Review

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Modern research on formulated granules of traditional Chinese medicines and Japanese Kampo medicines: A narrative review

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SUMMARY: The modernization of traditional medicine follows diverse pathways. This paper aims to provide a narrative review of the manufacturing processes, research on active ingredients, and models for the clinical use of formulated granules of traditional Chinese medicines (TCM) and Japanese Kampo medicines in the context of their modernization by comparing advances in research on the two and their challenges. By searching databases such as PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI), this review included relevant literature published up to 2026. After screening, a total of 48 relevant articles were included in the review. In TCM, formulated granules evolved from the need to modernize herbal medicines through multi-stage extraction and granulation. This enhances convenience while preserving medicinal properties. TCM enables flexible syndrome differentiation and it is working to industrially produce and standardize herbal medicines while refining quality standards. Japanese Kampo, based on fixed classical formulations and covered by National Health Insurance, has developed a highly standardized, evidence-based model. Research in China broadly investigates numerous formulations using omics technologies to explore their material basis and network pharmacology. Research in Japan focuses on in-depth analysis of "pathways to efficacious formulations" for select classic formulations. Faced with the challenge of providing modern evidence, granules can produce real-world data on TCM. This comparative analysis offers insights into the development of quality granules and their use internationally and it explores prospects for Sino-Japanese collaboration in complementary manufacturing processes and fundamental research.

Keywords: formulated granules of traditional Chinese medicine, Kampo medicine, modernization

1. Introduction

Traditional Chinese medicine (TCM) represents one of the most remarkable achievements of Chinese civilization, serving as a medical science with a heritage spanning millennia. Developed from empirical knowledge amassed in everyday life, TCM has been continuously refined through generations in the battle against diseases. It has made significant contributions to combating the SARS-CoV-2 virus and treating COVID-19 (*1*). In 2015, Tu Youyou's Nobel Prize elevated artemisinin to a new global status as "a gift from TCM to the world" (*2*). At present, TCM is extensively practiced in 183 countries and regions globally, with 103 countries having authorized the use of acupuncture therapy (*3*).

The modernization of TCM constitutes a central challenge to its preservation and innovation. In the process of promoting the modernization of the TCM industry, China has developed formulated granules as a significant dosage form. This innovation is designed to tackle the inconvenience associated with traditional decoction preparation and the challenges involved in quality control, while keeping pace with advances in modern healthcare. The path of development of formulated granules in TCM, as a representative foray into the modernization of traditional medicine, has been extensively studied and recognized for its innovative approach and significant impact. Japan, with its longstanding practice of TCM, has evolved a highly systematized form of traditional medicine known as Kampo. This system has been developed over centuries, with significant influence from ancient Chinese medical texts such as the *Shang Han Za Bing Lun*, and it has been integrated into the modern Japanese healthcare system. Kampo, which has fixed prescriptions and standardized extraction processes, has been integrated into Japan's National Health Insurance system, signifying its acceptance as a standardized form of traditional medicine. A systematic comparison of the similarities and differences between formulated granules in TCM and Kampo medicine in terms of manufacturing

processes, research efforts, and clinical uses will not only elucidate the unique features and challenges of TCM's development in China but also offer valuable insights from an international perspective. This review focuses on formulated granules in TCM, contrasting them with Kampo medicine to analyze differences in technological systems, active ingredient research, and regulations on clinical use. Formulated granules need to be standardized and their quality controlled, but at the same time the essence of TCM needs to be maintained while adopting modern scientific methods. This review aims to provide references for the continuous optimization and scientific advancement of traditional medicines.

2. Methods

To prepare this narrative review, the author conducted a systematic search of PubMed, Web of Science, Google Scholar, and China National Knowledge Infrastructure (CNKI). Search terms included "formulated granules of traditional Chinese medicine" and "Kampo medicine." Studies addressing process systems, active ingredient research, and clinical uses were included. After removing duplicates, conducting an initial screening of titles and abstracts, and conducting a secondary screening of full-text articles, a total of 48 studies were ultimately included in this review. As this is a narrative review aimed at providing a general overview of representative advances in the field, no assessment of study quality or meta-analysis was performed.

