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Oral bioavailability of celastrol following administration of pure celastrol and its related tablets in rats

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General characteristics of TCM

- TCM characteristics :

multi-component mixture, holistic-regulating, the history of long-term use by human (experience-based);

- TCM resources:

12807 species including 11146 herbs, 1581 animal-derived and 80 minerals; about 300-500 species commonly used in TCM clinical practice

- TCM Modernization:

a process of providing scientific evidence for the safety, quality and efficacy to develop evidence-based medicine.

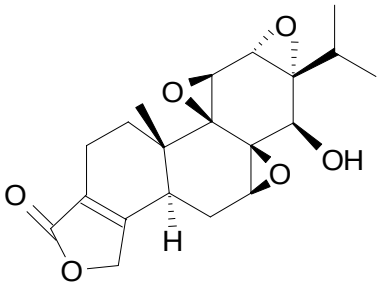
Background

- Thunder God Vine,
  Trypterygium wilfordii Hook F.,
  Shennong Bencao Jing (221BC- 200)
  Chinese name: 雷公藤

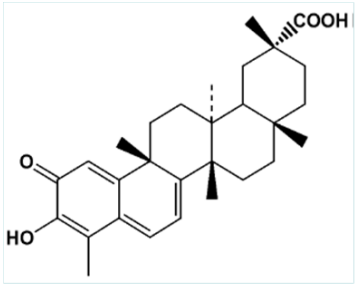
- The xylem, TGV root (removed away the scarfskin)
- To treat rheumatoid arthritis, systemic lupus erythematosus, and cancer, etc.

Background

- Pharmacological activities: immunosuppression, anti-inflammatory, antioxidant, anti-bacterial, anti-cancer, and anti-fertility, etc.
- Toxicity: hepatotoxicity, nephrotoxicity, and reproduction toxicity , etc.
- More than 450 compounds isolated from TGV. About 90% of them were terpenoids, containing 118 diterpenes, 130 triterpenes, 77 sesquiterpene pyridine alkaloids, 78 sesquiterpene polyol esters and 53 other compounds.
- Triptolide and Celastrol have become the hot issue of research in recent years. They have been demonstrated to be not only effective, but also poisonous.



