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Multiple Components in Chinese Medicine formula for Drug Discovery: State-of-art and future perspective

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Abstract

It has been the golden criterion in the drug discovery and development industry for hundreds of years that a single and identical component with a clear mechanism of action is a desirable candidate for potential drugs. However, this conventional strategy of drug discovery and development is facing challenges, including a low success rate and high development cost. In this review, we critically reviewed the state-of-the-art of drug discovery and development from multiple components of Chinese Medicine formulas. We reviewed the policies and status of the application of multi-component Chinese Medicine formula-based new drugs in the US, China, and the European Union, and illustrated several excellent cases of ongoing applications. We also discussed the biomedical technologies that may pave the way to facilitate drug discovery and development from multi-component Chinese Medicine formulas including network pharmacology, integrative OMICs, Crispr gene editing and chemometrics. Lastly, we discussed the possible problems and solutions in the pre-clinical and clinical research in drug discovery and development of multi-component Chinese Medicine formulas. We hope this review will facilitate the discussion on the role of multi-component Chinese Medicine formulas in the new drug discovery and development for the treatment of human diseases.

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

1. Introduction

From the historical evidence, humans have been using drugs since prehistoric times[1]. Since then, empirical methods have dominated the progress of human drug discovery for millennia, 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 are gradually discovered by scientists by accident. Examples include chloral

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hydrate used as an anaesthetic, and phenothiazine derivatives used for disinfection[3]. From the 20th century, with the development of the synthetic chemical industry and biology, drug discovery also ushered in a growth spurt[4]. This era gave birth to essential drugs such as antibiotics and vaccines[5]. Synthetic chemistry played a dominant role in drug discovery using spectrometers, separation techniques, and the computer revolution[6, 7]. These novel technologies allow 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 but through computer-aided drug, design to design new drugs rationally[8]. With the rapid development of technology today, scientists have access to more powerful computing tools, advanced recombinant DNA technology, and new technologies such as Omics Sciences[9]. However, the way to better integrate these technologies may be a challenge for the development of drug discovery.

As a traditional medical intervention in Asia, Chinese medicine has drawn interest from all around the world in life science[10, 11]. Chinese medicine is also a supplementary and alternative treatment in Western countries, with 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, due to the complexity of substances and multi-target features, the clarification of mechanisms of herbal medicines at a holistic level remains challenging. Furthermore, the discovery of bioactive compounds for a herb or herbal formula for a certain disease is a crucial procedure for Chinese medicine-related medication development. To address the problem, it is necessary to use advanced pharmacology techniques to discover bioactive chemicals and their associated targets/molecular mechanisms. The cutting-edge drug discovery approaches mainly include Network pharmacology, Integrative OMICs, CRISPR gene editing, and Chemometrics[13-15]. Network pharmacology is used to establish a biological network by analyzing the molecular relationship between Chinese medicines and molecular targets, which may offer novel perspectives for studying the complicated system in Chinese herbal medicine and its formula for treating diseases[16]. Integrative OMICs is a term recognized in multiple areas of biology, including genomics, transcriptomics, proteomics, etc. It is described as an information-rich approach to finding a series of molecular and biological features. Chinese medicine-related multiple targets for treating diseases may be discovered by this high-throughput technology[17]. CRISPR gene editing is a method that can be applied to modify genes[18]. Such technology is useful in validating Chinese medicine-related targets for disease precise treatment. Chemometrics is a branch of chemistry that makes use of mathematics, and statistics to identify the most effective assessment methods and experiments for the mining of bioactive compounds[19]. Through clinical and animal experiments, Chemometrics can provide the relevant chemical information for the treatment of a specific disease. In addition to the biological validations, the policies and cases in different countries for the approval of Chinese medicine as new drugs have been detailedly reviewed in this paper. Referring to these successful cases and ongoing applications, we can more effectively and appropriately perform drug development issues in Chinese medicine in terms of policies. In sum, the issue of how traditional Chinese medicine can successfully treat a wide range of diseases may be solved by current highly advanced biotechnology and artificial intelligence. These insights will aid the creation of Chinese medicine-related precision medicine. Additionally, an in-depth understating of policies

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may promote the successful development of new medications followed by getting them licensed smoothly. All these vital factors will contribute to the modernization of Chinese medicine in a precise and systematic manner.

2. Chinese Medicine formula-based products in drug discovery and development: The state-of-art

2.1 Food and Drug Administration (FDA)

The Food and Drug Administration (FDA) in the USA is an influential agency in the world[20]. Generally, FDA is in charge of protecting and advancing public health by monitoring and regulating drugs, biological products, medical devices, foods, cosmetics, tobacco products, and products with radical emissions. Over the years, FDA has changed the thinking that it is appropriate to apply different regulatory policies to botanical drugs that have been commonly used worldwide, due to their different nature from nonbotanical drugs, such as synthetic, semi-synthetic, highly purified, or chemically modified drugs. Thus, FDA launched draft guidance for botanical drugs in August 1996, release the draft version (entitled Guidance for Industry on Botanical Drug Products) in August 2000, issued the final version (with the same title as the draft version) in June 2004, and then issued the first modified version (entitled Botanical Drug Development: Guidance for Industry) in December 2016[21-23].

As shown, the title has been changed, indicating that the monitoring of botanical drugs has shifted from an end product-based mode to a drug development-based mode, namely supervision of the whole process from research and development to marketing and post-marketing. In addition, to better handle late-phase development and new drug applications (NDAs) filing for botanical medications, several particular suggestions have been amended, and additional sections have been introduced, which were based on improving the comprehension of drugs and experiences from NDAs and investigational new drug applications (INDs) for botanical drugs.

In detail, the new guidance specifically states the term BOTANICAL includes plant materials, algae, macroscopic fungi, and their combinations, and therefore does not include animal sections, 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 under OTC (over-the-counter, nondescription) 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, as well as NDAs for botanical drug products[24].

