to a "network target, multi-component therapeutics" perspective [97]. The molecular mechanisms of Gualou Xiebai decoction (GLXB), a well-known Chinese medicine formula for the management of cardiac disease, are unclear. By incorporating metabonomics and transcriptomics in an isoprenaline-induced rat model of chronic myocardial ischemia in the presence of GLXB, energy homeostasis and apoptosis have been found to be two core mechanisms responsible for GLXB's alleviation of chronic myocardial ischemia [98]. In addition, multi-omics data combined with virtual bioinformatic analysis, such as network pharmacology, can build target-drug interaction maps for promising candidate Chinese medicine targets. For example, a network pharmacology approach, together with single-cell and bulk transcriptomics, has been used to elucidate the antifibrotic mechanisms of Chaihu-Shugan-San and led to the discovery of 62 gene signatures associated with promising survival outcomes in patients with liver cirrhosis [99]. Multi-omics research is crucial for understanding the biological basis of Chinese medicine symptoms and providing molecular evidence for the creation of new Chinese medicine therapeutic medicines. A recent systematic review has summarized core factors of multi-omics data associated with Chinese medicine stroke syndromes, and has indicated that thioredoxin-dependent peroxidase reductase and mRNAs targeted by some microRNAs (miR-146b-5p, -199a-5p, and 23) are responsible for liver-Yang transforming into wind syndrome and blood-stasis syndrome, respectively [100]. Additionally, network pharmacology can be used to analyze and integrate data from various omics platforms to identify potential therapeutic targets and drug candidates. For example, network pharmacology can be used to analyze the interactions between proteins and small molecules within a biological system, and to identify key pathways and targets involved in disease progression. A key advantage of network pharmacology in omics research is that it allows for the identification of complex interactions between multiple molecular components within a biological system. This approach can be particularly useful in the study of complex diseases, such as cancer and neurological disorders.

4.3 CRISPR gene editing

CRISPR gene editing technology is a molecular biology tool to perform targeted genome modification in cultured cells or organisms. CRISPR technology uses an anti-viral defense enzyme found in bacteria and a guide RNA to locate gene-editing targets [101]. This platform, for which a Nobel prize has been awarded, is now widely used in various disease models, including inherited gene defects and cancers [102]. It is also applied in disease detection and diagnosis, genetically modified foods, and farming [103, 104]. CRISPR gene editing technology has been applied in research on Chinese medicine compound formulas.

A Chinese medicine formula, Ziyin Huatan Recipe (ZYHT), composed of three common herbs, Lilii Bulbus, Pinelliae Rhizoma, and Hedyotis Diffusa, has been clinically used for patients with advanced staged gastric cancer (GC) for many years [105]. Its effects on prolonging patient survival have been demonstrated, but the molecular mechanism was unclear. Through network pharmacology analysis, a gene hub associated with epithelial-mesenchymal transition and metastasis of GC has been identified. The transcription factor RUNX3 has been found to be upregulated after ZYHT treatment. CRISPR has been used to knock out the RUNX3 gene in a cell culture model to test whether RUNX3 might be the major target. The knockout of RUNX3 has been found to reverse the anti-tumor effect of ZYHT in a mouse model and to accelerate lung metastasis [105]. Thus, the application of CRISPR gene editing has increased the promise of research on the molecular mechanisms of Chinese medicine.

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Beyond conventional techniques, CRISPR-Cas9 knockout libraries can be used to identify critical genes involved in drug sensitivity. For example, a non-biased CRISPR knockout pooled library targeting nearly 20,000 human genes has been transfected into the HCC cell line 97L [106]. The throughput was controlled such that one gene was expected to be knocked out in each cell clone. The candidate drug toosendanin, a compound isolated from Chuanlianzi, was added to the cell culture for 7 days to allow for positive or negative selection. Gene Ontology analysis of the depleted or enriched genes revealed ribosome biogenesis-associated pathways. Finally, WW-domain containing oxidoreductase (WWOX) was identified and validated in further experiments to be the drug target of the anti-tumor effect of toosendanin.

