



# Quality control of herbal medicines

**Dr. Mei Wang**

**16 May 2023**



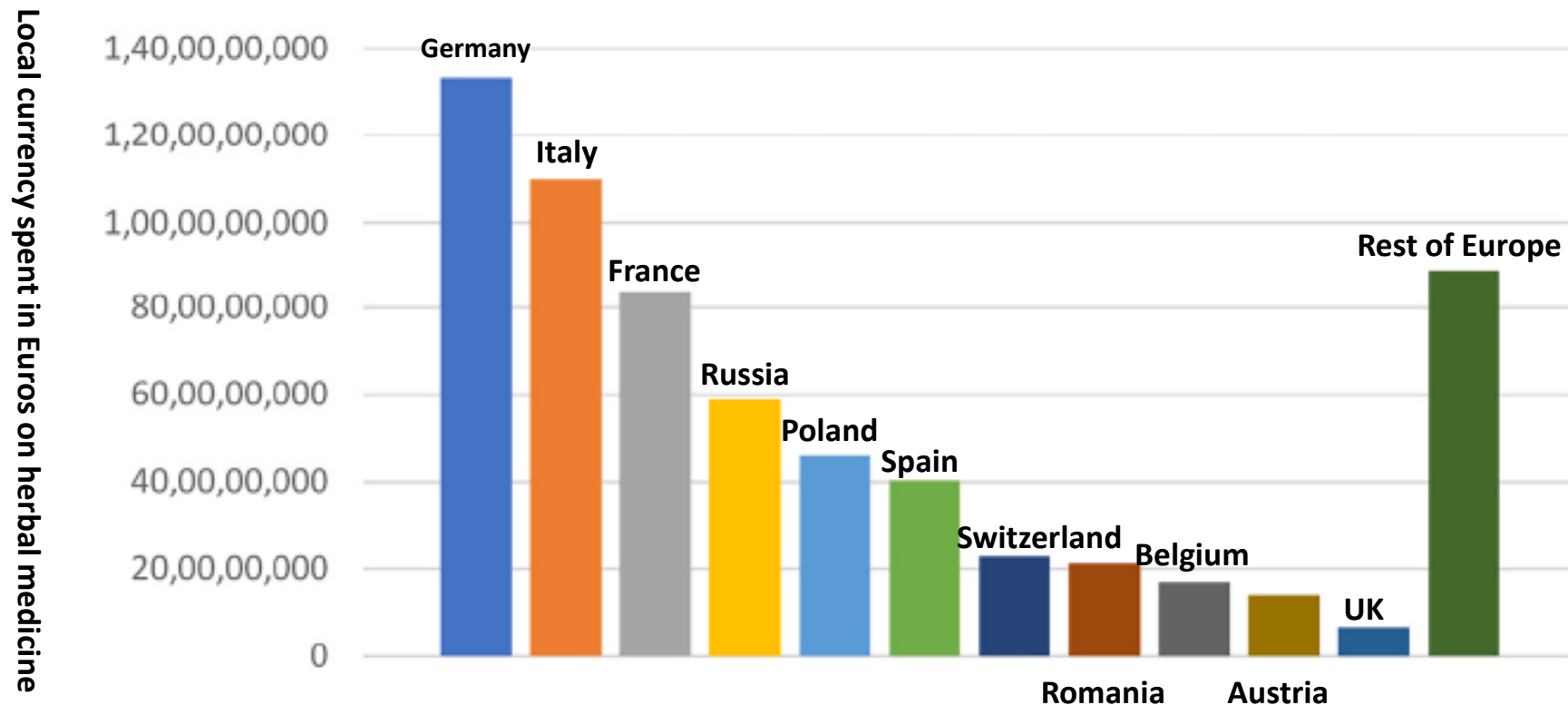
# Introduction and Disclaimer

## Dr. Mei Wang

- Graduated from Peking University (Biochemistry), China
- PhD from Leiden University (Biology and Genetics), The Netherlands
- Senior Scientist (plant biotechnology & plant metabolites), TNO, NL
- Member of European pharmacopeia TCM working party,
- Chairperson ISO TC249 (NEN) commission, NL
- Board member of NVF (Dutch Association of Phytotherapy), NL
- CEO SU Bio-Medicine consultancy company, NL
- Teaching master course “Pharmaceuticals from plants”, Leiden University; NL

# Significance of Herbal medicines in EU

(local currency spent in Euros at manufacturers prices)



Germany has the largest herbal medicine market in Europe for products with a medicinal claim and ones mostly dispensed in pharmacies. Based on manufacture price in Germany the Market has an annual costs of €1.33 billion equivalent to 20.7% of the total European market (2022).

# Example: Ginger (*Zingiber officinale*, family zingiberaceae)



01/2011:1522

**GINGER**  
*Zingiberis rhizoma*

**DEFINITION**  
Dried, whole or cut rhizome of *Zingiber officinale* Roscoe, with the cork removed, either completely or from the wide, flat surfaces only.  
*Content*: minimum 15 mL/kg of essential oil (anhydrous drug).

**CHARACTERS**  
Characteristic aromatic odour.  
Spicy and burning taste.

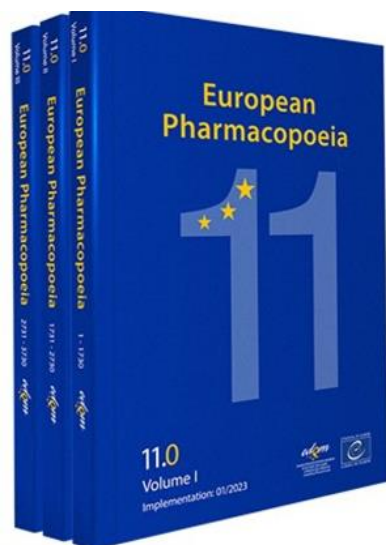
**IDENTIFICATION**  
A. The rhizome is laterally compressed, bearing short, flattened, obovate oblique branches on the upper side, each sometimes having a depressed scar at the apex; the whole rhizomes are about 5-10 cm long, 1.5-3 cm or 4 cm wide and 1-1.5 cm thick, sometimes split longitudinally.

