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Enlightenment of EU Herbal Medicinal Products regulation on the registration of Traditional Chinese Medicines in the Guangdong-Hong Kong-Macao Greater Bay Area

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ABSTRACT

Objective: This study analyzes the European Union's (EU's) regulatory practices of Herbal Medicinal Products (HMPs), aiming to provide implications for Traditional Chinese Medicines (TCMs) registration process within the Guangdong-Hong Kong-Macao Greater Bay Area (GBA).
Methods: This paper conducts a comparative analysis of the regulatory agencies, legal frameworks, registration classifications, market authorization procedures, and the number of applications and approvals for both HMPs in the EU and TCMs in the GBA, thereby identifying the distinctive regulatory features across these regions.
Results: Our study finds that the EU has established a scientific, efficient, and harmonized regulation system for HMPs, whereas the registration of TCMs in the GBA is characterized by complexity and jurisdictional disparities in requirements and procedures. Drawing on the EU's advanced regulatory practices, the study offers recommendations to enhance the mutual recognition and accessibility of TCMs within the GBA.
Conclusion: This study offers a comprehensive understanding of the EU's HMPs regulation and the GBA's TCMs registration, contributing to the synergistic development of TCMs in the GBA.

1. Introduction

In October 2019, the Central Committee of the Communist Party of China (CPC) and the State Council promulgated the "Opinions on Facilitating the Inheritance, Innovation and Development of Traditional Chinese Medicine" (hereinafter referred to as Opinions). The Opinions stress the strategic position of developing the Guangdong-Hong Kong-Macao Greater Bay Area (GBA) into a highland of Traditional Chinese Medicines (TCMs). In September 2020, the National Administration of Traditional Chinese Medicine (NATCM), GBA Leading Group Office and Guangdong Province have jointly issued the Construction Plan for the Chinese Medicine Highlands in the Guangdong-Hong Kong-Macao Greater Bay Area (2020–2025), officially commencing the construction of the TCMs highland in the GBA. Since then, the GBA has facilitated the harmonization of TCMs registration, promoting the Hong Kong and Macao registered proprietary Chinese medicines (pCms) for external use to be registered and sold in the GBA through the simplification of registration approval procedures, as well as the registration of high-quality TCMs in Hong Kong and Macao. However, the free flow of TCMs within the GBA is impeded by several challenges, primarily due to regional regulatory disparities, the absence of a mutual recognition mechanism for clinical trial data, quality standard inconsistencies, and the lack of a dedicated organization for TCMs coordination and evaluation.[1] Therefore, addressing these institutional barriers to achieve higher-level mutual recognition and interconnectivity of TCMs in the GBA is an urgent practical issue.

Since the implementation of Directive 2004/24/EC, the European Union (EU) has gradually developed a comprehensive regulatory system for Herbal Medicinal Products (HMPs), ensuring effective governance across member states and exerting a significant influence on global herbal market regulations.[2] The EU's regulatory model, characterized by a blend of "centralization" and "decentralization", maintains domestic harmonization in HMPs registration while respecting the autonomy of member states in the evaluation and approval processes. This efficient and flexible regulatory model offers valuable insights for TCMs registration in the GBA. Therefore, this study analyzes the regulatory agencies, legal frameworks, registration classifications, marketing authorization procedures, and granted numbers of HMPs within the EU.

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It summarizes the registration characteristics and explores the applicability of the EU's HMPs regulatory experience to the GBA, aiming to provide implications for the construction of a highland of TCMs under the background of inheritance and innovation.

2. Regulatory for HMPs registration in the EU

2.1. Regulatory agency

The European Medicines Agency (EMA) serves as the central regulatory authority within the EU, comprising representatives from each member state to harmonize and oversee drug regulation across the EU. The Committee on Herbal Medicinal Products (HMPC) under EMA is tasked with the regulation of HMPs. Each member state of the EU appoints 1 representative and 1 alternate representative to the HMPC, which also includes 5 experts in herbology. The HMPC's primary responsibilities encompass: 1) the development and update of herbal monographs and list entries to support HMPs registration; 2) the formulation of guidelines and standards for HMPs; 3) the provision of scientific opinions on the safety and efficacy of HMPs in response to inquiries from member states, research institutions, and enterprises.[3] Each EU member state is equipped with a National Competent Authority (NCA), which is responsible for the marketing authorization of HMPs within their respective countries. The European Directorate for the Quality of Medicines & HealthCare (EDQM) serves as the quality control agency for HMPs, regulating quality standards through the European Pharmacopoeia for HMPs entering the EU market.[4]

EMA, HMPC, NCAs, and EDQM form a cohesive regulatory network for HMPs within the EU. Through close collaboration among these agencies, with clear delineation of responsibilities and minimization of work redundancy, the quality, safety, and efficacy of HMPs across the EU market are stringently safeguarded.

2.2. Legal framework

The EU is among the pioneers in global HMPs regulation, having established a comprehensive legal framework encompassing directives, guidelines, herbal monographs, and list entries (see Fig. 1).

A directive, as a legally binding instrument, is issued by the European Commission or the Council of the EU. In 1965, the EU enacted the initial drug directive, Directive 65/65/EEC, which acknowledged the legal status of HMPs. In November 2001, the EU comprehensively reorganized and revised directives related to all human medicinal products, resulting in Directive 2001/83/EC. This directive serves as an overarching set of regulations governing the registration, manufacture, and marketing of human medicinal products, and it is central to HMPs regulation.