3. Historical context and industrialization

3.1. Emergence and development of formulated granules in TCM

The development of formulated granules in TCM signifies a major step in the modernization of Chinese herbal decoctions. Its conceptualization and implementation commenced in the late 20th century, and it entered a pilot exploratory phase in the early 21st century following the promulgation of the Interim Regulations on the Management of Formulated Granules of Traditional Chinese Medicine. Following more than two decades of development, the pilot phase concluded in 2021, marking the advent of a new era guided by national standards. This marked the transition from an "exploratory product" to a "standardized pharmaceutical" (*4*). This development was spurred by the urgent demand for greater convenience, consistency, and quality control in the clinical use of TCM. The primary goal is to offer, *via* industrialized production, a modern TCM in a dosage form that matches traditional decoctions in efficacy while being more convenient to dispense and administer. A core set of processes has been established, encompassing extraction of water, concentration, drying, and granulation, though special processing requirements for certain herbs (*e.g.*, pre-decoction or post-addition) are also addressed. Efforts are concentrated on developing a holistic quality assurance framework that encompasses the entire lifecycle of TCM products, from the selection of raw herbs and processing of herbal materials to quality control for the final product (*5*). As of this writing, provincial drug standards directories include 518 varieties, 350 of which are formulated granules that are recognized by national drug standards (*6*).

3.2. Revival and modernization of Japanese Kampo

The developmental trajectory of Japanese Kampo differs significantly from that of TCM. Once TCM was introduced to Japan, it underwent a process of local adaptation, resulting in the creation of Kampo medicine. However, Kampo was marginalized during the Meiji Restoration. A revival of Kampo took place in the mid-20th century, amid growing reflections on the side effects of chemical drugs. A pivotal moment in its modernization was the inclusion of Kampo extract preparations in the National Health Insurance system in 1967, which marked the first approval of Kampo medicines for reimbursement. This significantly expedited their industrial production, standardization, and clinical use (*7*). According to data from 2015, Kampo medicines constituted approximately 2.4% of Japan's total pharmaceutical sales, with the majority being prescription-only dry extract formulations, as reported by industry sources. Currently, 148 traditional medicine formulations that meet ethical standards, similar to Japanese Kampo medicine, are covered by national health insurance. While official certification standards for 294 over-the-counter traditional medicine products have been formally established, the number of such products has been steadily increasing, reflecting a shift towards greater accessibility and consumer autonomy in healthcare (*8*). Japan has established an industrial model centered on fixed classical formulations, primarily derived from texts such as the *Shang Han Za Bing Lun and Jin Gui Yao Lue* (Table 1), and featuring concentrated production by a few large enterprises, such as Tsumura Pharmaceutical. The national pharmacopoeia, industry GMP standards and stringent requirements for equivalence with standard decoctions together constitute a mature quality regulatory framework (*7*). Since 2001, Kampo medicine education has also been incorporated into Japan's core medical curriculum (*9*).

4. Comparison of process technology systems

4.1. Process characteristics of formulated granules in TCM

The core process of formulated granules in TCM involves the production of single-ingredient concentrated extracts from traditional Chinese herbs. Key technical

Table 1. Comparison of commonly used TCM prescriptions and Kampo prescriptions

No.	TCM Prescriptions	Kampo Prescriptions (*47*)	No.	TCM Prescriptions	Kampo Prescriptions (*47*)
1	Liujunzitang	Rikkunshito	21	Chaihuguizhiganjiangtang	Saikokeishikankyoto
2	Buzhongyiqitang/Buzhongyiqikeli (*46*)	Hochuekkito	22	Xiaojianzhongtang/ Xiaojianzhongkeli (*46*)	Shokenchuto
3	Gegentang/Gegentangkeli (*46*)	Kakkonto	23	Dangguisinijiawei	Tokishigyakukagoshuyushokyoto
4	Guizhifulingwan (*46*)	Keishibukuryogan	24	Chaihuguizhitang	Saikokeishito
5	Jiaweixiaoyaowan (*46*)	Kamishoyosan	25	Maimendongtang	Bakumondoto
6	Baweidihuangwan/Shenqiwan	Hachimijiogan	26	Sinisan	Shigyakusan
7	Jishengshenqiwan (*46*)	Goshajinkigan	27	Xiaoqinglongtang/ Xiaoqinglongkeli (*46*)	Shoseiryuto
8	Shaoyaogancaotang	Shakuyakukanzoto			
9	Wulingsan (*46*)	Goreisan	28	Mahuangfuzixixintang	Maobushisaishinto
10	Dangguishaoyaosan	Tokishakuyakusan	29	Guizhijiashaoyaotang	Keishikashakuyakuto
11	Banxiahouputang	Hangekobokuto	30	Xiaochaihutang/Xiaochaihukeli (*46*)	Shosaikoto
12	Yigansan	Yokukansan			
13	Lingguizhugantang	Ryokeijutsukanto	31	Wujisan	Goshakusan (Ojeoksan)
14	Dajianzhongtang	Daikenchuto	32	Zhulingtang	Choreito
15	Yigansanjiachenpibanxia	Yokukansankachinpihange	33	Guizhifulingwanjiawei	Keishibukuryogankayokuinin
16	Renshenyangrongtang/ Renshenyangrongwan (*46*)	Ninjinyoeito	34	Siwutangjiawei	Shichimitsukokato
			35	Maxingshigantang	Makyoyokukanto
17	Shiquandabutang/ Shiquandabuwan (*46*)	Juzentaihoto	36	Taohechengqitang	Tokakujokito
			37	Banxiaxiexintang	Hangeshashinto
18	Chaihujialonggumuli	Saikokaryukotsuboreito	38	Yinchenhaotang	Inchinkoto
19	Shujinghuoxuetang	Sokeikakketsuto	39	Fangjihuangqitang	Boiogito
20	Guipitang/Guipikeli (*46*)	Kamikihito	40	Mazirenwan	Mashiningan