Figure 1522.-1. – Illustration for identification test B of powdered herbal drug of ginger  
C. Thin-layer chromatography (2.2.27).  
*Test solution*. To 1.0 g of the powdered herbal drug (710)

## Community herbal monograph on *Zingiber officinale* Roscoe, rhizoma

### 4.1. Therapeutic indications

Well-established use	Traditional use
Herbal medicinal product for the prevention of <u>nausea and vomiting</u> in motion sickness.	<p><b>Indication 1)</b> Traditional herbal medicinal product for the symptomatic relief of motion sickness.</p> <p><b>Indication 2)</b> Traditional herbal medicinal product for symptomatic treatment of mild, spasmodic gastrointestinal complaints including bloating and flatulence.</p> <p>The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.</p>



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Example: Ginger (*Zingiber officinale*, family zingiberaceae)

## No benefit effects observed

Support Care Cancer (2017) 25:459–464  
DOI 10.1007/s00520-016-3423-8

34 breast cancer patients



ORIGINAL ARTICLE

**Efficacy of ginger for prophylaxis of chemotherapy-induced nausea and vomiting in breast cancer patients receiving adriamycin–cyclophosphamide regimen: a randomized, double-blind, placebo-controlled, crossover study**

Support Care Cancer (2009) 17:563–572  
DOI 10.1007/s00520-008-0528-8

162 cancer patients

ORIGINAL ARTICLE

**Phase II trial of encapsulated ginger as a treatment for chemotherapy-induced nausea and vomiting**

100 breast cancer patients

**Effect of Ginger on Acute and Delayed Chemotherapy-Induced Nausea and Vomiting: A Pilot, Randomized, Open-Label Clinical Trial**

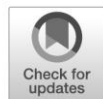
Integrative Cancer Therapies  
11(3) 204–211  
© The Author(s) 2012  
Reprints and permission: <http://www.sagepub.com/journalsPermissions.nav>  
DOI: 10.1177/1534735411433201  
<http://ict.sagepub.com>

Supportive Care in Cancer  
<https://doi.org/10.1007/s00520-019-05201-5>

47 cancer patients

ORIGINAL ARTICLE

**Effects of ginger adjunct to the standard prophylaxis on reducing carboplatin and paclitaxel-induced nausea vomiting: a randomized controlled study**



## Benefit effects observed

Support Care Cancer (2012) 20:1479–1489  
DOI 10.1007/s00520-011-1236-3

576 cancer patients

ORIGINAL ARTICLE

**Ginger (*Zingiber officinale*) reduces acute chemotherapy-induced nausea: a URCC CCOP study of 576 patients**

Volume 4, Number 4 • September 2007

706 cancer patients

**Key words:** Alternative medicine, Anticipatory nausea, Complementary and alternative medicine, Delayed nausea, Postchemotherapy nausea

current trial

A Phase II/III Randomized, Placebo-Controlled, Double-Blind Clinical Trial of Ginger (*Zingiber officinale*) for Nausea Caused by Chemotherapy for Cancer: A Currently Accruing URCC CCOP Cancer Control Study