FDA has received over 800 INDs, and pre-IND meeting requests related to botanical drugs in the years preceding 2018, however, the approval rate is extremely low. Until now, only two NDAs for botanical drugs have been approved by the FDA, namely Veregen in 2006 and Fulyzaq in 2012 [22]. Nevertheless, some herbal medicines, such as *Andrographis*, *Cinnamomum cassia* Twig, and *Ganoderma Lucidum* fruiting body, have been included in the United State Pharmacopeia (USP 44-NF 39-2021) after approval by FDA. Still, many botanical drug candidates based on Chinese medicine formulas, such as Kanglaite Injection, Fuzheng

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Huayu Tablet, Compound Danshen Dripping Pill (T89), Guizhi Fuling Capsule (KYG0395), Xuezhikang Capsule, and Lianhua Qingwen Capsule have been approved by FDA to conduct clinical trials in America[25-29]. Owing to the multiple and abundant bioactive components, Chinese Medicine formula-based products and other botanical products can surely 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 have great impacts on the development and application of botanical drugs and related products and will also bring us critical thinking about drug discovery and development based on traditional Chinese medicine and related products. Most of all, the therapeutic consistency of botanical drugs should be supported by a “totality of the evidence”, regarding 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, one of the characteristics of Chinese medicine formulae and medicinal herbs is their reliance on accumulated human experience; yet, to use this wealth of information to support regulatory approval, standardization of data collection techniques and criteria is essential [24].

2.2 National Medicinal Products Administration (NMPA)

Over the past few years, China has placed a premium on expanding its 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 aiming to help evaluate the benefits and risks of the decisions, which is used by drug regulatory authorities (DRAs) to make strategies on medicinal products. For instance, The FDA in the USA, the European Medicines Agency (EMA) in European, and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan both emphasized the value of RS as a foundation of high-quality assessment in strategic plans through their ways[32]. In China, NMPA drew up the Chemistry, Manufacturing, and Controls (CMC) Guidance System for Chinese medicine as well as 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 being emphasized in the development of Chinese medicine-related RS.

First of all, the main NMPA’s responsibility is associated with supervising the safety, efficacy, and quality of Chinese medicines and approval for marketing. To achieve these goals, strengthening the regulatory systems through the development of the RS is considered a critical step. Unlike chemically synthesized drugs, Chinese medicine is a complex multiple components system whose quality depends on the chemical composition of many structurally diverse compounds. There is no doubt that the quality standard setting of most herbal materials and final processed products is extremely challenging. Moreover, the research mode of "single component and single target" in modern medicine is difficult to clarify the characteristics of synergistic response between different components, action pathways, and effect targets [34]. Therefore, it is essential to implement a scientific and efficient evaluation approach for Chinese medicine quality control. Fundamental studies and processes of Chinese medicines have made significant

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strides forward. Biological testing, for example, has been advocated to guarantee Chinese medicine sources [35]. Additionally, the concepts of biological response, biological activity, and quality markers are suggested to apply in the quality evaluation. Moreover, during the RS development, new techniques and methods such as chemometrics and mass spectrum are exploited to advance quality standards [33].

Secondly, drug discovery should meet the clinical needs of various therapeutic areas. Following the "Requirements for Registration Classification and Application Materials of Chinese medicines" issued by the NMPA, the research and development of new drugs have shown vigorous vitality. Up to 2021, there are fifty-four applications of innovative Chinese Medicine formulas have been accepted, and eleven of them have been approved. Among them, Qingfei Paidu Granules, Huashi Baidu Granules, and Xuanfei Baidu Granules are the most effective anti-coronavirus prescriptions selected by many academicians and experts in Wuhan since the outbreak of COVID-19. They are derived from ancient recipes, which are also the first variety being reviewed following the reform “Requirements”. From 2010 to 2020, NMPA approved 58 innovative drugs[36]. Although innovative drugs are abundantly distributed in different fields, the discovery of Chinese medicine drugs should be paid more attention to.

2.3 European Medicines Agency (EMA)

The Committee on Herbal Medicinal Products (HMPC) in the European Union is known as European Medicines Agency (EMA). EMA is responsible for collecting and obtaining scientific data on herbal medicinal products, herbal substances and herbal preparations to facilitate the harmonization of the European market. The mission of 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, herbal medicinal products development in the European Union is systemically conducted, with an emphasis on legal safeguards and thorough ethics [38]. Meanwhile, a simplified registration procedure for (traditional) herbal medicines has been introduced in the EU to encourage their benefits to outweigh their risks. Using the rigorous scientific standard, it could be more convenient to facilitate assessing medicine worldwide and provide partners and stakeholders with independent, science-based information about herbal medicinal products [39]. Moreover, EMA is also having the obligation to confront issues related to herbal medicinal products which have been previously marketed outside the EU as well as the growing number of combination products in the member state. Therefore, EMA revises its scientific guidelines on herbal medicinal products from time to time, aimed to facilitate drug developers to prepare marketing-authorization applications on medicinal products for human and veterinary use. The latest version of the EMA guideline on the quality of (traditional) herbal medicinal products (EMA/HMPC/CHMP/CVMP/201116/20051 Rev. 3) was published on 12 May 2022. Nowadays, excellent molecular pharmacology research is conducted by Chinese medicine practitioners and researchers on isolated, well-characterized small molecules and substances. The primary objective is to expedite the decipherment of biological processes, with a particular emphasis on the development and deployment of computationally demanding methods for innovative therapeutic applications. Moving forward, it is urgently needed to establish a more inclusive resource that represents public medical diversity more accurately to better serve

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humanity in the modernization and normalization of the traditional herbal medicinal field in the EU.