CRISPR technology can also be applied to identifying novel drug metabolic enzymes responding to Chinese medicine treatment. In a research in 2021, a triple-target CRISPR/Cas9 system was used to generate multiple mutagenesis of cytochrome P450 enzymes (CYPs) [107]. The target sequences were cloned into different sets of sgRNAs driven by different promoters. These sets of vectors were then transformed into Danshen explants, thus yielding multiple mutants of CYP enzymes. The content of tanshinones was diminished in some mutants, and two novel P450 enzymes, CYP76AK2 and CYP76AK3, were identified to be involved in terpenoid synthesis pathways—an essential route for metabolism of active compounds from Danshen.

4.4 Chemometrics

Herbal products from Chinese medicine typically contain multiple components. The stability and consistency of their chemical profiles are critical for drug development [108]. Processing, calculation, and analysis of the chromatographic data of complex component information in Chinese medicine must be performed with proper mathematical techniques. Chemometrics is a interdisciplinary scientific approach method comprising mathematics, statistics, and other logical methods [109]. Its primary goal is to resolve chemistry-associated issues in experimental design through analysis of results, to provide a more thorough and effective understanding of chemical issues [110]. The large amounts of data produced by chromatographic analysis of Chinese medicine can be processed and analyzed with high efficiency through chemometrics, Moreover, chemometrics can be used for Chinese medicine quality control [111]. Inadequate quality control is a major scientific issue preventing Chinese medicine from being modernized, because numerous factors are involved in herbal production, including the growth environment, climate, harvest season, processing methods, and storage. All these factors may result in variations in the quantities of the chemical constituents in Chinese medicines [38], thus challenging adequate assessment of the quality of Chinese medicines and the determination of quality profiles through a simple-index evaluation system. Multiple approaches should be used for the quality control and standardization of Chinese herbal medicine products, such as high-performance liquid chromatography, thin-layer chromatography, gas chromatography, capillary zone electrophoresis, and micellar electrokinetic capillary chromatography. These approaches been extensively used in the study of Chinese medicine, owing to its exceptional specificity and precision [112].

For statistical analysis in chemometrics, chemometric analyses of fingerprint data are aimed primarily at classifying samples. Subsequently, unsupervised analytical methods are often used to understand the characteristics of the data obtained. Principal component analysis (PCA) is commonly used [113]. After the data profile is determined, samples with known information must be divided into a training set and test set. Through adjustment of the parameters of the model through the training set, a test set can be used to evaluate the model. However, the applications and processes are not always the same: for example, PCA is commonly used in machine learning to simplify data and eliminate redundant information, whereas partial least squares discriminant analysis is used to identify key variables of feature differences in pattern recognition models [114]. With chemometrics, unique features for specific Chinese medicines can be obtained. For instance, the chromatographic signature of Shuang-huang-lian has been generated by fingerprints from many batches of pharmaceutical firms to evaluate the uniformity of quality [115]. In another example, PCA has been applied to data analysis to precisely identify the uniformity of various samples. By measuring similarity, Qing-kai-ling markers for use in industrial quality control have been identified [116]. Additionally, because the effectiveness of Chinese medicine often arises from the synergistic action of multiple components and targets, pharmacological research and chemometrics can be combined to accurately and efficiently determine the most effective components in Chinese medicine contributing to a certain therapy, thus providing substantial time and money savings in the drug development process. Overall, chemometrics can feasibly determine the key anti-disease targets of medicinal materials with powerful statistical analysis. In addition, chemometrics is an effective tool for identifying characteristic compounds for a single herb or Chinese medicine formula.

5. DISCUSSION

5.1 The scientific foundation of Chinese medicine Zheng: a novel approach for identifying therapeutic mechanisms of multi-component Chinese medicine formulas

In modern Chinese medicine research, two novel methods—network pharmacology and integrative omics technology—are commonly integrated to investigate the therapeutic mechanisms of multi-component Chinese medicine formulas at a systematic investigation [117-119].