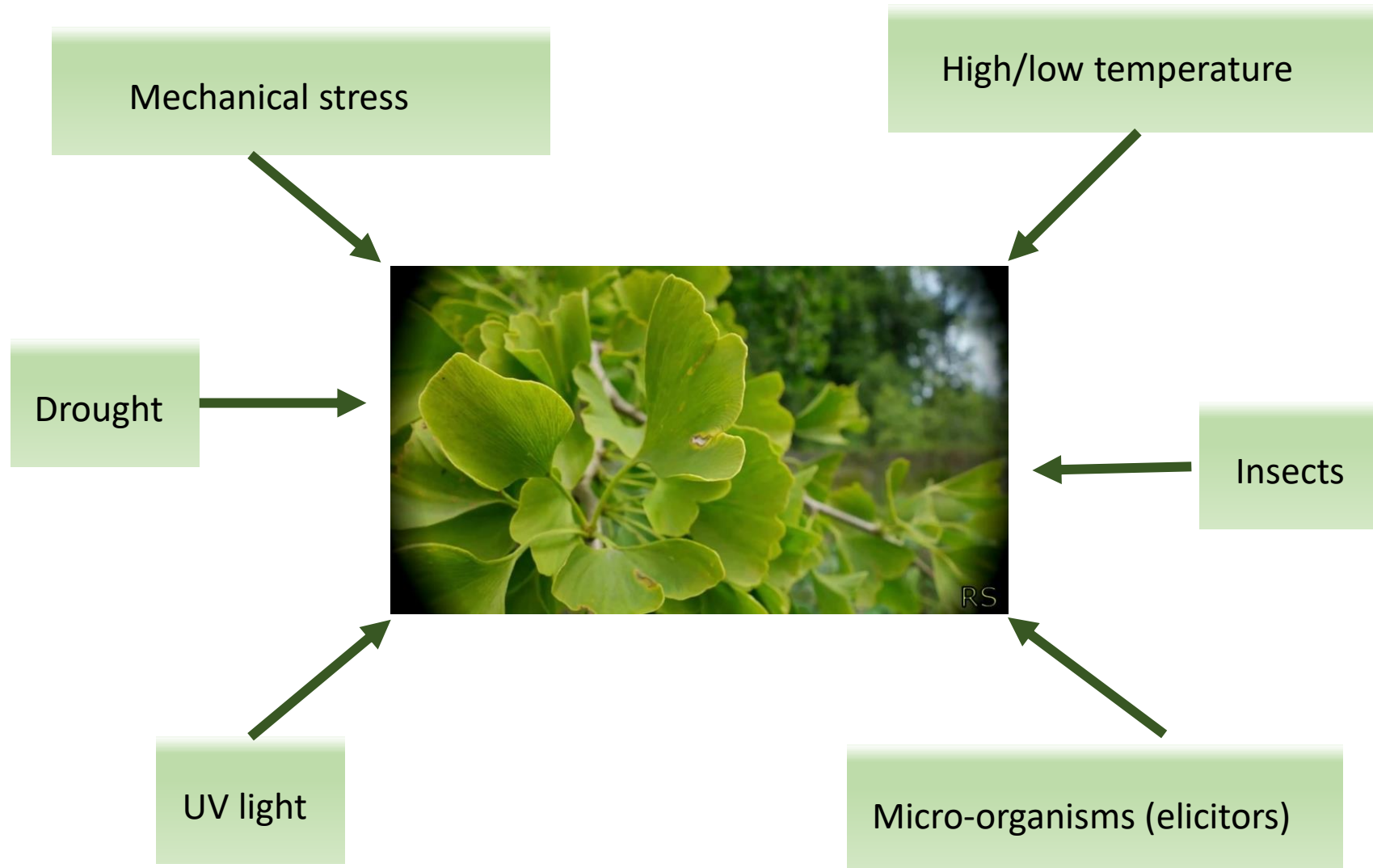
60 cancer patients

Pediatr Blood Cancer 2011;56:234–238

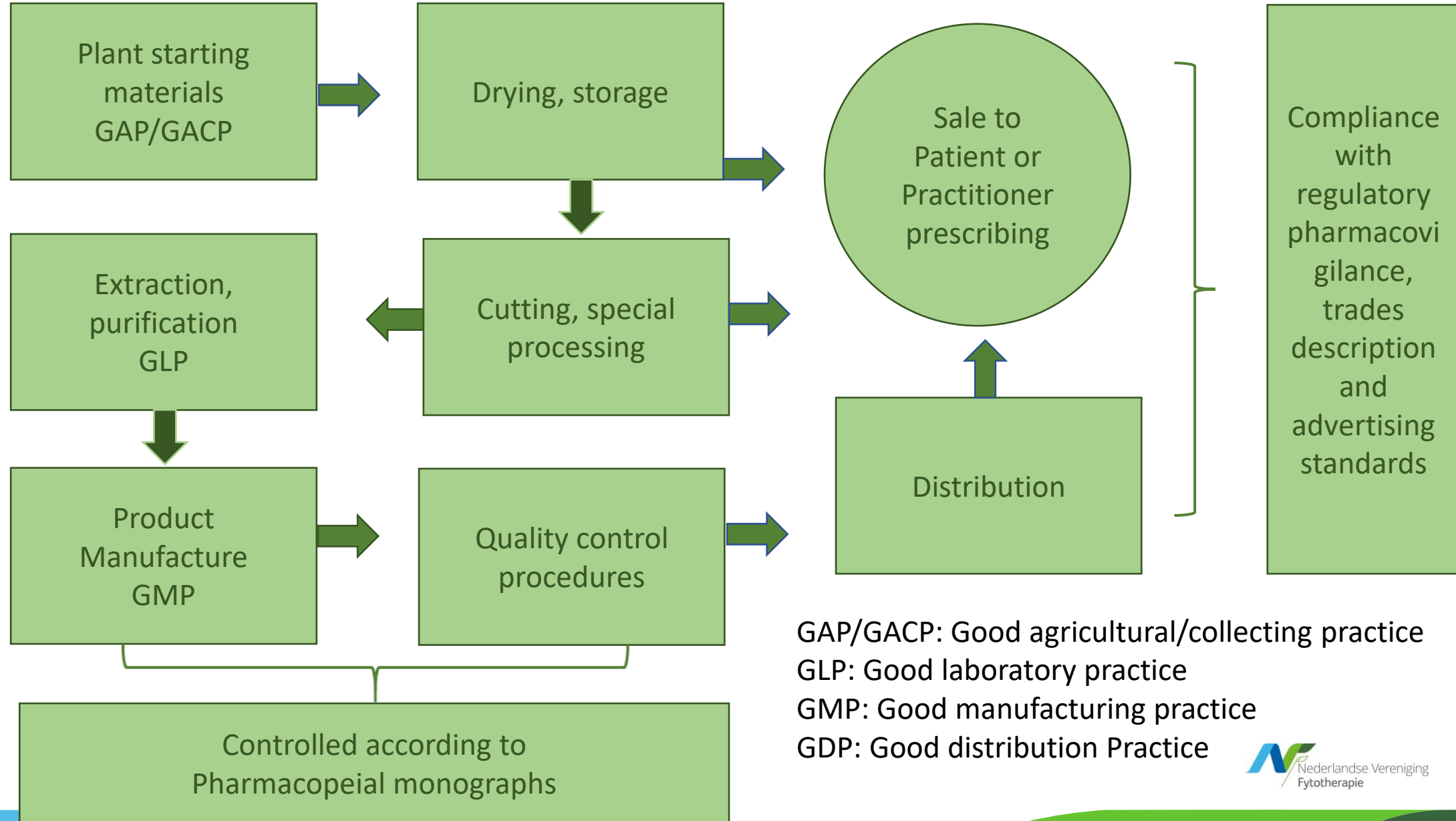
**Anti-Emetic Effect of Ginger Powder Versus Placebo as an Add-On Therapy in Children and Young Adults Receiving High Emetogenic Chemotherapy**