Directives 2003/63/EC, 2004/27/EC, and 2004/24/EC are subsequent regulatory documents for HMPs. Among these, Directive 2003/63/EC primarily addresses the specific characteristics of HMPs and provides detailed regulations for the requirements of their application materials; Directive 2004/27/EC mainly revises and clarifies provisions related to the marketing authorization, research and development, and pharmacovigilance of medicinal products. Directive 2004/24/EC specifically supplements the regulation of HMPs within the text of Directive 2001/83/EC. This directive holds significant importance for the improvement of HMPs regulation, particularly in two aspects: 1) it empowers the EMA to establish the HMPC and assigns it the role of formulating herbal monographs; 2) it recognizes the legal status of traditional use HMPs for the first time and introduces a simplified registration procedure.[5–7]

Guidelines are scientific opinions formulated and published by the EMA, based on directives, to address specific regulatory issues for medicinal products. The EU has established a series of guidelines focusing on the quality, clinical, non-clinical, and safety of the HMPs. These guidelines are categorized as follows: 1) the Concept Paper (CP), representing less mature proposals and ideas; 2) the Reflection Paper (RP), offering suggestions on specific issues; 3) the Guideline (G), a category of more mature guidance documents; 4) the Questions and Answers (Q&A), explaining common issues in the review process in a question-and-answer format; 5) the Public Statement (PS), primarily addressing pharmacovigilance-related issues. By April 2024, the HMPC has released 41 guidelines for the regulation of HMPs. The document classification reveals a mature guideline framework, with 14 PS, 12 RP, and 10 G,

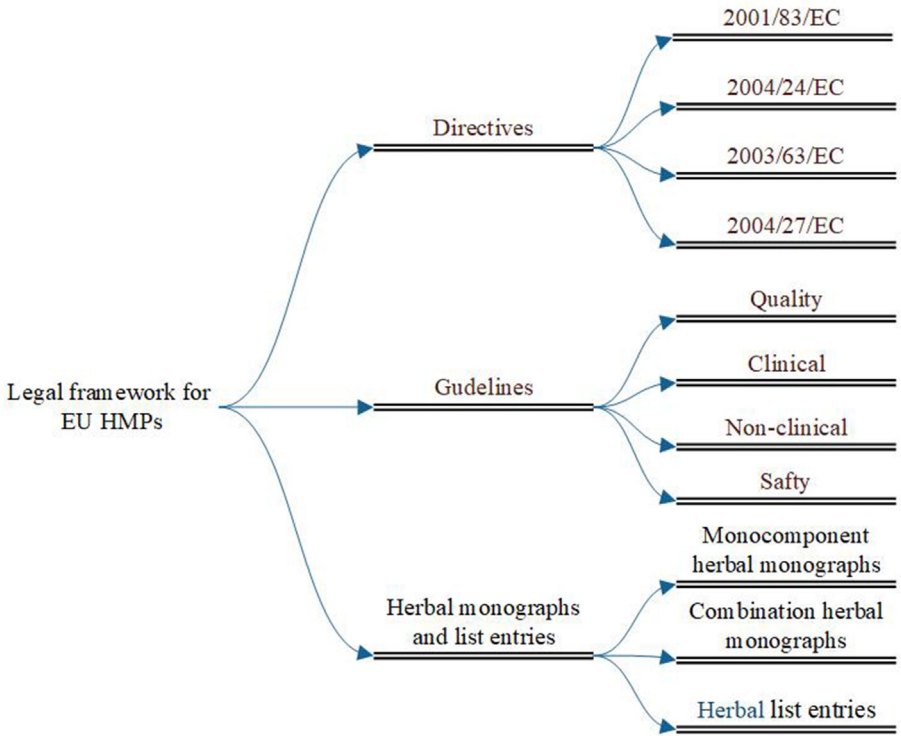

Fig. 1. Regulatory legal framework for the EU HMPs registration.

suggesting robust support for the underlying directives. Regarding content, the distribution is as follows: 17 documents pertain to quality control, 4 focus on clinical evaluation, 3 cover non-clinical evaluation, and 17 address specific safety concerns (The HMPs guidelines data is sourced from the EMA, which may be accessed for further details: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/multidisciplinary-guidelines/herbal-medicinal-products-scientific-guidelines).

Herbal monographs and list entries are also components of the EU regulatory legal framework for HMPs. These official documents are published by the HMPC, in accordance with the Directives 2001/83/EC and 2004/24/EC, and they present the HMPC's scientific evaluation of the safety and efficacy of HMPs based on a review of relevant literature. The purpose of herbal monographs and list entries is to serve as a reference for the evaluation and approval of HMPs by NCAs.[8] Monographs can be directly incorporated into the application materials for HMPs, and NCAs are expected to fully consider and adhere to the content of the herbal monographs during their evaluation process.[9] List entries, which are legal documents established on the basis of herbal monographs, provide a further evaluation of the safety of HMPs. These are published by the European Commission and carry greater legal binding force compared to herbal monographs. By April 2024, the HMPC had released 169 herbal monographs, while the European Commission had officially promulgated 14 herbal list entries (The herbal monographs and list entries data is collected from the EMA: https://www.ema.europa.eu/en/human-regulatory-overview/herbal-medicinal-products/european-union-monographs-list-entries).

2.3. Registration classification

HMPs in the EU are categorized into three distinct registration classes: 1) new HMPs, which are registered through a full application; 2) well-established use HMPs, registered via a literature application; 3) traditional use HMPs, which undergo a simplified registration procedure (see Table 1).[10]

New HMPs are subject to registration requirements analogous to those for new chemical entities, necessitating the completion of a full suite of research projects, including physicochemical, pharmacological, and toxicological studies and clinical trials as mandated by the directive. This comprehensive application process is followed by a full application submission. Well-established use HMPs, also known as literature-based applications, pertain to HMPs that have been in use for over 10 years within the EU, with quantifiable usage data and scientific literature substantiating their safety and efficacy. The crux of this application type lies in the provision of literature, such as published controlled trial studies, which can supplant the clinical and non-clinical study reports typically required for registration. Traditional use HMPs face the least stringent registration requirements but are subject to strict criteria regarding medicinal history, indications, and dosage forms: 1) A medicinal history of at least 30 years, with over 15 years of use within the EU; 2) Indications are confined to self-medication; 3) Dosage forms are limited to oral, topical, and inhalation routes; 4) The marketing authorization holder must be a company registered within the EU. Traditional use HMPs applying for market authorization through a simplified registration procedure can forgo the need for clinical and non-clinical data, provided they furnish literature, expert evidence, and a safety report demonstrating substantial evidence of traditional use and the safety and efficacy of the HMPs.[11] For traditional use HMPs with established herbal monographs and list entries, the application materials can be further reduced, eliminating the need to provide records of human use within the EU and a literature review of its safety.[12] It is important to clarify that the pharmaceutical quality requirements for all three registration types are uniform, necessitating compliance with the quality standards of the European Pharmacopoeia.[13]

Table 1
The EU HMPs registration classifications.

