

REGIONAL REPORT (SHANGHAI)



Zhengtao Wang
Shanghai University of TCM
19th CGCM Meeting, Chengdu, 2023

10 CGCM Member Institutes in Shanghai

- Shanghai University of TCM / Shanghai Academy of TCM 上海中医药大学/上海市中医药研究院(SHUTCM)
- Shanghai R&D Center for Standardization of Chinese Medicines 上海中药标准化研究中心(SHCSCM)
- School of Pharmacy, Fudan University 复旦大学药学院(FUDAN)
- School of Pharmacy ,Shanghai JiaoTong University 上海交通大学药学院(SJTU)
- School of Sciences and Technology, Tongji University 同济大学生命科学与技术学院(TONGJI)
- School of Pharmacy, East China University of Science and Technology 华东理工大学药学院(ECUST)
- Modern Research Center for TCM, Second Military Medical University 第二军医大学现代中药研究中心(SMMU)
- Shanghai Research Center for TCM Modernization, Shanghai Institute of Materia Medica 中国科学院上海药物研究所, 上海中药现代化研究中心(SIMM)
- Institute Pasteur of Shanghai ,Chinese Academy of Sciences 中国科学院,上海巴斯德研究所
- Shanghai PharmValley Innovation Institute of Biomedicine 上海药谷生物医药创新研究院(New member)



Major Research Fields in TCM

- Quality Evaluation and Standardization of Chinese Medicines
- Natural Products Chemistry
- Pharmacological activities of TCM compounds, herbs and formula
- Pharmaceutics of TCMs
- Biotechnology of medicinal plants and natural products
- Innovative medicines development and preclinical studies
- TCM informatics (databases, target prediction, etc)
- healthcare products
- Technical service

Representative R&D

- Quality Criteria of ISO/TC 249 Traditional Chinese Medicine**
- Quality Criteria of Shanghai TCM Formula Granules**
- Basic research supporting the registration and marketing of TCM formula Dannin Tablets (Biliflow) in Canada**

1. ISO/TC 249 Traditional Chinese Medicine (国际标准化组织中医药技术委员会)



International Organization for Standardization (ISO)

- ISO is an independent, non-governmental international organization with a membership of 168 national standards bodies.
- 《ISO STRATEGY 2030》 vision:
 - ***To make life easier, safer and better***



ISO/TC 249 Traditional Chinese Medicine

<https://www.iso.org/committee/598435.html>

- The secretariat of ISO/TC 249 has been allocated to Shanghai University of Traditional Chinese Medicine since 2009.
- The Committee is now composed of more than 1,000 experts from 45 member countries on five continents.

Scope

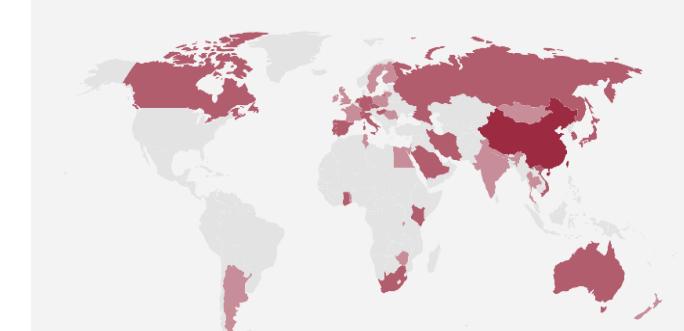
Standardization in the field of medical systems derived from ancient Chinese medicine which shall be able to share one common set of standards. Both traditional and modern aspects of these systems are covered. The committee focuses on quality and safety of raw materials, manufactured products and medical devices and of informatics, including service standards limited to involving the safe use and delivery of devices & medicine, but not into the clinical practice or application of those products.

21

Participating members

24

Observing members



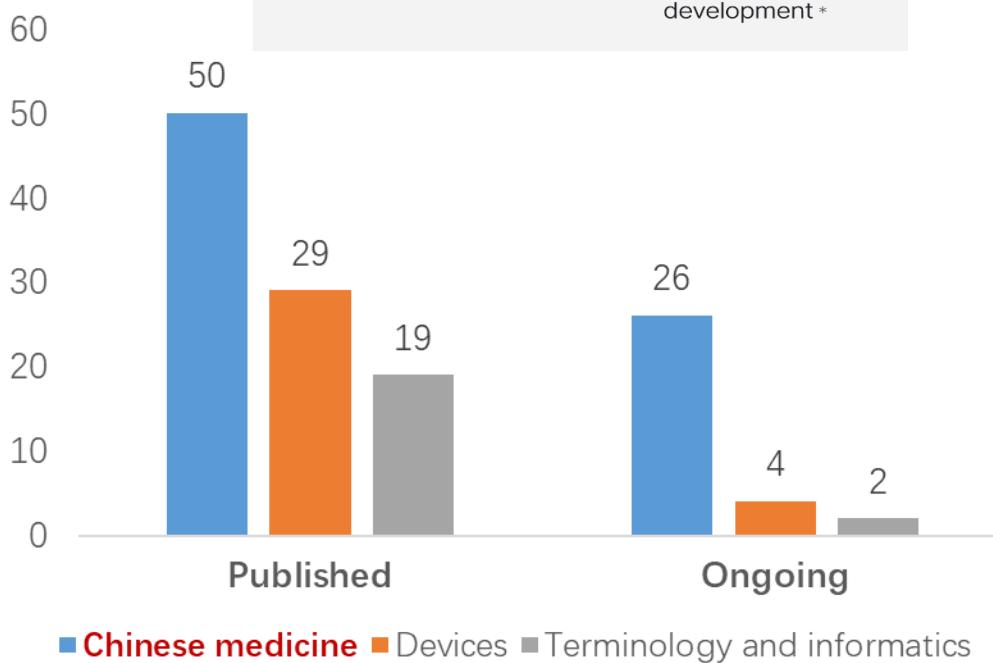
Published international standards led by ISO/TC 249

(ISO/TC249主导发布的国际标准)