Description of the preparation of Ginger product

# Plant Stresses



# Regulatory processes involved in monitoring the quality of herbal products



# Monographs used for providing evidence in EU legislation

**Validated methods  
Pharmacopeia monographs,  
EQDM, Strasbourg**



**Evidence of Quality**

**Monographs or listed entries  
by HMPC  
EMA, Amsterdam**

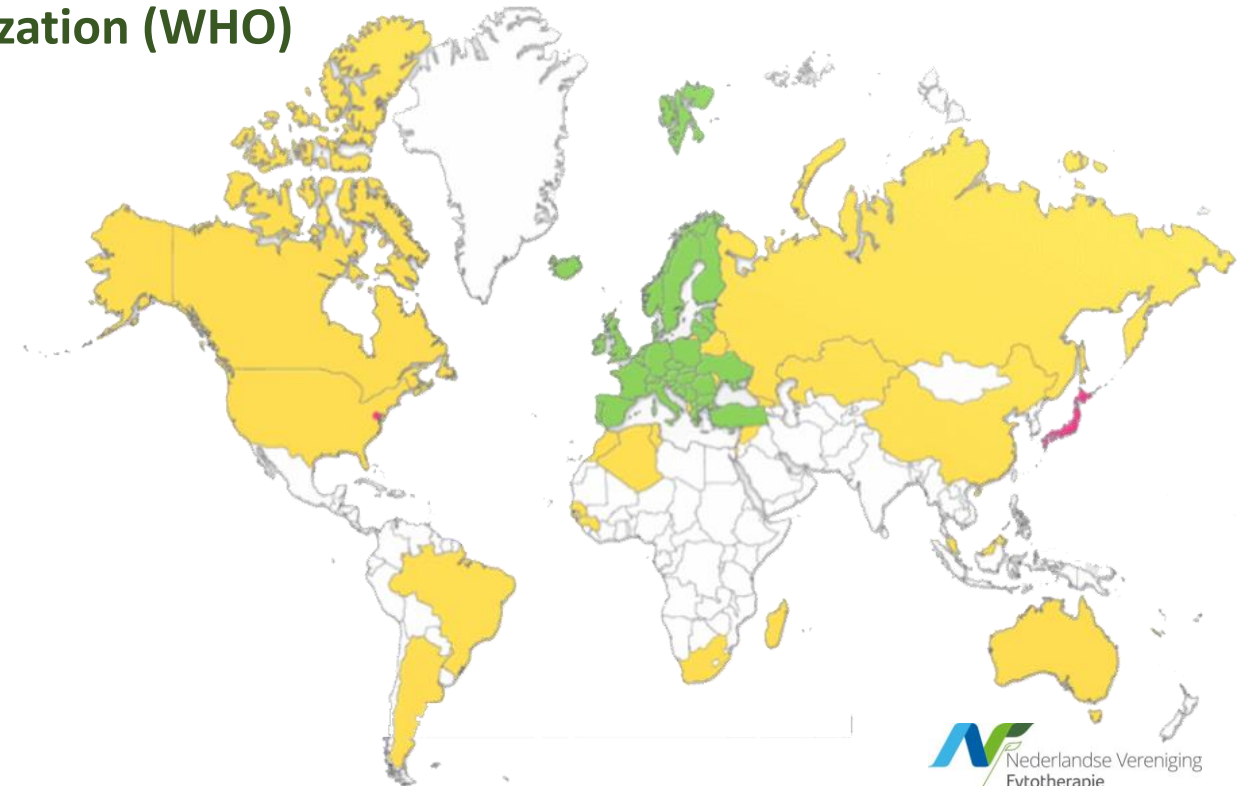
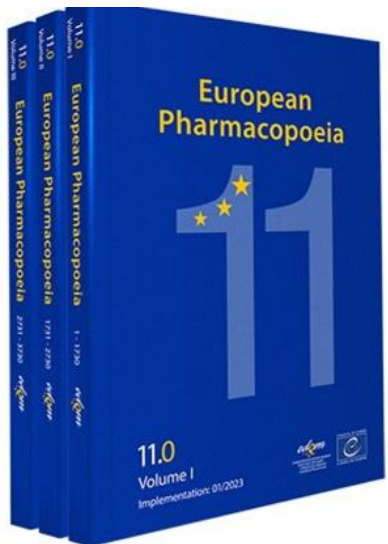


**Evidence of Efficacy and safety**



# Ph Eur Membership & Observer ship

- **37 member states + the European Union Ph. Eur. is the official Pharmacopoeia in Europe common to all member states - national pharmacopoeias to cover subjects of solely national interest. Mandatory at the same date in 37 Member States(CoE) and the EU.**
- **24 observer countries + the World Health Organization (WHO)**

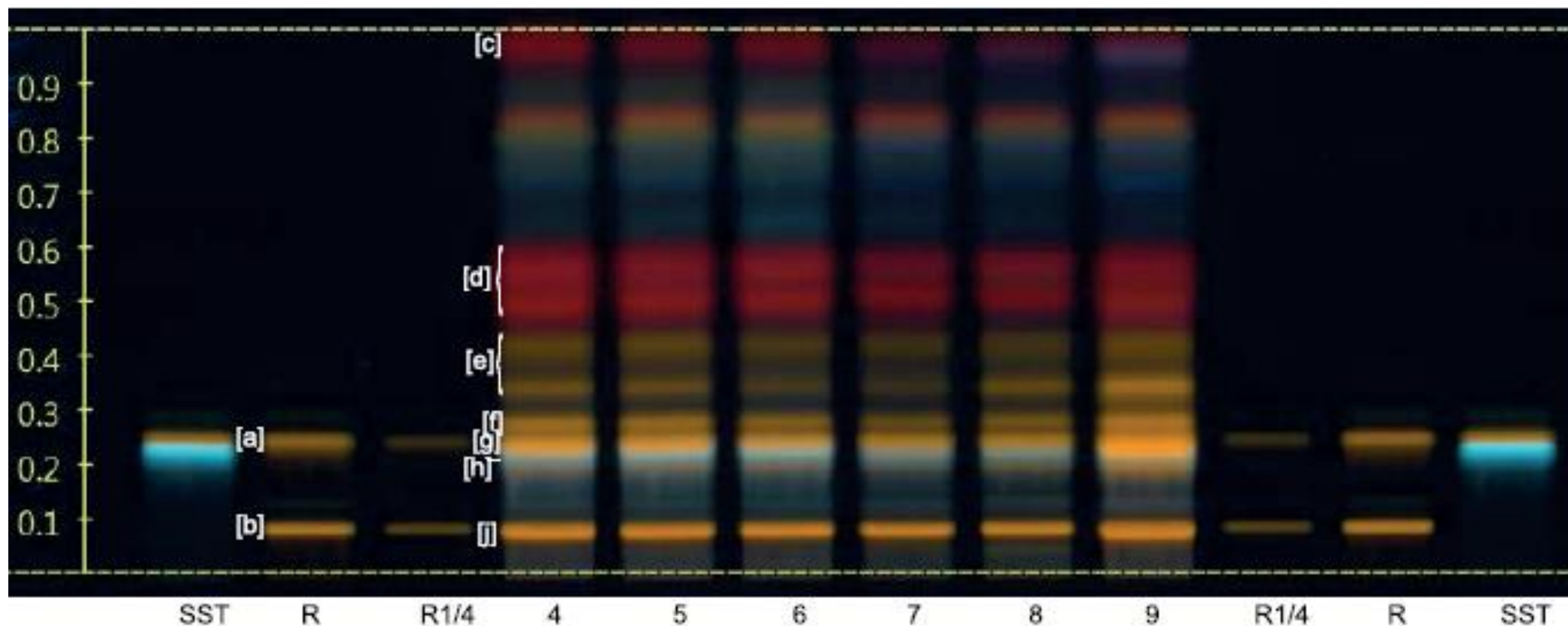




# Example of Ph Eur Herbal Drug Monographs

Hyperici herba:

HPTLC chromatogram for identification test C of different batches of St. John's wort



SST: reference solution (c) R: reference solution (a)

R1/4: reference solution (b) 4-9: test solutions for different batches

**Reference solution (a).** Dissolve 2.5 mg of hyperoside R and 3.5 mg of rutoside trihydrate R in methanol R and dilute to 10.0 mL with the same solvent.