Registration classifications	New HMPs	Well-established use HMPs	Traditional use HMPs
Medicinal history	Unused experience	Human use history in EU ≥ 10 years	Human use history ≥ 30 years (≥ 15 years in EU)
Application type	Full application	Literature application	Simplified registration application
Legal basis	2001/83/EC	2001/83/EC	2004/24/EC

2.4. Marketing authorization procedure

HMPs in the EU pursue market authorization through four principal procedures: the centralized procedure, the decentralized procedure, the mutual recognition procedure, and the national procedure (see Table 2). The centralized procedure is predominantly applicable to HMPs intended for the treatment of serious conditions, such as cancer, AIDS, and diabetes. It involves evaluation by the EMA, with the European Commission making the final decision on the marketing authorization. The evaluation period for this procedure is approximately 210 days, and HMPs granted marketing authorization through this route are authorized for sale across all EU member states. The decentralized procedure refers to an applicant submitting materials to multiple EU member states simultaneously. A designated reference member state initiates the evaluation, conducting a technical assessment and drafting a preliminary evaluation report. Other concerned member states do not perform separate evaluations but are primarily responsible for reviewing the evaluation report provided by the reference member state. If consensus is reached between the reference member state and the concerned member states, the applicant can obtain marketing authorization for the HMPs in multiple member states. The mutual recognition procedure occurs when an HMP, already approved by one member state, seeks market authorizatin in other member states. The country that has granted authorization for the HMPs is referred to as the reference member state. The NCA of this state submits the evaluation report for review by the concerned member states. If the concerned member states agree with the evaluation opinion of the reference member state, they grant a marketing authorization for their respective region. Except in extraordinary circumstances, such as serious threats to public health, the concerned member states are expected to recognize the decision of the reference member state.

New HMPs and well-established use HMPs can apply through any of the aforementioned procedures. Traditional use HMPs are not eligible to apply through the centralized procedure, and the decentralized and mutual recognition procedures are only applicable to HMPs that have established herbal monographs and list entries.[14]

2.5. Numbers of HMPs application and authorization

The EMA has documented the registration and approval of HMPs within the EU and its member states from the inception of Directive

Table 2
The EU HMPs marketing authorization procedures.

Procedures	Centralized procedure	Decentralization procedure/ Mutual recognition procedure	National procedure
Scope	Throughout the EU	2 or more Member States	1 Member State
Evaluation	EMA	NCA	NCA
Requirement	Treatment of cancer, AIDS, diabetes.	Applicable to drugs that have established herbal monographs and list entries	None

Table 3
Number of granted HMPs in the EU.

Registration classifications	New HMPs	Well-established use HMPs	Traditional use HMPs
Monocomponent	3	701	1078
Combination	0	158	641
Total	3	859	1719

2004/24/EC through December 31, 2016.[15] A comprehensive analysis reveals that the EU has granted marketing authorization for a total of 3 new HMPs, 859 well-established use HMPs, and 1719 traditional use HMPs, as detailed in Table 3.

In the category of new HMPs, Birch Bark Extract Gel was the inaugural HMP to receive EMA approval under the centralized procedure in 2016, securing marketing authorization for the entire EU market. The remaining two new HMPs, Tea Polyphenol Ointment and Cannabis Mucosal Spray, were both granted marketing authorization via the mutual recognition procedure. For well-established use HMPs, EU member states have received 1428 applications, with 859 approvals and 245 instances of non-approval or withdrawal. The average approval rate, calculated as the ratio of approvals to the total number of approvals, non-approvals, and withdrawals, stands at 77.81%. In the case of traditional use HMPs, EU member states have received 2730 applications, resulting in 1719 approvals and 437 non-approvals or withdrawals, achieving an average approval rate of 79.73%.

Table 4 presents the number of granted marketing authorizations for HMPs in several EU member states. The new HMP, Tea Polyphenol Ointment, was approved for marketing through the mutual recognition procedure, with Germany as the designated reference member state and 22 other countries, including Austria, France, and Italy, as concerned member states. Similarly, Cannabis Mucosal Spray received marketing authorization via the mutual recognition procedure, with the Netherlands as the reference member state and 17 other countries, including France, Denmark, and Finland, as concerned member states.

In the case of well-established use HMPs, Germany has accepted 447 applications, representing 33.01% of the total number of applications received by the EU, while other member states have received fewer than 100 applications each. Analyzing the approval rates of each member state, many have approval rates exceeding the EU average of 77.81%. Notably, Austria, Romania, and Slovenia have achieved a perfect approval rate of 100%. For traditional use HMPs, Germany, Poland, and Austria have each accepted over 200 applications, collectively accounting for 55.02% of the total application volume. Among the top 10 member states by number of received applications, 7 have approval rates above the EU average of 79.73%, with Hungary demonstrating a remarkable 100% approval rate. In contrast, Spain and Germany exhibit stricter approval criteria for traditional use HMPs, with non-approval rates of 34.84% and 23.45%, respectively.

3. Registration of TCMs and pCms in the GBA

3.1. TCMs in the Chinese mainland

3.1.1. Regulatory agency

The National Medical Products Administration (NMPA) serves as the central regulatory authority for pharmaceuticals in the mainland of China. Within the NMPA, the Division of Traditional Chinese Medicines and Ethno-Medicines, which is part of the Department of Drug Registration, is specifically tasked with the registration management of TCMs. The Center for Drug Evaluation (CDE) is responsible for the reception and review of applications for the marketing authorization of TCMs. To facilitate drug evaluation and inspection efforts, the CDE has established sub-centers in the Yangtze River Delta and the GBA. The regulation of ancient HMPs is also a collaborative effort with the NATCM, which works in conjunction with the NMPA to formulate the "Catalogue of Ancient Famous Classical Formulas". Additionally, the National Pharmacopoeia Commission, as the technical authority for the formulation, revision, and compilation of the "Chinese Pharmacopoeia", plays a crucial role in the quality control of TCMs.[16]

The Guangdong Medical Products Administration (GDMPA) is designated as the authority for the registration of TCMs within Guangdong province. Its responsibilities include the acceptance and evaluation of pCms for external use registered in Hong Kong and Macao, the management of post-authorization changes and re-registration of TCMs, and the development of localized standards and technical guidelines. Additionally, to facilitate the transition of medical institution preparations into new TCMs, the GDMPA has spearheaded the selection of "Lingnan Famous Classical Formulas" and is actively promoting their clinical application and pursuit of marketing authorization in Hong Kong and Macao.