features include: (1) Adaptive extraction: For materials with distinct properties, such as minerals, toxic components, precious herbs, and volatile constituents, strategies like pre-decoction, post-addition, separate extraction, and wrapped decoction are traditional techniques used in TCM to ensure the effective display of medicinal properties and to mitigate toxicity. Mineral and shell-based materials like *Gypsum Fibrosum* and *Ostreae Concha* require pre-decoction. Chinese medicinal materials that exhibit thermal instability, heat-induced volatility, or pose toxicity risks due to prolonged boiling, such as *Menthae Haplocalycis Herba* and *Foeniculi Fructus*, are added later in the extraction process. Chinese medicinal materials that may cause decoction viscosity or turbidity, like *Typhae Pollen* and *Plantaginis Semen*, require enclosed decoction. Chinese medicinal materials with a high viscosity (*e.g.*, *Asini Corii Colla* and *Testudinis Carapacis et Plastri Colla*) require melting to minimize interference with other materials during extraction. Certain precious Chinese medicinal materials, such as *Ginseng Radix et Rhizoma* and *Panacis Quinquefolii Radix*, need to be decocted separately to maintain their activity. Highly valuable materials, such as *Bovis Calculus* and *Moschus*, are typically pulverized and taken as an infusion with a decoction of other materials; (2) Full-process quality control: Emphasizes the correlation of characteristic spectra or fingerprint spectra across "decoction pieces-intermediates-finished products" to demonstrate consistency with the material basis of traditional decoctions. The Technical Requirements for Quality Control and Setting Standards for Formulated Granules of Traditional Chinese Medicines stipulate that the specific or fingerprint spectra of Chinese medicinal materials , decoction pieces, intermediates, and granules must be correlated. This standard emphasizes that extraction should be based on traditional decoctions, ensuring consistency in extraction yield, key components, and characteristic spectra. Standardized decoctions are usually analyzed alongside extracts or granules to pinpoint factors influencing the consistency of quality during extraction (*10*); and (3) Technological diversification: Widespread adoption of dry granulation, spray-drying granulation, and wet granulation (*e.g.*, extrusion granulation, fluidized bed granulation, and high-shear wet granulation) (*11*). The underlying process logic involves flexibly using formulated components in industrial production in order to strike a balance between production efficiency and the inherent complexity and individualization of traditional Chinese clinical prescriptions.

4.2. Characteristics of Japanese Kampo manufacturing processes

Japanese Kampo technology centers on the core principles of "restoration and standardization" and seeks to modernize and standardize the production of traditional formulations. Its key characteristics include: (1) Fixed formulations and raw materials: Utilizing pre-formulated mixtures of "crude drugs" as starting materials; (2) Standardized decoction and drying: Preparing standardized decoction extracts under strictly controlled conditions (time, temperature, and solvent) that are primarily processed into granules *via* spray-drying technology. This decoction essentially originates from traditional decoction methods, in which raw herbs

are boiled to extract their soluble medicinal components; and (3) Stringent equivalence criteria: Finished products are required to exhibit "equivalence" with standard decoctions based on an analysis of the content of target components and/or fingerprint patterns. Production processes strictly comply with pharmaceutical GMP standards and are supported by established quality control systems. This approach embodies the principle of "fixed ancient formulations, precise replication," guaranteeing a high level of product consistency and stability (*8*).