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An important aspect of network pharmacology is that it can be applied not only in identifying bioactive compounds in multi-component formulae, as well as their potential molecular targets, but also in elucidating pharmacological mechanisms and exploring the scientific evidence base of a formula [120]. For example, network pharmacology has indicated that Lianhua Qingwen capsules suppress the apoptosis caused by viral infection via the NF-κB and p38 MAPK pathways [121]. The application of a herbal formula tailored to an individual syndrome ("Zheng" in Chinese) is a key element of Chinese medicine theory [122]. Zheng refers to a pattern of symptoms and signs associated with a specific disease or condition. In traditional Chinese medicine, several different Zhengs can be used to describe a patient's condition, such as Yin deficiency, Yang deficiency, Qi stagnation, and blood stasis. Each Zheng is associated with a set of symptoms and signs, and a specific treatment approach based on herbal medicine, acupuncture, and other Chinese medicine modalities. By identifying the specific Zheng associated with a patient's condition, Chinese medicine practitioners can develop a customized treatment plan that addresses the root cause of the problem, to restore balance to the body's energy. To understand Zheng by using modern approaches, network pharmacology can also provide a systematic method for revealing the molecular basis of the association between a multi-component formula and Chinese medicine Zhengs [117]. Through network pharmacology, biomarkers for a variety of Zhengs can be identified in multiple diseases, thereby enabling the mechanistic interpretation of Chinese medicine herbal formulas and Zhengs [117]. For example, Li has investigated hot/cold herbal formulas and cold/hot Zhengs through a network-based study [123]. The hot formula (Wen-Luo-Yin) targeted the hub nodes of the cold Zheng network, whereas the cold formula (Qing-Luo-Yin) acted on the hub nodes of the hot Zheng network. The results were in accordance with the Chinese medicine therapeutic theory of "cooling the hot and warming the cold" [123].

Integrative omics focuses on discovering functional activities and changes from a system-wide perspective, such as through combining genomics, transcriptomics, proteomics, and metabolomics [124]. In Chinese medicine, Zheng, which emphasizes integrity and dynamics, involves a similar perspective. The use of integrative omics, which can provide evidence of Chinese medicine as a whole, has become increasingly important in the determination of Chinese medicine Zheng through the comparison of differences in DNA, RNA, proteins, and metabolites [118]. For example, a study conducted by Guo et al. has detected gene expression in two different Zhengs: liver stagnation and spleen deficiency Zheng, and liver-gallbladder dampness-heat Zheng developed in the congenital heart block [125]. Consequently, different gene expression has been observed for the same disease with two different Chinese medicine Zhengs [125]. Furthermore, integrative omics can be used to uncover the therapeutic mechanisms of multi-component Chinese medicine formulas. For instance, in people with coronary artery disease and blood clots, Zheng, Xue, and colleagues have discovered that Xuefu Zhuyu oral liquid might improve hemorheological indicators as well as clinical symptoms [126]. A change in the human platelet antigen-3 polymorphism of membrane glycoprotein IIb has been identified through the use of integrative omics [126].

5.2 Pragmatic clinical trials: new SOPs for clinical trials in the drug discovery and development of multi-component Chinese medicine formulas

In June 2022, the NMPA issued the Annual Report on the Progress in Clinical Trials of New Drug Registration in China (2021) [127]. This annual report used clinical trial information for drugs registered in 2021, to summarize and analyze the overall trends, main characteristics, and outstanding problems in clinical trials, and guide improvements in SOPs for new drug discovery and development. To extensively analyze the clinical efficacy of new drugs against disease and avoid controversy, we recommend the following procedures as a reference.

First, study design is critical. The trial should be approved by the relevant ethics committee and registered with the Clinical Trials Database. The number of clinical trials on new drugs has markedly increased. Moreover, the number of clinical trials of traditional Chinese medicine is not adequate.

Second, the criteria for the inclusion and exclusion of participants should be standardized. Authoritative clinical evaluation criteria such as symptoms, signs, and laboratory tests could be used. Exclusion criteria might include having prior treatments or other diseases. An urgent problem to be solved is that clinical trials have an uneven regional distribution. Written informed consent from participants should be obtained. According to a recent report [128], participants may have limited capacity to provide informed consent and owing to the "limited or lost capacity for informed consent and capacity for right protection" of some participants, typically minors, prisoners, and older people in nursing homes, etc. These vulnerable participants require special attention from researchers, ethics committees, and management departments.

Third, the allocation to the test group and control group should involve randomization and blinding. To ensure sufficient allocation concealment, randomization should be performed with an electronic case report form, using computer-generated blocks of varying sizes. The blinding of researchers and participants is also important.

Fourth, the medication procedures should be determined in the experimental design, including the dose, administration mode, administration time, and administration period. Importantly, attention should be paid to clinical trials of drugs for special populations, such as the older people [129].

