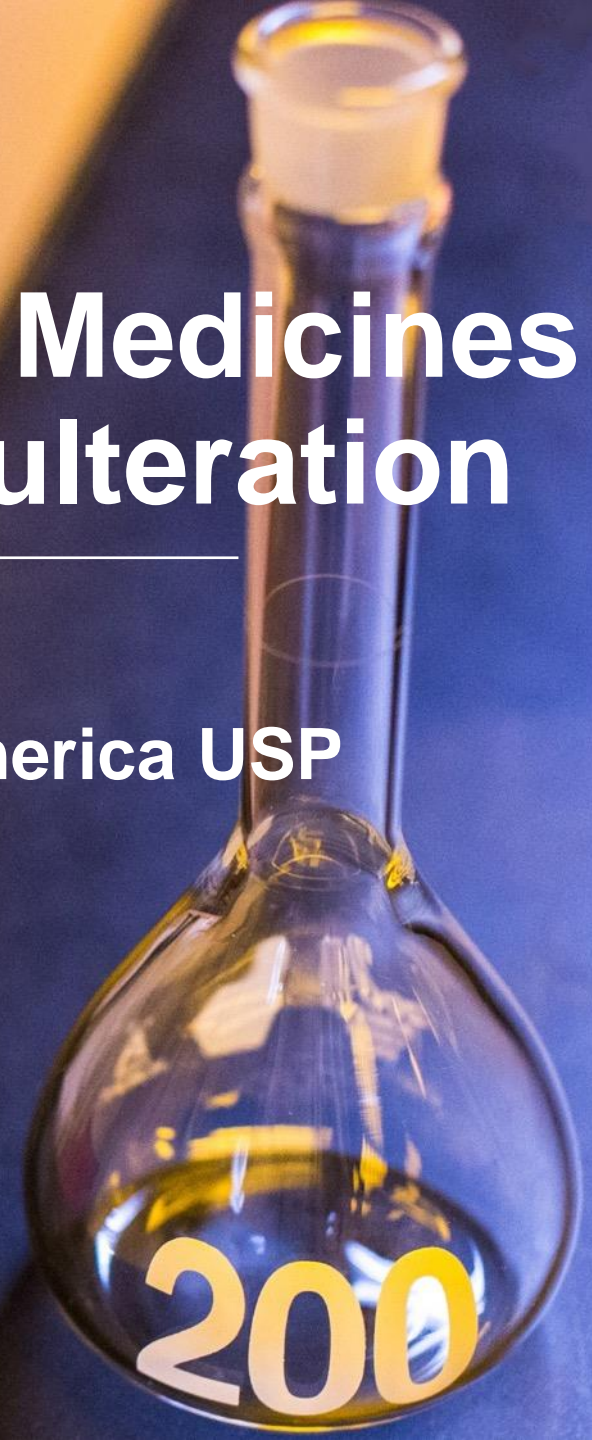


Basis for Detecting Falsified Medicines and Dietary Supplements adulteration

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- ▶ WHO Overview
- ▶ USP Quality medicines approach
 - Value of USP Public Standards for monitoring of counterfeit and substandard products
 - DS&HM USP Quality approach and adulteration
- ▶ Q & A



Up to two billion people around the world lack access to necessary medicines, vaccines, medical devices including in vitro diagnostics, and other health products, which creates a vacuum that is too often filled by substandard and falsified products



A modelling exercise developed by the University of Edinburgh estimates that 72 000 to 169 000 children may be dying each year from pneumonia due to substandard and falsified antibiotics.

An estimated 1 in 10 medical products circulating in low- and middle-income countries is either substandard or falsified, according to new research from WHO

WHO definitions of substandard and falsified medicines



- ▶ **Substandard** Also called “out of specification”, these are authorized medical products that fail to meet either their quality standards or their specifications, or both.
- ▶ **Falsified medicines** Medical products that deliberately/fraudulently misrepresent their identity, composition or source.
- ▶ **Unregistered/Unlicensed** Medical products that have not undergone evaluation and/or approval by the national and/ or regional regulatory authorities for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

S&F Medicines Impact



- ▶ The negative impact of S&F medicines spans beyond health system inefficiency



USP Quality Medicines approach

Value of USP Public Standards for monitoring of counterfeit and substandard products



Who we are



Mission

To improve global health through public standards and related programs that help ensure the quality, safety and benefit of medicines and foods