ISO standards of Traditional Chinese medicine

98
Published ISO standards *

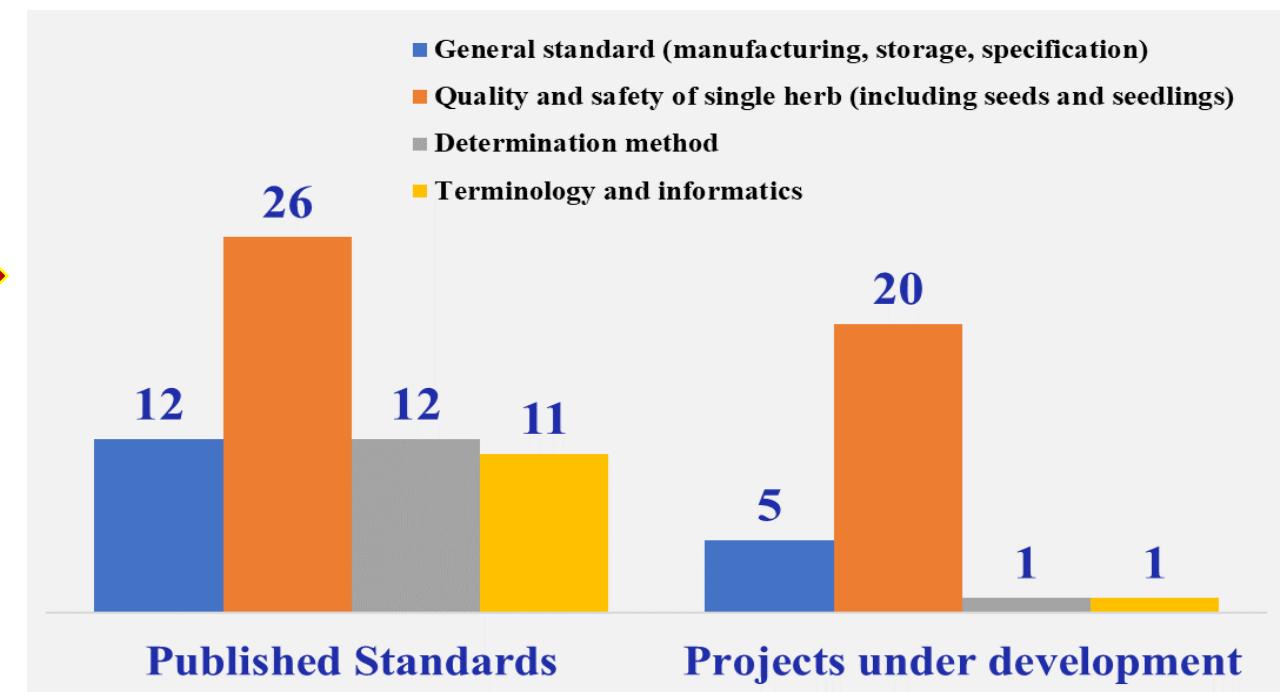
32
ISO standards under development *



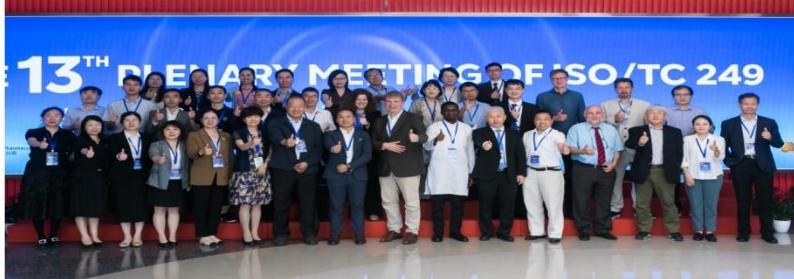
➤ ISO standards of Chinese Materia Medica (CMM)

- Of the 98 standards released, 61 (63.3%) were CMM and its related standards;
- 27 (84.4%) are CMMs standards in the 32 underdevelopment ISO standards.

- General standard (manufacturing, storage, specification)
- Quality and safety of single herb (including seeds and seedlings)
- Determination method
- Terminology and informatics



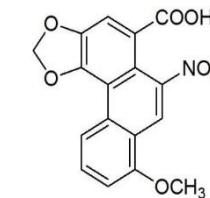
13th Plenary Meeting of ISO/TC249, 2023.6.4~6.9, Shanghai)



Work experience of our team on ISO/TC 249 CMM

Published ISO standards of single herbs

- Project leader: 7
- Participation: 5



ISO 21316: 2019 ISO 22584: 2019 ISO 23193: 2020 ISO 22585: 2022 ISO 22586: 2022 ISO 23190: 2021 ISO/TR 23975: 2019

1. ISO_21316: 2019 中医药—板蓝根, ISO_21316: 2019 Traditional Chinese medicine — *Isatis indigotica* root
2. ISO_22584: 2019 中医药—当归, ISO_22584: 2019 Traditional Chinese medicine — *Angelica sinensis* root
3. ISO_23193: 2020 中医药—枸杞子, ISO_23193: 2020 Traditional Chinese medicine — *Lycium barbarum* and *Lycium chinense* fruit
4. ISO_22585: 2022 中医药—党参, ISO_22585: 2022 Traditional Chinese Medicine — *Codonopsis pilosula* root
5. ISO_22586: 2022 中医药—白芍, ISO_22586: 2022 Traditional Chinese Medicine — *Paeonia lactiflora* root
6. ISO_23190: 2021 中医药—天然药物中马兜铃酸的HPLC含量测定方法, ISO_23190: 2021 Traditional Chinese medicine — Determination of aristolochic acids in natural products by HPLC
7. ISO/TR 23975: 2019 中医药—单味中草药国际标准制定优先级, ISO/TR 23975: 2019 Traditional Chinese medicine — Priority list of single herbal medicines for developing standards

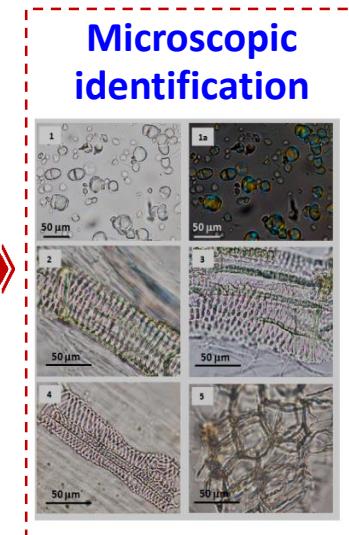
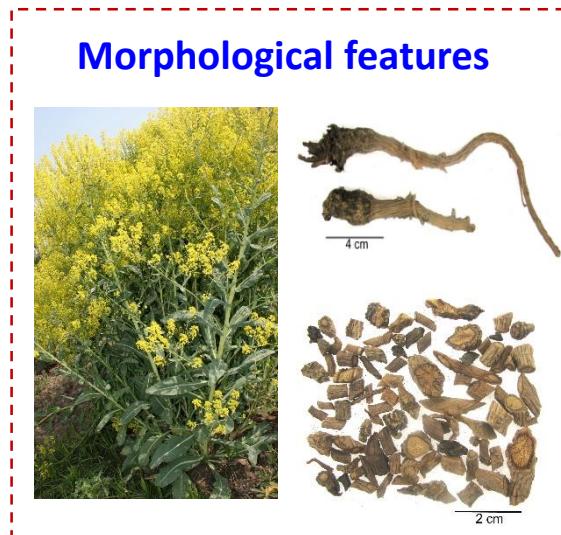
Underdevelopment ISO standards of single herbs

1. ISO/FDIS 7450 Traditional Chinese Medicine — *Pinellia ternata* tuber 半夏
2. ISO/DIS 13619 Traditional Chinese Medicine — *Gardenia jasminoides* fruit 梔子
3. ISO/CD 19047 Traditional Chinese Medicine — *Polygonum multiflorum* root 何首乌
4. ISO/CD 19842 Traditional Chinese Medicine — *Dioscorea opposita* rhizome 山药
5. ISO/CD TR 18962 Traditional Chinese medicine — Report on Panax ginseng in terms of industry and standardization development 人参产业化与标准化发展报告

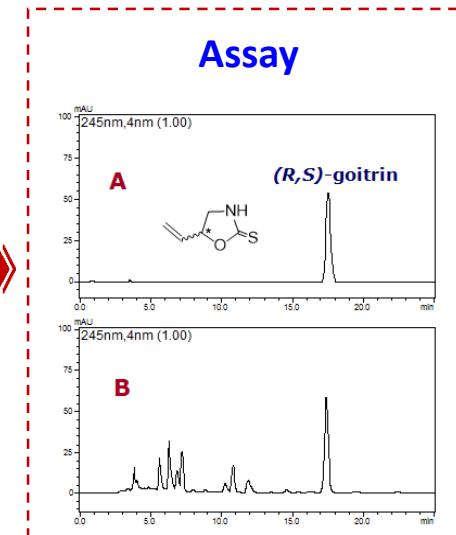
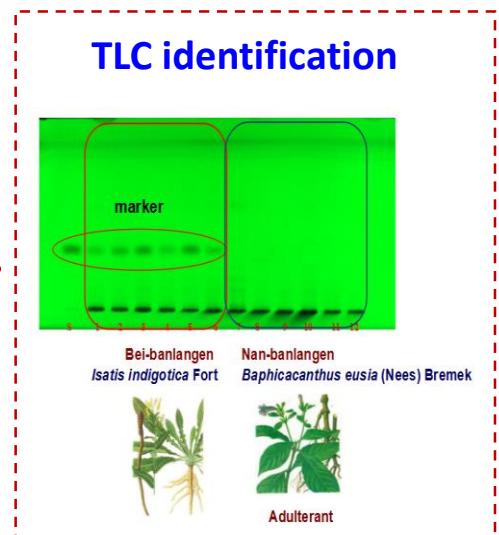