To safeguard the quality of Kampo formulations, Japan's Ministry of Health, Labor, and Welfare issued the Guide to Data Requirements for Ethical Kampo Formulations in 1985. This requires systematic comparisons between Kampo extract formulations and standard decoctions to determine whether their quality control markers are equivalent. Related studies are required to provide data from at least three batches, and each batch needs to be tested at least three times (*12*).

In addition, Japan developed a system of abbreviated English notation for Kampo preparations to promote the international spread of Kampo medicine. This system covers all 298 Kampo preparations listed in the 2013 New Guidelines for Over-the-Counter Kampo Preparations, including non-prescription Kampo extract preparations (*13*).

In summary, the strength of Chinese manufacturing processes lies in their high degree of flexibility, which effectively aligns with the clinical practice of TCM syndrome differentiation and treatment, thereby meeting individual therapeutic needs. The complexity of those processes hampers the achievement of a high level of consistency across different manufacturers and batches, since quality standards are still being standardized. Japanese manufacturing processes are renowned for their rigorous standardization, which ensures consistent quality and facilitates systematic pharmacological and clinical research. A drawback is the use of fixed formulations, which cannot be adjusted based on syndrome differentiation, leading to limited flexibility.

5. Research on active components and pharmacologically active substances

5.1. Research on active components in formulated granules

Research on formulated granules in TCM primarily focuses on two directions: (1) Validation studies on the "equivalence" between formulated granules and traditional decoctions. Recent studies have systematically compared the chemical profiles of traditional decoctions and formulated granules using modern analytical techniques such as high-resolution mass spectrometry, revealing that formulated granules may offer advantages in terms of convenience and effectiveness. Evidence of their consistent quality is being provided. For example, a quantitative analysis of 64 components, including glycyrrhizic acid and naringin, in Erchen Decoction Granules using UPLC-Q-Exactive Orbitrap MS corroborated the chemical equivalence of those components (*14*); and (2) Research on the pharmacological mechanisms and action pathways of formulated granules. This research direction comprehensively utilizes network pharmacology, proteomics, metabolomics, and animal models to elucidate the multi-target mechanisms by which formulated granules are effective in treating complex diseases. Below are a few examples.

Biyuan Tongqiao Granules: Ultra-high-performance liquid chromatography-electrospray ionization-quadrupole-linear ion trap-mass spectrometry (UHPLC-ESI-QE-Orbitrap-MS) was used to identify 58 compounds in that medicine (*15*). By combining an ovalbumin (OVA)-induced allergic rhinitis mouse model with proteomics analysis, that study revealed that it acted to regulate the PI3K/AKT and STAT3/MAPK pathways to inhibit the expression of E-selectin, VCAM-1, and ICAM-1, thereby alleviating allergic rhinitis.

Jingfang Granules: In a bleomycin-induced acute lung injury model, Jingfang Granules were confirmed to have a lung-protective effect by downregulating the PI3K/Akt/mTOR signaling pathway and modulating glycolysis/gluconeogenesis and pyruvate metabolism (*16*).

Qishen Granules: In an adriamycin-induced cardiac toxicity model, Qishen Granules were found to alleviate oxidative damage, protect mitochondrial function by activating the SIRT3/Ac-SOD2 signaling pathway, and thereby improve doxorubicin-induced cardiotoxicity (*17*).

Jieduhuayu Granules: Using a combined metabolomics and proteomics analysis approach, a study evaluated changes in proteins and metabolites in liver tissue from rats with alcoholic fatty liver disease before and after treatment with Detoxifying and Blood-Stasis-Resolving Granules (*18*). The findings suggest that the mechanism may involve activation of the PI3K-AKT pathway and inhibition of hepatic glycolysis, thereby alleviating hepatic inflammatory stress.

Additionally, studies on the correlation between spectra and effects are ongoing. For example, high-performance liquid chromatography fingerprinting technology was used to systematically analyze the relationship between the active component groups (total flavonoids, total saponins, total alkaloids, *etc.*) in Yinyang Tongnao Granules and the pharmacological efficacy indicators of chronic intermittent hypoxic-ischemic reperfusion injury in rats, providing elucidation of the material basis underlying that medicine's holistic effects (*19*).