3.1.2. Legal framework

The regulatory framework governing TCMs registration in the mainland of China is founded on two fundamental legal pillars: the "Drug Administration Law of the PRC" and the "Laws of the PRC on Traditional Chinese Medicine". These are further elaborated by the "Regulations for Implementation of the Drug Administration Law of the PRC", which provides specific requirements for TCMs registration. The core framework is supplemented by departmental regulations, including the "Provisions for Drug Registration" and the "Special Provisions for Traditional Chinese Medicines Registration". Additionally, technical guidance such as the "Guidance for the Preparation of Application Dossiers for TCM Theory of Compound Preparations of New Chinese Medicines" is provided, which refines the standards and technical requirements at each stage of the TCMs registration process. The current "Provisions for Drug Registration" officially came into effect on July 1, 2020, introducing the concept of life-cycle drug supervision and establishing a registration system and technical evaluation framework tailored to the characteristics of TCMs.[17]

Table 4
Numbers of granted HMPs in EU member states.

Type	Member states	Application	Approval	Non-approval	Withdrawn	Approval rate
Traditional use HMPs	Germany	513	285	106	61	63.05%
	Poland	315	215	19	19	84.98%
	Austria	224	209	0	1	99.52%
	France	171	33	0	11	75.00%
	Spain	162	100	54	1	64.52%
Well-established use HMPs	Germany	447	286	24	67	75.86%
	Austria	74	56	0	0	100%
	Croatia	73	41	7	12	68.33%
	Czech Republic	73	36	6	15	63.16%
	Romania	66	29	0	0	100%

Guangdong Province has promulgated a series of regulations to enhance the management of TCMs registration, including the "Guangdong Provincial Traditional Chinese Medicine Regulations", the "Detailed Rules for the Registration and Record-Filing of Medical Institution Preparations in Guangdong Province", and the "Guangdong Province Lingnan Chinese Medicinal Materials Protection Regulations". Moreover, to facilitate the simplified registration for Hong Kong and Macao registered pCms for external use to be registered and sold in the GBA, Guangdong Province has issued guiding documents such as the "the Work Plan for Regulatory Innovation and Development of Pharmaceutical and Medical Device in the Guangdong-Hong Kong-Macao Greater Bay Area".

3.1.3. Registration classification and marketing authorization procedure

According to the "Provisions for Drug Registration", the existing classifications for TCMs in the Chinese mainland include four categories: innovative TCMs, modified new drugs of TCMs, compound preparations of TCMs originated from classic recipes, and TCMs with identical names and identical recipes.[18] From the perspective of market authorization, the NMPA has established four special procedures to accelerate the authorization of TCMs: priority review and approval procedure, conditional approval procedure, special review and approval procedure, and simplified registration procedure (see Fig. 2). Among them, the simplified registration procedure is primarily designed for market authorization of compound preparations of TCMs from ancient famous classical formulas. The registration of Hong Kong and Macao registered pCms for external use also adopts the simplified registration procedure, which does not require the submission of information related to drug clinical studies.

3.1.4. Numbers of granted TCMs

The Drug Review Annual Report, as published by the NMPA CDE, reveals the following statistics regarding TCMs applications accepted for evaluation from 2021 to 2023: 444, 421, and 1163 applications, respectively. Within this period, there was a notable increase in the number of clinical trial applications (IND), rising from 52 to 75, and an increase in the number of new drug marketing authorization applications (NDA), which grew from 14 to 26. In terms of approvals, the figures for INDs and NDAs granted were as follows: in 2021, 34 INDs and 14 NDAs were approved; in 2022, 45 INDs and 8 NDAs were approved; and in 2023, 63 INDs and 11 NDAs were granted approval. Detailed data can be found in Table 5.

In Guangdong Province, a total of 18 new TCMs have been reported for registration over the past three years, demonstrating a consistent annual increase in both the level of innovation and the number of applications. Since 2020, Guangdong has been entrusted by the NMPA to conduct the review and approval processes of Hong Kong and Macao registered pCms for external use. By December 31, 2023, 2 pCms from Macao and 9 from Hong Kong have been granted registration and sale permissions within the GBA, with an additional 5 pCms currently under evaluation. Furthermore, 6 in-hospital preparations within Guangdong have been approved for clinical use in Macao, and 18 in-hospital preparations have been included in the "Lingnan Famous Classical Formulas" repository.

Table 5
Numbers of acceptance and approval of TCMs in the Chinese mainland.

Acceptance/Approval	Number of acceptance		Number of approvals	
Type	IND	NDA	IND	NDA
2021	52	14	34	14
2022	57	14	45	8
2023	75	26	63	11

3.2. pCms in Hong Kong

3.2.1. Regulatory agency

In Hong Kong, western medicines and pCms are regulated separately, with the registration of pCms involving two primary authorities: the Chinese Medicine Council of Hong Kong and the Department of Health Chinese Medicine Regulation Office. The Chinese Medicine Council of Hong Kong is in charge of the registration applications for pCms, with its subordinate Chinese Medicines Committee responsible for reviewing these applications and providing scientific opinions. The final decision to approve or reject applications resides with the Chinese Medicines Board. The Department of Health Chinese Medicine Regulation Office serves as the central regulatory agency for pCms, with its main functions including the establishment of standards for Chinese medicinal materials, the provision of administrative support to the Chinese Medicine Council of Hong Kong, and the implementation of regulatory measures for pCms. Furthermore, Hong Kong has established the Chinese Medicine Development Committee to offer strategic guidance and recommendations for the development and regulation of pCms.