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Fifth, the collection and analysis of outcome indicators should be completed, including the primary outcome measure, secondary efficacy outcome measures, and safety outcomes. An independent data safety and monitoring board should assess the study data regarding treatment efficacy, safety, and futility at regular intervals. Meanwhile, researchers must frequently monitor participant status. During statistical analysis, if the researchers discover that the study has an odds ratio greater than 1, this finding may indicate the superiority of the experimental treatment over the control for each ordinal scale category [129]. Otherwise, the researchers must assess whether the effect size appears to be statistically relevant. The withdrawal decision of personnel should be endorsed by the corresponding steering committee.

Sixth, according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (ICH-GCP), drug discovery and development of multi-component Chinese medicine formulas should involve a comprehensive process including identification of potential drug candidates, preclinical testing, clinical trials, regulatory approval, and post-marketing surveillance. The ICH-GCP guidelines provide a standard framework for designing, conducting, recording, and

Figure 1 | Schematic diagram of strategies of Chinese medicine-associated drug discovery through multiple approaches.

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Table 1 | Potential drug discovery of Chinese medicines for treating modern diseases, analyzed on the basis of the HERB high-throughput database.

Single or combined compounds	Chinese medicine	Latin name	Main medicinal parts	Diseases ($p < 0.05$)	Main gene targets ($p < 0.05$)
Ephedrine, pseudoephedrine	Ma Huang	Herba Ephedrae	Herbaceous twigs	Amnesia, anorexia, anxiety disorders	EBAG9, INS, ALOXE3
Cinnamaldehyde	Gui Zhi	Ramulus Cinmomi	Twigs	Neuroendocrine tumors, arthritis, sialorrhea	DUSP6, ATF3, ISYNA1
Cimicillin glycoside, 5-O-methylvisammiol glycoside	Fang Feng	Radix Saposhnikoviae divaricatae	Root	Lymphopenia, pulmonary edema, hemorrhoids	ADRA1A, GRIA2, THEM6
Menthol	Bo He	Herba Menthae	Dried aerial parts	Atrial premature complexes, respiratory tract infections, salivary gland neoplasms	FCER2, GSSOS2, JUN
Baicalin	Huang Qin	Radix Scutellariae	Root	Pneumonitis, vein thrombosis, trichoepithelioma	TP53COR1, RELA, CDK2
Berberine, rpiberberine, coptisine	Huang Lian	Rhizoma Coptidis	Rhizome	Intrauterine adhesions, mumps, radicular pain	CCND1, SDHB, CASP9
Phellodendrine	Huang Bai	Phellodendron amurense	Bark	Eye inflammation, intestinal cancer, gastroenteritis	ALOXE3, TP53, BAX
Chlorogenic acid, luteolin 3,5-di-O-caffeoylquinic acid	Jin Yin Hua	Flos Lonicerae	Flower bud	Meningitis, lipid metabolism disorders, ganglioneuroma	ADTRP, ARNTL2, RXRA
Harpagide, harpagoside	Xuan Shen	Radix Scrophulariae	Root	Bone necrosis, pituitary neoplasms, Hurthle cell tumor	RAC1, NOS3, CXCL8
Osthol, dihydrocaryol angelate	Du Huo	Radix Angelicae Pubescentis	Root	Anemia, odontogenic cysts, Alzheimer disease	PTGS1, ETFDH, SMAD1
Notopterygium alcohol, Isoimperatorin	Qiang Huo	Radix et Rhizoma Notopterygii	Rhizome or root	Disseminated neuroblastoma, autoimmune thyroiditis, lupus vulgaris	RBP2, RNASE3, Dpml
Tetrandrine, fangchinoline	Fang Ji	Radix Stephaniae Tetrandrae	Root	Tracheal diseases, prostate carcinoma, brain infarction	IGHG1, IFNG, BCL2
Magnolol, honokiol	Hou Po	Magnolia Officinalis	Bark	Retinal neovascularization, large hyperpigmented retinal spots, chronic post-traumatic stress disorder	OXA1L, PM20D2, SLC6A4
Pachyman, pachymaran	Fu ling	Poria	Sclerotium	Hemophilia A, phototoxicity, Brooke-Spiegler syndrome	POLD1, HMBS, CXCL8
23-Acetate alisol B, 23-acetate alisol C	Ze Xie	Rhizoma Alismatis	Tuber	Glucose metabolism disorders, avascular necrosis, hemolytic anemia	NR3C1, SREBF2, SLC44A2
Jujuboside A, spinozol	Suan Zao Ren	Semen Ziziphi Spinosae	Seed	Obesity, hyperglycemia, malignant neoplasm of the breast	Dpml, CSE1L, CSTF1
β-asarone, α-asarone, eugenol	Shi Chang Pu	Rhizoma Acori Talarinowii	Rhizome	Urinary tract infections, heart diseases, acoustic neuroma	SCN5A, AKR1C12, TRPA1
Astragaloside IV, Pistil isoflavone glucoside	Huang Qi	Radix Astragali	Root	Oligodendroglioma, diabetes, autoimmune diseases	AKT1, PPARA, TP53
Ferulic acid, butylidenephthalide	Dang Gui	Radix Angelicae sinensis	Root	Chronic sinusitis, acute pancreatitis, musculoskeletal diseases	PCYT1A, ADRA1A, AHCYL1
Monoside, strychnine	Shan Zhu Yu	Fructus Corni	Fruit	Nephritis, cardiomyopathy, chronic urticaria	MYC, EIF6, CASP8