**Reference solution (b).** Dilute 2.5 mL of reference solution (a) to 10.0 mL with methanol R.

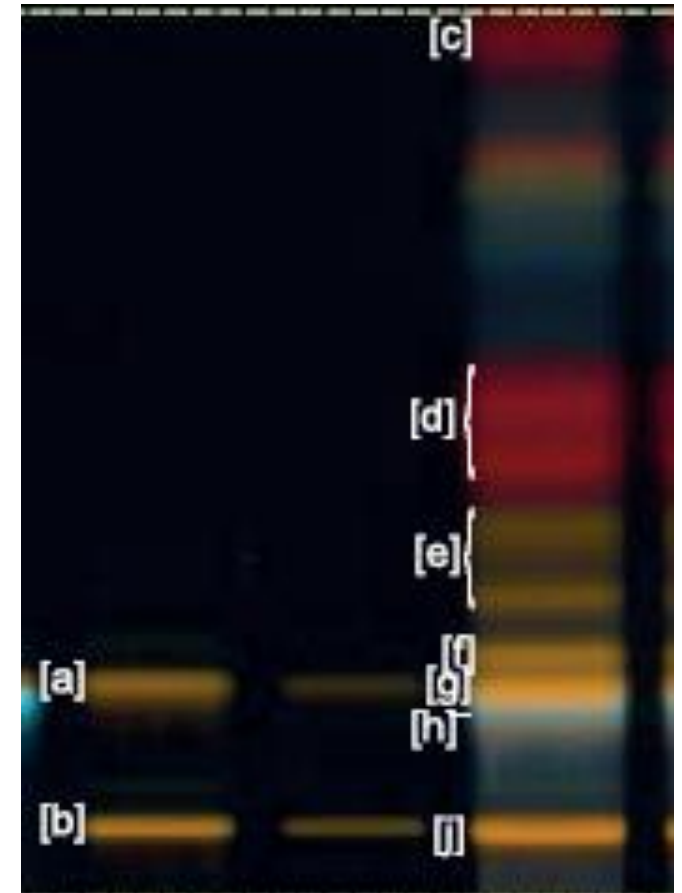
**Reference solution (c).** Dissolve 2.5 mg of hyperoside R and 3 mg of chlorogenic acid R in methanol R and dilute to 10.0 mL with the same solvent.



# Example of Ph Eur Herbal Drug Monographs



Top of the plate	
	[c] A red fluorescent zone or a faint red fluorescent zone
	[d] 2 red fluorescent zones (hypericin and pseudohypericin)
	[e] 2 yellow or orange fluorescent zones or 2 faint yellow or orange fluorescent zones
	[f] A yellow or orange fluorescent zone or a faint yellow or orange fluorescent zone
[a] Hyperoside: a yellow or orange fluorescent zone	[g] A yellow or orange fluorescent zone or an intense yellow or orange fluorescent zone (hyperoside)
	[h] A light blue fluorescent zone or a faint light blue fluorescent zone (chlorogenic acid)
[b] Rutoside: a yellow or orange fluorescent zone	[j] A yellow or orange fluorescent zone (rutoside)
Reference solution (a)	Test solution



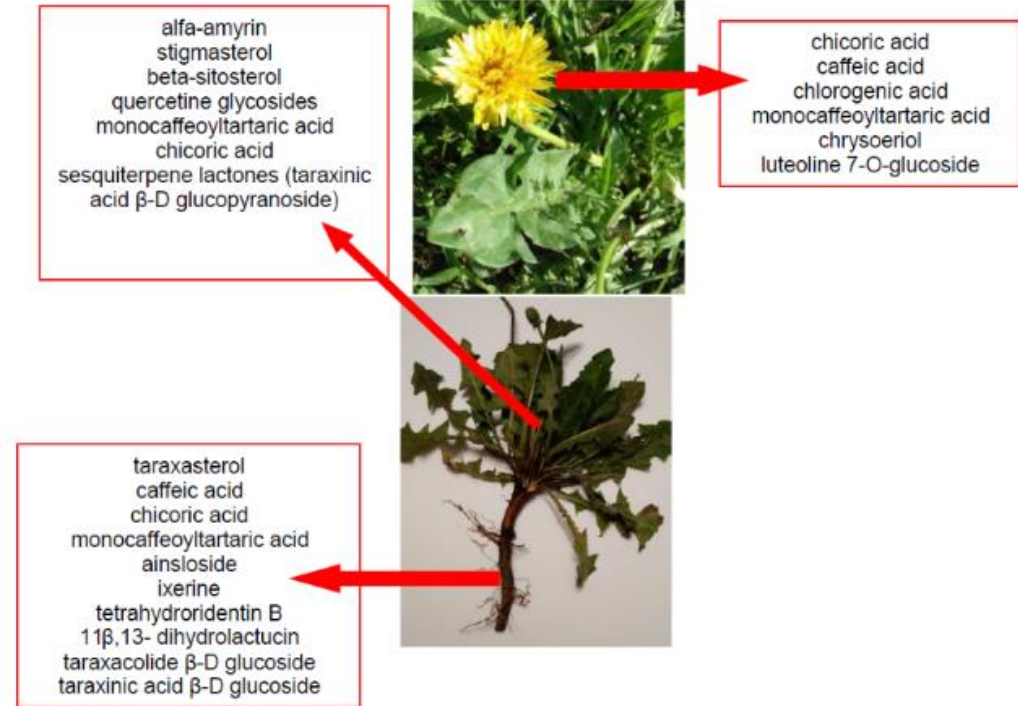
Identification : HPTLC

# Right plant part: therapeutic applications

Community herbal monograph on *Taraxacum officinale* Weber ex Wigg., radix cum herba