2.4 Common features among FDA, NMPA, and EMA

Several characteristics can be found in common throughout the FDA, NMPA, and EMA policies:

- Safety and efficacy: For a product to be approved for use, all three organisations demand proof that it is both safe and effective.
- Good manufacturing practices: In order to guarantee quality and consistency, the agencies demand that items be produced in compliance with GMPs.
- Post-marketing surveillance: It is necessary for all three organisations in order to keep track of a product's safety after it has hit the market.
- Regulatory authority: The FDA, NMPA, and EMA all have the power to enact laws and take action against goods that don't adhere to 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 how crucial it is to guarantee that products are reliable and safe for use by the general public, as well as the necessity of regulatory monitoring to ensure this is the case. The use and regulation of Chinese medicine products differ in the US, China, and the EU. The detailes are shown below:

3. Discovery and development of multi-component Chinese Medicine formula for disease intervention: a case study

The drug discovery of multi-component Chinese Medicine formula is an important area of research for disease intervention. This case study aims to focuse on three Chinese medicines: PHY906, Realgar-Indigo formula (RIF), and Compound Danshen dripping pills (CDDPs). These 3 drugs were selected as representative Chinese medicines with well-known therapeutic effects. PHY906 is a Chinese medicine that has been used in TCM for centuries. PHY906 has been shown to reduce the toxicity and enhance the efficacy of chemotherapy in animal models and clinical trials. RIF is a Chinese medicine formula that has been 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 Acute Promyelocytic Leukemia in China. CDDPs is a widely used Chinese medicine formula that has been approved in China for treating cardiovascular disease. Belows are the detailed discussion.

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*

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Pall (peony), and *Ziziphus jujuba* Mill (Chinese date), and the main ingredients are found baicalin, baicalein, glycyrrhizic acid and wogonin [40]. It was first documented over 1800 years ago for treating gastrointestinal disorders like diarrhoea, nausea, and vomiting [41]. Each of the four herbs has various biological properties like anticancer, hepatoprotective, and immune-regulatory activities. Teams led by Professor Yung-Chi Cheng at Yale University have developed the applications of PHY906 as an adjuvant agent in cancer treatment. Preclinical and clinical studies find that PHY906 is used to not only potentiate the anticancer activity of drugs and therapies but also diminish the toxicity and resistance induced by anticancer drugs and chemo-, radio-, or targeted therapy [42-45]. The current preparations of PHY906 are consistent and available in the market, which is demonstrated by Phytomics QC with standardized chemical and biological fingerprints. PHY906 is different from the Huang Qin Tang mixture and it exhibits strong enhancement for anticancer agents while the Huang Qin Tang mixture fails to do it [41].

In colon cancer treatment, PHY906 enhanced the anticancer activity of irinotecan (CPT11) on HCT116 cells and reduced its gastrointestinal toxicity [40]. The metabolomics study demonstrated that PHY906 ameliorated CPT11-induced gastrointestinal toxicity mainly by regulating the glycine, serine and threonine pathway [46, 47]. The potential mechanisms of action included intestinal epithelial protection, a decrease in neutrophil or macrophage infiltration, tumour necrosis factor-alpha expression in the intestine, and a reduction in pro-inflammatory factors such as nuclear factor kappa B (NF-B), cyclooxygenase-2 (COX2), and inducible nitric oxide synthase (iNOS). PHY906 is capable of inhibiting the growth and proliferation of colorectal cancer cells (CRC) by inducing apoptosis, and it increased the cytotoxicity of 5-fluorouracil (5-FU) against the resistant cells and CRCs, which may be due to its inhibition of the thymidylate synthase (TS) expression [48]. PHY906, on the other hand, may maintain the epithelial barrier against colon cancer cell invasion and control cancer cell death via the response to steroid hormone stimuli, for which the genes E2f1, Hsfy2, and Nfyb were possible therapeutic targets in the therapy [49].

Additionally, PHY906 may be used in combination with the chemotherapeutic medication capecitabine to treat advanced hepatocellular cancer (HCC). The phase II clinical trial found that PHY906 not only increased the anticancer effects of capecitabine but also reduced its side effects like diarrhoea, pain, fatigue and liver injuries [50]. And it also acted as a modulator for adaptive and innate immunity and potentiated anticancer activity for immunotherapies in HCC treatment by reducing the immune tolerance and monocytic myeloid-derived suppressor cell (MDSC), inducing the inflammation in the microenvironment with more M1-like macrophages and potentiating the action of interferon-gamma (IFN-γ)[51]. Besides, the anticancer activity of sorafenib was enhanced by PHY906 against liver cancer, which increased expression of monocyte chemoattractant protein-1 (MCP1), infiltration of macrophages and autophagy, and changing the cancer microenvironment [52].

Moreover, According to the phase I trial, patients receiving the combination of PHY906 and capecitabine for the treatment of advanced pancreatic and other gastrointestinal cancers tolerated the drugs well; the highest tolerated dose was 1500 mg/m2 for capecitabine and 800 mg/m2 for

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PHY906 twice a day [53]. In addition, it might target IL-6 in the treatment of pancreatic cancer in patients [54]. In short, PHY906 is thought to be a promising supplementary medication for the treatment of cancer since it has the potential to increase anticancer effectiveness while reducing adverse effects and alleviating post-operative discomfort. As a result, the uses of PHY906 have raised awareness of the use of both Chinese and Western medicine in the treatment of cancer.

3.2 Realgar-Indigo Formula

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, while the others are adjuvant components. The main active elements are tetraarsenic tetrasulfide (As4S4), indirubin, and tanshinone IIA [55] It was initially created in the 1980s and was given medical approval in 2009 in China [56]. The effectiveness of RIF in treating acute promyelocytic leukaemia (APL) has been demonstrated. A multi-centre, phase II clinical trial with consolidation phases showed RIF (60 mg/kg daily) plus all-trans retinoic acid (ATRA) without chemotherapy proved effective as the first-line consolidation treatment for individuals with high-risk APL [57]. A non-inferiority, randomized phase 3 trial revealed that 97% (67 of 69) of patients treated with RIF-ATRA had event-free survival at two years, compared to 94% (34 of 36) of patients treated with arsenic trioxide-ATRA[58]. There was no significant difference between the effects of intravenous arsenic trioxide (ATO) paired with ATRA and oral RIF administered with ATRA [59]. In addition to being effective in adult patients, the RIF has also been effective and safe in pediatric acute promyelocytic leukaemia. A randomized, multicenter, and noninferiority trial demonstrates that oral RIF, which has the benefit of shortening hospital stays, is just as efficient and secure as intravenous ATO for treating pediatric APL [60]. According to the pharmacokinetic analysis, children experienced a more excellent steady state through concentration with RIF (60 mg/kg/d) dosage regimen than adults. This finding indicated that patients with pediatric APL who have just received a diagnosis could safely use the formula [61]. For the mechanisms of RIF, the combination yields synergy of As4S4, indirubin, and tanshinone IIA in the murine model has been illustrated. They increased G1/G0 arrest in APL cells, greater myeloid differentiation regulator reprogramming, and promyelocytic leukaemia (PML)-retinoic acid receptor (RAR) oncoprotein degradation. Furthermore, the study showed the compatibility principle of "monarch, minister, assistant, and envoy" in traditional Chinese medicine [55].