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Table 2 | Newly repurposed and developed Chinese medicines for treating diseases after drug development and marketing.

Notable Chinese medicine drugs (compound, fraction and formula)	Main source (Chinese medicine)	Latin name of main source	Main diseases	References
Artemisinin	Qin Hao	Artemisia apiacea	Malaria	[131]
Arsenic trioxide	Pi Shuang	Arsenic	Acute promyelocytic leukemia	[132]
Berberine	Huang Lian	Coptis chinensis	Cancer and metabolic disorders	[133-135]
Pueraria flavonoid	Ge Gen	Radix Puerariae	Cardiovascular dysfunction	[136]
Panax notoginseng saponins	San Qi	Radix Notoginseng	Obesity, cardiac dysfunction	[137, 138]
Elemene injectable emulsion	Yu Jin	Curcuma wenyujin	Cancer	[139]
Compound Huangdai tablets	Qin Dai, Xiong Huang (levigating), Tai ZiShen, Dan Shen	Indigo naturalis, Realgar, Radixpseudostellariae Salvia miltiorrhiza	Acute promyelocytic leukemia	[59]
Qi Li Qiang Xin capsules	Huang Qi, Ren Shen, Fu Zi (detoxity), Dan Shen, Ting LiZi, Ze Xie, Yu Zhu, Gui Zhi, Hong Hua, Xiang JiaPi, Chen Pi	Astragalus membranaceus, Ginseng, Radix aconiti lateralis, Radix Salviae liguliobae, Pepperweed seed, Rhizoma alismatis, Radix polygonati officinalis, Cassia twig, Red flower, Cortex periplocae, tangerine peel	Cardiac metabolism dysfunction	[140]
Jinhua Qinggan granules	Jin YinHua, Shi Gao, Ma Huang, Rhizoma Anemarrhee, Ku Xing Ren, Huang Qin, Lian Qiao, Zhe BeiMu, Zhi Mu, Niu BangZi, Qing Hao, Bo He, Gan Cao	Flos Lonicerae, Gypsum Fibrosum, Herba Ephedrae, Prunus armeniaca, Radix Scutellariae, Bulbus Fritillariae thunbergii, Fructus Arctii lappae, Herba Artemisiae Annuae, Herba Menthae, Radix Glycyrrhizae	Lung diseases, COVID-19	[141, 142]
Lianhua Qingwen capsules	Lian Qiao, Jin YinHua, MaHuang, Xing Ren, Shi Gao, Ban LanGen, Guan Zhong, Yu XingCao, Huo Xiang, Da Huang, Hong JingTian, Bo He, Gan Cao	Fructus Forsythiae, Flos Lonicerae, Herba Ephedrae, Prunus armeniaca, Gypsum Fibrosum, Radix Isatidis seu Baphicacanthi, Rhizoma Dryopteris crassirhizomae, Herba Houttuyniae, Agastache rugosus, Radix et Rhizoma Rhei, Radix et Rhizoma Rhodiolae, Herba Menthae, Radix Glycyrrhizae	Lung diseases, COVID-19	[143, 144]
Xue Bi Jing injection	Hong Hua, Chi Shao, Chuan Xiong, Dan Shen, Dang Gui	Flos Carthami, Radix Paeoniae Rubra, Radix chuanxiong, Radix Salviae liguliobae, Radix Angelicae sinensis	Intestinal injury Cardiac dysfunction COVID-19	[145-147]
Qingfei Paidu decoction	Ma Huang, Gui Zhi, Chai Hu, Sheng Jiang, Huo Xiang, Fu Ling, Zhu Ling, Ze Xie, Ban Xia, Xi Xin, Chen Pi, Bai Zhu, Zi Yuan, Kuan Dong Hua, She Gan, Huang Qing, Shi Gao, Zhi Shi, Xing Ren, Shan Yao, Gan Cao	Herba Ephedrae, Ramulus Cinmomi, Radix Bupleuri, Rhizoma Zingiberis Recens, Agastache rugosus, Poria, Polyporus umbellatus, Rhizoma Alismatis, Rhizoma Pinelliae, Herba asari, Pericarpium Citri Reticulatae, Rhizoma Atractylodis macrocephalae, Asteris Radix et Rhizoma, Flos farfarae, Rhizoma Belamcandae, Radix Scutellariae, Gypsum Fibrosum, Fructus Aurantii Immaturus, Prunus armeniaca, Rhizoma Dioscoreae, Radix Glycyrrhizae	COVID-19	[148]