## 4.1. Therapeutic indications

Well-established use	Traditional use
	<p><b>Indication a)</b></p> <p>Traditional herbal medicinal product for the relief of symptoms related to mild digestive disorders (such as feeling of abdominal fullness, flatulence, and slow digestion) and temporary loss of appetite.</p> <p><b>Indication b)</b></p> <p>Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.</p> <p>The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.</p>



Roots: sesquiterpene lactones and triterpenes and sterols

**antidiabetic potential**

Leaves and flowers: hydroxycinnamic acid derivatives and flavonoids

**antioxidant and hypocholesterolemic properties**

**The main active compounds of dandelion**

# Right plant part: therapeutic applications

Community herbal monograph on *Urtica dioica* L., *Urtica urens* L., their hybrids or their mixtures, radix

## 4.1. Therapeutic indications

Well-established use	Traditional use
	<p>Traditional herbal medicinal product for the relief of lower urinary tract symptoms related to benign prostatic hyperplasia after serious conditions have been excluded by a medical doctor.</p> <p>The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.</p>



## Urtica dioica for Treatment of Benign Prostatic Hyperplasia

A Prospective, Randomized, Double-Blind, Placebo-Controlled, Crossover Study

- To determine the effects of therapy with *Urtica dioica* for symptomatic relief of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH).
- A 6-month, double-blind, placebo-controlled, randomized, partial crossover, comparative trial of *Urtica dioica* with placebo in 620 patients was conducted.
- Conclusion: *Urtica dioica* has beneficial effects in the treatment of symptomatic BPH.**

Journal of Herbal Pharmacotherapy, Volume 5, 2005 - Issue 4

Stinging nettle, *Urtica dioica* L.: botanical, Phytochemical & pharmacological overview

Activities	leaves	stems	roots
Antioxidant	+	+	+
Anti-prostatic	-	-	+
Antiulcer	+	-	-
Cytotoxic	+	+	-
Hematopoietic	-	+	-
Immuno-modulatory	+	-	+
Prevention of atherosclerosis	+	-	-

Phytochem. Rev (2020) 19:1341–1377

# Impurity in herbal medicine products:

## Foreign materials

- Visible
  - Animal original e.g insects, larvae
  - Vegetable origin, e.g. other plants, or other plant parts
  - Mineral origin, e.g. sand or adulteration (calcium carbonate, barium sulphate to increase weight)
- Invisible
  - Contaminants
    - Toxic metals (Cu, Ni, Zn, As, Cr, Cd, Hg, Pb)
    - Radioactive substances (Cs-134 & Cs 137)
    - Microorganisms and Mycotoxins (Ochratoxin, Aflatoxins)
    - Polycyclic aromatic hydrocarbons

# Impurity in herbal medicine products:

## Foreign materials

- Invisible
  - Contaminants
    - Toxic metals (Cu, Ni, Zn, As, Cr, Cd, Hg, Pb)
    - Radioactive substances (Cs-134 & Cs 137)
    - Microorganisms and Mycotoxins (Ochratoxin, Aflatoxins)
    - Polycyclic aromatic hydrocarbons
    - Pyrrolizidine alkaloids
  - Residues
    - Fumigants (methylenebromid, phosphine, ethylene oxide)
    - Solvents residues
    - pesticides
  - Degradation products



# Impurity in herbal medicine products:

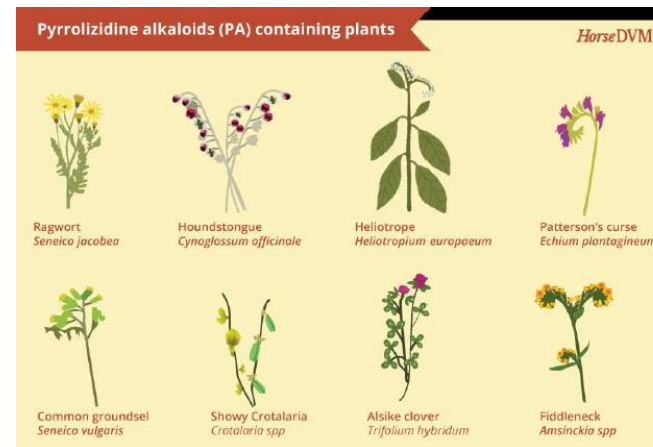
## Pyrrolizidine alkaloids

The occurrence of potentially toxic pyrrolizidine alkaloids (PAs) in herbal medicines is currently intensely being discussed in Europe. Pyrrolizidine alkaloids, particularly the 1,2-unsaturated PAs, are undesired compounds in Herbal medicines due to their potential hepatotoxic and carcinogenic properties.

The results showed that about **63% of the HMs were PA positive**, whereas the average PA concentration of the samples was 201 µg/kg, the **highest concentration of PAs (3270 µg/kg)** was attributed to a product that was purchased from the pharmacy and contained *Hypericum perforatum* L. (**St. John's Wort**) as an active ingredient.