RIF has been in use for approximately 30 years, and the efficacy and safety of regiments based on RIF have both been well-proven during this time. Oral arsenic, which is a naturally occurring substance, has the potential to be the first oral arsenical formulation to be utilized in APL. The combination of oral arsenic and ATRA will, in the long run, make treatment more secure, less expensive, and more readily available to patients.

3.3 Compound Danshen Dripping Pills

Compound Danshen dripping pills (CDDPs) are well-recognized Chinese medicine formulas, which have been approved for treating cardiovascular diseases in China since 1994. The CDDPs

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is primarily composed of three nature-derived ingredients, namely Salvia miltiorrhiza, Panax notoginseng, and Borneol. The 28-year clinical application and experience demonstrated that CDDP is effective in improving circulation, removing stasis and alleviating pains, which collectively contribute to its substantial efficacy in treating cardiovascular diseases [62]. As multi-component Chinese medicine formula, CDDP without exception have complex active pharmacodynamic molecules, which include but are not limited by 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 CDDP have been systemically evaluated in rat and healthy human volunteers. The TMAX for the main ingredients of CDDP was below 1 hour, showing that CDDP could be rapidly absorbed after oral administration [63]. CDDP have multiple pharmacological effects owing to its multi-component nature. Salvia miltiorrhiza extracts are effective in inhibiting peroxidative damage and improving myocardial by regulating energy metabolism [64, 65]. Notoginseng extracts exert an effect on inhibiting platelet adhesion and aggregation, anti-inflammation, and inhibition of lipid deposition [66]. Borneol not only serves as an adjuvant for drug formulation but also has coronary dilating and analgesic effects [67]. When formed into CDDP, complementary and synergistic therapeutic effects could be achieved in terms of Chinese medicine theories.

CDDP is the first Chinese medicine formulation to complete phase II clinical trials under FDA supervision. For the phase II study, 125 participants with chronic stable angina pectoris were randomized into 3 groups, including placebo, low dose, and high dose. The low-dose group was treated with 20 pills of CDDP twice per day while 30 pills were in the high dose group. The treatment last for 8 weeks. After 4 weeks, the average improvement of Total Exercise Duration (TED) was 20 seconds in the low-dose group ($P = 0.18$) and 43 seconds in the high-dose group ($P = 0.005$) when compared with the placebo group. There were no adverse drug effects observed during the clinical trial, suggesting that CDDP could effectively improve coronary heart disease with minimal side toxic effects [63].

The advances in biomedicine technology provide researchers with a versatile toolbox to evaluate the pharmacological effects of CDDP more clearly. In a current investigation, Hu et al. discovered the critical pharmacological actions of CDDP for treating coronary heart disorders by the network pharmacology, in which they found that CDDP activated angiogenesis-associated signalling through PI3K/AKT pathway. Subsequent in vivo experiments corroborated that CDDP indeed promoted angiogenesis in zebrafish [68]. In a different study, Guo et al. utilized a metabolomics platform to explore the underlying mechanism of CDDP in cardiac disease. Their observation showed that CDDP reduced ischemia by driving a metabolic shift in the ischemic heart toward fatty acid metabolism [69].

4. New technologies in drug discovery from multi-components Chinese Medicine formula

4.1 Network pharmacology

Multiple Component Chinese Medicine formulas are commonly considered to possess multi-component, multi-pathway, and multi-target effects. [70-72]. Due to the shortage of quantitative and objective data supporting their efficacy and safety, it is relatively hard to clarify the

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pharmacological action of multiple components in a single herb or Chinese Medicine formula, which resulted in the difficulty in the international community to accept Multiple Components Chinese Medicine formula [73]. With the rapid development of systems biology, multidirectional pharmacology, computational biology, and other disciplines, as well as the cross-penetration of cutting-edge technologies such as artificial intelligence and big data analysis, network pharmacology, a new systematic drug research discipline, has emerged in recent years [74-76].

Hopkins developed the concept of network pharmacology in 2007 [77]. This methodology highlights the system level and biological network investigation of molecular connections between medications and treatment items. Its research philosophy is in line with the holistic concept of traditional Chinese medicine, which explains why network pharmacology has been widely used in the discovery of active compounds of drugs and traditional Chinese medicine, the explanation of the overall mechanism of action, the analysis of drug combination and prescription compatibility law, which provides new ideas for the study of traditional Chinese medicine's complex system and 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 also shows that traditional Chinese medicine research can be at the forefront of the international related fields in terms of methodology[77].

Databases such as TCMSP, TCMID and Uniprot were used to retrieve the active components, target proteins and gene conversion of related drugs. At the same time, databases such as GeneCards were used to retrieve the disease targets[80]. After the intersection of drug targets and disease targets, the "drug-intersection target gene-disease" network was constructed. The interaction between drugs and diseases is explored through visualization tools and related algorithms to reveal the potential mechanism of drug treatment for diseases[81, 82].

The functional characteristics of the Multiple Components of Chinese Medicine formula and the research advantages of network pharmacology have promoted the research and development of Chinese medicine compounds and new drugs [83]. Studies have confirmed that the effective substances and mechanism of the Multiple Components of the Chinese Medicine formula play an important role in revealing the compatibility mechanism of Chinese medicine and realizing the modernization of Chinese medicine[84-86].

Due to the diversity and complexity of network pharmacology research, as well as the limitations of current research levels and conditions, there are still many problems to be solved. Network pharmacology research in the future also needs to further standardise data, the development of an original algorithm and improve the precision of the algorithm, combine the experimental and clinical, sufficient scientific inspection, require more in-depth mining of the overall characteristics of traditional Chinese medicine and principle, need more in-depth information and medical life science disciplines cross innovation.

