

# REGIONAL REPORT (SHANGHAI)



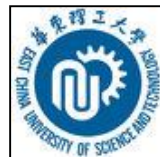
**Zhengtao Wang**

**Shanghai University of TCM**

**19<sup>th</sup> 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

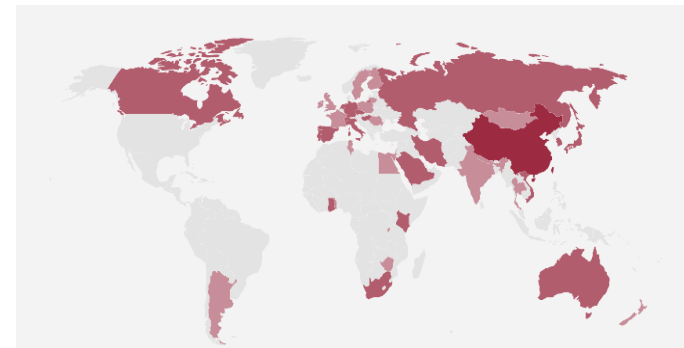
Standardization in the field of medical systems derived from ancient Chinese medicine which shall be able to share one common set of standards. Both traditional and modern aspects of these systems are covered. The committee focuses on quality and safety of raw materials, manufactured products and medical 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)

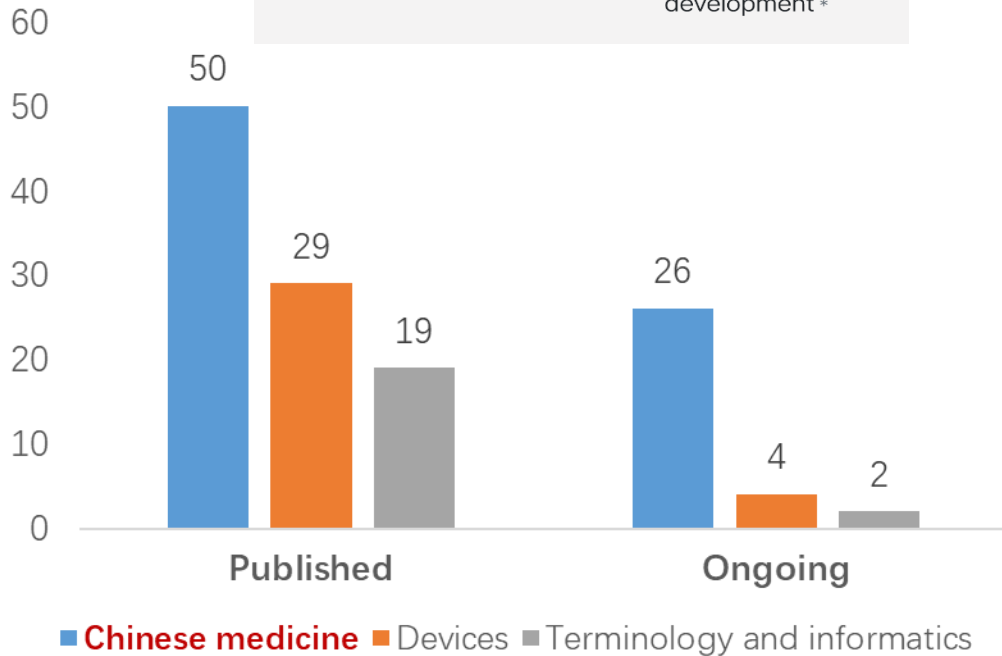
### ISO standards of Traditional Chinese medicine

98

Published ISO standards \*

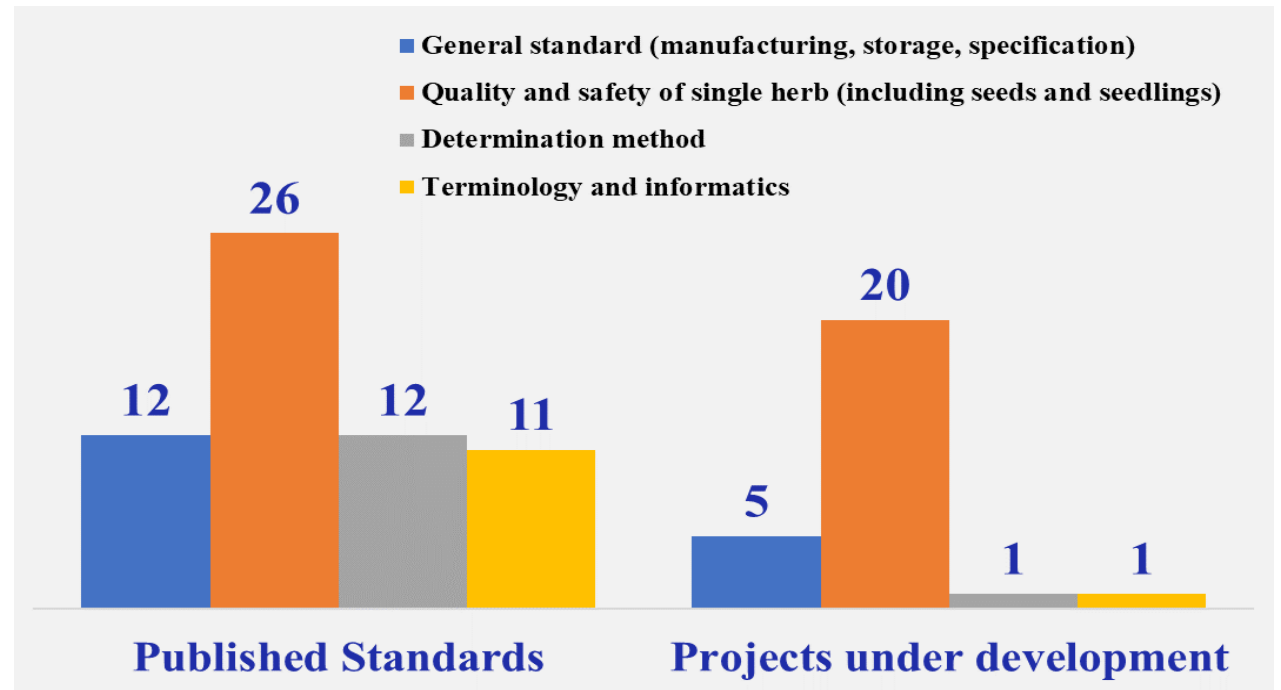
32

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.