200

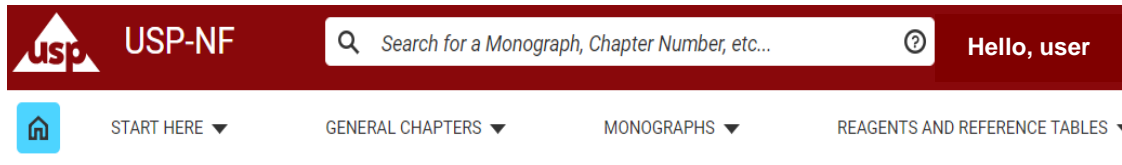
**years building quality
foundations for a
healthier world**



USP – Public Standards



USP standards used in over 140 countries

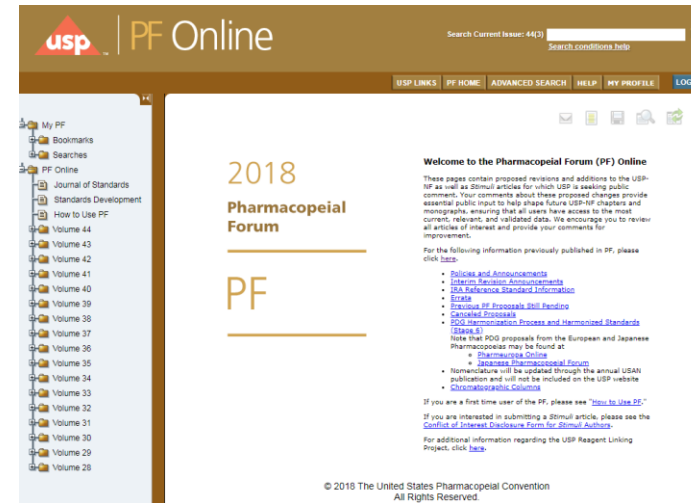


New USP-NF Online Dashboard

Get the most out of your new USP-NF Online! Explore this area for helpful video tutorials and links to USP resources.

NEW USP-NF ONLINE DASHBOARD

Please Read: Release Notes Please read for known issues on this release.	Improved Search Tutorial Get relevant contextual results much faster.	Navigation Basics Tutorial Browse smartly with information arranged relevantly.	Understanding Official Status Tutorial What you need to know about USP-NF versions and official status.
PLEASE READ: RELEASE NOTES Please read for known issues on this release	IMPROVED SEARCH TUTORIAL Watch a video tutorial on the improved search tool!	NAVIGATION BASICS TUTORIAL Learn how to navigate the new USP-NF Online	OFFICIAL STATUS TUTORIAL Understand official dates for monographs and general chapters
Dissolution Toolkit View the Dissolution Toolkit.	Reference Standard Mobile App Stay notified. USP compliance made easy. Download the USP Reference Standard App today!	Access to the old (legacy) USP-NF Online platform. Click here for access.	Update Delayed Implementation for Second Supplement to USP41-NF36
DISSOLUTION TOOLKIT Click here for helpful information on Dissolution	REFERENCE STANDARD APP Download the free USP Reference Standards App today	LEGACY USP-NF ONLINE Access the legacy (old) USP-NF Online	IMPORTANT COMPENDIAL UPDATES Keep up with the latest compendial updates.



Go to www.usppf.com to access the PF





3,600+

reference standards

are available for prescription and OTC drugs, biologics, excipients, dietary supplements and foods



USP Reference Standards

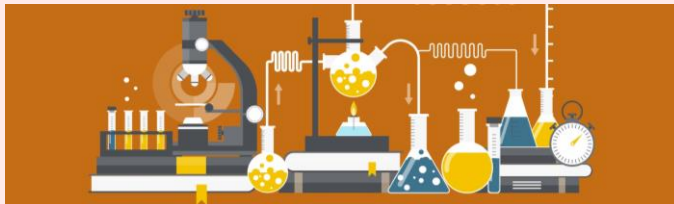


Highly characterized specimens of



- Drug substances
- Excipients
- Impurities
- Degradation products
- Biologics

- Food ingredients
- Dietary supplements
- Compendial reagents
- Performance test tablets



The Value of Public Quality Standards



- ▶ Helps provide scientific basis for decision-making in regulatory review, manufacturing and enforcement
- ▶ Contribute to research and development, fostering innovation
- ▶ Helps ensure a consistent approach to quality for innovator and generic products
- ▶ Assess the quality of drug products in commerce
- ▶ Aids in monitoring for counterfeit and substandard products and quality of imported drug products



USP Quality Institute



- ▶ The USP Quality Institute sponsors much-needed research to enable evidence-based policy decisions that can help increase the availability of quality medicines everywhere, building a foundation for a healthier world.
- ▶ Global health leaders are faced with a proliferation of falsified and substandard medicines that threaten public health.
- ▶ The Fellowship in Quality of Medical Products is the signature program of the USP Quality Institute.