St. John's Wort



<http://www.cowdvm.com/disease/pyrrolizidine-alkaloid-toxicity/>

# Question: Can the quality monograph represent the therapeutic efficacy?



- Cucuminoids

**Curcumin**

Demethoxycurcumin

Bisdemethoxycurcumin



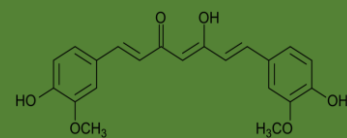
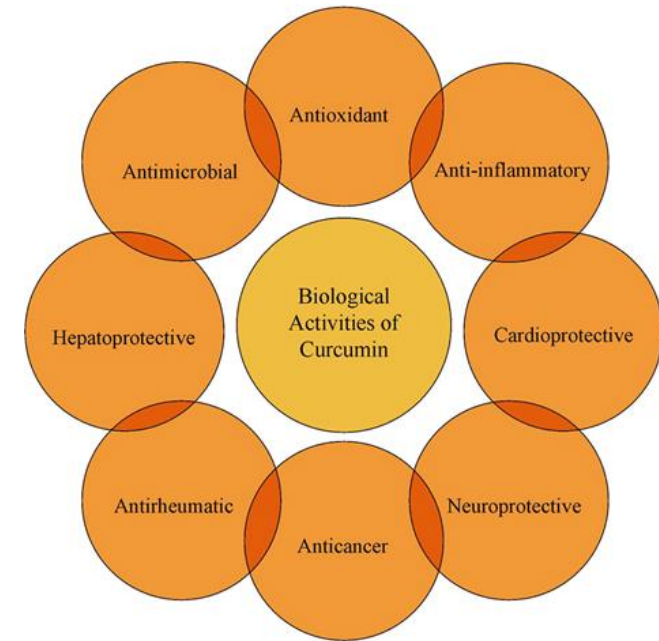
Curcumae Longae Rhizoma

- Volatile oils

**Tumerone**

Natlantone

Zingiberone

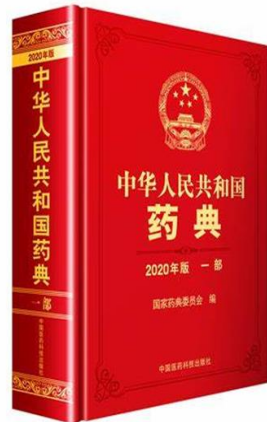


**Anti-inflammatory**  
**chronic inflammation**  
**Antioxidant**  
**Anti-cancers**

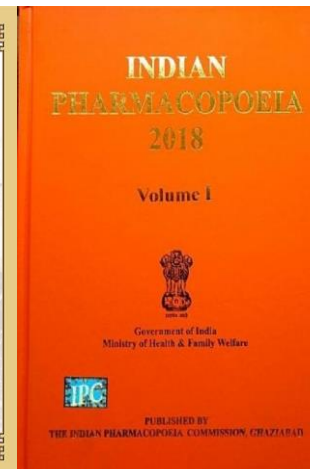
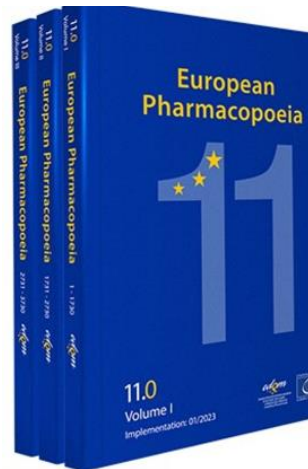
**Treat: Hyperglycemia, insulin resistance**

# Question: Can the quality monograph represent the therapeutic efficacy?

Pharmacopoeia/standards: USA, UK, Europe, China, India, etc.



*JP XVII*  
**THE JAPANESE PHARMACOPOEIA**  
*SEVENTEENTH EDITION*  
*Official from April 1, 2016*  
English Version



# Question: Can the quality monograph represent the therapeutic efficacy?

Test indicators		Chinese Pharmacopoeia (2020)	Hong Kong Chinese Materia Medica Standards (Volume 2)	Japanese Pharmacopoeia (JP17)	United States Pharmacopoeia (USP43)	European Pharmacopoeia (EP10)
Water (%)		≤16	≤16	≤17	≤10	≤12
Total ash (%)		≤7	≤6.5	≤7.5	≤7	≤8
Ash insoluble in hydrochloric acid (%)		/	≤1	≤1	≤1	/
Extractives (%)		≥12	≥13	≥9	≥9	/
Volatile oil (mL/g)		≥7	/	/	≥3	≥2.5
<b>Curcumin (%)</b>		≥1	/	/	/	≥2
<b>Sum of Demethoxycurcumin, curcumin and Demethoxycurcumin (%)</b>		/	≥1.5	≥1、≤5	≥3	/
Foreign matter (%)		/	≤1	/	≤2	/
Heavy metals	mg/kg	/	≤5	≤20	≤5	≤5
	mg/kg	/	≤2	≤5	≤2	/
	mg/kg	/	≤0.3	/	≤0.3	≤12
	mg/kg	/	≤0.2	/	≤0.2	≤0.1
Aflatoxin	Aflatoxin B1 μg/kg	/	≤5	/	≤5	≤2
	Aflatoxin (B1, B2, G1, G2) μg/kg	/	≤10	/	≤10	≤4