3.2.2. Legal framework

The regulatory legal framework governing the registration of pCms in Hong Kong is anchored by the "Chinese Medicine Ordinance", which was enacted in 1999. This ordinance primarily encompasses measures to regulate the use, sale, and manufacturing of pCms. Subsequent to the

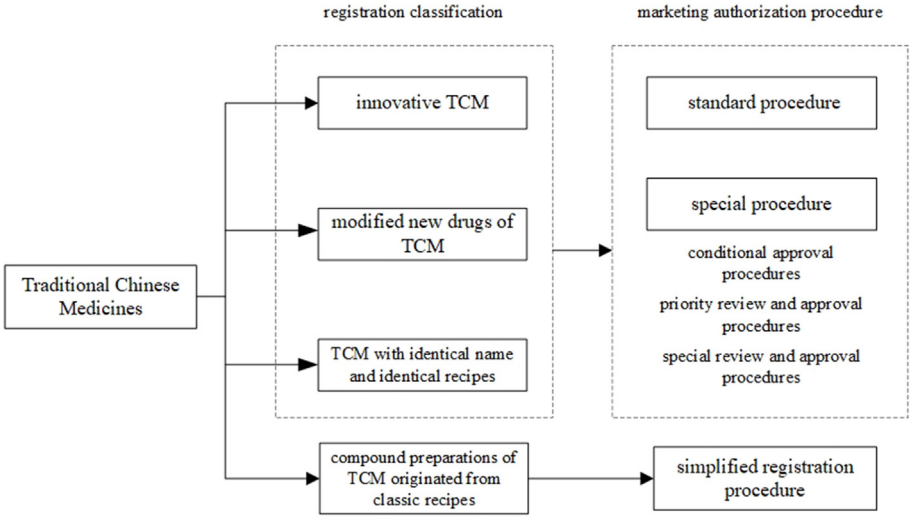

Fig. 2. Registration classification and marketing authorization of TCMs in the mainland of China.

implementation of the "Chinese Medicine Ordinance", Hong Kong has introduced relevant legislative provisions in 2008 and 2010, which established the licensing system for Chinese medicine traders and the registration framework for pCms. The procedural and technical requirements for pCm registration are further detailed by subsidiary legislation, including the "Chinese Medicines Regulations" and the "Chinese Medicines (Fees) Regulations".

3.2.3. Registration classification and marketing authorization procedure

Hong Kong's regulatory framework classifies pCms into three distinct categories based on their composition, usage, and sales history: established medicines, non-established medicines, and new medicines.[19] Established medicines include ancient prescriptions, modified ancient prescriptions, and pharmacopoeia prescriptions. The non-established medicines category is further divided into health-preserving medicines and other medicines, with the latter category encompassing single Chinese medicine granules that fall within the definition of pCms. New medicines are defined as those involving a newly discovered Chinese herb, a new medicinal part of a Chinese herb, Chinese medicine injections, preparations of a new Chinese medicine prescription, or pCms that have altered the route of administration, have new indications, or have changed dosage forms. The registration of pCms in Hong Kong is divided into three groups: Group I, Group II, and Group III (see Fig. 3). Each registration group has specific requirements and necessitates the submission of different documentation. For pCms falling under the categories of established and non-established medicines, applicants have the option to apply for registration in any of the three groups. However, new medicines must be registered in accordance with the requirements of Group III.

3.2.4. Numbers of granted pCms

The Chinese Medicine Council of Hong Kong has published a list of approved pCms. By April 18, 2024, the Chinese Medicines Board has cumulatively issued 2816 "Notice of confirmation of Transitional Registration of pCms" and 5327 "Certificate of Registration of pCms" (These figures were sourced from the official website of the Chinese Medicine Council of Hong Kong: https://www.cmchk.org.hk/pcm/chs/index.html#main_listpcm_2023.htm). In addition, on July 25, 2023, a new compound pCms developed by the Center for Chinese Herbal Medicine Drug Development at Hong Kong Baptist University, intended for the treatment of chronic constipation, received approval to conduct Phase I clinical trials in the United States. This marks the first instance where a new botanical drug, based on the traditional Chinese herbal formulation "MaZiRenWan", has been authorized to undergo clinical trials in the United States.

3.3. pCms in Macao

3.3.1. Regulatory agency

On January 1, 2022, the Pharmaceutical Administration Bureau of Macao was established, marking the creation of an independent administrative authority for drug regulation. The Pharmaceutical Administration Bureau is responsible for the regulation of pCms, and operates under the guidance of a Committee of Experts and Advisors. This committee is charged with conducting technical reviews and providing recommendations on the approval, refusal, and modification of pCms registration applications. Comprising 17 experts from the mainland and Macao of China, the committee members bring a minimum of 10 years of professional experience in the field of pCms, playing a crucial role in the decision-making process of pCms evaluation.[16]

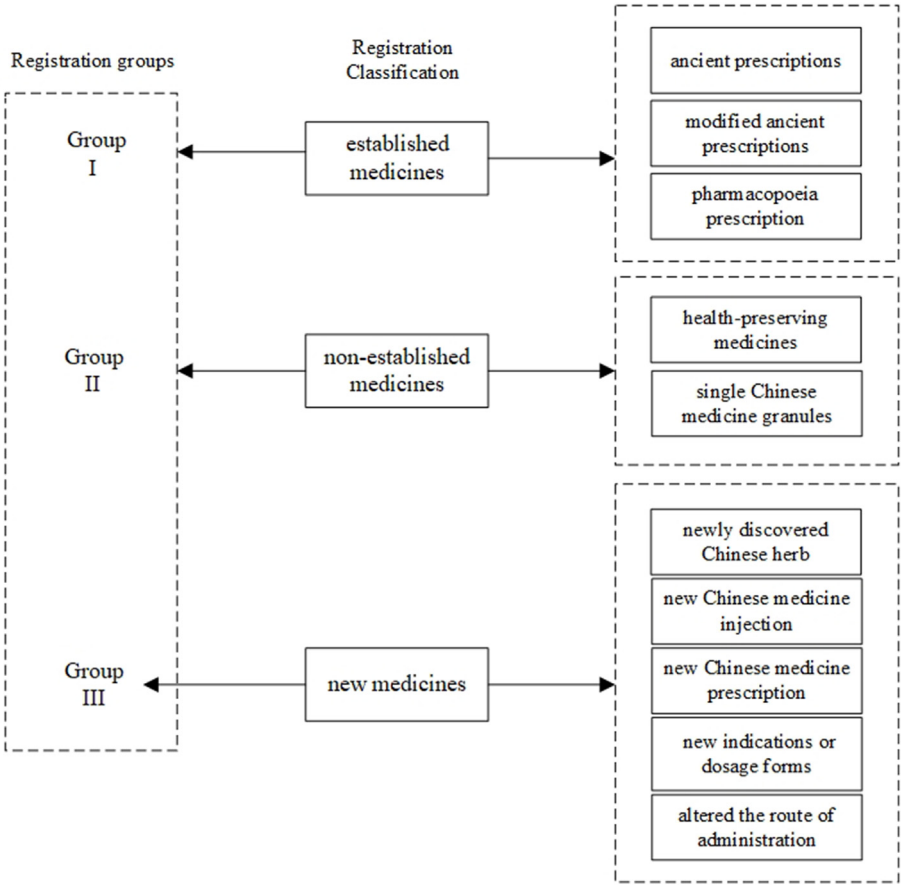

Fig. 3. Classification and registration of pCms in Hong Kong.