# 13<sup>th</sup> 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



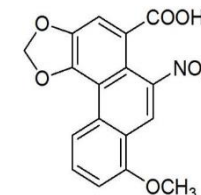
ISO 23193: 2020



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



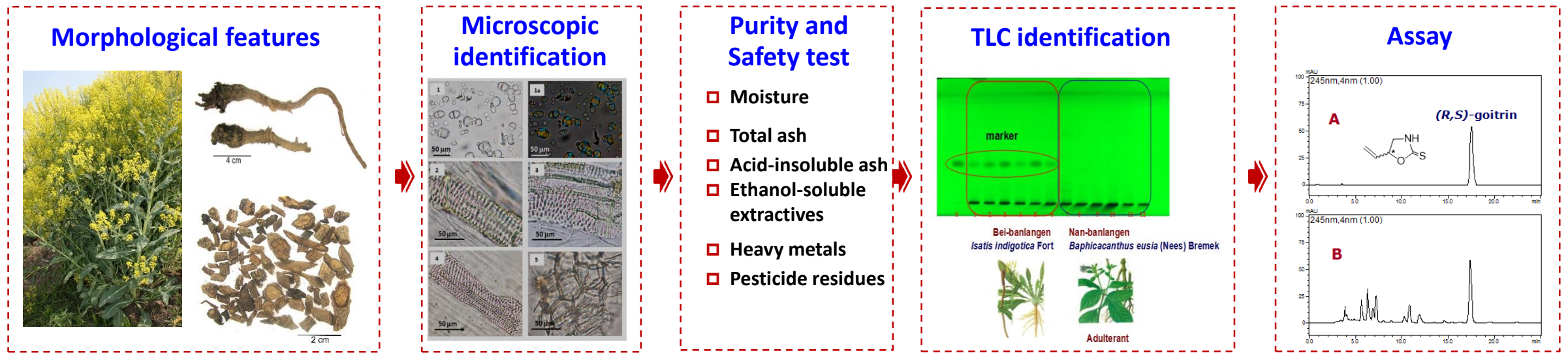
# Underdevelopment ISO standards of single herbs

1. ISO/FDIS 7450 Traditional Chinese Medicine — *Pinellia ternata* tuber 半夏
2. ISO/DIS 13619 Traditional Chinese Medicine — *Gardenia jasminoides* fruit 栀子
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

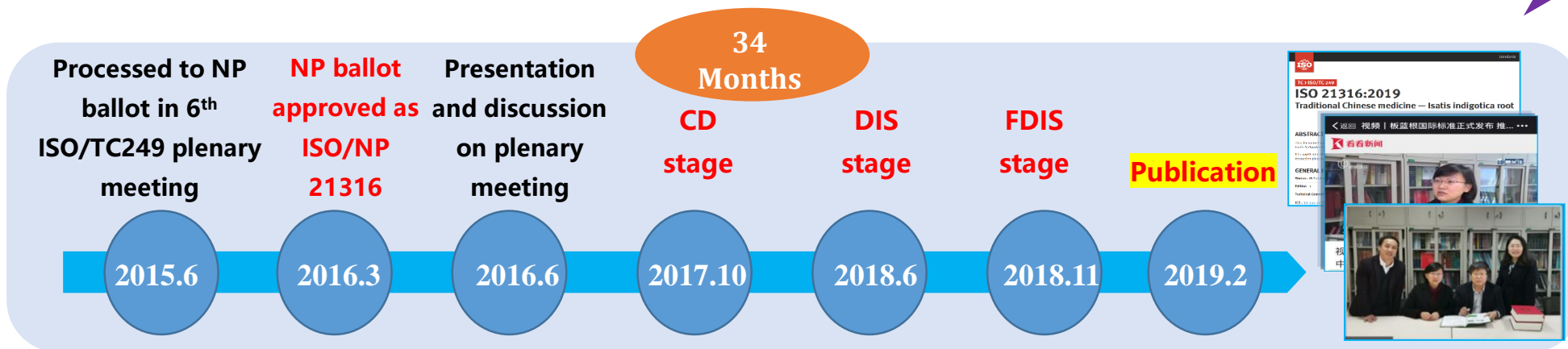


# ISO 21316: 2019 Traditional Chinese medicine — *Isatis indigotica* root

## ➤ Quality contents and Requirements



## ➤ Process of standard development



## ➤ Achievements

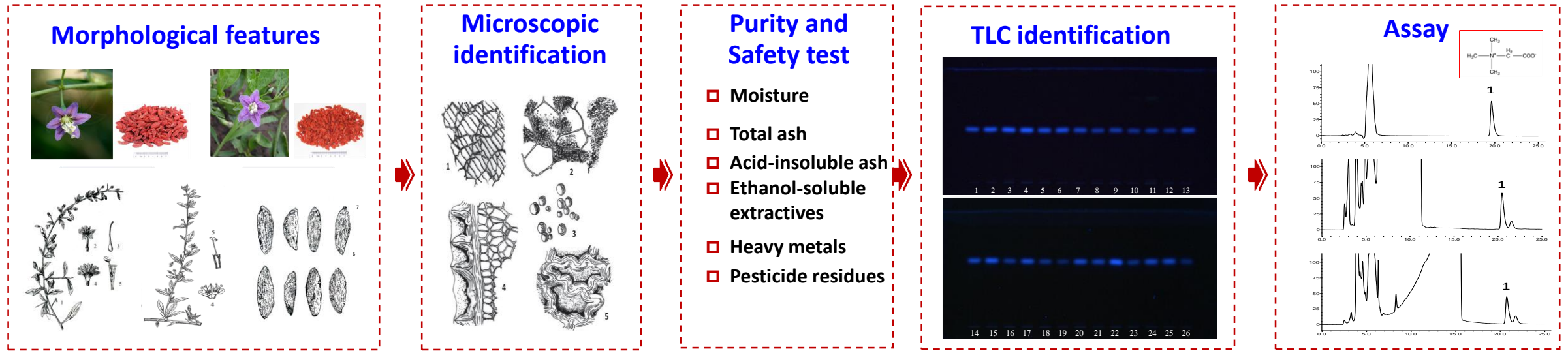
**Published papers: 20**  
**Patents: 2**