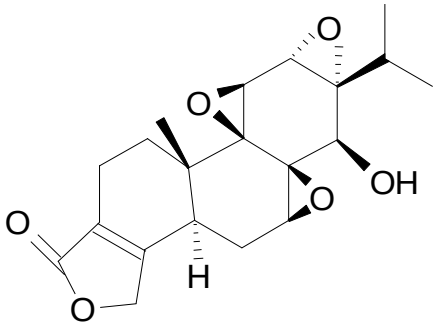
Celastrol



Triptolide

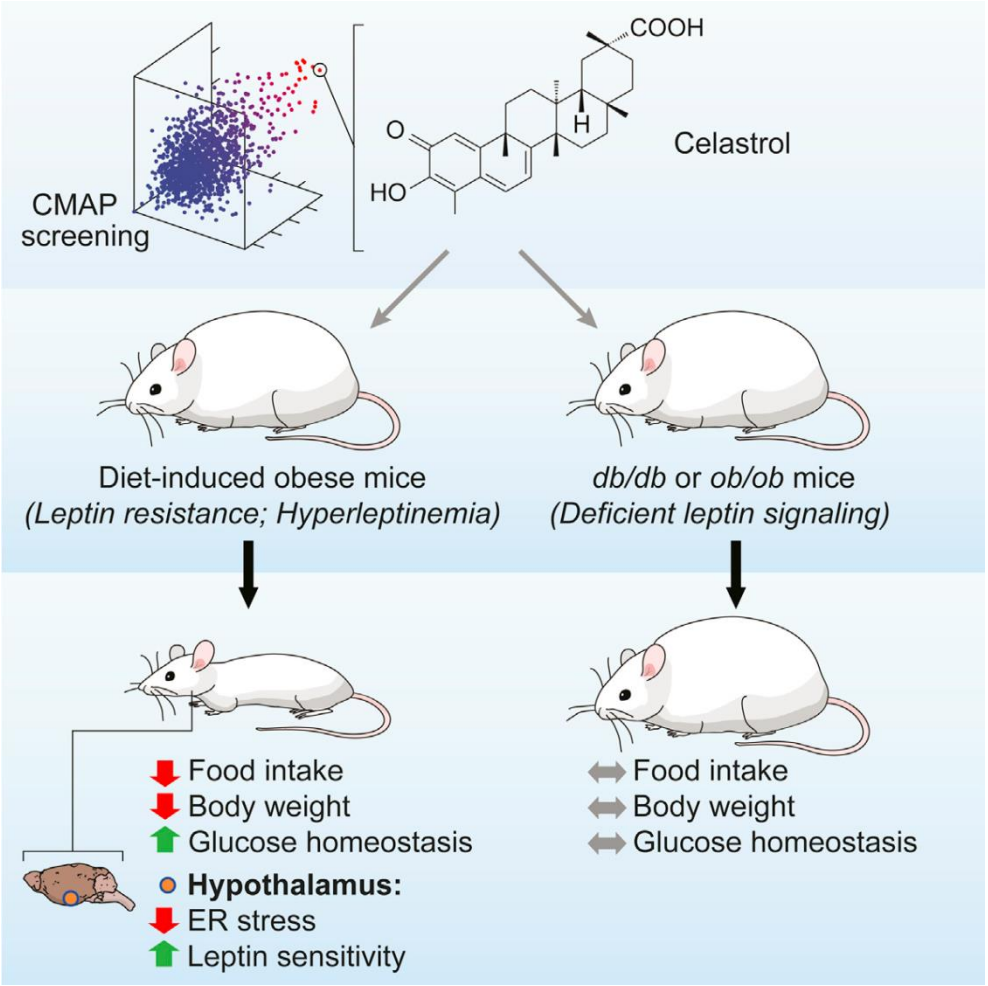
Background

- Celastrol, isolated from TGV in 1936.
- Properties: anti-oxidant, anti-inflammation and anti-cancer.
- Therapeutic usefulness: Alzheimer's disease, arthritis rheumatoid, asthma, hypertension, systemic lupus erythematosus and different types of cancer.



Celastrol

Treatment of Obesity with Celastrol



Liu et al., 2015, Cell 161, 999-1011

Content outline

- Oral bioavailability of celastrol following administration of pure celastrol
- Gender-related pharmacokinetics of celastrol following oral administration of TGV tablets

Oral bioavailability of pure celastrol

Animals and treatment:

✓ Two groups (female rats, n = 6, pure celastrol) :

administered an oral dose: 1000μg·kg^{-1} by gavage;

intravenous dose: 100μg·kg^{-1} via the tail vein.

✓ Blood samples collection:

intravenous injection: 0, 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48 h;

oral administration: 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48 h.

Instrumentation and LC-MS conditions

Agilent 1200 HPLC coupled with a API4000 mass spectrometer,

Analyst software version 1.4.1.

ESI+, with acquisition in MRM mode.

m/z 451.3→201.1 for celastrol, m/z 471.4→317.4 for I.S.

Chromatographic condition:

Phenomenex Luna C8 column (2.0×50 mm, 3 μm) ; Mobie phase: methanol, acetonitrile, isopropanol, formic acid and water (15/27.5/27.5/0.03/29.97) ; Column temperature: 35 ℃； Flow rate: 0.3mL/min

The optimized electrospray conditions :

ion spray voltage (ISV) : 5500 V; turbo heater temperature (TEM): 500℃; collision activation dissociation (CAD) : 10 psi; curtain gas (CUR) : 20 psi. declustering potential (DP) and collision energy (CE) were optimized at 40 and 30 for celastrol and 25 and 15 for I.S.