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Table 2 | Continued

Notable Chinese medicine drugs (compound, fraction and formula)	Main source (Chinese medicine)	Latin name of main source	Main diseases	References
Huashi Baidu decoction	Ma Huang, Xing Ren, Shi Gao, Gan Cao, Huo Xiang, Hou Po, Cang Zhu, Cao Guo, Ban Xia, Fu Ling, Da Huang, Huang Qi, Ting LiZi, Chi Shao	Herba Ephedrae, Prunus armeniaca, Gypsum Fibrosum, Radix Glycyrrhizae, Agastache rugosus, Magnolia officinalis, Rhizoma Atractylodis, Fructus tsaoko, Rhizoma Pinelliae, Poria, Radix et Rhizoma Rhei, Radix Astragali, Semen Lepiddi seu Descurainiae, Radix Paeoniae Rubra	COVID-19	[149]
Xuanfei Baidu decoction	Jin YinHua, Shi Gao, Ma Huang, Xing Ren, Huang Qin, Lian Qiao, Zhe Bei Mu, Zhi Mu, Niu Bang Zi, Qing Hao, Bo He, Gan Cao	Flos Lonicerae, Gypsum Fibrosum, Herba Ephedrae, Prunus armeniaca, Radix Scutellariae, Fructus Forsythiae, Bulbus Fritillariae thunbergii, Rhizoma Anemarrhee, Fructus Arctii lappae, Herba Artemisiae Annuae, Herba Menthae, Radix Glycyrrhizae	Lung diseases, COVID-19	[150, 151]
TaiWan Qing Guan Yi Hao Extract granules (NRICM101)	Huang Qin, Yu XingCao, Gua Lou, Ban LanGen, Hou Po, Bo He, Jing Jie, Sang Shen, Fang Feng, Gan Cao	Radix Scutellariae, Herba Houttuyniae, Angina pectoris, Radix Isatidis seu Baphicacanthi, Magnolia officinalis, Herba Menthae, Herba Schizonepetae, Fructus Mori, Radix Saposhnikoviae divaricatae, Radix Glycyrrhizae, Radix Scutellariae, Herba Houttuyniae,	COVID-19	[152]
TaiWan Qing Guan Er Hao extract granules (NRICM102)	Huang Qin, Yu XingCao, Gua Lou, Fu Zi, Hou Po, Fu Ling, Yu Zhu, Ban Xia, Yin Chen, Gan Cao	Angina pectoris, Radix aconiti lateralis, Magnolia officinalis, Poria, Rhizoma Polygoti Odorati, Rhizoma Pinelliae, Herba Artemisiae Scopariae, Radix Glycyrrhizae	COVID-19	[153]

reporting clinical trials, with a focus on patient safety, data quality, and regulatory compliance. The guidelines cover all aspects of conducting clinical trials, including study design, investigator selection, ethics committee review, informed consent, study monitoring, data management, adverse event reporting, and study completion. The goal of ICH-GCP is to harmonize clinical trial standards worldwide and facilitate the registration of new pharmaceuticals for human use.

Finally, the involvement of funding sources should be clarified to indicate whether the sponsors participated in the study conception, data collection, data analysis, data interpretation, or writing of the report.