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

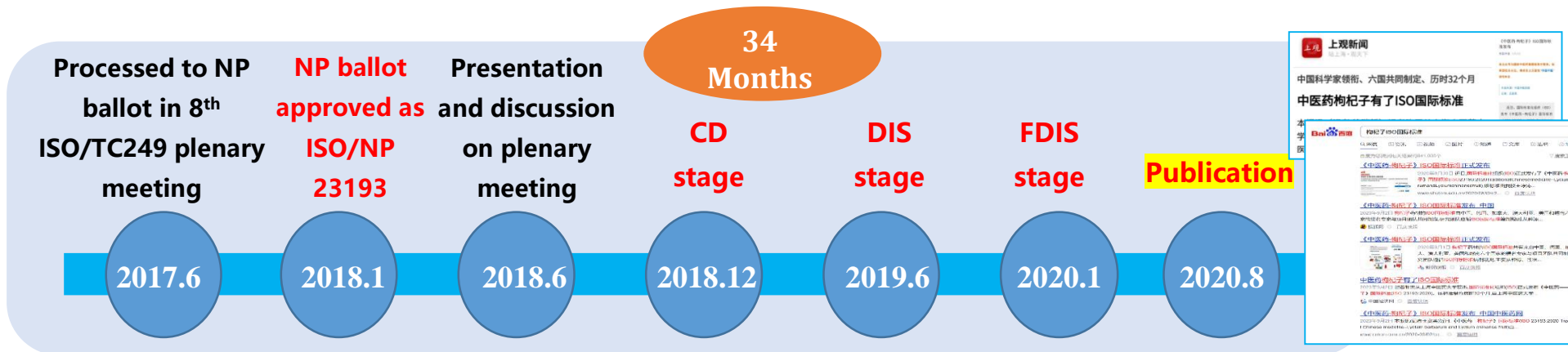


# ISO 23193: 2020 Traditional Chinese medicine — *Lycium barbarum* and *Lycium chinense* fruit

## ➤ 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

**上海市药品监督管理局**  
**上海市中药配方颗粒标准**  
SH-PFKL-2022002

**炒椿皮配方颗粒**  
Chaochunpi Peifangke

**【来源】**本品为苦木科植物臭椿 *Ailanthus altissima* (Mill.) Swingle 的干燥根皮或干皮经炮制并按标准汤剂的主要质量指标加工制成的配方颗粒。

**【制法】**取炒椿皮饮片 12000g, 加水煎煮, 滤过, 滤液浓缩成清膏 (干浸膏出膏率为 4.2%~8.3%), 加入辅料适量, 干燥 (或干燥、粉碎), 再加入辅料适量, 混匀, 制粒, 制成 1000g, 即得。

**【性状】**本品为棕黄色至棕褐色的颗粒; 气微, 味苦。

**【鉴别】**取本品 2g, 研细, 加乙醚 20ml, 超声处理 15 分钟, 滤过, 滤液挥干, 残渣加乙醇 1ml 使溶解, 作为供试品溶液。另取椿皮对照药材 2g, 同法制成对照药材溶液。照薄层色谱法 (中国药典 2020 年版通则 0502) 试验, 吸取供试品溶液 15 $\mu$ l, 对照药材溶液 10 $\mu$ l, 分别点于同一硅胶 G 薄层板上, 以石油醚 (60~90 $^{\circ}$ C)-乙酸乙酯 (4:1) 为展开剂, 展开, 取出, 晾干, 置紫外光灯 (365nm) 下检视。供试品色谱中, 在与对照药材色谱相应的位置上, 显相同颜色的荧光斑点。

**【特征图谱】**照高效液相色谱法 (中国药典 2020 年版通则 0512) 测定。

**色谱条件与系统适用性试验** 以十八烷基硅烷键合硅胶为填充剂; 以乙腈为流动相 A, 以 0.1%磷酸溶液为流动相 B; 按下表中的规定进行梯度洗脱; 检测波长为 254nm。理论板数按铁屎米酮峰计算应不低于 10000。

时间 (分钟)	流动相 A (%)	流动相 B (%)
0~8	10~15	90~85
8~45	15~25	85~75
45~65	25~29	75~71

**参照物溶液的制备** 取炒椿皮对照饮片 5g, 加水 50ml, 加热回流 1.5 小时, 放冷, 滤过, 滤液蒸干, 残渣加 10%氨水溶液 25ml 使溶解, 用二氯甲烷振摇提取 2 次, 每次 25ml, 合并

二氯甲烷液, 挥干, 残渣加甲醇 2ml 使溶解, 摇匀, 滤过, 取续滤液, 作为对照饮片参照物溶液。另取铁屎米酮对照品适量, 精密称定, 加甲醇制成每 1ml 含 40 $\mu$ g 的溶液, 作为对照品参照物溶液。

**供试品溶液的制备** 取本品适量, 研细, 取约 1.0g, 精密称定, 置具塞锥形瓶中, 加入 10%氨水溶液 25ml, 振摇使溶解, 用二氯甲烷提取 2 次, 每次 25ml, 合并二氯甲烷液, 挥干, 残渣用适量甲醇溶解并转移至 5ml 量瓶中, 加甲醇至刻度, 摇匀, 滤过, 取续滤液, 即得。

**测定法** 分别精密吸取参照物溶液和供试品溶液各 10 $\mu$ l, 注入液相色谱仪, 测定, 即得。

供试品色谱中应呈现 9 个特征峰, 并应与对照饮片参照物色谱中的 9 个特征峰保留时间相对应, 其中峰 9 应与铁屎米酮对照品参照物峰的保留时间相对应。与铁屎米酮参照物峰对应的峰为 S 峰, 计算各特征峰与 S 峰的相对保留时间, 其相对保留时间应在规定值的 $\pm$ 10%之内。规定值为: 0.13 (峰 1)、0.25 (峰 2)、0.27 (峰 3)、0.36 (峰 4)、0.46 (峰 5)、0.75 (峰 6)、0.79 (峰 7)、0.82 (峰 8)。

对照特征图谱

峰 1: 5-羟甲基-1H-吡咯-2-甲腈 峰 4: 松杉醇 峰 9 (S): 铁屎米酮

**【检查】**应符合颗粒剂项下有关的各项规定 (中国药典 2020 年版通则 0104)。

**【浸出物】**取本品适量, 研细, 取约 3g, 精密称定, 精密加入乙醇 100ml, 照醇溶性浸出物测定法 (中国药典 2020 年版通则 2201) 项下的热浸法测定, 不得少于 15.0%。

**【含量测定】**照高效液相色谱法 (中国药典 2020 年版通则 0512) 测定。

**色谱条件与系统适用性试验** 以十八烷基硅烷键合硅胶为填充剂; 以乙腈-0.1%磷酸溶液 (29:71) 为流动相; 检测波长为 360nm。理论板数按铁屎米酮峰计算应不低于 10000。

**对照品溶液的制备** 取铁屎米酮对照品适量, 精密称定, 加甲醇制成每 1ml 含 7.5 $\mu$ g 的溶液, 即得。

**供试品溶液的制备** 取本品适量, 研细, 取约 0.4g, 精密称定, 置具塞锥形瓶中, 精密加入甲醇 20ml, 密塞, 称定重量, 超声处理 (功率 100W, 频率 40kHz) 30 分钟, 放冷, 再称定重量, 用甲醇补足减失的重量, 摇匀, 滤过, 取续滤液, 即得。

**测定法** 分别精密吸取对照品溶液与供试品溶液各 20 $\mu$ l, 注入液相色谱仪, 测定, 即得。

本品每 1g 含铁屎米酮 (C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O) 应为 0.070mg~1.0mg。

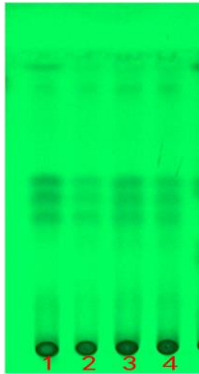
**【规格】**每 1g 配方颗粒相当于饮片 12g。

**【贮藏】**密封。

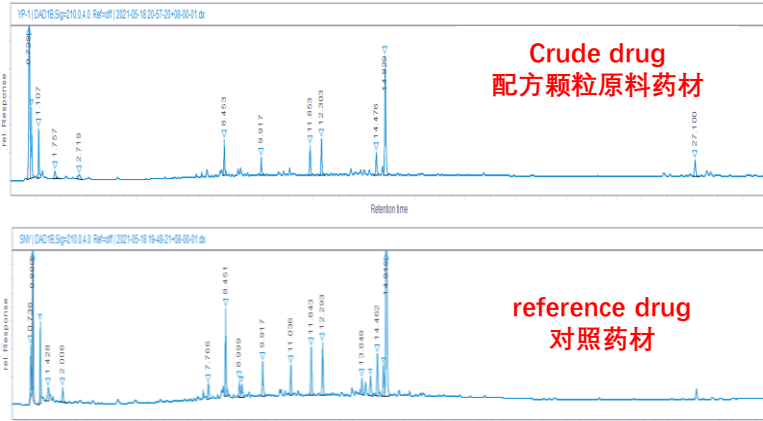
# Criteria of Shanghai TCM Formula Granules——

## 石斛 DENDROBII CAULIS

### Identification of the crude drug



1. reference drug;  
2-4. Crude drug;