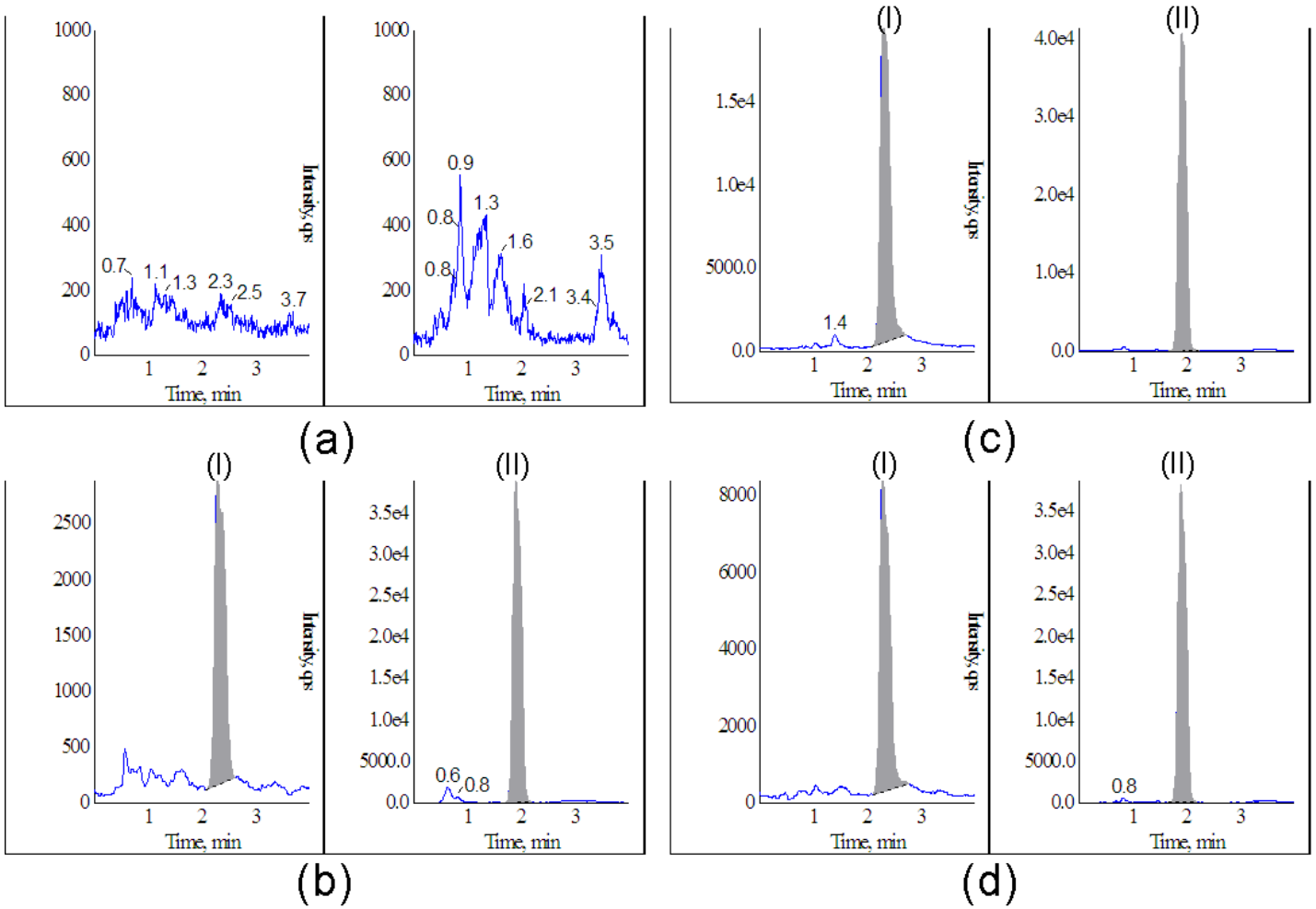


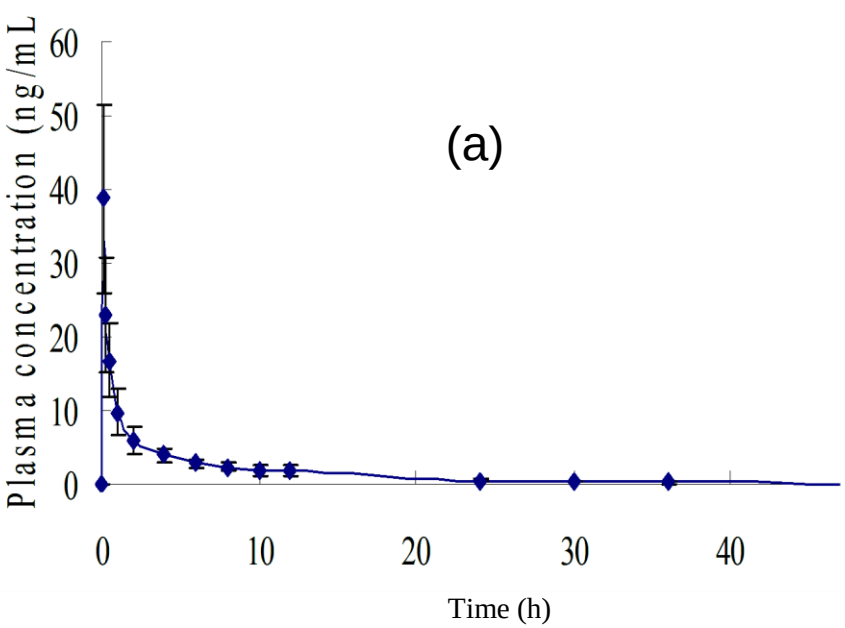
Fig. 2 Typical MRM chromatograms of celastrol (I) and glycyrrhetinic acid (I.S., II)