5.3 Limitations of current methods applied in drug discovery and development

The present approaches used in drug discovery and development have several drawbacks. First, many current methods rely heavily on in vitro assays and animal models, which may not accurately reflect human biological systems. Consequently, false positives or false negatives may arise, thus posing a major obstacle in the drug development process. Second, current methods are often time-consuming and expensive, and many compounds fail clinical trials after years of development, thus posing a major financial burden for pharmaceutical companies and potentially deterring investment in drug development. Third, understanding of the complex mechanisms underlying many diseases is lacking, thus hindering the identification of effective drug targets and development of drugs that are both safe and effective. Finally, the current regulatory environment presents challenges in drug development. The strict requirements for safety and efficacy data before a drug can be approved for use can hinder the market entry of new drugs, particularly those developed through novel methods.

6. CONCLUSION

Drug discovery is a systematic process with large investments and long time periods. Owing to the multi-component and multi-target characteristics of Chinese medicine, the drug development of Chinese medicines has been greatly hindered. General strategies of drug discovery in Chinese medicine are illustrated in **Figure 1**; these mainly include systematic review of the traditional Chinese medicine literature, in silico screening using databases and bioinformatic analysis, pharmacological evaluation, clinical trials, development of standardized formulations, and integration of multi-omics data. Moreover, using HERB, a recently available database (high-throughput experiment- and reference-guided database of Chinese medicine published in 2021), we further investigated and summarized the potential therapeutic effects of common Chinese medicines in treating modern diseases. The statistical analysis (p-value) indicated the underlying relationship between "herbs" and "diseases/gene targets" (**Table 1**), on the basis of

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Table 3 | Policies and status of drug discovery in Chinese medicine in the US, China, and the European Union.

Country	Policy	Status
United States	The regulation of Chinese medicine products in the US is complicated, with the FDA regulating some aspects and dietary-supplement regulations covering others.	Chinese medicine is gaining popularity in the US, but is regulated as dietary supplements, thus leading to concerns regarding product quality and safety.
China	The National Medical Products Administration (NMPA) regulates new Chinese medicine products, with specific requirements for safety, efficacy, and quality.	Chinese medicine is widely used in China, and the government has been promoting its development.
European Union	The EU regulates Chinese medicine products under the Traditional Herbal Medicinal Products Directive (THMPD), which requires evidence of safety, quality, and efficacy.	Chinese medicine is gaining popularity in the EU. Interest in integrating Chinese Medicine into mainstream healthcare is growing.

an "herb-target big data"-dependent Fisher's exact text [130]. The main active and characteristic compounds of an herb was based primarily on the Chinese Pharmacopoeia (2020 version). In addition, newly developed and repurposed Chinese medicines in China are listed. The targets of these drug treatments include cancer, metabolic diseases, and COVID-19 (**Table 2**). In conclusion, five crucial elements are highlighted to facilitate the discovery of Chinese medicine: 1) Identifying the active compounds of specific herbs is important to improve quality control. 2) The clarification of compounds that may be responsible for the principal effects of multi-component herbal medicines must be performed through advanced approaches. 3) Precise understanding of the pharmacological action of Chinese medicine by using cutting-edge approaches will promote drug discovery; methods include integrated omics, CRISPR gene editing, and chemometrics. This understanding may greatly accelerate the internationalization and modernization of Chinese medicine, if the underlying mechanisms are scientifically determined. 4) Clinical trials should follow SOPs whose rules are well accepted worldwide (e.g., ICH-GCP) [154]. 5) Better understanding of the policies for the approval of new drugs in various areas (US, China, and the European Union) is a prerequisite for the successful approval of novel drug applications (**Table 3**). Additionally, the rapid growth of artificial intelligence will provide considerable technical and algorithmic support for identifying new drugs. Supervised and unsupervised multi-dimensional mathematical model construction will enable more precise and scientific discovery of the ideal therapeutic doses of medicines and their distinctive components. For instance, artificial neural networks, a deep learning method, can be used to hierarchically classify relationships between drug dosages and therapeutic effects in pre-clinical animal studies [155]. High-specificity, high-intelligence analytical approaches may dramatically decrease the physical effort required and increase the success rate of clinical trials. Scientific researchers should continually optimize technologies, theories, and policies of drug discovery to promote the development and modernization of the Chinese medicine industry.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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