Crude drug  
配方颗粒原料药材

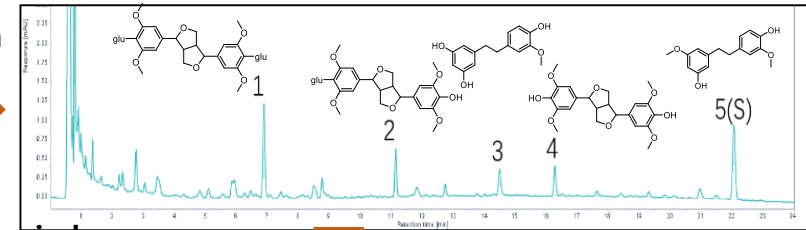
reference drug  
对照药材

### Identification of Characteristic peak and selection of chemical reference standard

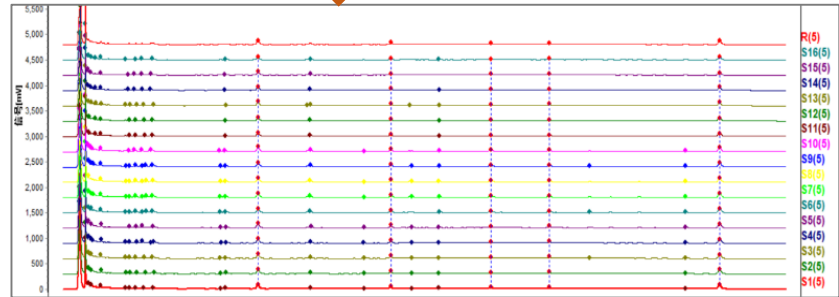
Literature research



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



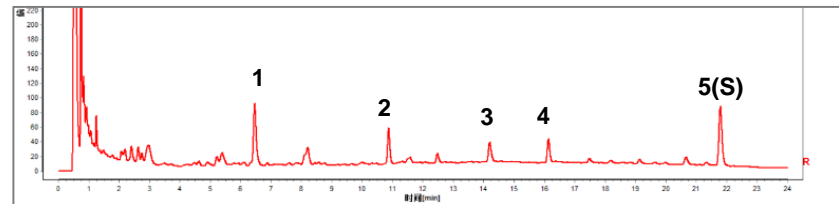
HPLC/UPLC/GC analysis



Assay



Mass  
Transfer  
Analysis

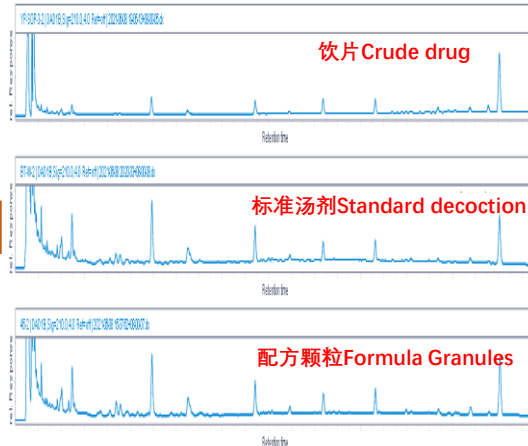


### Characteristic chromatogram

Quality standard  
( Draft )



Content  
range



饮片Crude drug

标准汤剂Standard decoction

配方颗粒Formula Granules

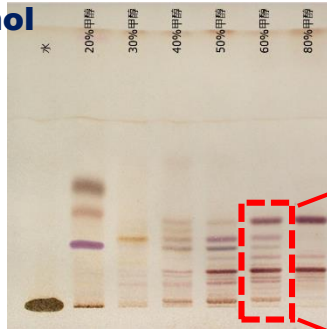
1: Liriodendrin 2: Episyringaresinol 4'-O- $\beta$ -D-glycopyranoside 3: Tristin

4: Syringaresinol 5 (S) : gigantol (Characteristic peak, chemical reference standard)

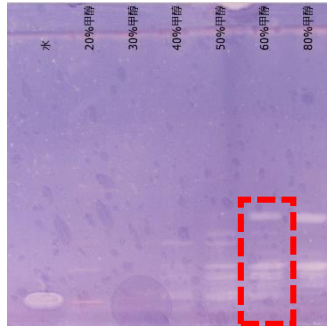
# Criteria of Shanghai TCM Formula Granules—— 白扁豆 LABLAB SEMEN ALBUM

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

10% solution of Sulfuric acid in ethanol



TLC-Bioautography

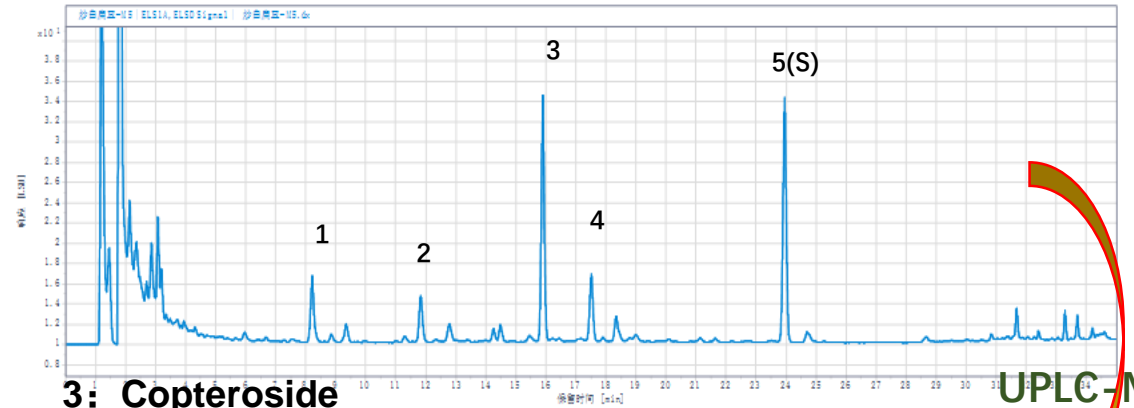


8  
7  
6  
5  
4  
3  
2  
1

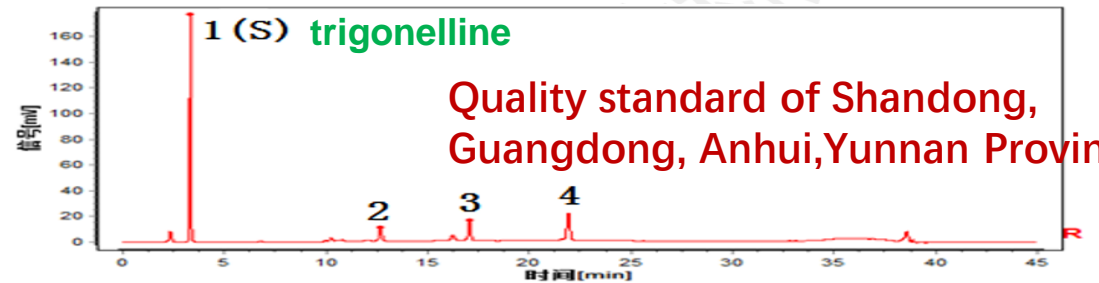
TLC-MS

- B1: Lablaboside E B2: Lablaboside B B3: Lablaboside D  
 B4:  $3\beta$ -[(2-O- $\alpha$ -L-rhamnopyranosyl-2-O- $\beta$ -D-galactopyranosyl)-1- $\beta$ -D-glucuronopyranosyl]oxy]-22 $\alpha$ ,24-dihydroxyolean-12-en-28-al  
 B5: Sandosaponin B B6: Azukisaponin III B7: Quinoasaponin-9  
 B8: Chikusetsusaponin IVa