5.2. Active component research in Japanese Kampo

Japanese research adopts a "fewer but more refined" strategy, concentrating on classical fixed formulations covered by National Health Insurance to conduct in-depth and systematic analyses of their pharmacological mechanisms. Studies underscore the importance of incorporating chemical analysis, cellular assays, animal experimentation, and clinical observations to comprehensively understand the integrated pathways of compound formulations.

For example, Choreito has been found to alleviate detrusor overactivity and bladder pain symptoms induced by tranilast in a rat model, mimicking interstitial cystitis/painful bladder syndrome, as evinced by a recent study (*20*). This aligns with the broader context of interstitial cystitis treatment, which includes a range of approaches such as drug therapy and surgical interventions, as discussed in various medical sources. An exploratory study with an open-label, single-arm design further demonstrated significant improvement in bladder pain scores following treatment with this formulation, indicating its therapeutic efficacy for bladder pain (*21*). This type of study design is often used in early clinical trials, such as Phase I and II, to explore safety and efficacy, as well as to provide preliminary data on the treatment's potential benefits.

Yokukansan is clinically recognized as beneficial for dementia patients. Recent studies using tauopathy cell models have demonstrated that a specific formulation can decrease levels of phosphorylated and oligomeric tau by suppressing GSK3β kinase activity and promoting autophagy. This mechanism holds promise for intervening in the pathology of Alzheimer's disease, as evinced by the success of GSK-3β inhibitors in reducing phosphorylated Tau protein levels (*22*).

Retrospective clinical analysis combined with molecular mechanism studies of Boiogito have revealed that this formulation promotes LRRC8A transport to the plasma membrane and activates the VSOR chloride channel, thereby inducing chloride ion release and water excretion (*23*). This provides scientific evidence of its clinical efficacy.

These studies exemplify Japanese Kampo medicine's emphasis on translational research—from cellular and animal model studies to clinical observations—in deciphering "pathways to efficacious formulations," establishing a research avenue where basic and clinical evidence merge.

In summary, Chinese research covers a broad range of medicines and involves cutting-edge techniques, actively exploring the material basis and mechanisms of numerous formulated granules on the market. However, systematic studies on individual formulations need to go into further depth and clinical translation needs to be enhanced further. Japanese research, and particularly that in the field of Kampo medicine, excels in depth and clinical integration, building robust evidence chains from molecular mechanisms to clinical efficacy through the use of modern research methodologies and fixed formulations. These differing strategies reflect distinct industrial models: China has a vast formulation system in the early stages of industrialization and a vast need, while Japan focuses on in-depth development of a limited number of formulations for industrial production.

6. Clinical use system and regulatory framework

6.1. Formulated granules of TCM

The clinical use of formulated granules of TCM is centered on syndrome differentiation and treatment in TCM, enabling physicians to tailor prescriptions to an individual patient's condition. This approach ensures personalized treatment and has been found to be effective in various clinical settings, as evinced by studies demonstrating the efficacy and convenience of granules. TCM's regulatory framework has evolved from trial local standards to unified national standards (*6*). As a further example, a prospective cohort study demonstrated that Jingyin Granules can enhance nucleic acid conversion rates, shorten conversion time, and reduce the duration of hospitalization for patients with mild COVID-19 (*24*). A recent randomized controlled trial, following the CONSORT guidelines and utilizing statistical software for data analysis, demonstrated that Qingjin Yiqi Granules significantly alleviated dyspnea and fatigue symptoms in patients with post-COVID-19 sequelae (*25*). These studies offer preliminary contemporary evidence supporting the clinical use of formulated granules.

6.2. Japanese Kampo

Kampo medicine in Japan is deeply embedded within the national healthcare framework, with robust support from three pillars: widespread health insurance coverage, high rates of physician prescriptions, and a well-established system of real-world evidence.

Japan's health insurance system covers 148 ethical Kampo formulations and 187 crude drugs, with multiple clinical guidelines recommending Kampo as a treatment option (*26*). This has established an institutional foundation for its routine use. Surveys indicate that 92.7% of Japanese family physicians have prescribed Kampo formulations, frequently using them for patients with health-related anxiety or mental disorders (*27*). Of 679 clinicians, 30% regularly prescribe Kampo, while 45% prescribe it occasionally (*28*). A 2020 public survey revealed that 71% of respondents had taken Kampo medicines (*29*). Kampo is widely used for psychiatric disorders (*e.g.*, dementia, schizophrenia spectrum disorders, mood disorders, and anxiety disorders) (*30*) as well as cancer-related anorexia, general malaise, and peripheral neuropathy (*31*).