3.3.2. Legal framework

The legislation titled "Pharmaceutical Activity in the Field of Traditional Chinese Medicines and the Registration of Proprietary Chinese Medicines" officially came into effect on January 1, 2022, and serves as the foundational legal framework for the registration of pCms in Macao. Concurrent with the implementation of this law, Macao issued a series of complementary rules and requirements to guide the registration of pCms. These include the "Detailed Rules for the Implementation of the Chinese Medicine Pharmaceutical Activities and the Registration of Proprietary Chinese Medicines", which outline the procedural aspects of registration; the "Technical Requirements for the Registration Dossier of Proprietary Chinese Medicines", which specify the documentation standards for pCm applications; and the "Technical Requirements for Clinical Trial Application", which establish the criteria for clinical trial applications involving pCms.

3.3.3. Registration classification and marketing authorization procedure

Macao's registration system for pCms is consistent with the four types established by the Chinese mainland. However, there are notable differences in the definitions of medicines with identical names and recipes. In Macao, the scope of imitable products includes botanical drugs, traditional medicines, natural medicines, and Kampo medicines that have been registered in any country or region, whereas the Chinese mainland limits imitation to medicines that have completed clinical trials. Additionally, the definition of compound preparations derived from classic recipes varies; Macao recognizes prescriptions documented in ancient medical literature from over 180 countries or regions globally, while the Chinese mainland only acknowledges prescriptions from classical Chinese medical literature.

The registration materials required for pCms in Macao are analogous to those on the Chinese mainland, but with streamlined technical requirements. Macao has also implemented a priority review and approval procedure to accelerate the marketing authorization of pCms that are urgently needed and clinically scarce, as well as modified new drugs or innovative drugs intended for the prevention and treatment of major infectious diseases and rare diseases. Upon receiving marketing authorization, pCms are granted a "Certificate of Registration of Proprietary Chinese Medicines" by the Pharmaceutical Administration Bureau. This certificate is valid for a period of 5 years and is eligible for renewal for an additional 5-year term after expiration.

3.3.4. Numbers of granted pCms

Between the implementation of the "Pharmaceutical Activity in the Field of Traditional Chinese Medicines and the Registration of Proprietary Chinese Medicines" in January 2022 and April 2023, the Macao Pharmaceutical Administration Bureau received a total of 85 applications for the registration of pCms, including 31 online applications. During this period, the bureau issued 11 registration certificates and had 38 applications under review. Additionally, the bureau provided 317 pre-registration consulting services, with the average approval time recorded at 52 working days (The application and marketing authorization data for pCms were collected and calculated from the Pharmaceutical Administration Bureau of Macao: www.isaf.gov.mo).

4. Characteristics of HMPs and TCMs registration

4.1. EU regulatory model for HMPs registration

The coexistence of "centralization" and "decentralization" is the most distinctive characteristic of the EU's regulatory framework for HMPs. On one hand, marketing authorization for HMPs can be granted through a centralized procedure by the EMA, mutual recognition, and national procedure by each member state. On the other hand, the legal framework, including directives, guidelines, herbal monographs, and list entries issued by the European Commission, EMA, or HMPC, serves as the foundation for the regulatory of HMPs registration by each member state.[20] However, the marketing authorization of HMPs within their territory being evaluated and approved by their respective NCAs. This regulation model has achieved significant success in facilitating HMPs registration within the EU. More specifically, the EU HMPs registration system also exhibits the following characteristics:

Firstly, the EU places a high premium on the human use experience of HMPs and has established a diversified registration framework based on the evidence of application. The EU delineates three distinct registration classifications for HMPs: new HMPs, well-established use HMPs, and traditional use HMPs. There are substantial differences in the human use experience and application evidence required for each type of registration, and the EU has crafted targeted technical requirements to address these variations.[21,22] For well-established use and traditional use HMPs, the EU has developed evaluation criteria grounded in their long-term history of human use and has granted exemptions for certain research data, aligning with the scientific rigor of their application evidence. Concurrently, the EU values the diversity and comprehensiveness of application evidence. For instance, the scientific literature supporting well-established use of HMPs should encompass at least one high-quality clinical study, alongside a broad spectrum of evidence including pre-authorization and post-authorization analyses, epidemiological studies, and pharmacovigilance data.

Secondly, the EU has instituted an efficient regulatory model that utilizes herbal monographs and list entries in conjunction with the evaluation and approval of HMPs. This approach fosters technical harmonization and optimizes the use of assessment resources. Herbal monographs and list entries encapsulate the scientific opinions of the HMPC regarding the safety and efficacy of specific HMPs. Directive 2004/24/EC legally integrates these documents with the marketing authorization process for HMPs, permitting them to be directly utilized as application materials and mandating their use as reference documents during the marketing authorization by EU member states.[23,24] Among the well-established use and traditional use HMPs approved within the EU, a significant proportion—77.10% and 69.80% of registrations, respectively—had corresponding herbal monographs prior to registration.[25] Moreover, in the context of decentralized and mutual recognition procedures, only HMPs with established monographs and list entries are eligible to apply for marketing authorization within the EU through these pathways. It is evident that herbal monographs and list entries are indispensable components of the HMPs registration process, and their significance in marketing authorizations is escalating with the increasing number and diversity of HMPs.

Thirdly, the EU places a high priority on quality control and has developed a series of strict yet flexible quality standards for HMPs. The quality control of HMPs within the EU is predominantly governed by the European Pharmacopoeia, which is compiled by the EDQM and establishes quality standards for each herbal ingredient. The European Pharmacopoeia is recognized globally as a benchmark for drug quality and carries legal force across all EU member states. It is crucial to highlight that the EU's quality control requirements for HMPs focus primarily on the reproducibility of the production process and the stability of product quality. Moreover, the EU's quality requirements for HMPs exhibit flexibility. On one hand, the European Pharmacopoeia takes into account new HMPs from non-European countries by establishing the TCM Working Party, which formulates pharmacopoeia monographs for herbal substances used in traditional Asian medicines, including TCMs and Ayurveda medicines.[26] On the other hand, the EU permits a certain degree of fluctuation in the composition of HMPs. For instance, in the case of compound well-established and traditional use HMPs, a reduction in some ingredients is permissible if the safety and efficacy of the remaining herbal components can be demonstrated.