ISO 21316: 2019 Traditional Chinese medicine — *Isatis indigotica* root

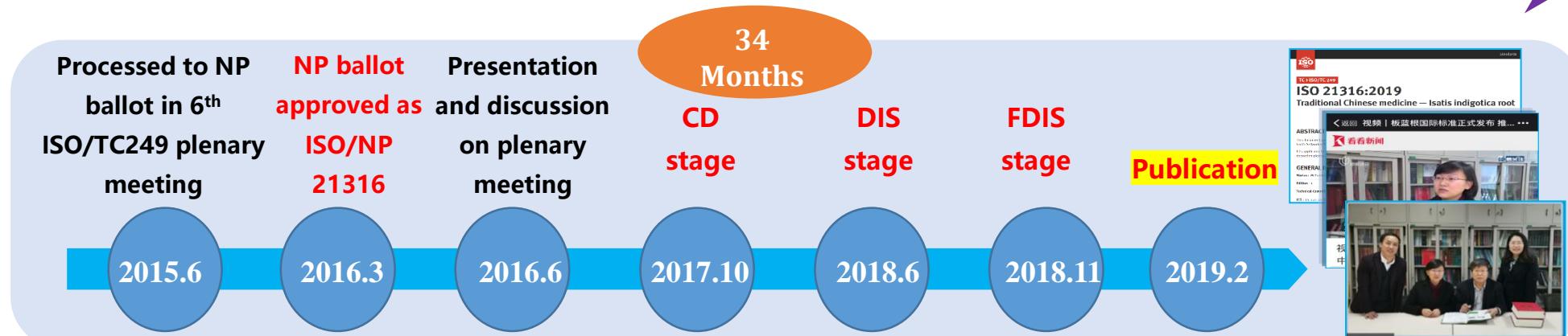
➤ Quality contents and Requirements



- Purity and Safety test**
- Moisture
 - Total ash
 - Acid-insoluble ash
 - Ethanol-soluble extractives
 - Heavy metals
 - Pesticide residues



➤ Process of standard development



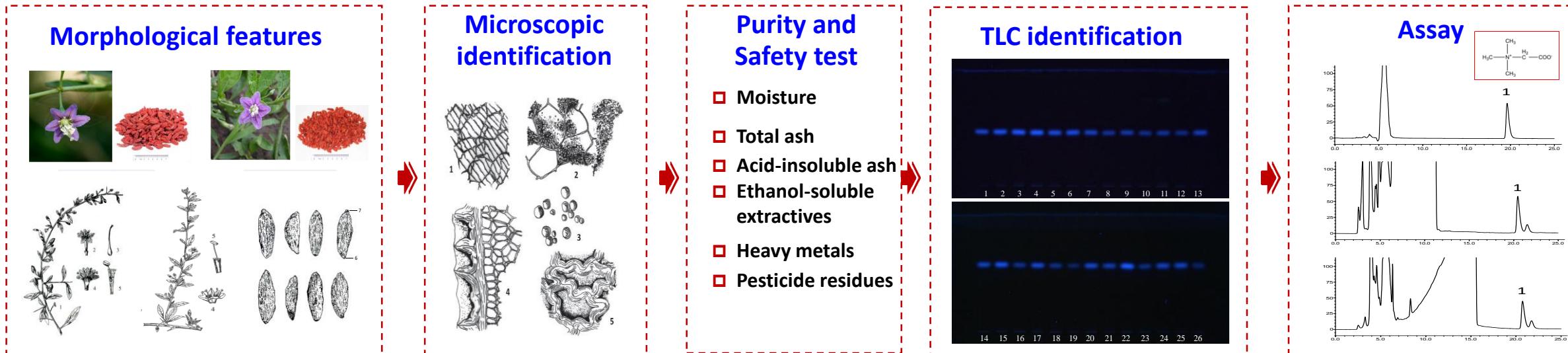
➤ Achievements

**Published papers: 20
Patents: 2**

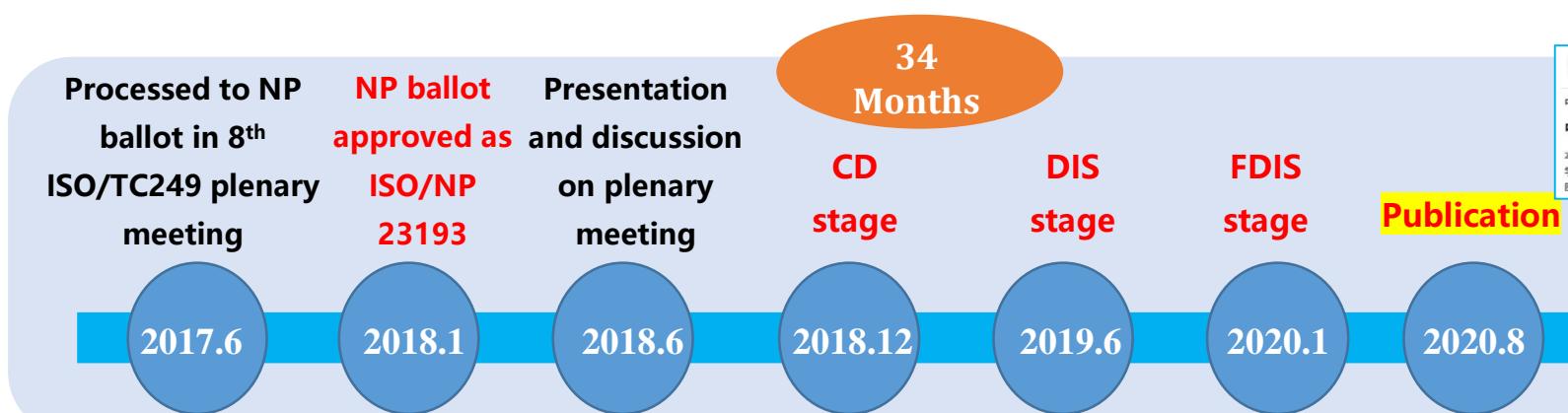
- *J. Agr. Food Chem.*, 2011
- *RSC Adv.*, 2014
- *Biomed. Chromatogr.*, 2019
- *Phytochemistry*, 2020
- *Nat. Prod. Res.*, 2021
-

ISO 23193: 2020 Traditional Chinese medicine — *Lycium barbarum* and *Lycium chinense* fruit

➤ Quality contents and Requirements



➤ Process of standard development



➤ Achievements

Published papers: 6

- *Food Funct.*, 2023
- *Front. Chem.*, 2022
- *J. Sep. Sci.*, 2021
-



2. Criteria of TCM Formula Granules

National : Total 272

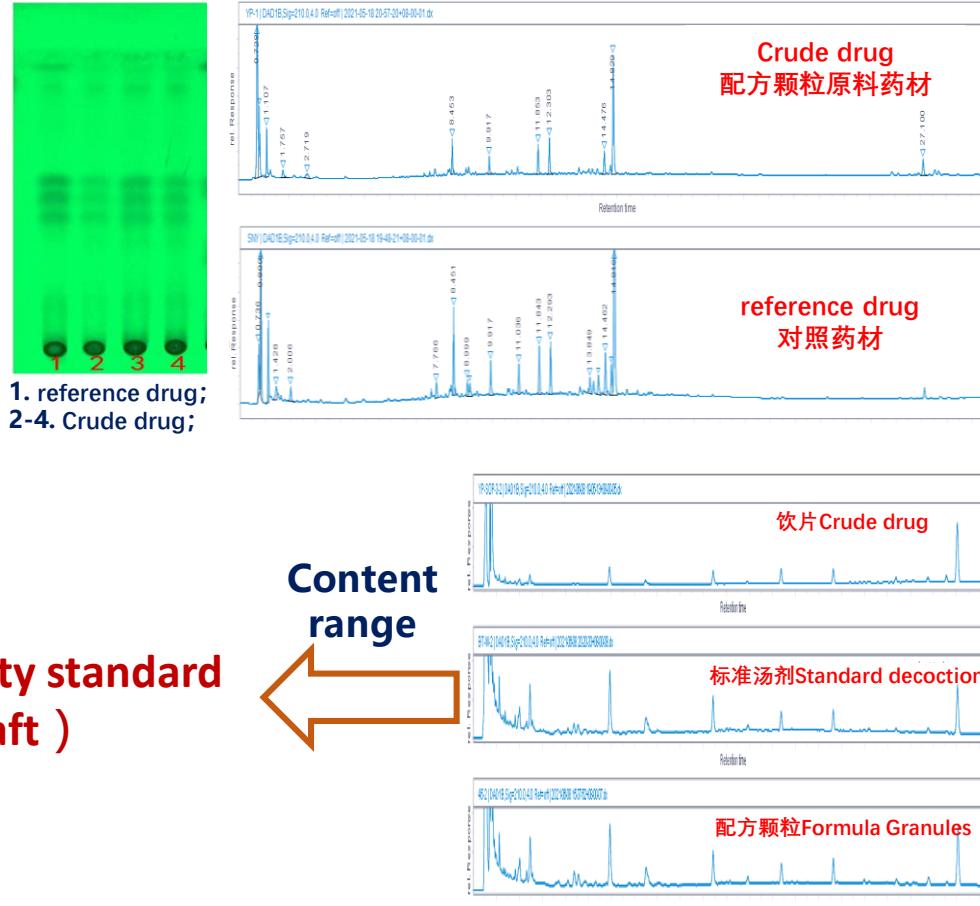
Shanghai : Total 365 (Our team's work 44)