(a) blank plasma, (b) blank plasma spiked with celastrol (4.34 ng·mL-1) and I.S. (960 ng·mL-1),

(c) rat plasma sample 5 h after oral administration of pure celastrol,

(d) rat plasma sample 7 h after intravenous administration of pure celastrol.

Oral bioavailability



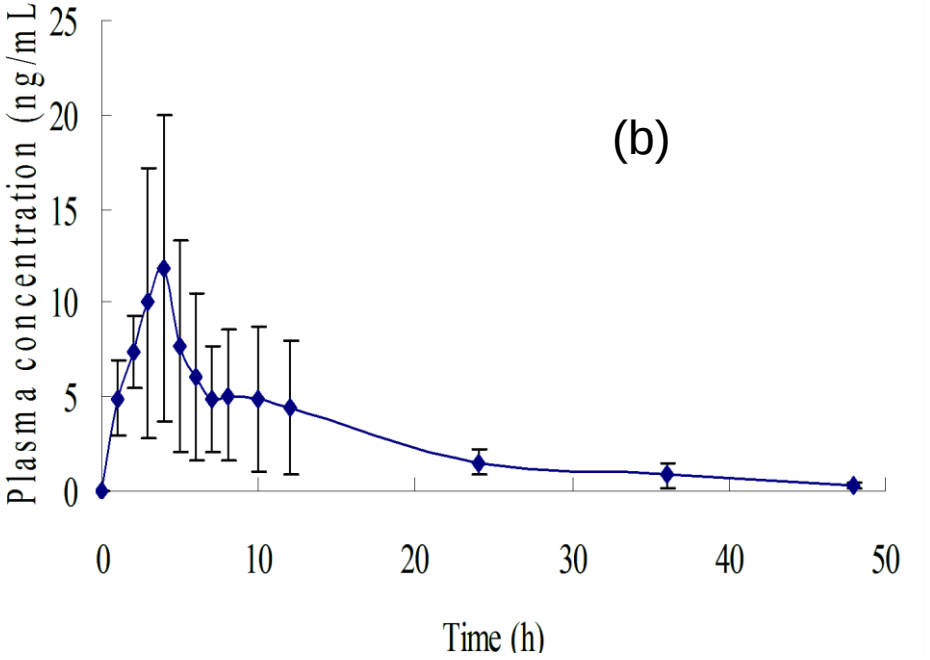


Fig. 3 Plasma concentration–time profiles of celastrol following

(a) intravenous injection and (b) oral administration of pure celastrol in female rats(n=6)

Oral bioavailability

Table 1 Pk parameters of celastrol following single intravenous and oral administration of pure celastrol in female rats (n=6, mean values ± SD)

Parameter	Oral group (1000 μg·kg^{-1})	intravenous group (100 μg·kg^{-1})
*T*max (h)	3.00±0.89	0.083
*C*max(μg·L^{-1})	13.75±7.94	38.83±12.83
$AUC_{(0\text{-}tn)}$ (μg·h·L^{-1})	130.90±79.39	76.74±19.03
$AUC_{(0\text{-}\infty)}$ (μg·h·L^{-1})	135.50±79.76	79.35±19.85
$T_{1/2\beta}$ (h)	10.20±2.17	8.33±0.84
CL/F (L·h^{-1})	11.29±6.16	0.45±0.16
$MRT_{(0\text{-}tn)}$ (h)	12.04±1.20	7.63±0.75
$MRT_{(0\text{-}\infty)}$ (h)	14.11±1.60	9.46±1.43

The oral absolute bioavailability: 17.06%

Which ?