Common formulations and indications: Frequently prescribed medicines include Shakuyakukanzoto (an

analgesic, for neuralgia and joint pain) (*32*), Kakkonto (for acute upper respiratory tract inflammation) (*33*), Hochuekkito (for recovery from fatigue) (*34-36*), Rikkunshito and Daikenchuto (for upper and lower gastrointestinal discomfort) (*37,38*). Additionally, Yokukansan is frequently used to treat dementia and ICU delirium; Goreisan is used not only for gastrointestinal and renal diseases (*39,40*), but also for lymphedema following retroperitoneal lymph node resection (*41*); and formulations like Hachimijiogan have been found to enhance the quality of life for dialysis patients and potentially delay the initiation of dialysis, as evinced by studies on the impact of dialysis treatment on patient well-being and the importance of supportive care in improving outcomes (*42*). Data from a university hospital inpatient registry has indicated that Daikenchuto was prescribed most frequently (485 cases), primarily for postoperative and psychosomatic gastrointestinal symptoms (*43*).

According to the Yasui Classification, Kampo formulations are often combined with Western medications to enhance therapeutic efficacy (*e.g.*, Shichimitsukokato in combination with antihypertensive drugs), to mitigate adverse reactions to Western drugs (*e.g.*, Hochuekkito for treating severe diarrhea caused by azacytidine in patients with myelodysplastic syndromes), or to serve as substitutes when Western drugs are contraindicated (*e.g.*, Goreisan for treating headaches during pregnancy) (*44*).

The Evidence-Based Medicine Committee of the Japanese Society of Oriental Medicine has systematically screened over 500 randomized controlled trials (RCTs) and published the Kampo Best RCTs, providing a crucial clinical reference (*45*).

In summary, the Chinese model can be characterized as follows: personalized prescriptions serve as the foundation, a standardized system is in the process of development, and evidence-based data continues to accumulate. Its strengths reside in its strong clinical adaptability and its capacity to fully reflect the characteristics of TCM. Challenges include achieving unified regulation, ensuring consistent quality, and producing high-level evidence-based data. The Japanese model is characterized by a prerequisite of standardized prescriptions, a safeguard of unified medical insurance coverage, and a support system of evidence-based practice. Japanese Kampo medicine, rooted in TCM, has gained a significant market share globally, and particularly in Japan, due to its standardized production, consistent quality, and systematic clinical evidence. This approach has led to its popularity and dominance in the international market, with a focus on quality and safety. However, this standardized approach may limit the flexibility of tailoring prescriptions to individual symptoms.

7. Discussion

The different pathways to modernization in China and Japan as described in this review (formulated granules *vs.* Kampo medicines) are by no means merely a matter of differing technical choices; rather, they stem from divergences in regulatory philosophies, healthcare systems, and industrialization goals. An in-depth analysis of these institutional roots will help explain why the two models have diverged systematically in terms of quality standards, clinical evidence, and potential use internationally.

7.1. Structural contradictions between RCT design and consistent quality

The fixed formulation model of Japanese Kampo medicine essentially transforms traditional formulations into standardized industrial products. Its regulatory pathway requires that product ingredients, proportions, and manufacturing processes be completely fixed, making Kampo medicine naturally suited to classic placebo-controlled RCTs—where interventions are uniform and reproducible, in line with the paradigm of drug evaluation. However, this high level of reproducibility comes at the expense of the flexibility inherent in the core TCM principle of "differentiation of syndromes and treatment." In clinical practice, Japanese physicians rarely adjust formulations even when they observe changes in a patient's syndrome. While this ensures internal validity in RCTs, it undermines the need for individualized treatment in the real world.

In contrast, the "full-spectrum extraction plus clinical adjustment" model of formulated granules of TCM allows physicians to dynamically formulate, add, or subtract ingredients based on changing clinical presentations. While this preserves the flexibility of TCM, it poses a fundamental challenge to RCT design: how to create a comparable control group while maintaining individualized treatment? A deeper issue lies in the difficulty of ensuring the inter-manufacturer equivalence of formulated granules—differences in raw material sources, extraction processes, and excipients among manufacturers lead to significant variations in the chemical fingerprint profiles and dissolution profiles of the same standardized formulated granules. This not only diminishes the generalizability of multicenter RCT results but also prevents drug regulatory authorities from implementing uniformity controls as effectively as in Japan.