- Source
- Procedure
- Description
- Identification
- Characteristic chromatogram
- Other requirements
- Extractives
- Assay
- Strength
- Storage



Criteria of Shanghai TCM Formula Granules— 石斛 DENDROBII CAULIS

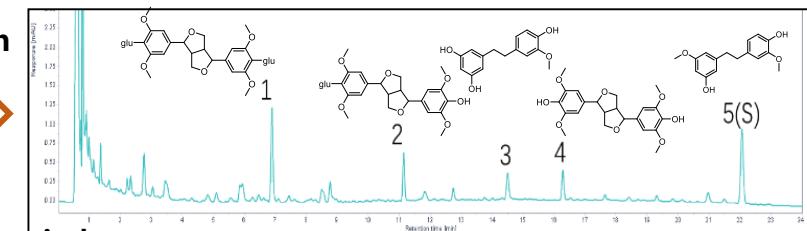
Identification of the crude drug



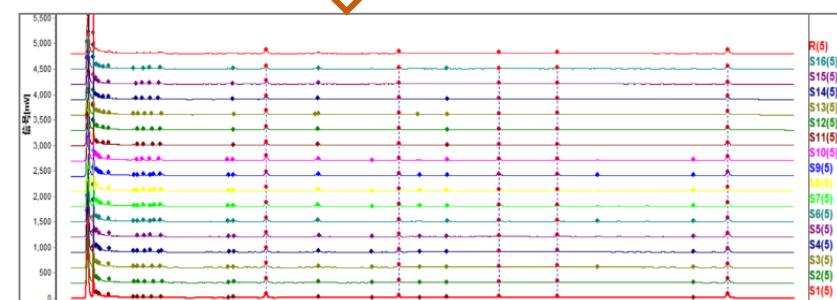
Identification of Characteristic peak and selection of chemical reference standard

Literature research

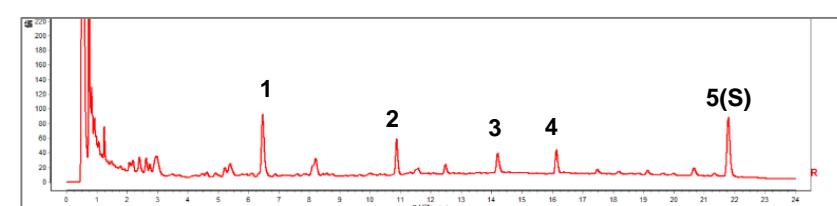
HPLC/UPLC/GC-MS analysis
comparison with chemical
Reference
Isolation and preparation



HPLC/UPLC/GC analysis



Mass Transfer Analysis



Quality standard
(Draft)

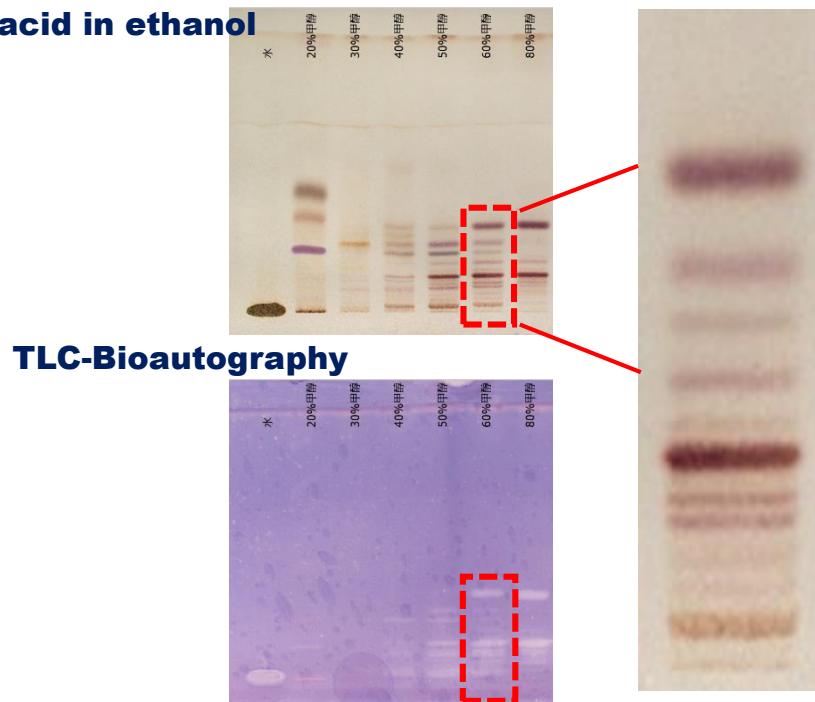
Characteristic chromatogram

- 1: Liriodendrin 2: Episyringaresinol 4'-O- β -D-glucopyranoside 3: Tristin
4: Syringaresinol 5 (S) : gigantol (Characteristic peak, chemical reference standard)

Criteria of Shanghai TCM Formula Granules—— 白扁豆 LABLAB SEMEN ALBUM

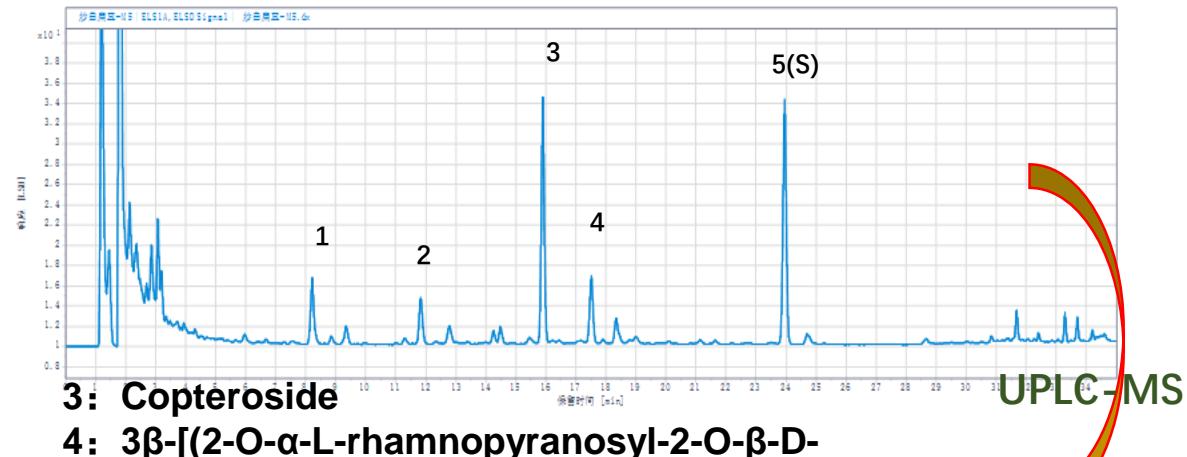
Screening and Identification of Lipase Inhibitors (TLC-Bioautography-MS)