There are 16 drug approval numbers.

Determination of celastrol in TGV tablets

Chromatographic condition:

Zorbax Eclipse XDB-C8 column (5μm, 4.6mm×150mm) Mobie phase: methanol:1% glacial acetic acid solution (83:17)

Column temperature: 30 ℃； injection volume: 5μL

Detection wavelength: 425nm

Flow rate: 1.0 mL/min.

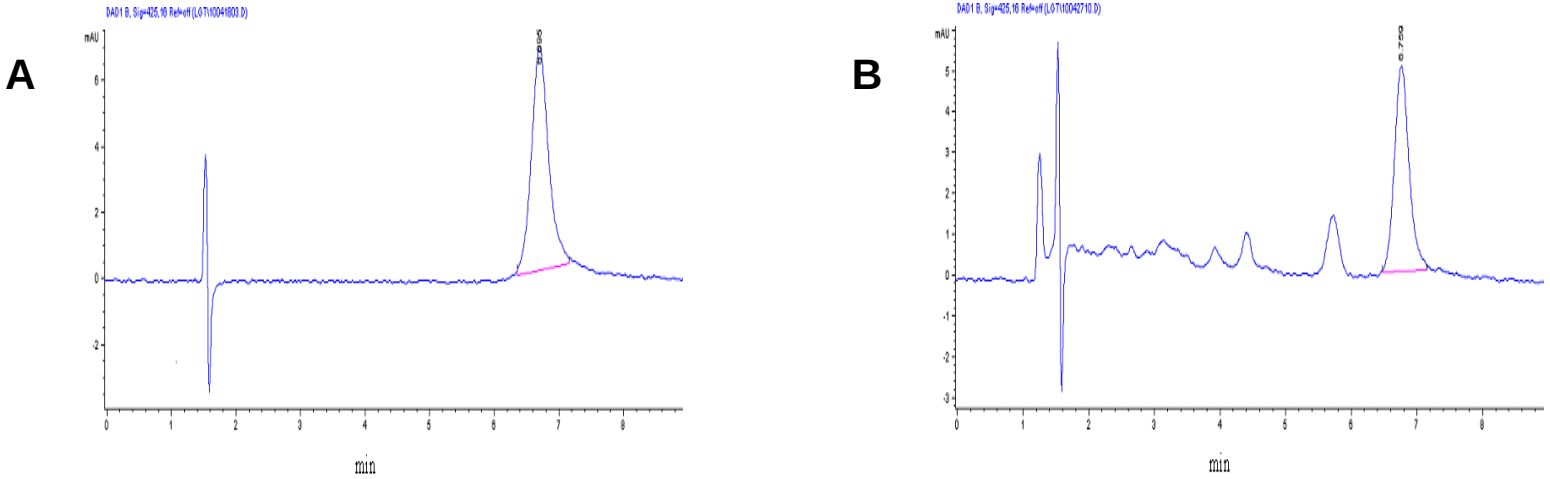
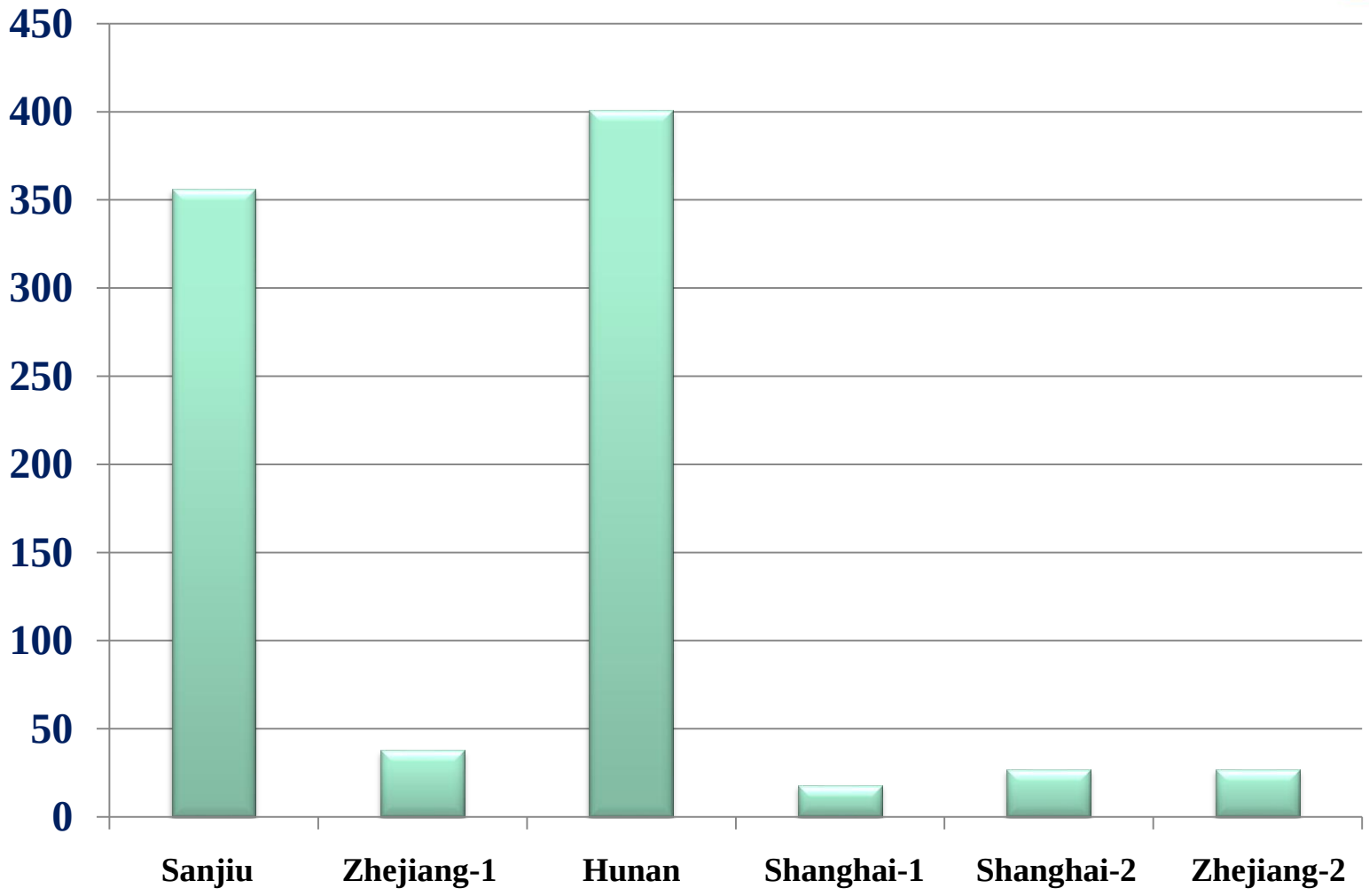