Additionally, the establishment of the HMPC plays a pivotal role in ensuring the harmonization and coordination of regulatory efforts within the EU, which is a significant characteristic of the EU HMPs registration. Furthermore, the comprehensive transition to electronic submission of

applications is another notable feature. Since 2018, the EU has required that applications for centralized, decentralized, mutual recognition, and national procedures be submitted in the Electronic Common Technical Document (eCTD) format. This mandate has positioned the EU as one of the pioneering regions globally in the full implementation of electronic submission for drug registration.

4.2. TCMs registration characteristics in China

4.2.1. The Chinese mainland

The "Drug Administration Law of the PRC", the "Laws of the PRC on Traditional Chinese Medicine" and the "Special Provisions for Traditional Chinese Medicines Registration" have collectively strengthened the regulatory framework for TCMs registration and have optimized the environment to stimulate innovative vitality within the TCM sector. Specifically, the registration of TCMs in the Chinese mainland is characterized by the following features:

Firstly, the evaluation and approval process for TCMs has been strategically extended to the pre-submission phase, establishing a diversified evidence system and special procedures aimed at accelerating market authorization. The TCMs registration process encompasses a series of stages, including initial drug development, application for market authorization, post-authorization research, and re-registration. The current regulatory strategy for TCMs registration has shifted focus towards front-end technological innovation, emphasizing thorough communication with regulatory authorities prior to the submission of registration applications. Concurrently, during the evaluation process, a comprehensive evidence system and special registration procedures are implemented to accelerate the market authorization of TCMs, based on their demonstrated clinical value.[27]

Secondly, the quality control measures for TCMs have been consistently strengthened, with a particular emphasis on the sourcing of ingredients. In recent years, the NMPA CDE has issued nearly 10 technical guidance principles, offering essential directives for the development and refinement of a quality control system that is tailored to the unique characteristics of TCMs. Collectively, China has made preliminary strides in establishing a quality control system for TCMs and has issued the "Good Agricultural Practice for Chinese Crude Drugs" in March 2022. This guidance is of significant importance for enhancing the quality of TCMs from the source.

Thirdly, Guangdong Province has prioritized the transformation of medical institution preparations into new TCMs, by conducting a selection process for "Lingnan Famous Classical Formulas", thereby deeply exploring the region's TCMs heritage. In-hospital preparations of TCMs possess a substantial foundation of human use experience and clinical practice, acting as a significant "incubator" for new TCMs. Through the selection of "Lingnan Famous Classical Formulas", Guangdong has strategically supported the conversion of certain in-hospital preparations, known for their stable quality and proven efficacy, into new TCMs. In July 2023, the first batch of "Lingnan Famous Classical Formulas" was announced, with 18 out of 113 applicants being selected. The chosen "Lingnan Famous Classical Formulas" are eligible to receive policy support aimed at expanding the scope of application of these preparations, promoting their transformation into new drugs, and facilitating medical insurance coverage for their use.

4.2.2. Hong Kong and Macao

The registration of pCms in Hong Kong has concluded its transitional phase and is now in the process of constructing a more stringent and comprehensive regulatory framework. This regulatory system is characterized by two distinct features: Firstly, there is a separation of regulatory agencies between western medicines and pCms, with the Pharmacy and Poisons Board and the Chinese Medicine Council being the respective authorities. This division reflects a tailored approach to the regulation of different types of medicines. Secondly, a rigorous regulatory system has been instituted to ensure the quality of Chinese medicinal materials from their origin. Hong Kong's regulations concerning the permissible levels of heavy metals are aligned with international standards and are notably more stringent than those observed in the Chinese mainland, as well as in Japanese Kampo medicine and Traditional Korean medicine.[28]

Macao's registration system for pCms has been informed by the experience of the NMPA, particularly in terms of application classification, evaluation, and approval mechanisms, thereby gradually forming a distinctive regulatory pattern. This pattern is characterized by two features: Firstly, Macao's pCms regulatory adopts a model that integrates regulation with service, introducing pre-registration consultation services and online registration measures to facilitate the registration of pCms. These initiatives aim to streamline administrative procedures and enhance the efficiency of the registration process. Secondly, Macao's pCms registration system exhibits a high degree of harmonization with international HMPs registration regulations. The generic targets for pCms with identical names and identical recipes in Macao encompass plant medicines and traditional medicines that have been registered in the majority of countries and regions worldwide. Furthermore, compound preparations of pCms derived from classic recipes in Macao recognize prescriptions documented in ancient medical classics from over 180 countries and regions globally.[29]

4.2.3. GBA

The GBA features a unique structure of one country, two systems, and three customs territories, with differences in political systems and legal frameworks, posing significant challenges to the integration of regional resources.[30] In light of this, Chinese authorities have issued the "Outline Development Plan for the Guangdong-Hong Kong-Macao Greater Bay Area" alongside a suite of complementary documents. These policy initiatives are designed to foster the harmonization of regulatory standards and facilitate the unfettered movement of essential factors within the GBA, thereby capitalizing on the distinct advantages of each region to foster synergistic development.[31]

In terms of TCMs, the establishment of the Macao Pharmaceutical Administration Bureau in 2022 and the enactment of the "Pharmaceutical Activity in the Field of Traditional Chinese Medicines and the Registration of Proprietary Chinese Medicines" mark a significant milestone. These developments indicate that Guangdong, Hong Kong, and Macao have each instituted comprehensive registration management systems for TCMs, providing a robust organizational foundation and institutional safeguard for the collaborative advancement of the TCMs regulatory within the GBA. Furthermore, the abundant cultural heritage in TCMs in Guangdong, Hong Kong, and Macao has cultivated a substantial grassroots foundation, which is instrumental in propelling deeper cooperation in TCMs registration throughout the GBA.[32]

5. Enlightenment for TCMs registration in the GBA

The EU has achieved significant success in the regulation of HMPs registration, accumulating mature experience in the development of regulatory networks, legal frameworks, and evaluation and approval mechanisms. This experience offers significant reference value for the registration of TCMs within the GBA.