Testing with USP Reference Standards

A graphic of a silver chain link, with one link being larger and containing text. The text is '3 Finished Product'.

3 Finished Product



ID Tests
Impurity Tests
Related Compounds
Limit Tests
Residual Solvents
Dissolution
Assay

Partnerships at the heart of quality



Partners in science

With academics,
practitioners



Partners in industry

R&D companies and
generic
manufacturers



Partners in government

With regulatory and
health authorities



Dietary Supplements & Herbal Medicines USP Quality approach and Adulteration



Dietary supplements global situation



- ▶ \$106.4B global sales in 2018 and expected to continue to grow to \$138B by 2023*
- ▶ Consumers/patients expect quality & safety
- ▶ USA / Dietary Supplement Health & Education Act (DSHEA):
 - Quality means that the dietary supplement consistently meets the established **specifications for identity, purity, strength, and composition, and limits on contaminants**
 - Methods should be **scientifically valid and fit for the purpose**
- ▶ USP has >500 monographs for dietary supplements and >50 monographs for herbal medicine ingredients

*Source: Euromonitor

Complexity of Botanical Products



Whole

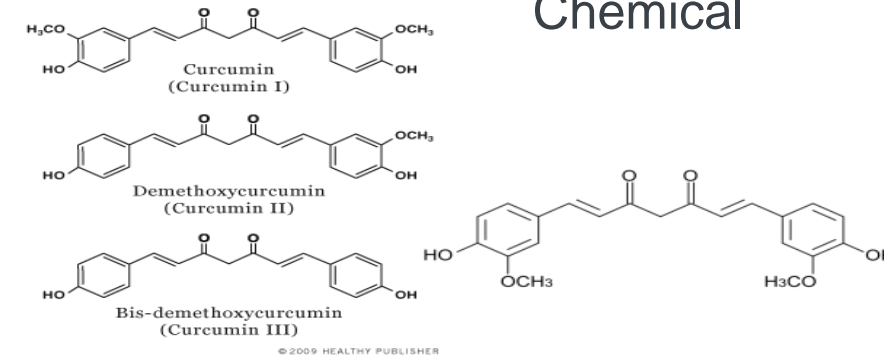
Powdered
plant material

Native/
Full spectrum
Extracts

Enriched
Extracts

Isolated
Class of
compounds

Purified
Single
Chemical



Turmeric Root

Turmeric
Powder

Turmeric
Dry Extract

Turmeric
Curcuminoid
Extract

Curcuminoids

Curcumin

Degree of Complexity

Intact plant material-----

-----Single chemical entity

Degree of Purification

Degree of Purification

USP General Chapters



Specific for Dietary Supplements:

- <2021> Microbial Enumeration Tests, Nutritional and Dietary Supplements
- <2022> Microbiological Procedures for Absence of Specified Microorganisms, Nutritional and Dietary Supplements
- <2023> Microbiological Attributes of Non-sterile Nutritional and Dietary Supplements
- <2040> Disintegration and Dissolution of Dietary Supplements
- <2091> Weight Variation of Dietary Supplements
- <2232> Elemental Contaminants in Dietary Supplements
- <2250> Detection of Irradiated Dietary supplements
- <2251> Screening Methods for Undeclared Drugs and Drug analogs
- <2750> Manufacturing Practices for Dietary Supplements

USP General Chapters



Non-specific for Dietary Supplements:

<203> HPTLC

<467> Residual Solvents

<561> Articles of Botanical Origin

<563> Identification of Articles of Botanical Origin

<621> Chromatography

USP public standards for dietary supplements



- ▶ Monographs + chapters + reference standards = comprehensive set of scientifically validated methods, supporting RS, and specifications to assess quality
 - Identity
 - Purity/Strength/Content
 - Limits for Contaminants
 - Performance
 - Specific Tests



Common tests by monograph type



Test \ DS Type	Vitamin	Minerals	Non Botanicals	Botanicals
Identity	IR, HPLC RT, UV, Chemical	Chemical	IR, HPLC RT, UV, Chemical	Microscopy, TLC, HPLC, GC
Purity/ Contaminants	Chromatographic purity, Limit Tests, Microbial, Heavy Metals	Chemical Limit tests, Limit of foreign metals by AA, ICP	Chrom. purity, Limit Tests, Microbial, Heavy Metals, PCBs-Dioxins	Toxins, Aflatoxins, Heavy Metals, Pesticides, Foreign Matter, Residue On Ignition, Microbial, Negative Markers
Performance	Packaging, Labeling, Uniformity, Dissolution, Disintegration	Packaging, Labeling, Uniformity, Dissolution, Disintegration	Packaging, Labeling, Uniformity, Dissolution, Disintegration	Packaging, Labeling, Extractable Matter, Uniformity, Dissolution, Disintegration
Strength/ Composition	Spectroscopy, HPLC, Microbial	AA, ICP, Titration	Spectroscopy, HPLC, Titration	HPLC, GC