4.2 Integrative OMICs

The term omics is recognized in multidiscipline biology whose name end in the suffix -omics, such as genomics, transcriptomics, proteomics, epigenomics, metabolomics, lipidomics,

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microbiomics, and other omics methods, and defined as high-throughput, information-rich assays to obtain a set of molecules measurements within cells or tissues[87-89]. Advances in system biology and personalized medicine in the clinic have driven the paradigm shift from single target specificity to holistic views of biology systems with dynamic complexity, allowing omics technologies rapidly applied in almost all biomedical studies, including Chinese medicine[90]. In light of the broad recognition of Chinese medicine in modern medicine, the advent of multi-omics platforms could help Chinese medicine to meet the demand for precision medicine proposed by Western medicine and gain new insights into Chinese medicine.

There have been over ten thousand papers published in a PubMed search restricted to the keywords of OMICs techniques together with Chinese medicine in the titles or abstracts, which is a tenfold increase from ten years ago. It was documented the omics approaches at different levels assist Chinese medicine studies to address concerns from modern society, including quality control, cellular target, molecular mechanism, pharmaco-toxicity studies and clinical validation[91]. In Chinese herbal medicine, the use of phytocomplex, the mixture of plant parts or their extracts, is very common in Chinese medicine formulas and requires a critical analytical procedure for quality control to meet the demand for reproducibility and standardization in herbal preparations. The high-throughput multi-omics provide a quick and cost-effective platform for the identification and quality control of CHM. For example, metabolomic approaches using MALDI-TOF-MS and UPLC-Q/TPG/MS could facilitate the characterization of metabolites of Chinese medicines[92, 93]. Phytochemomics and herbogenomics could conduct toxicity assessments of herbal remedies[94, 95]. Consistent with the holistic view of Chinese medicine, multi-component Chinese medicine formulas work against certain Chinese medicine syndromes or diseases often simultaneously affecting various cellular functions instead of a single target. However, conventional Chinese medicine research is incapable of investigating the system actions of bioactive components in the associated molecular mechanisms due to the complexity of the chemical components[91, 96]. Through integrating omics data and robust analytic strategies (e.g., bioinformatics and computational tools), current Chinese medicine study has zoomed out the focus from “one target, one drug” to “network target, multicomponent therapeutics”[97]. Gualou Xiebai decoction (GLXB) is a well-known Chinese medicine formula for the management of cardiac disease but lacks clear molecular mechanisms. By incorporating metabonomics and transcriptomics in an isoprenaline-induced rat model of chronic myocardial ischemia (CMI) in the presence of GLXB, it was revealed that energy homeostasis and apoptosis were two core mechanisms responsible for alleviating CMI by GLXB[98]. In addition, multi-omics data combined with virtual bioinformatic analysis such as network pharmacology can build target-drug interaction maps for promising candidate targets for Chinese medicines. For example, the network pharmacology approach together with a single cell and bulk transcriptomics were used to elucidate the antifibrotic mechanisms of Chaihu-Shugan-San (CHSGS) and discovered 62-gene signature associated with promising survival outcomes of patients with liver cirrhosis[99]. Multi-omics research appears to be crucial in comprehending the biological basis of Chinese medicine symptoms and providing molecular evidence for the creation of new Chinese medicine therapeutic medicines. The most recent systematic review summarized core factors from multi-omics data associated with Chinese medicine stroke syndromes and discovered that thioredoxin-dependent peroxidase reductase and mRNAs targeted

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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]. Addtionally, Network pharmacology can be used to analyse and integrate data from various OMICS platforms to identify potential therapeutic targets and drug candidates. For example, network pharmacology can be used to analyse the interactions between proteins and small molecules within a biological system, and to identify key pathways and targets that are involved in disease progression. One of the key advantages 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

Clustered regularly interspaced short palindromic repeats (CRISPR) gene editing technology is a molecular biology tool to perform targeted modifications on the genome in cultured cells or organisms. The CRISPR technology utilizes an enzyme isolated from the anti-viral defence mechanism of bacteria and uses guided RNA to mark the gene-editing target [101]. This Nobel-prize-awarded platform is now widely used in various disease models, including inherited gene defects, and cancers [102]. It is also applied to disease detection and diagnosis, as well as genetic-modified food and farming [103, 104]. CRISPR gene editing technology is now also applied in the research of 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 used for patients with advanced staged gastric cancer (GC) at the bedside for many years [105]. Its effect in prolonging patient survival was demonstrated but the molecular mechanism was not clear. By using network pharmacology analysis, a gene hub associated with epithelial-mesenchymal transition and metastasis of GC was identified. A transcription factor RUNX3 was identified to be upregulated after the ZYHT treatment. CRISPR was applied to knock out the RUNX3 gene in the cell culture model to test whether RUNX3 is the major target . The knockout of RUNX3 reversed the anti-tumour effect of ZYHT in mice model, and accelerate lung metastasis [106]. This typical application of CRISPR gene editing makes researczin the molecular mechanism of Chinese medicine more promising.

Further than the conventional technique, the CRISPR-Cas9 knockout library could 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 was transfected into an HCC cell line 97L [107]. By controlling the amount of throughput, one gene is expected to be knockout in each cell clone. The candidate drug, toosendanin (TSN), a compound isolated from Chuanlianzi, was added to the cell culture for 7 days to allow positive or negative selection. Gene ontology analysis on the depleted or enriched genes showed ribosome biogenesis-related pathways. WW-domain containing oxidoreductase (WWOX) was identified and proved by further experiments that the drug target the anti-tumour effect of TSN.

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On the other hand, the CRISPR technology could be applied to look for 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 mutageneses of cytochrome P450 enzymes (CYPs) [108]. The target sequences were cloned into different sgRNA sets, which are driven by different promoters. These sets of vectors were transformed into danshen explants and multiple mutants of CYP enzymes were achieved. Contents of tanshinones were reduced in some mutants, and it was proved that two novel P450 enzymes, CYP76AK2 and CYP76AK3, were identified to be involved in the terpenoid synthesis pathways, which is an essential route to metabolize active compounds from Danshen.