Fig 1 HPLC profiles of reference standards (A, containing 50.65μg ·mL^{-1} celastrol) and Tripterygium Preparation (B, from one pharmaceutical company in Zhejiang province)

The contents of celastol of Tripterygium Preparations in 6 different batches (n=5)

Product Name	Manufacturer	Batches	Contents of celastol (μg per tablet)
Tripterygium Tablets	Sanjiu	090604	356.03
Tripterygium Glycosides	Zhejiang-1	090602	37.84
Tripterygium Glycosides	Hunan	090601	400.62
Tripterygium Glycosides	Shanghai-1	091010	17.66
Tripterygium Glycosides	Shanghai-2	090603	26.77
Tripterygium Glycosides	Zhejiang-2	0910107	26.77



China pharmacist, 2011, 14(4):483-484

Gender-related pharmacokinetics of celastrol

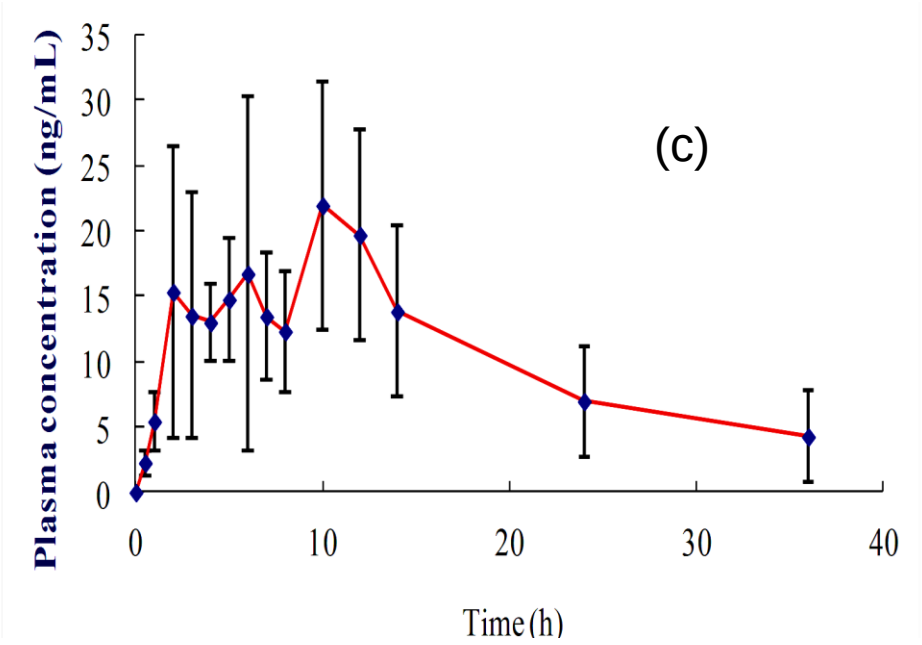
Animals and treatment:

- ✓ Group1: seven male rats, Group2: seven female rats.
- ✓ Dose: 1.5 tablets·kg^{-1} by gavage.

- ✓ Blood samples collection:

  0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48 h.

Gender difference, TGV tablets



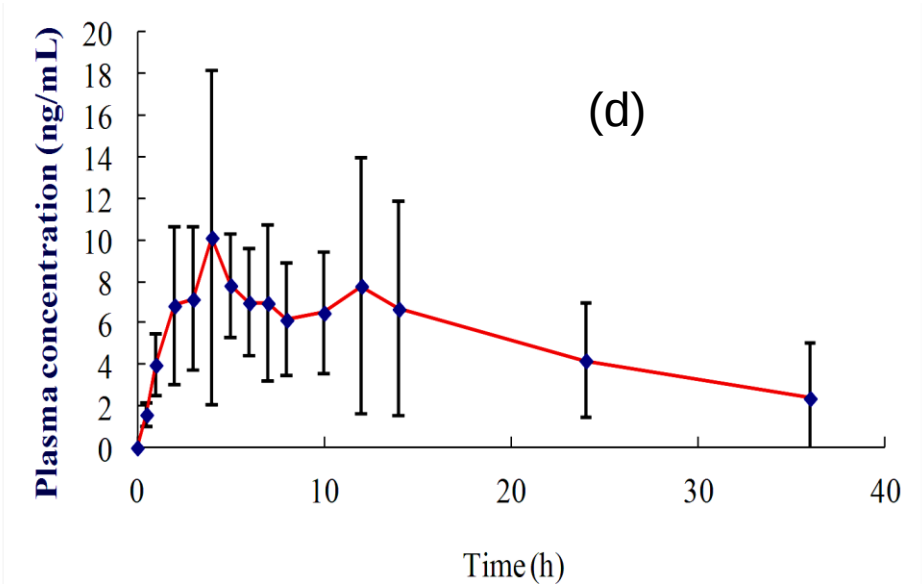


Fig. 3 Plasma concentration–time profiles of celastrol following oral administration of TGV tablets in (c) female and (d) male rats

Gender difference, TGV tablets

Table 2 PK parameters of celastrol following single oral administration of TGV tablets (1.5 tablets·kg^{-1}) in female and male rats (n=7)

Parameter	Female group	Male group
*T*max (h)	6.71±4.57	5.14±3.58
***C*max(μg·L^{-1})	32.03±8.41↑	14.31±7.33
***AUC*$_{(0\text{-}tn)}$ (μg·h·L^{-1})	379.49±118.19 ↑	188.17±92.33
***AUC*$_{(0\text{-}\infty)}$ (μg·h·L^{-1})	443.52±138.95 ↑	221.87±135.44
$T_{1/2\beta}$ (h)	10.02±3.36	8.38±1.98
***CL/F* (L·h^{-1})	0.96±0.53 ↓	2.58±0.66
MRT$_{(0\text{-}tn)}$ (h)	13.87±1.72	14.19±2.31
MRT$_{(0\text{-}\infty)}$ (h)	16.72±1.43	16.96±2.56