## Characteristic chromatogram and Assay



- 3: Copteroside  
 4:  $3\beta$ -[(2-O- $\alpha$ -L-rhamnopyranosyl-2-O- $\beta$ -D-galactopyranosyl)- $\beta$ -D-glucuronopyranosyl]oxy]-22 $\alpha$ ,24-dihydroxyolean-12-en-28-al  
 5(S): Chikusetsusaponin IVa



Quality standard of Shandong, Guangdong, Anhui, Yunnan Province

对照特征图谱

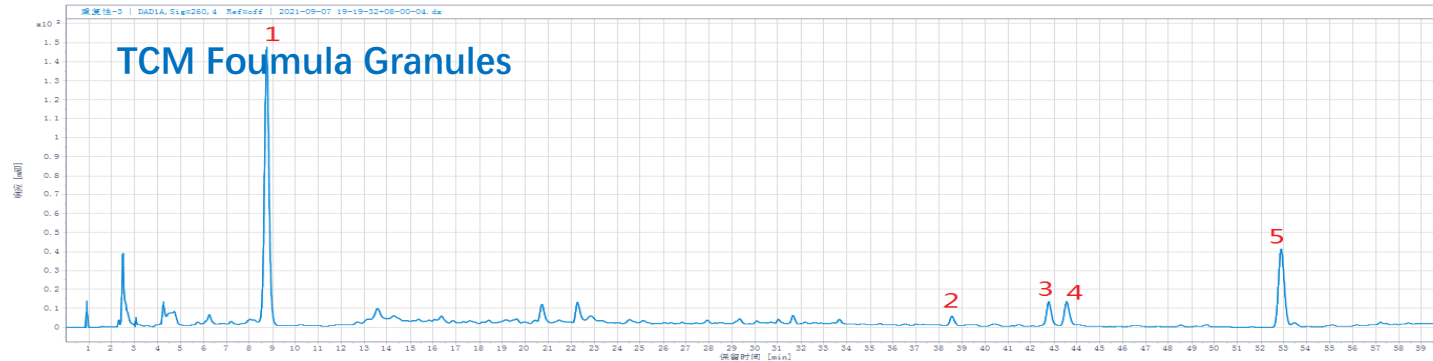
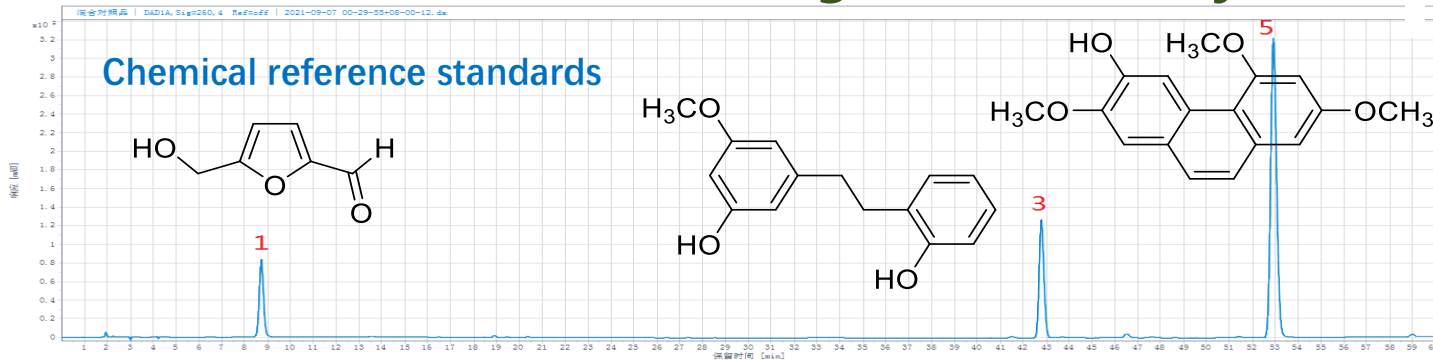
峰 1 (S): 葫芦巴碱