10% solution of Sulfuric acid in ethanol



- B1: Lablaboside E B2: Lablaboside B B3: Lablaboside D
B4: 3β -[(2-O- α -L-rhamnopyranosyl-2-O- β -D-galactopyranosyl)- β -D-glucuronopyranosyl]oxy]-22 α ,24-dihydroxyolean-12-en-28-al
B5: Sandosaponin B B6: Azukisaponin III B7: Quinoasaponin-9
B8: Chikusetsusaponin IVa

Characteristic chromatogram and Assay

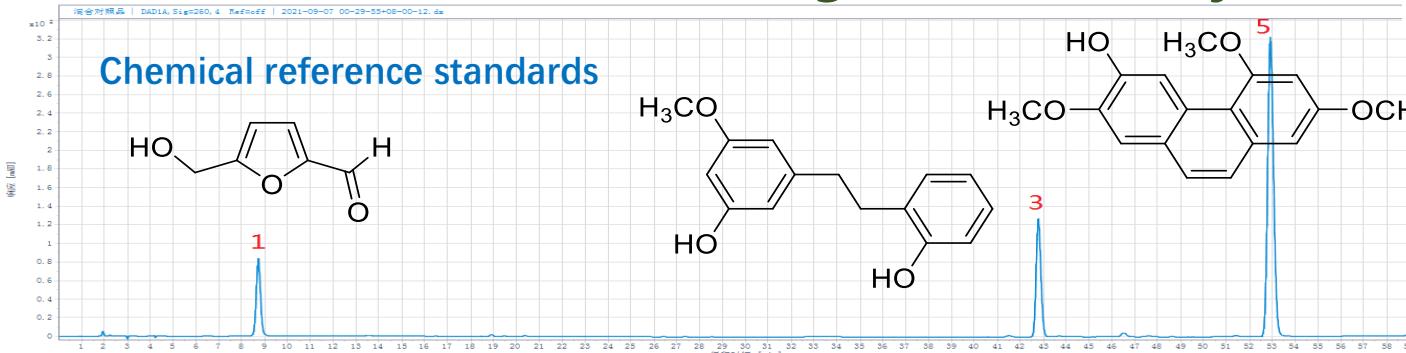


Criteria of Shanghai TCM Formula Granules—

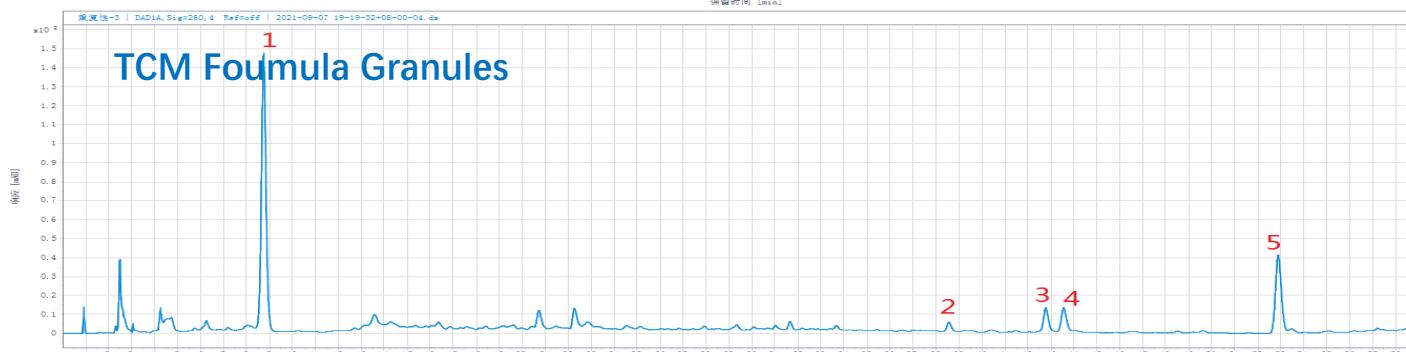
山药/蜜麸山药 DIOSCOREAE RHIZOMA

Characteristic chromatogram and Assay

Chemical reference standards

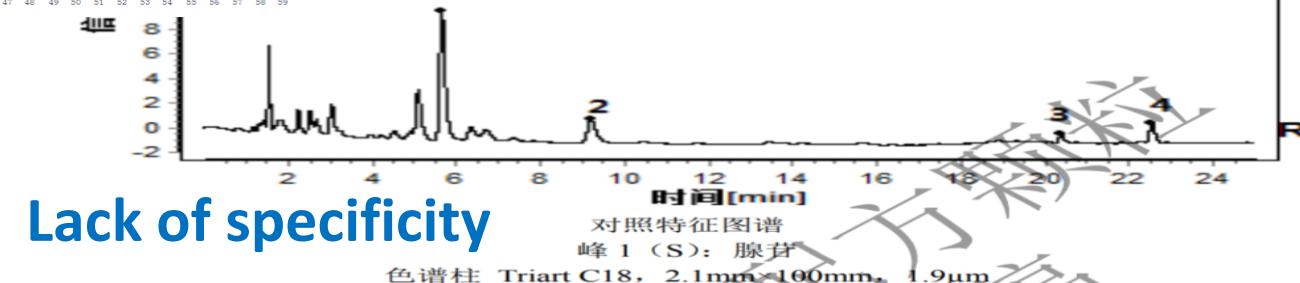


TCM Formula Granules



Quality standard of Shandong province

Adenosine



3、Interpreting effective substances, improving Cretaria, and strongly supporting the registration and marketing of TCM formula Dannin Tablets (Biliflow) in Canada

诠释科学内涵，提升质量标准，力助胆宁片在加拿大注册并上市



- 上海和黄药业独家品种
- 国家中药保护品种
- 上海市名牌产品
- 国家中医药科技进步三等奖
- 上海市科技进步二等奖
- 上海市优秀新产品奖
- 上海市第一届优秀产学研工程一等奖

【功能与主治】疏肝利胆，清热通下。临床用于治疗慢性胆囊炎，胆结石症。

胆宁片 – 需解决的问题

- 保肝利胆药效物质基础与作用机制？
- 质量控制与标准提升？
- 国际化途径

多基源药材：

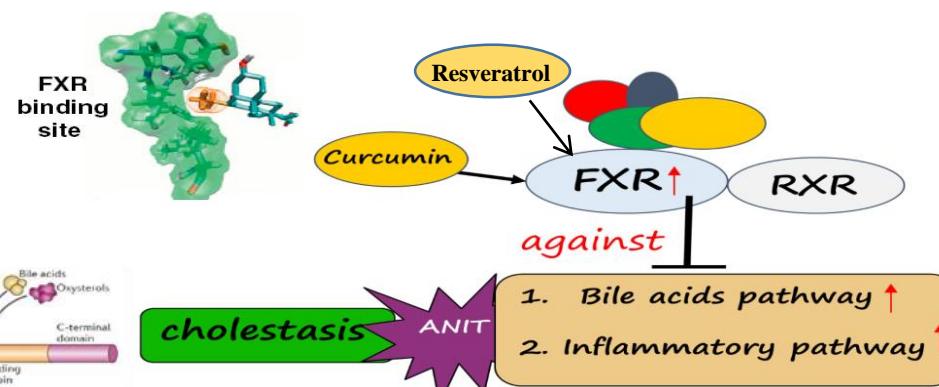
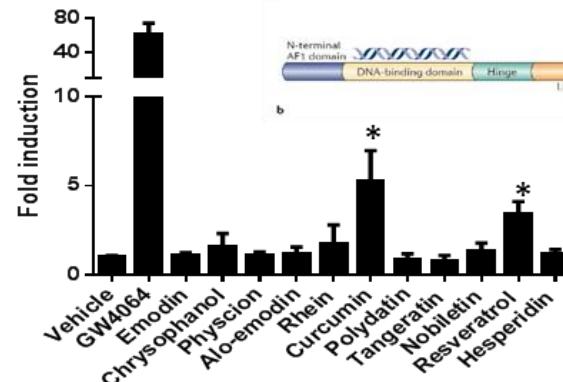
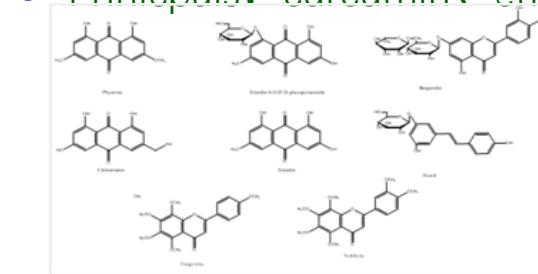
- 大黄：3 种植物来源
- 药用大黄
 - 掌叶大黄
 - 唐古特大黄