7.2. The cost of high reproducibility and clinical flexibility

The high reproducibility of Japanese Kampo medicines stems from its unique regulatory system of "pharmacy formulations combined with GMP uniformity." While this system ensures batch-to-batch consistency and the stability of Kampo medicines, it simultaneously imposes

institutional constraints on the prescribing freedom of Japanese Kampo physicians. While this model facilitates industrial production and evidence generation, it may lead to a dilution of therapeutic efficacy due to "inappropriate formulation-patient matching"—for example, the widespread use of Shosaikoto in Japan has been linked to cases of interstitial pneumonia due to insufficient syndrome differentiation (*48*). This illustrates that high reproducibility, when detached from clinical flexibility, may obscure the fundamental principles of traditional medicine.

Formulated granules of TCM offer immense clinical flexibility, but at the cost of an exponential increase in the complexity of source-level quality control. Since physicians are permitted to freely combine single-herb granules and an effectively infinite number of "potential formulations" exist on the market, but regulators can only control the quality of each type of granule once it is marketed and they cannot verify the final prescription as a whole. Due to differences in manufacturing processes, granules of the same type produced by different companies may exhibit varying bioequivalence, which directly leads to a crisis of prescription reproducibility across manufacturers and hospitals. This flexibility has become a fundamental obstacle to the international spread of formulated granules of TCM—particularly when entering markets such as the EU and the U.S., which require strict proof of bioequivalence for generic drugs.

There is essentially no perfect answer to how to balance the strengths and weaknesses of formulated granules of TCM and Japanese Kampo medicines. However, a potential breakthrough for Chinese formulated granules in the future may come from several approaches as described below.

Enhancing and unifying quality standards: Accelerating the development of a comprehensive system with quality standards and traceability that covers the entire process from raw materials to finished products. Focusing on resolving equivalence issues among products from different manufacturers, which arise due to variations in production processes, is a core task once national standards are fully implemented.

The systematic advancement of clinical evidence-based research can be informed by Japan's evidence-based path for development of Kampo medicine, and particularly by focusing on disease categories where Kampo has proven advantageous and on clinical formulations that are frequently utilized. More methodologically rigorous RCTs and real-world studies need to be designed and conducted to amass internationally recognized high-level medical evidence, providing robust support for the clinical use of TCM.

Holistic elucidation of compound mechanisms: Using integrative strategies such as multi-omics and bioinformatics, conducting more in-depth network pharmacology and systems pharmacology research into the synergistic mechanisms of granules with multiple components, targets, and pathways. Using modern scientific language to describe the scientific basis for their traditional efficacy.

Further exploring the potential for Sino-Japanese cooperation: Both countries are capable of achieving technological complementarity in areas including in-depth analysis of active ingredients, screening the material bases for broad-spectrum formulations, and collaboratively developing novel dosage forms. Additionally, they can jointly undertake targeted clinical research projects that comply with international standards.

Actively promoting international harmonization of regulations and standards: Jointly exploring strategies to evaluate traditional medicines within international frameworks like the World Health Organization, thereby removing obstacles for formulated granules of TCM to be registered internationally and to be allowed market access.

8. Conclusion

Formulated granules in TCM and Japanese Kampo preparations represent two distinct paradigms in the modernization of traditional medicine. Formulated granules, rooted in the traditional theory of syndrome differentiation and treatment, serve the vast and complex clinical needs of the Chinese population. Formulated granules are developing on a path toward industrial production and flexible clinical formulations, and a standardized system of those formulations is being created. Japanese Kampo, which relies on fixed prescriptions and a universal healthcare system, has enabled highly standardized and intensive production as well as evidence-based use. Although the paths of their development diverge, both face the common challenge of demonstrating efficacy and safety within a modern scientific framework while ensuring precise, end-to-end quality control. The future development of formulated granules of TCM relies on maintaining the core principles of TCM theory while also enhancing quality standards, advancing pharmacodynamic research, and amassing persuasive clinical evidence. Rationally learning from Japan's mature experience in Kampo medicine and particularly standardization, evidence-based medical practice, and the close integration of industry and healthcare, TCM can also draw on the unique advantages of formulated granules in terms of clinical flexibility and technological innovation. TCM can offer significant practical and long-term strategic value by contributing to global health.

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