# Criteria of Shanghai TCM Formula Granules——

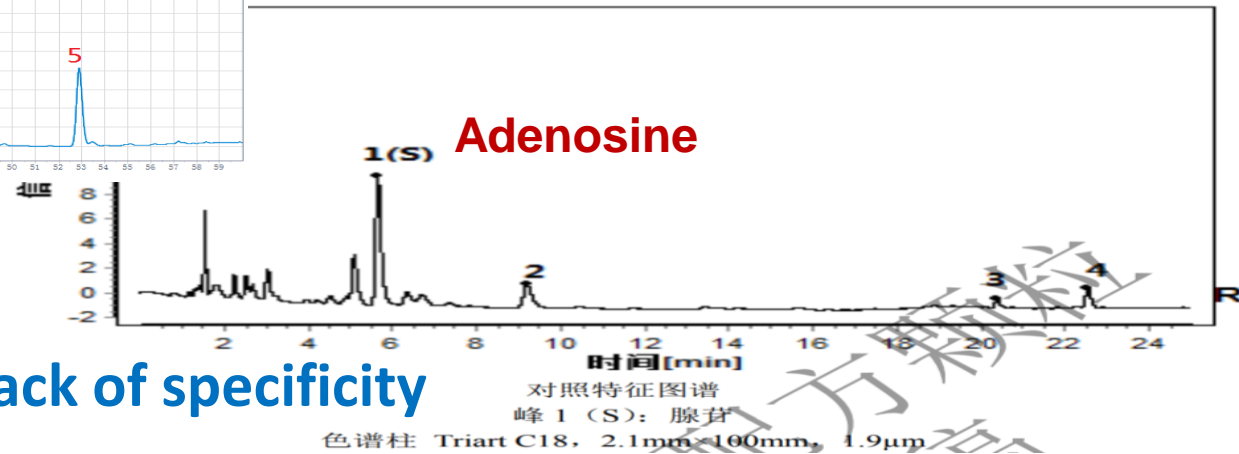
## 山药/蜜麸山药 DIOSCOREAE RHIZOMA

### Characteristic chromatogram and Assay



1:5-Hydroxymethylfurfural; 3: Batatasin IV IV;  
5 (s) : Batatasin I

Quality standard of Shandong province



Lack of specificity

### 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:

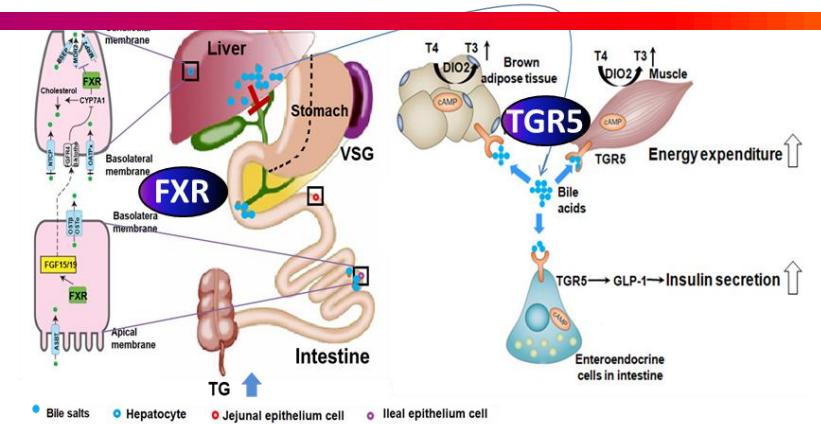
- 大黄：3 种植物来源
- 药用大黄
  - 掌叶大黄
  - 唐古特大黄

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

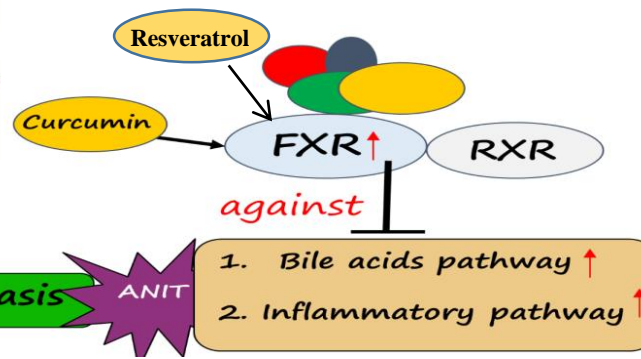
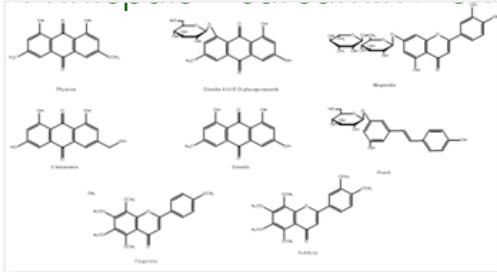
# Elucidation of Bioactive substances and Underling Mechanism of Biliflow

## 揭示胆宁片功效物质基础、作用机理

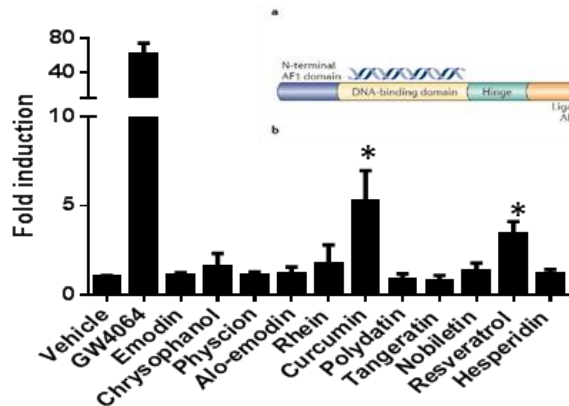
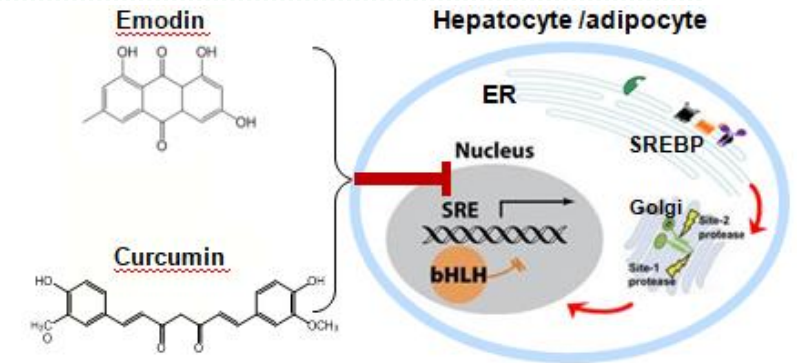
- it exerts cholagogic effect By activating bile acid receptors and downstream signaling pathways
  - Regulating bile acid receptors FXR and TGR5, improving bile stasis and glucose lipid metabolism;
  - nhibiting the downstream gene SREBP of FXR and improving non-alcoholic fatty liver disease;



- Principals: curcumin, emodin, polydatin



Hepatology 2016, 64: 760-773



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

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

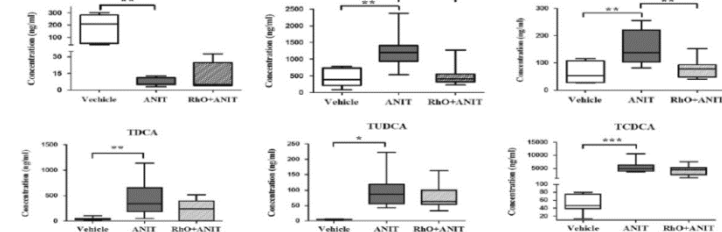
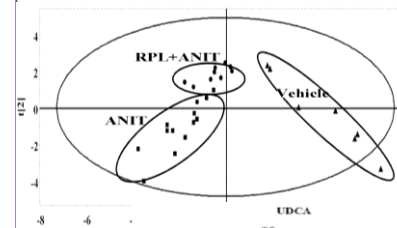
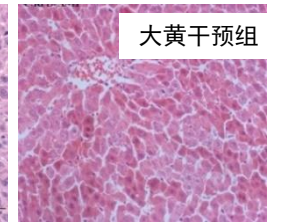
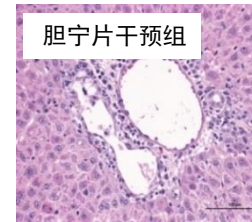
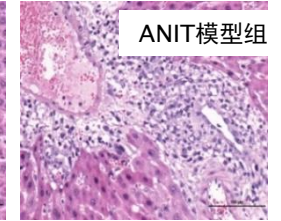
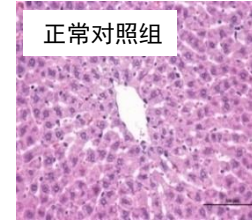
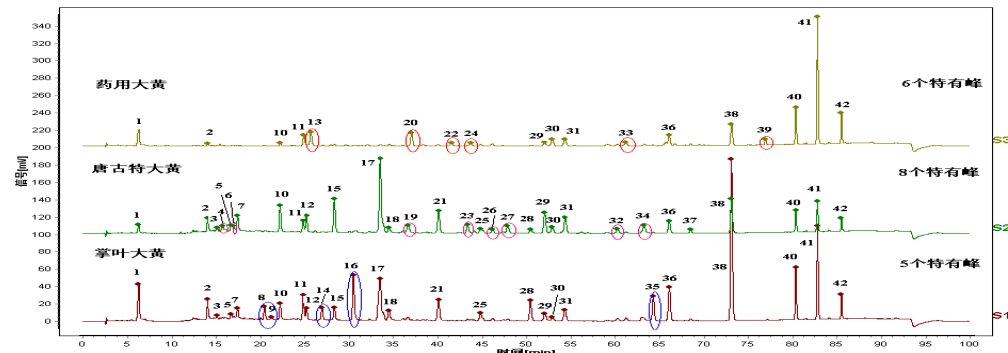
- 药用大黄 (*Rheum officinale*)

High free anthraquinones but low sennosides

- 掌叶大黄 (*R. palmatum*)