- 郁金：4 种植物来源
- 黄丝郁金
 - 绿丝郁金
 - 温郁金
 - 桂郁金

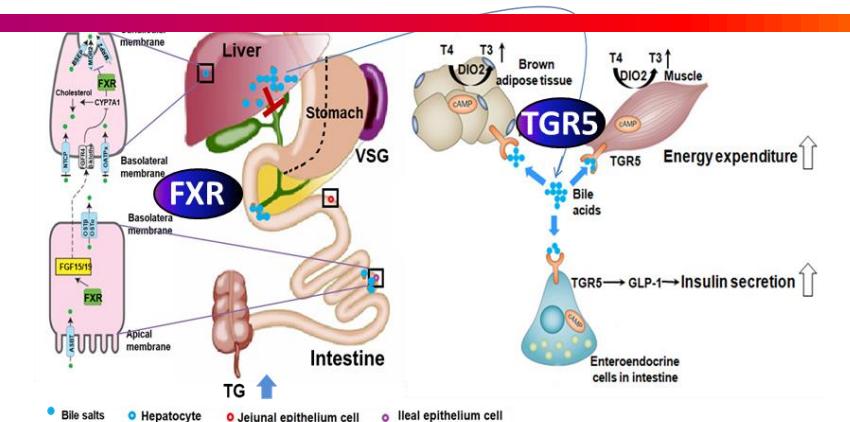
Elucidation of Bioactive substances and Underling Mechanism of Biliflow

揭示胆宁片功效物质基础、作用机理

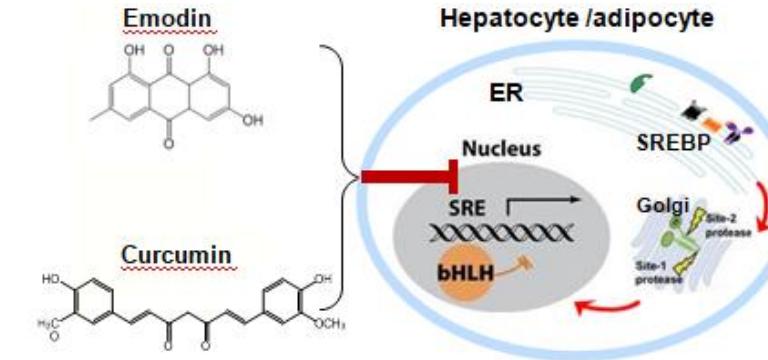
- it exerts cholagogic effect By activating bile acid receptors and downstream signaling pathways
 - Regulating bile acid receptors FXR and TGR5, improving bile stasis and glucose lipid metabolism;
 - Inhibiting the downstream gene SREBP of FXR and improving non-alcoholic fatty liver disease;
- Principals: curcumin、emodin、polydatin



J Ethnopharmacol, 2021, 279:114320
Acta Pharmacol Sin 2016, 37: 1218-1228
J Ethnopharm. 2016, 194, 63-71



Hepatology 2016, 64: 760-773



Molecular Medicine Reports, 2018, 1863-1872
Toxicol Appl Pharmacol, 2016, 304: 99-109
Eur J Pharmacol, 2016, 770:99-109

Rheum officinale, rich in free anthraquinones, shows the best liver protecting and gall promoting effects and low toxicity

大黄 Rhubarb

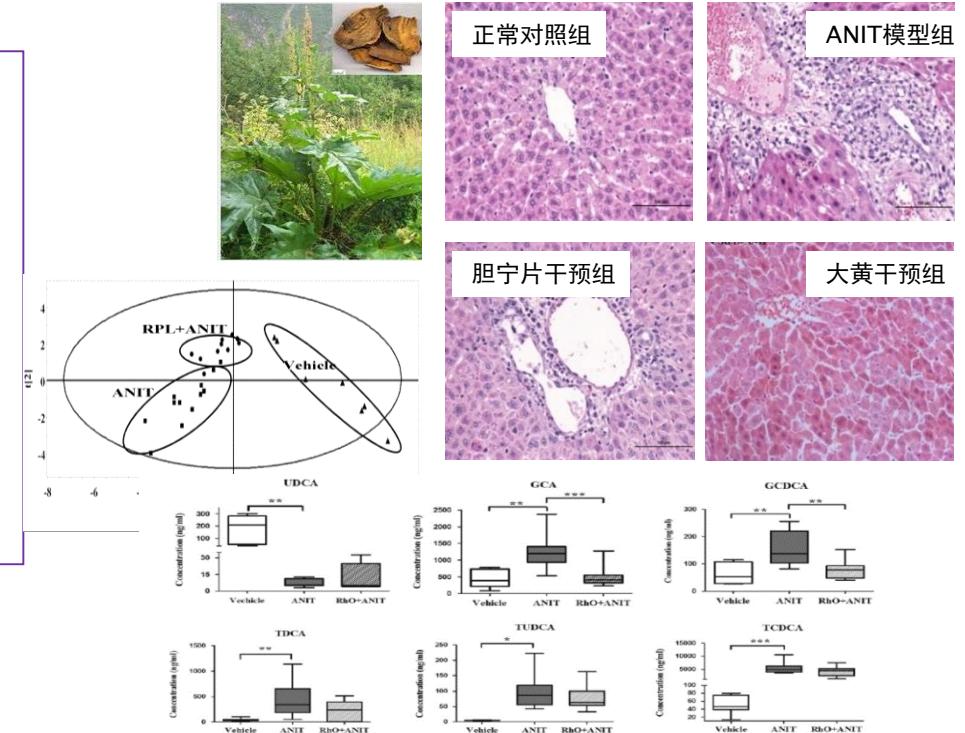
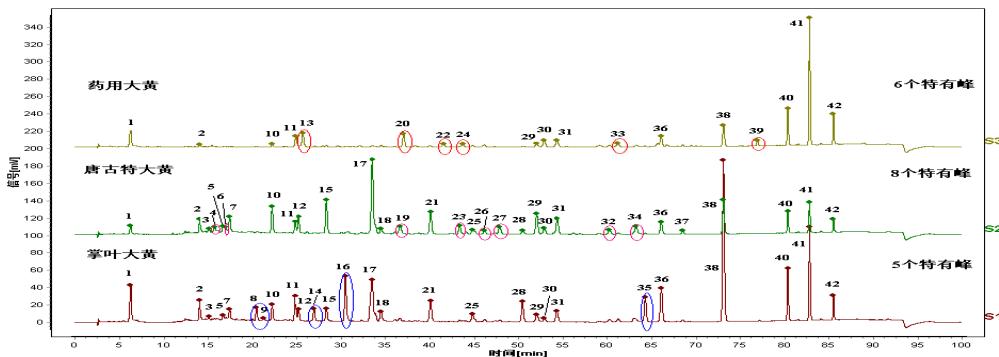
● 药用大黄(*Rheum officinale*)

High free anthraquinones but low sennosides

● 掌叶大黄(*R. palmatum*)

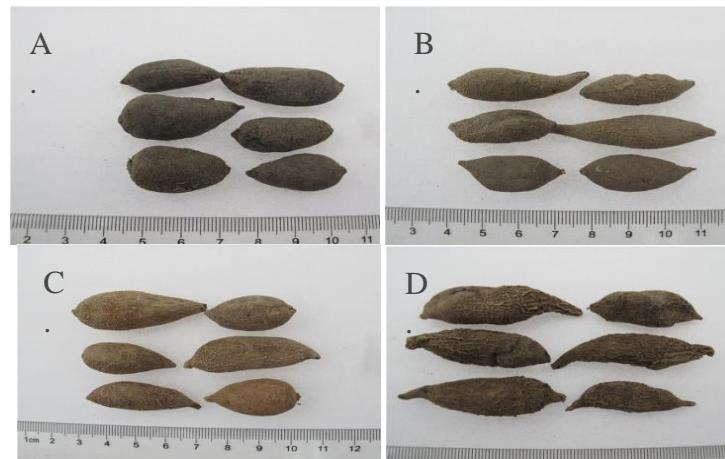
● 唐古特大黄(*R. tanguticum*)

High sennosides which are responsible for the side effects of diarrhea and colon melanosis of Rhubarb.