5.1. Establishing the GBA TCMs Drug Evaluation Center for integrated registration management

Inspired by the EMA's establishment of the HMPC for the regulation of HMPs registration within the EU, the GBA could benefit from the creation of a dedicated TCMs Drug Evaluation Center. This center would play a pivotal role in managing registration applications for new TCMs from China's mainland, Hong Kong, and Macao, addressing the current regulatory fragmentation arising from varying regulatory models and legal frameworks that hinder effective connection in registration across these regions. The proposed GBA TCMs Drug Evaluation Center would fulfill several critical functions: 1) Formal communication and cooperation:

organize formal communications among drug regulatory agencies in China's mainland, Hong Kong, and Macao to deepen cooperation in TCMs regulation; 2) Enterprise support: provide comprehensive support for the development of TCMs by enterprises in the GBA; 3) Guidelines development: formulate a series of guidelines to offer technical support throughout the entire lifecycle of TCMs regulation; 4) Scientific opinion and coordination: provide scientific opinion for the evaluation and approval of TCMs and coordinate or resolve specific issues related to TCMs registration in the GBA.

The establishment of GBA TCMs Drug Evaluation Center would not only provide technical support for TCMs regulation but also promote the harmonization and unification of TCMs registration across the GBA, drawing on the successful model of the HMPC within the EU context.

5.2. Introducing the decentralized and mutual recognition procedures to consolidate the evaluation resources of TCMs within the GBA

The evaluation procedures for HMPs in the EU include four primary types: centralized procedure, mutual recognition procedure, decentralized procedure, and national procedure. In comparison to the national procedure, both the decentralized and mutual recognition procedures prevent duplicate evaluations by different member states for the same medicinal product, thus conserving evaluation resources and enhancing registration efficiency, complementing the centralized and national procedures.[11] These procedures within the EU offer valuable insights for TCMs registration in the GBA, necessitating the adoption of these two procedures.

Specifically, for applicants intending to market their TCMs across multiple regions within the GBA, including Guangdong, Hong Kong, and Macao, the decentralized procedure could be employed. In this procedure, materials are simultaneously submitted to the regulatory agencies of each region, with one designated as the reference region to initiate the assessment and draft an evaluation report. Should consensus be reached among the other regions and the reference region, the applicant may obtain marketing authorization for TCMs across these regions. Furthermore, once an applicant has secured TCMs marketing authorization in any region within the GBA, they may seek authorization in other regions through the mutual recognition procedure. In such instances, the region that has granted authorization becomes the reference region, with its regulatory agency submitting the relevant evaluation report to other regions. If all of the bodies reach an agreement, the applicant is granted authorization for the TCMs in the other regions. However, in cases where any region dissents from granting marketing authorization for the TCMs during the coordination and communication process, the GBA TCMs Drug Evaluation Center is expected to make the final decision.

5.3. Integrating herbal monographs into the TCMs registration process within the GBA

The EU has developed a regulatory model that combines the herbal monographs with the registration and evaluation of HMPs. This model not only improves the efficiency of evaluation but also conserves review resources, facilitating technical coordination and unification in HMPs registration. In the Chinese mainland, TCM monographs such as the "Zhonghua Bencao" and the "Chinese-English Dictionary of Traditional Chinese Medicine" exist; however, these are not legally linked to the registration of TCMs and are primarily oriented towards guiding clinical medication. This inclination limits their utility as official evaluation guidelines for the safety and efficacy of TCMs. Therefore, drawing on the EU's experience with herbal monographs and considering the characteristics of TCMs in the GBA, it is essential to confer significant value and legal status upon these herbal monographs in the registration and evaluation processes of TCMs within the GBA. This integration would streamline the evaluation process, aligning with international best practices and enhancing the regulatory framework for TCMs in the region.

5.4. Developing international standards for TCMs in the GBA to facilitate registration systems interconnectivity

The EU stands as a global leader in establishing monographs that address the quality controllability, safety, and efficacy of HMPs.[10] The herbal monographs, in conjunction with the European Pharmacopoeia, offer unified technical standards for the registration and marketing authorization of HMPs, ensuring efficient evaluation within the EU. Moreover, the EU's internal implementation of decentralized and mutual recognition procedures has effectively facilitated the mutual recognition and interconnection of HMPs among its member states.

The efficient and flexible regulatory model of the EU provides valuable lessons for enhancing the mutual recognition and interconnection of TCMs registration systems within the GBA. Firstly, the role of the Expert Committee on TCMs Standards should be leveraged to expedite the establishment of mutually recognized TCMs standards for the GBA, formulating unified evaluation norms and guiding principles to offer technical support for the evaluation of TCMs across the three regions.[33] Secondly, the current simplified approval procedures for registering and selling Hong Kong and Macao registered pCms for external use in the GBA could be expanded, with further efforts aimed at promoting the mutual recognition and interconnection of a broader range of Chinese medicine products within the GBA. Thirdly, the scope of mutual recognition and use of hospital preparations of TCMs in the GBA should be broadened, with special policies issued to encourage the transformation of hospital preparations into new TCMs. Lastly, deepening the mutual recognition of clinical trial data among the GBA, breaking down geographical restrictions in development, clinical transformation, and manufacturing faced by TCMs registration in the three regions.

6. Conclusion

TCMs are revered as a treasure within the Chinese civilization, and the establishment of a TCMs highland in the GBA holds unique advantages in historical context, geographical location, and human resources. Despite differences in definitions, manufacturing processes, and other aspects between EU HMPs and Chinese TCMs, the EU's close-knit regulatory network, efficient evaluation and approval mechanisms, and unified quality standards offer substantial reference value for the recognition and interconnection of TCMs registration within the GBA.

The regions of Guangdong, Hong Kong, and Macao should fully absorb the advanced regulatory experience of the EU and explore innovative models and pathways for the mutual recognition and interconnection of TCMs registration. This focus should encompass regulatory agencies, evaluation and approval mechanisms, and the construction of international standards. Such an endeavor will stimulate the endogenous driving force and institutional vitality necessary for the high-quality development of TCMs, providing strong support for the creation of a Healthy Bay Area.

CRediT authorship contribution statement

Ran Xiong: Writing – original draft. **Hui Zhang:** Conceptualization. **Yueyun Li:** Investigation. **Guihao Zeng:** Investigation. **Yonghui Liu:** Writing – review & editing. **Yeyou Xu:** Supervision.

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Declarations of interest

The authors declare no conflict of interest.

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