# Example of Refined and Quantified ginkgo dry Extract:

**Definition:** Refined and quantified dry extract from *Ginkgo leaf*.

## Content:

Quantity of the genuine extract: 100% genuine extract

DER genuine: 35 – 67: 1

**flavonoids expressed as flavone glycosides:** 22.0 to 27.0 % (dry extract)

**ginkgolides A, B and C:** 2.8 to 3.4 % (dry extract)

**Bilobalide:** 2.6 to 3.2 % (dry extract)

**Ginkgolic acid:** maximum 5 ppm (dry extract)

**Other excipients:** 0%

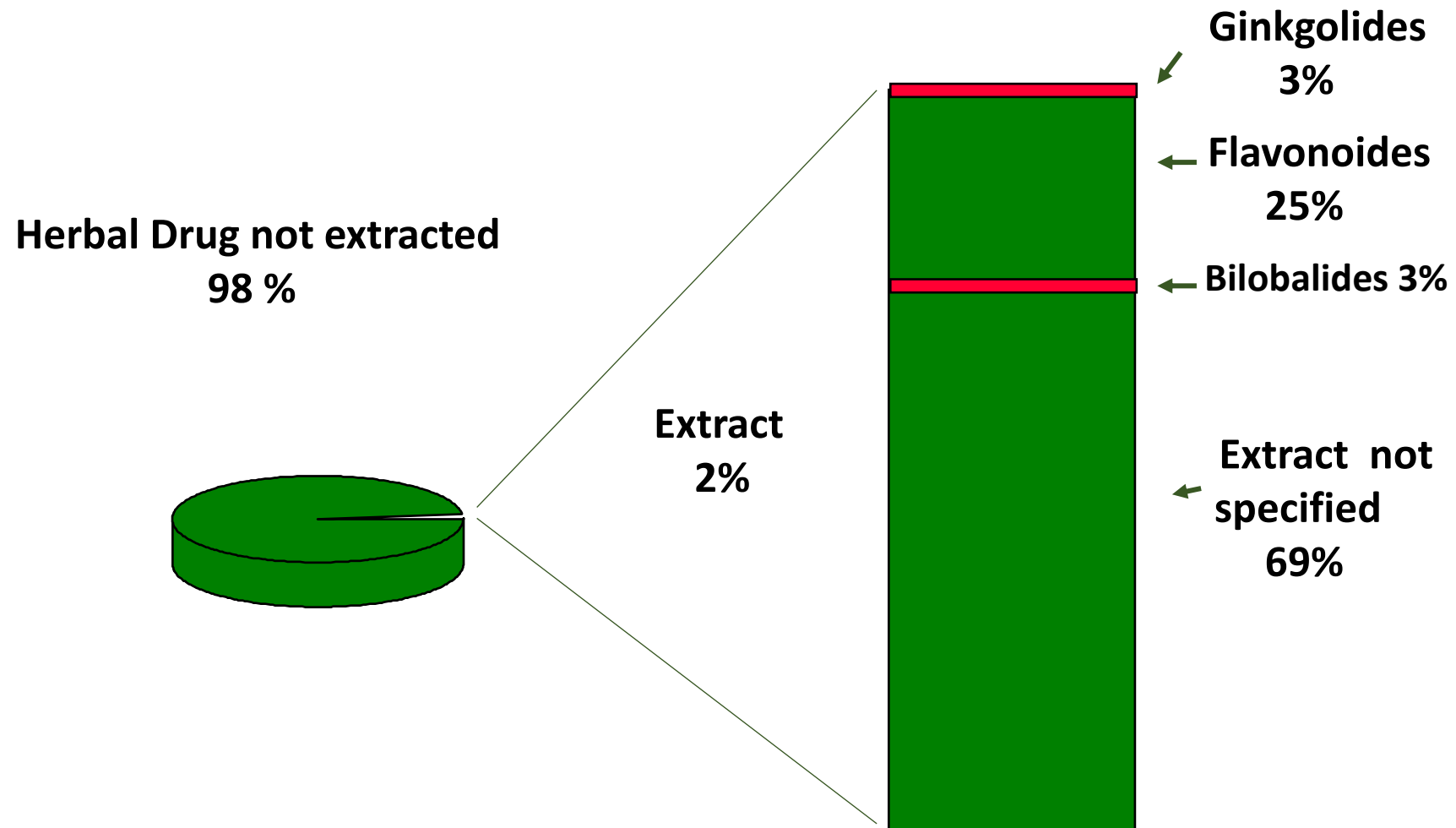
**Extraction solvent :** acetone 60%

### European Union herbal monograph on *Ginkgo biloba* L., folium

#### 4.1. Therapeutic indications

Well-established use	Traditional use
Herbal medicinal product for the improvement of (age-associated) cognitive impairment and of quality of life in mild dementia.	Traditional herbal medicinal product for the relief of heaviness of legs and the sensation of cold hands and feet associated with minor circulatory disorders, after serious conditions have been excluded by a medical doctor.

# Example of Refined and Quantified ginkgo dry Extract:

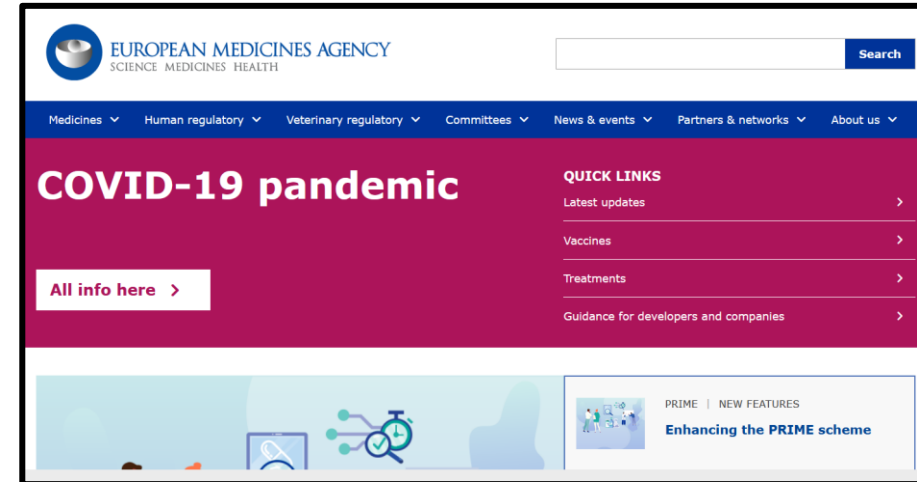


# What is the difference between an EMA community/ESCOP monograph for an herbal drug and a Ph Eur monograph?



<https://www.edqm.eu/>

Quality standard



<https://www.ema.europa.eu/en>



You are here: [Home](#) / [Online viewing](#) / ESCOP herbal monographs: Online viewing

ESCOP herbal monographs: Online viewing

Example of monograph: [Psylli semen \(Psyllium seed\)](#). [Free access](#)

Prices and registration forms

[Members of societies belonging to ESCOP](#) **FREE ACCESS**

→ Members of societies belonging to ESCOP (FREE ACCESS)

- Registered: [Log in](#)
- Not yet registered in ESCOP: go to [Registration forms](#) or ask your society

Safety and efficacy

# Take home messages

A growing interest for integrating phytomedicines into future conventional patient care.

An urgency for phytomedicines with guaranteed quality, safety, and efficacy

A need for database relating to these for integrating practice of phytomedicines and pharmaceutical medicines

A necessity for good documentation and research into interactions between phytomedicines & pharmaceutical medicines during practice

The research team should include a phytomedicine practitioner, a conventional medicine GP, a clinical pharmacologist, a biomedical scientist and a bio informaticist to analyse and produce the reliable data.





**Thank you for your attention!**

E-mail: [m.wang@biology.leidenuniv.nl](mailto:m.wang@biology.leidenuniv.nl)