The effect of *Rheum officinale* on bile acid metabolism in rats

Curcuma longa shows the best both in curcumin content and liver protecting and gall promoting effects

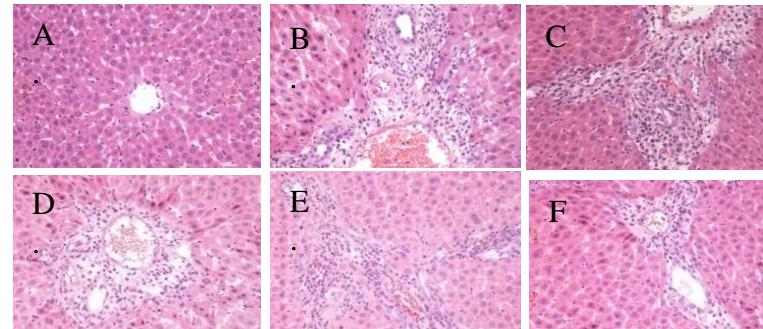


A. 蓬莪术 *Curcuma phaeocaulis*

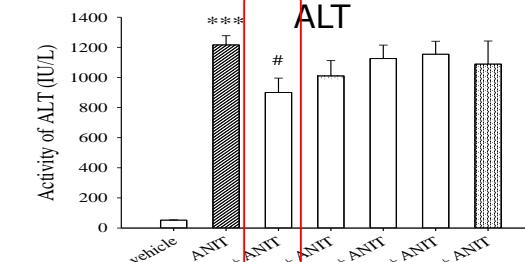
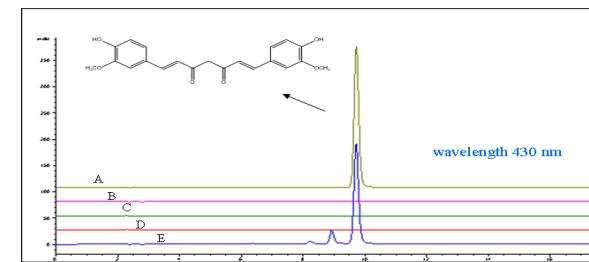
B. 黄丝郁金 (姜黄) *Curcuma longa*

C. 桂郁金 *Curcuma kwangsiensis*

D. 温郁金 (温莪术) *Curcuma wenyujin*

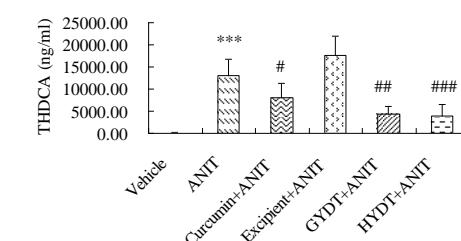
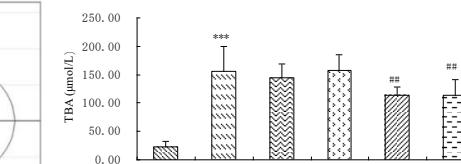
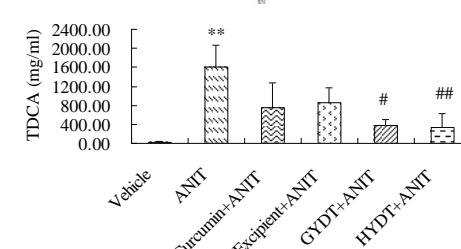
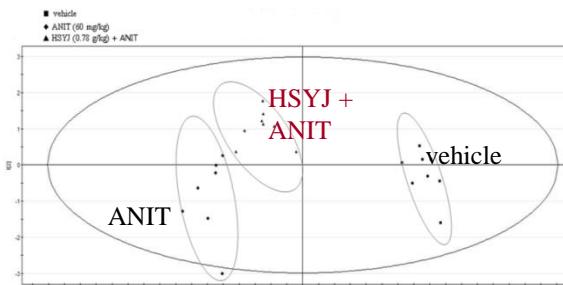


A. Control ; B. ANIT ; C. *Curcuma kwangsiensis*; D. *Curcuma wenyujin*
E. *Curcuma phaeocaulis* ; F. *Curcuma longa* (H&E, $\times 200$)