4.4 Chemometrics

Herbal products from Chinese medicine typically contain several components. The stability and consistency of their chemical profile are critical for drug development [109]. It is necessary to process, calculate, and analyze the chromatographic data of complex component information in Chinese medicine using the proper mathematical techniques. Chemometrics is a potential scientific approach to deal with it, which is an interdisciplinary method that includes many disciplines, including mathematics, statistics, and other logical methods[110]. Its primary goal is to resolve chemistry-related issues from experiment design through result analysis to gain a more thorough and effective understanding of chemical issues[111]. The large amounts of data produced by chromatographic analysis of Chinese medicine can be processed and analyzed with great efficiency by chemometrics, Moreover, Chemometrics can be used for Chinese medicine-related quality control[112]. Inadequate quality control is also a major scientific issue that is preventing Chinese medicine from being modernized, because numerous factors are involved in herbal production, including the growth environment, climate, harvest season, methods of processing, and storage. All these factors may result in variations in the quantities of the chemical constituents of Chinese medicine[38]. Therefore, it isn't easy to adequately assess the quality of Chinese medicine and describe its quality profile through the examination of 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. It has been extensively employed in the study of Chinese medicine due to its exceptional specificity and precision[113].

For the statistical analysis in Chemometrics, chemometric analysis of fingerprint data is mainly aimed at classifying samples. After that, unsupervised analytical methods are often used to understand the characteristics of the data obtained. Principal Component Analysis (PCA) is commonly used at present[114]. After understanding the data profile, it is necessary to distribute the samples with known information according to the training set and test set. By adjusting the parameters of the model through the training set, a test set can be used to evaluate the model. However, the above applications and processes are not always the same. For example, PCA is also commonly used in the popular machine learning field in recent years to simplify data and eliminate redundant information, while Partial Least Squares Discriminant Analysis (PLS-DA) is also used to find key variables of feature differences in pattern recognition models[115]. With

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the use of Chemometrics, a unique and well-acknowledged recognition feature for a specific Chinese medicine can be obtained. For instance, the chromatographic signature of the Shuang-huang-lian (SHL) can be generated by fingerprints from many batches of pharmaceutical firms for evaluating the uniformity of quality [116]. For another instance, PCA was applied to data analysis to precisely identify the uniformity of various samples. By measuring similarity, the marker of the Qing-kai-ling for industry quality control can be identified [117]. Additionally, Since the effectiveness of Chinese medicine frequently results from the synergistic action of multiple components and targets, we can combine pharmacological research and Chemometrics to accurately and efficiently determine the most effective and contributive components in Chinese medicine for a certain therapy, which can save a significant amount of time and money during the drug development process. In sum, Chemometrics is feasible to find out the key anti-disease targets of medicinal materials with ideal statistical analysis. Also, Chemometrics is an effective tool for the identification of 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 the identification of the therapeutic mechanism of multi-component Chinese Medicine formula?

In modern Chinese medicine research, two novel methodologies are being employed, including network pharmacology and integrative OMICs technology, which have been commonly integrated to investigate the therapeutic mechanism exerted by multi-component Chinese Medicine formulas on a systematic level[118-120]. An important aspect of network pharmacology is that it is not only a novel approach to identifying bioactive compounds in multi-component formulae, as well as their potential molecular targets, but also an approach to elucidate the pharmacological mechanisms and explore scientific evidence of a formula[121]. For example, network pharmacology found that the Lianhua Qingwen capsule could suppress apoptosis caused by viral infection via NF - κB and p38 MAPK pathway[122]. The application of a herbal formula that is differentiated according to the individual syndrome (ZHENG in Chinese) is a key element of Chinese medicine theory[123]. ZHENG refers to a pattern of symptoms and signs that are associated with a specific disease or condition. In traditional Chinese medicine, there are a number of different ZHENG that 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 customised treatment plan that addresses the root cause of the problem and aims to restore balance to the body's energy. For the understanding the ZHENG using modern approaches, the study of network pharmacology can also provide a systematic methodology for understanding the molecular basis of the association between a multi-component formula and Chinese medicine ZHENGs[118]. Using network pharmacology, biomarkers for a variety of ZHENGs can be identified in multiple diseases, enabling the mechanistic interpretation of

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Chinese medicine herbal formulas and ZHENGs[118]. For example, Li investigated Hot/Cold herbal formulas and Cold/Hot ZHENGs through a network-based study[124]. 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"[124].

Integrative OMICs are focused on discovering functional activities and changes from a systems-wide viewpoint such as combining genomics, transcriptomics, proteomics, and metabolomics[125]. Chinese medicine's ZHENG, which emphasize integrity and dynamic, is similar to this. The use of integrative OMICs, which can provide evidence for Chinese medicine as a whole, has become increasingly significant in the determination of Chinese medicine ZHENG through the comparison of the differences in DNA, RNA, proteins, and metabolites[119]. For example, in a study conducted by Guo et al., gene expression was detected in two different ZHENGS, including liver stagnation and spleen deficiency ZHENG, and liver-gallbladder dampness-heat ZHENG developed in the congenital heart block[126]. As a result, different gene expressions were observed for the same disease with two different Chinese medicine ZHENGs[126]. Furthermore, Integrative OMICs can be used to uncover the therapeutic mechanisms of Chinese medicine's multi-component formulas. For instance, in people with coronary artery disease and blood clots, ZHENG, Xue, and colleagues discovered that Xuefu Zhuyu Oral Liquid might improve hemorheological indicators as well as clinical symptoms [127]. A change in the human platelet antigen-3 polymorphism of membrane glycoprotein IIb was found through the use of Integrative OMICs [127].

5.2 Pragmatic clinical trials: new SOP of clinical trials in the drug discovery and development of multi-component Chinese Medicine formula?