Comparison of major PK parameters

species	drug	Targeted compound	Dose ($\mu g \cdot kg^{-1}$)	Tmax(h)	Cmax(ug/L)	AUC0-t	AUC0-∞	t1/2
Rat	celastrol	celastrol	100 (i.v.)	0.083h	38.83±12.83	76.74±19.03	79.35±19.85	8.33±0.84
Rat	celastrol	celastrol	1000 (i.g.)	3.00±0.89	13.75±7.94	130.90±79.39	135.50±79.76	10.20±2.17
Rat (♂)	TGV tablets	celastrol	534(i.g.)	6.71±4.57	32.03±8.41	379.49±118.1	443.52±138.95	10.02±3.36
Rat (♀)	TGV tablets	celastrol	534(i.g.)	5.14±3.58	14.31±7.33	188.17±92.33	221.87±135.44	8.38±1.98
Dog	TGV tablets	Triptolide	356(i.g.)	1.75±0.76	2.78±0.39	11.54±1.49	13.18±1.69	2.59±0.6

The oral absolute bioavailability of celastrol significantly increased from 17.06% for pure celastrol to 94.19% for TGV tablets containing equivalent celastrol.

Challenges

- Large content variance in different TGV tablets.
- Choose which ingredient for the quality control of TGV
- The low concentration of compounds in blood makes it detect difficultly.
- when TGV was administrated with other drugs, is there potential drug–drug interaction?

Resolution

- The plant of TGV should be cultivated according to Good Agricultural Practices.
- Multi-marker quantification plus fingerprint analysis is the future direction for the comprehensive quality control of TGV.
- Investigate the effects of TGV extract on CYP activity to predict the potential clinical drug–drug interaction.

Publications

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5 Zhang J, Chen M, Xu MJ, Ju WZ, Xiong NN. Rapid Determination of Tripterine in Tripterygium Preparations by HPLC. China pharmacist, 2011,(04): 483-485.

6 Liu L , Zhang J , Wang Z , Xu D , Jiang Z , Wang T , Ju W , Zhang L. Gender Differences in the Toxicokinetics of Triptolide after Single- and Multiple-dose Administration in Rats. Drug Research, 2015

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2 Leading Talents of scientific research in TCM of Jiangsu Province, LJ200906

3 A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions, 2010


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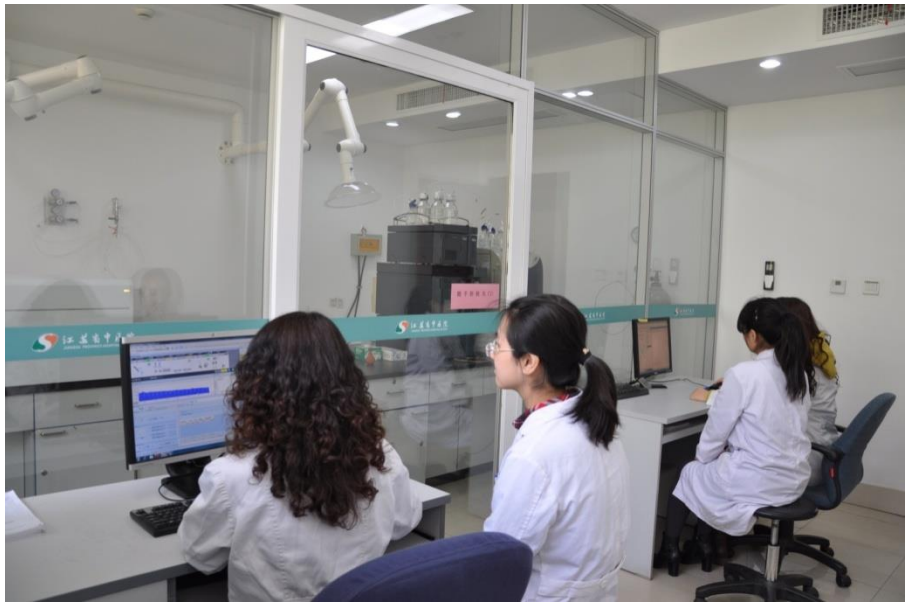

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