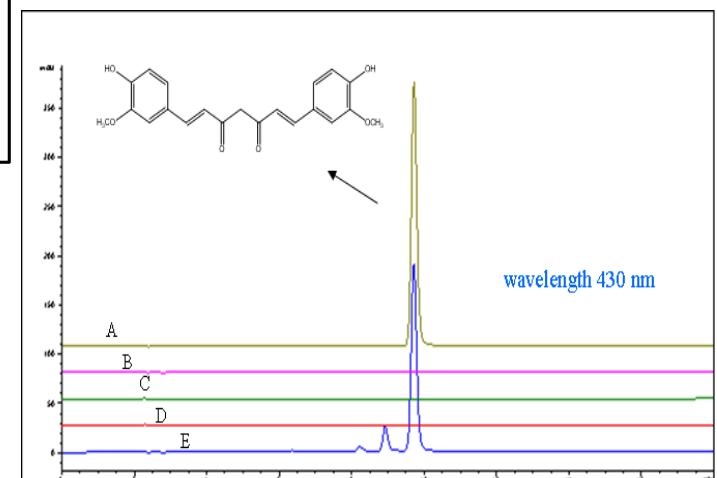
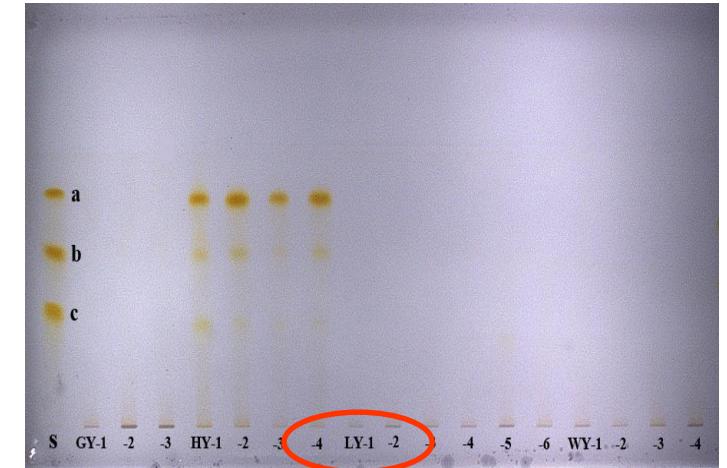
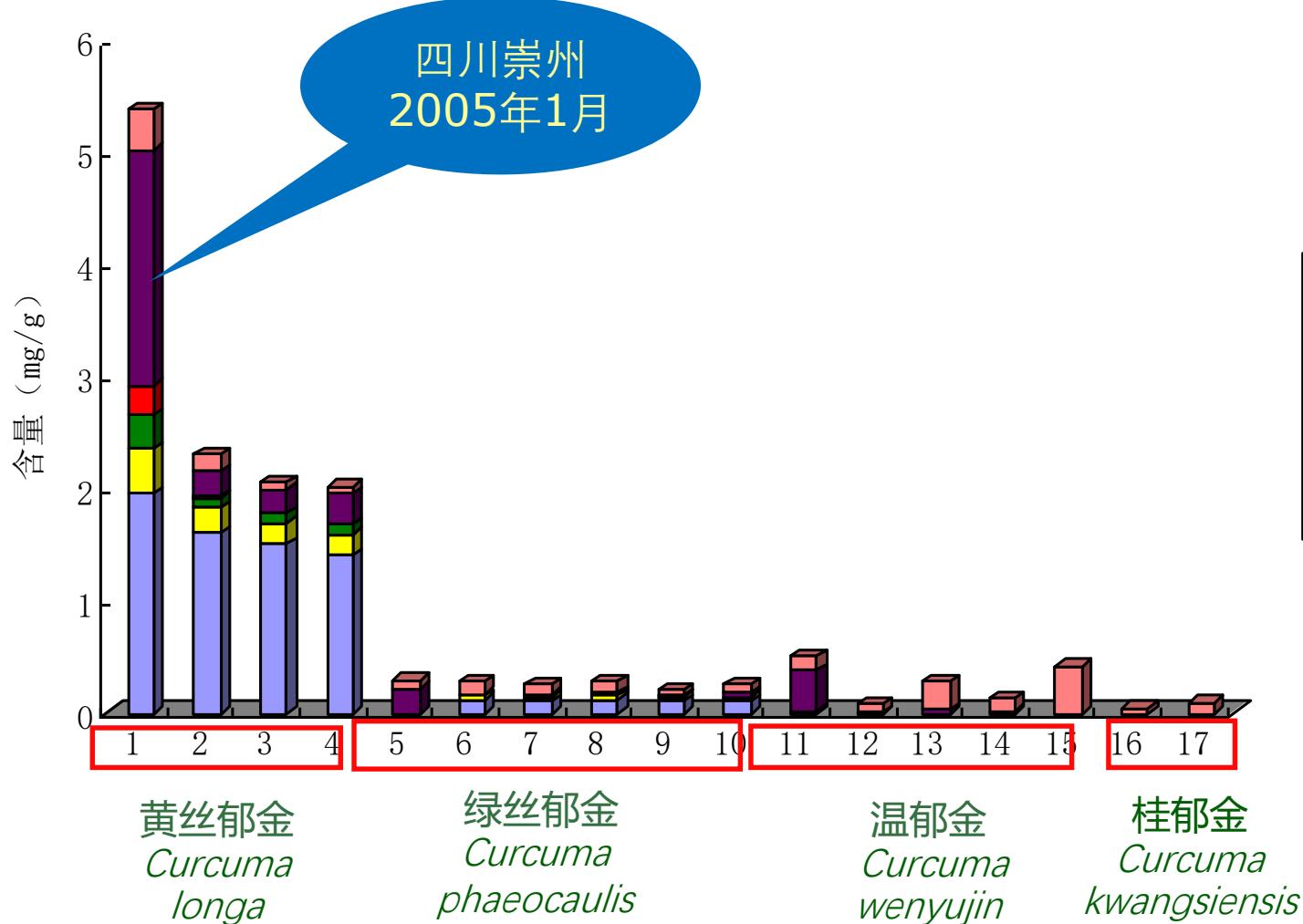
Curcuma longa shows the highest curcumin content and accordingly the more potent liver protecting and gall promoting effects

● The effect of Curcuma longa on bile acid metabolism in rats



Contents of Curcumin and sesquiterpenoids in multi-original Curcumae Radix

不同种郁金中姜黄素及倍半萜类成分含量



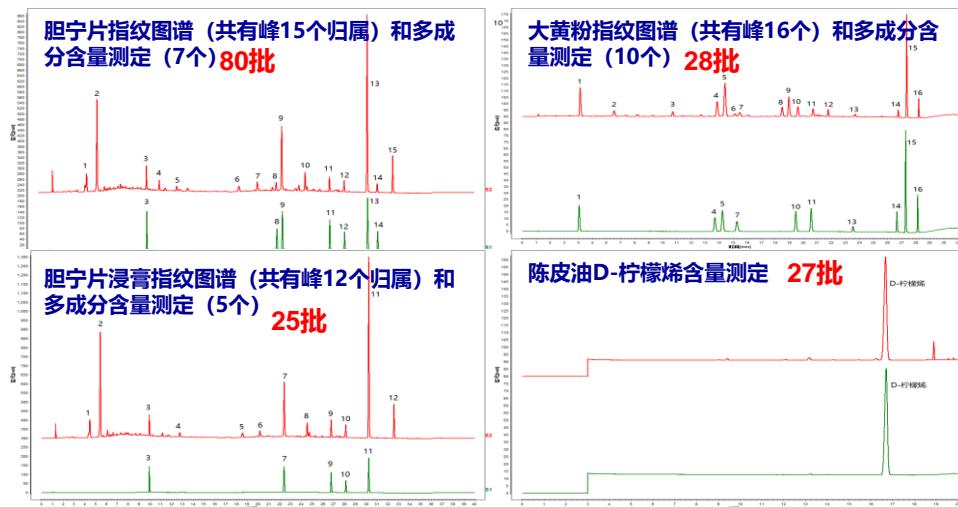
Whole process quality control system of “Raw materials-Intermediates-Preparations” of Biliflow

建立胆宁片“原料药-中间体-制剂”全过程质控体系

Construction of Crude drugs
farming field



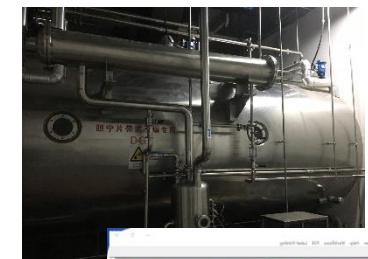
Establishment of intermediate and finished
product standards for Biliflow



J Chromatogr A, 2022, 1678:463342
Analytical Chimica Acta 2019, 1046:148-153
Molecules, 2016, 21: 631

Manufactory process
improvement

- 设备优化：提取自动化、带干设备、干燥粉碎一体化；
- 微生物控制：大黄药材；
- 质量系统控制建立：QMS,LIMS

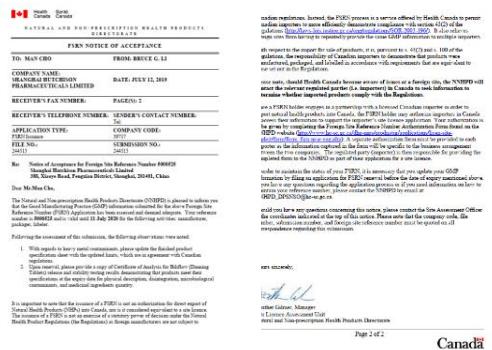


An example of basic research contributing to the internationalization of TCM



上海重点中药产品成首个“功能主治”全部被欧美国家政府认可的复方中药
讲清七味药，胆宁片“走出国门”

标志我国中药现代化、国际化重要进展，其“路径选择”值得国内企业借鉴



Biliflow (胆宁片) 加拿大药品注册标准

FSRN证书 (5000525)

- Danning Tablets (Biliflow) licensed in Canadian in 2016 (NPN: 80073325), and obtained the Overseas Site Registration Certificate and Foreign Site Reference Number (FSRN), started marketing in Canada in 2022.
- It serves as a demonstration of the internationalization of traditional Chinese compound medicines.



2022年上海市科技进步奖（一等奖）

中药质量评鉴技术集成创新与应用

**Integrated Innovation and Application in
Quality Evaluation Technologies of TCMs**

**完成单位：上海中医药大学
上海中药标准化研究中心**



Thanks and welcome to visit our institute !

Institute of Chinese Meteria Medica,
Shanghai University of Traditional Chinese Medicine