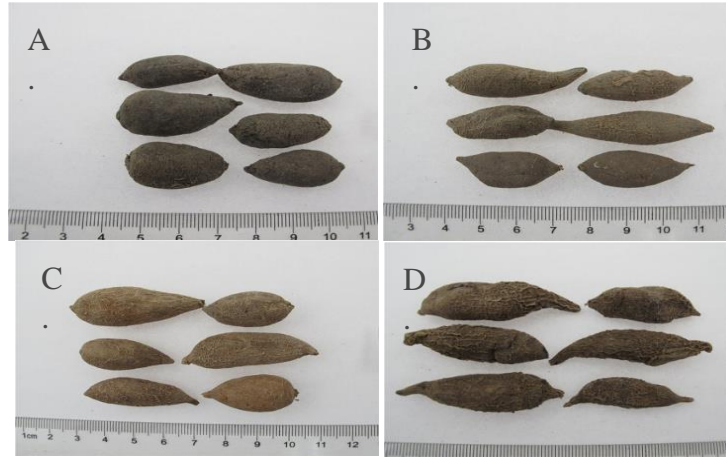
- 唐古特大黄 (*R. tanguticum*)

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

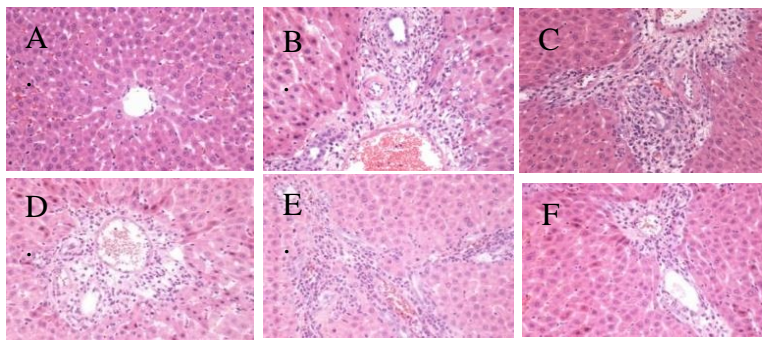


The effect of *Rheum officinale* on bile acid metabolism in rats

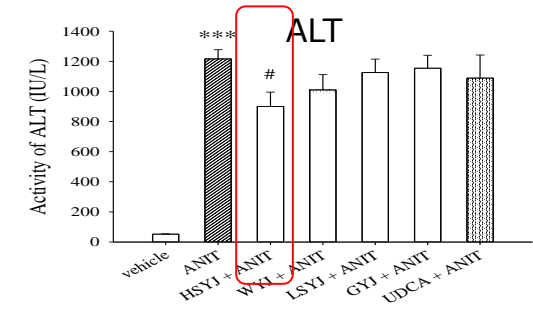
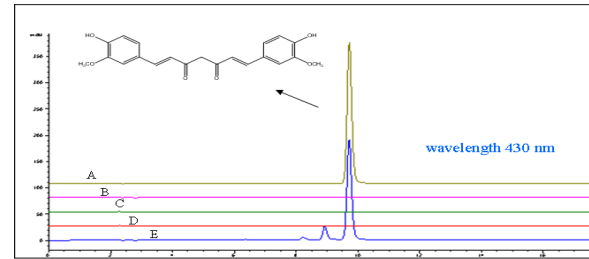
# Curcuma longa shows the best both in curcumin content and liver protecting and gall promoting effects



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*

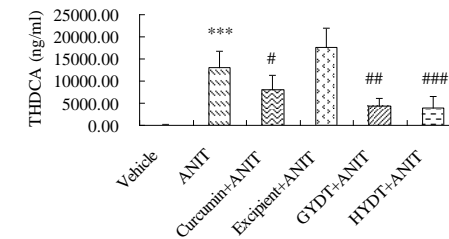
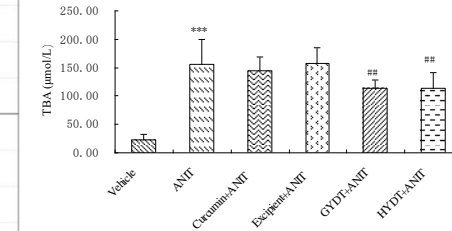
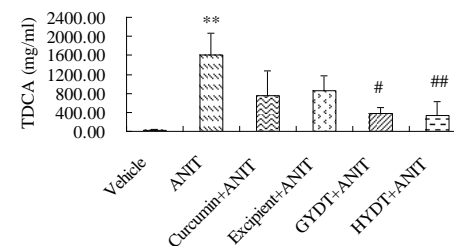
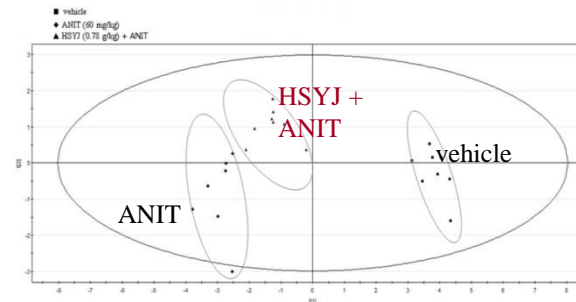


A. Control ; B. ANIT ; C. *Curcuma kwangsiensis*; D. *Curcuma wenyujin*  
 E. *Curcuma phaeocaulis* ; F. *Curcuma longa* (H&E, × 200)