In June 2022, the CENTER FOR DRUG EVALUATION, NMPA issued the Annual Report on the Progress of Clinical Trials of New Drug Registration in China (2021) [128]. This annual report is mainly based on the clinical trial information of drugs registered in 2021 to summarize and analyze the overall trend, main characteristics and outstanding problems of clinical trials, guiding the improvement of the SOP for new drug discovery and development. To analyse the clinical efficacy of the new drug against disease deeply, avoiding controversy, we recommended the following procedures for reference:

First, a study design is vital. The trial should be approved by the Ethics Committee and registered with the Clinical Trials Database. The number of clinical trials of new drugs has increased significantly, however, the homogeneity is still obvious. Moreover, the number of clinical trials of traditional Chinese medicine is not adequate, and the implementation efficiency needs to be improved.

Second, the criteria for the conclusion as well as the exclusion of participants should be standardized. Authoritative clinical evaluation criteria such as symptoms, signs and laboratory tests could be used. Exclusion criteria of the participants might include having been treated as well as suffering from other basic diseases. The regional distribution of clinical trials is uneven, becoming an urgent problem to be solved. It is worth noting that written, informed consent from

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participants should be obtained. According to a new report [129], potential participants may have limited capacity for informed consent and civil conduct. Due to the "insufficient or loss of informed consent ability and rights protection ability" of some participants, typically minors, prisoners, applicants' workers and elderly people in welfare homes, etc. These vulnerable subjects need special attention from researchers, ethics committees and management departments.

Third, the division of the test group and control group should have randomisation and masking. To guarantee sufficient allocation concealment, randomisation was performed in the electronic case report form, using computer-generated blocks of varying sizes. The blinding of researchers and subjects is also important.

Fourth, the operation of the medication Procedures according to the experimental design, deciding on a dose, administration mode, administration time and administration period. Importantly, more attention should be paid to clinical trials of drugs for special populations [130].

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 (DSMB) assessed the study data regarding treatment efficacy, safety, and futility at regular intervals. Meanwhile, the researchers need to observe participant status at a certain frequency. During the process of statistical analysis, if the researchers discover the study for an odds ratio (OR) being greater than 1, it may indicate the superiority of the experimental treatment over the control for each ordinal scale category [130]. Otherwise, the researchers need to measure if this size effect appeared statistically relevant. The withdrawal decision of personnel should be endorsed by the corresponding steering committee in case of unclear missing data.

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 formula involves a comprehensive process, including identifying potential drug candidates, preclinical testing, clinical trials, regulatory approval, and post-marketing surveillance. The ICH-GCP guidelines provide a standard framework for the design, conduct, recording, and reporting of clinical trials, with a focus on patient safety, data quality, and regulatory compliance. The guidelines cover all aspects of clinical trial conduct, 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 harmonise clinical trial standards across different regions of the world and facilitate the registration of new pharmaceuticals for human use.

Last but not least, we should clarify the involvement of the funding source, indicating whether the sponsors participated in the study's conception, data collecting, data analysis, data interpretation, or report authoring.

5.2 Limitations of the current methodologies applied in drug discovery and development.

The present approaches used in drug discovery and development have a number of drawbacks. First, many of the current methodologies rely heavily on in vitro assays and animal models,

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which may not accurately reflect the human biological system. This can lead to false positives or false negatives and can be a major obstacle in the drug development process. Second, the current methodologies are often time-consuming and expensive, with many compounds failing in clinical trials after years of development. This can be a significant financial burden for pharmaceutical companies and may deter investment in drug development. Third, there is a lack of understanding of the complex mechanisms underlying many diseases, which can make it difficult to identify effective drug targets and develop drugs that are both safe and effective. Finally, the current regulatory environment can also present challenges for drug development. With strict requirements for safety and efficacy data before a drug can be approved for use, this can make it difficult for new drugs, particularly those developed using novel methodologies, to make it to market.

6. Conclusion

Drug discovery is a systematic project with large investments and long periods. Due to the multi-component and multi-objective characteristics of Chinese medicine, the drug development of Chinese medicine is greatly postponed and hampered. In general, the summarised strategies of drug discovery in Chinese medicine are illustrated in Figure 1, it mainly includes systematic review of traditional Chinese medicine literature, in silico screening using database and bioinformatic analysis, pharmacological evaluation, clinical trials, development of standardized formulations, integration of multi-omics data. Moreover, using a recently available database termed HERB (a high-throughput experiment- and reference-guided database of Chinese medicine published in 2021), we further investigated and summarised the potential therapeutic effect of common Chinese medicines in treating modern diseases. The statistical inference (p-value) indicated the underlyging relationship between “herbs” and “diseases/gene targets” (Table 2), which is conducted based on “herb-target big data”-dependent Fisher’s exact text[131]. The main active and characteristic compound of a herb is mainly referred to Chinese Pharmacopoeia (2020 version). In addition, we also listed newly developed and repurposed Chinese medicines in China. The targeted treatments of these drugs include cancer, metabolic diseases and COVID-19, etc (Table 3). In conclusion, 5 crucial elements may be highlighted to facilitate the discovery of Chinese medicine as follows: 1) It is important to identify the characteristic compound of a specific herb, which aims to improve quality control by recognising a component. 2) The clarification of the high-impact factors in a multi-component system by advanced approaches is really necessary, which may be responsible for the principal effect of herbal medicine. 3) Precise understanding of the pharmacological action of Chinese medicine using cutting-edge approaches will promote drug discovery, such as integrated Omics, CRISPR gene editing, and Chemometrics. It may greatly accelerate the internationalization and modernization of Chinese medicine if the underlying mechanism is scientifically addressed. 4) It is recommended to implement the clinical trials in terms of the notable SOPs, whose rules are well-accepted (e.g. ICH-GCP) worldwide[132]. It may be widely adopted for Chinese medicine-related clinical studies all over the world. 5) We should have a better understanding of the policies for the approval of new drugs in various areas (US, China and the Europe Union). It is a prerequisite for the successful approval of the application of novel drugs. Additionally, the quick growth of artificial intelligence will give the creation of new drugs considerable technical and algorithmic

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support. By using supervised and unsupervised multi-dimensional mathematical model construction, it is possible to more precisely and scientifically discover the ideal therapeutic dose of medicine and its distinctive components. For instance, the Artificial Neural Network (ANN), as a kind of Deep Learning method, can be used to hierarchically classify the relationship between "drug dosage - therapeutic effect" in pre-clinical animal studies[133]. High-specificity and high-intelligence analytical approaches may dramatically save manpower and increase the success rate of clinical trials. Scientific researchers should continuously optimize technologies, theories, and policies of drug discovery to promote the development and modernization of the Chinese medicine industry.