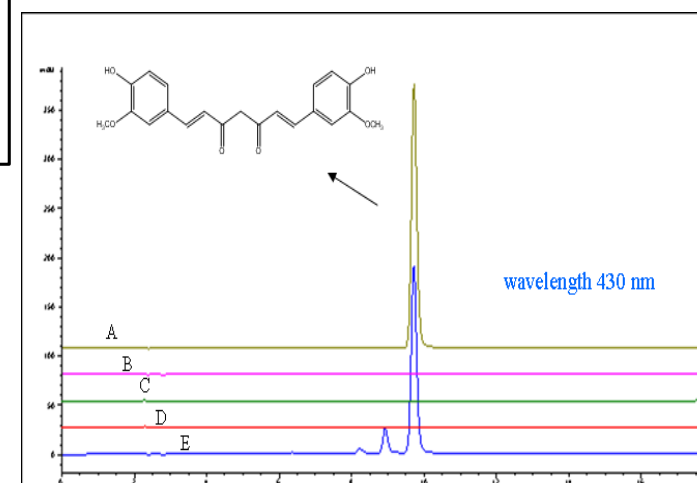
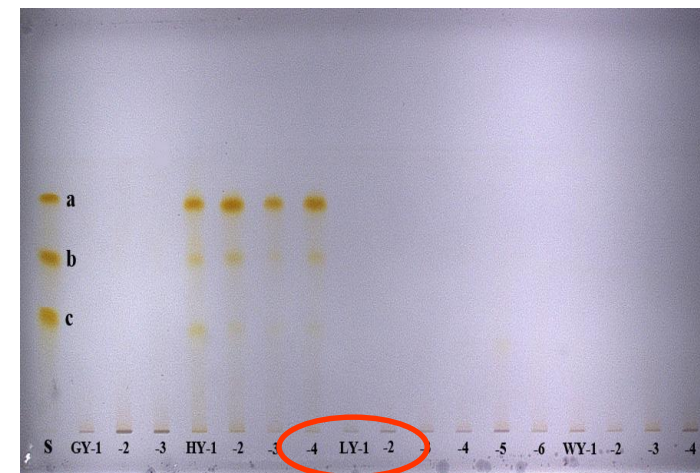
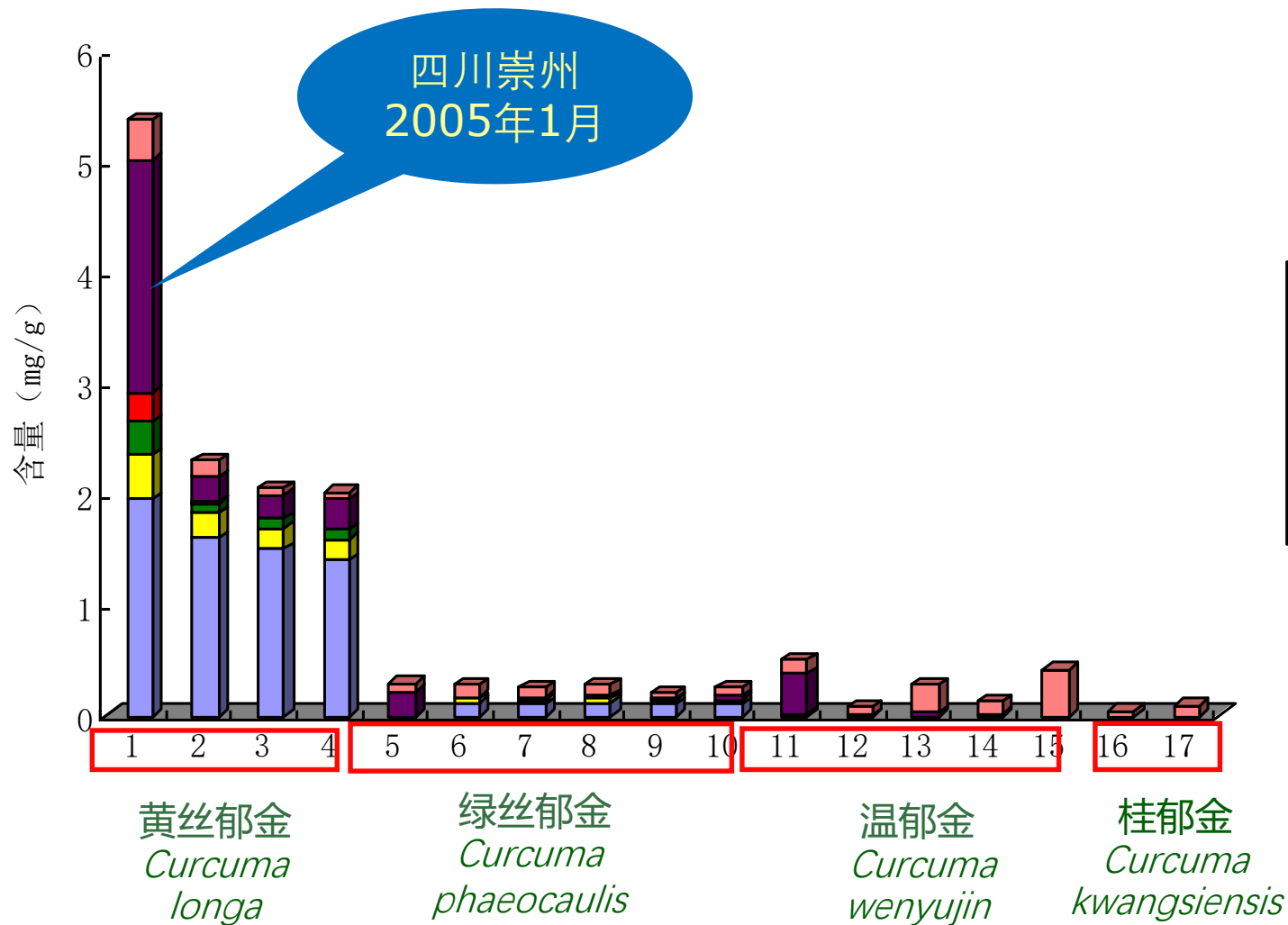
Curcuma longa shows the highest curcumin content and accordingly the more potent liver protecting and gall promoting effects

## ● 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



大黄



郁金

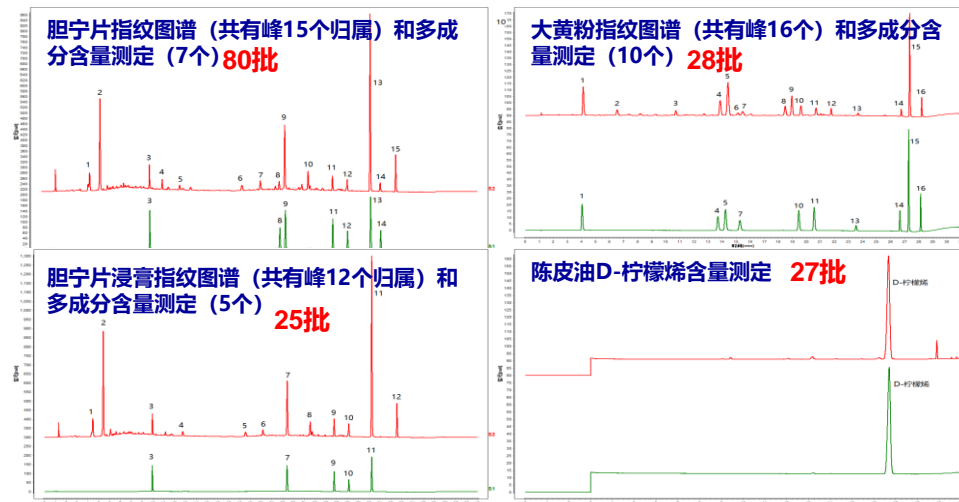
药用大黄基地 (四川北川)



郁金基地 (广西玉林)



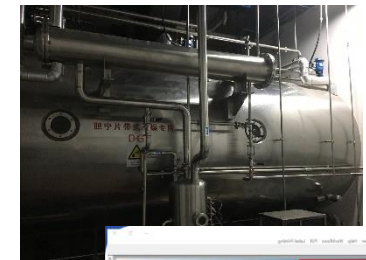
Establishment of intermediate and finished  
product standards for Biliflow



*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



- Danning Tablets (Biliflow) licensed in Canadian in 2016 (NPN: 80073325), and obtained the Overseas Site Registration Certificate and Foreign Site Reference Number (FSRN), started domestic marketing in Canada in 2022.

- It serves as a demonstration of the internationalization of traditional Chinese compound medicines.

Product Name	Manufacturer	Country of Origin	Product Category	Registration Status
Biliflow (胆宁片)	Shanghai Zhongyao	China	Traditional Chinese Medicine	Registered

Product Name	Manufacturer	Country of Origin	Product Category	Registration Status
Biliflow (胆宁片)	Shanghai Zhongyao	China	Traditional Chinese Medicine	Registered

Product Name	Manufacturer	Country of Origin	Product Category	Registration Status
Biliflow (胆宁片)	Shanghai Zhongyao	China	Traditional Chinese Medicine	Registered

Foreign Site Reference Number (FSRN) issued to Shanghai Zhongyao for Biliflow (胆宁片) in Canada. The FSRN is 5000525. The document includes details about the manufacturer, product, and the regulatory process.

22

Biliflow (胆宁片) 加拿大药品注册标准

FSRN证书 (5000525)



胆宁片在和黄药业奉贤基地发货，运往多伦多港

**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 Materia Medica,  
Shanghai University of Traditional Chinese Medicine**