Author contributions

YF and NW conceived and designed the study. CZ, GMC, GYT, XYX, ZXF,YJL, YTC, JYW, YYC, LX, QR, HCY drafted the manuscript. YF, ZSC, NW and CZ revised the manuscript. The final version of the manuscript was read and approved by all authors.

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Tables (Table 1-Table 3):

Table 1: Policies and status of the drug discovery in Chinese Medicine in US, China and the Europe Union.

Country	Policies	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 it is regulated as dietary supplements, which has raised concerns about product quality and safety.
China	The National Medical Products Administration (NMPA) regulates new Chinese medicine products, and there are 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. There is growing interest in integrating Chinese Medicine into mainstream healthcare.

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Table 2：Potential drug discovery of Chinese medicines for treating modern diseases analyzed by database.

Single or combined compounds	Chinese medicine	Latin name	Main medicinal parts	Current modern diseases (p<0.05)
Ephedrine, Pseudoephedrine	Ma Huang	Herba Ephedrae	Herbaceous twigs	Amnesia, Anorexia, Anxiety disorders
Cinnamaldehyde	Gui Zhi	Ramulus Cinmomi	Twings	Neuroendocrine tumor, Arthritis, Sialorrhea
Cimicillin glycoside, 5-O-methylvisammiol glycoside	Fang Feng	Radix Saposhnikoviae divaricatae	Root	Lymphopenia, Pulmonary Edema, Hemorrh
Menthol	Bo He	Herba Menthae	Dried aerial parts	Atrial Premature Complexes, Respiratory T Salivary Gland Neoplasms
Baicalin	Huang Qin	Radix Scutellariae	Root	Pneumonitis, Vein Thrombosis, Trichoepith
Berberine, Epiberberine, coptisine	Huang Lian	Rhizoma Coptidis	Rhizome	Intrauterine adhesions, Mumps, Radicular p
Phellodendrine	Huang Bai	Phellodendron amurense	Bark	Eye Inflammation, Intestinal Cancer, Gastro
Chlorogenic acid, Luteolin 3,5-Di-O-caffeoylquinic acid	Jin Yin Hua	Flos Lonicerae	Flower bud	Meningitis, Lipid Metabolism Ganglioneuroma

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Single or combined compounds	Chinese medicine	Latin name	Medicinal parts	Current modern diseases (p<0.05)
Harpagide, Harpagoside	Xuan Shen	Radix Scrophulariae	Root	Bone necrosis, Pituitary Hurthle Cell Tumor
Osthol, Dihydrocaryol angelate	Du Huo	Radix Angelicae Pubescentis	Root	Anemia, Odontogenic Cysts, Alzheimer Dis
Notopterygium alcohol, Isoimperatorin	Qiang Huo	Radix et Rhizoma Notopterygii	Rhizome or root	Disseminated neuroblastoma, Autoimmu Lupus Vulgaris
Tetrandrine, Fangchinoline	Fang Ji	Radix Stephaniae Tetrandrae	Root	Tracheal Diseases, Prostate carcinoma, Brai
Magnolol, Honokiol	Hou Po	Magnolia Officinalis	Bark	Retinal neovascularization, Large hyperpig spots, Chronic Post-Traumatic Stress Disorder
Pachyman, Pachymaran	Fu ling	Poria	Sclerotium	Hemophilia A, Phototoxicity, Brooke-Spieg
23-acetate Alisol B, 23-acetate Alisol C	Ze Xie	Rhizoma Alismatis	Tuber	Glucose Metabolism Disorders, Avasc Hemolytic anemia
Jujuboside A, Spinozol	Suan Zao Ren	Semen Ziziphi Spinosae	Seed	Obesity, Hyperglycemia, Malignant neoplas
β-asarone, α-asarone, Eugenol	Shi Chang Pu	Rhizoma Acori Talarinowii	Rhizome	Urinary tract infection, Heart Diseases, Aco
Astragaloside IV, Pistil isoflavone glucoside	Huang Qi	Radix Astragali	Root	Oligodendroglioma, Diabetes, Autoimmune
Ferulic acid, Butylidenephthalide	Dang Gui	Radix Angelicae sinensis	Root	Chronic sinusitis, Acute Musculoskeletal Diseases
Monoside, Strychnine	Shan Zhu Yu	Fructus Corni	Fruit	Nephritis, Cardiomyopathy, Chronic urticar

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Table 3：Newly repurposed and developed Chinese medicines for treating diseases after drug develop

Notable Chinese medicine drugs (Compound, fraction and formula)	Main source (Chinese Medicine)	Latin name of main source
Artemisinin	Qin Hao	Artemisia apiacea
Arsenic trioxide	Pi Shuang	Arsenic
Berberine	Huang Lian	Coptis chinensis
Pueraria Flavonoid	Ge Gen	Radix Puerariae
Panax notoginseng Saponins	San Qi	Radix Notoginseng
Elemene injectable emulsion	Yu Jin	Curcuma wenyujin
Compound Huangdai Tablets	Qin Dai, Xiong Huang (levigating), Tai ZiShen, Dan Shen	Indigo naturalis, Realgar, Radixpseudostellariae Salvia miltiorrhiza
Qi Li Qiang Xin Capsule	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

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Notable Chinese medicine drugs (Compound, fraction and formula)	Main source (Chinese Medicine)	Latin name of main source
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
Lianhua Qingwen Capsule	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
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

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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

Notable Chinese medicine drugs (Compound, fraction and formula)	**Main source (Chinese Medicine)**	**Latin name of main source**
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
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

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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,
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

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Figure 1: Schematic diagram regarding strategies of Chinese medicine-related drug discovery using multiple approaches.