▶ Identification Tests

- Orthogonality
- Spectroscopy: IR, NMR, UV, etc
- Chromatographic: HPLC, TLC, GC, CE
- Chromatographic fingerprints for complex ingredients
- Salts and counter ion tests
 - *Identification Tests—General <191>*

DNA Methods for Botanical Identification

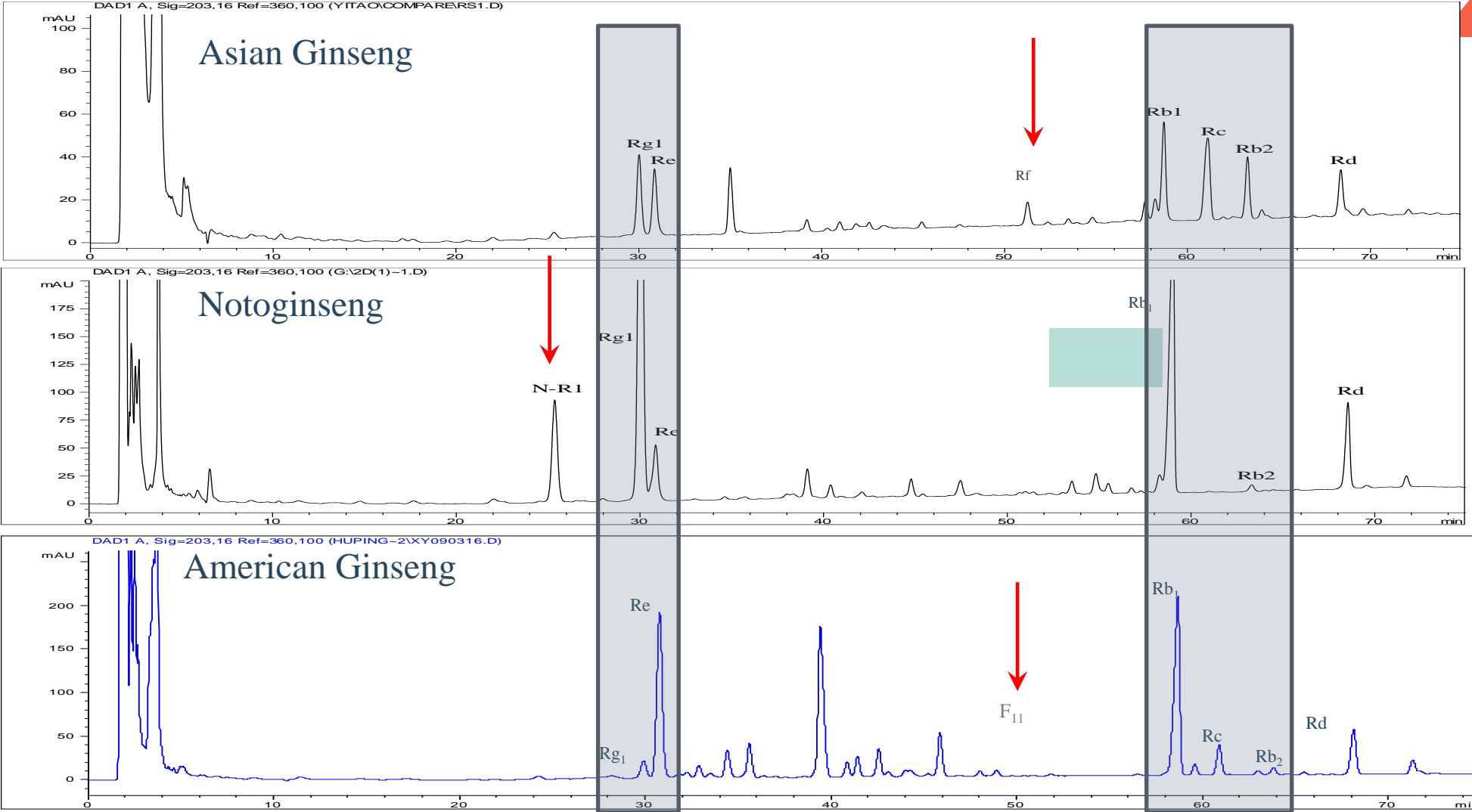


American Ginseng (A)

Asian Ginseng (B)

Tienchi Ginseng (C)

Chromatographic fingerprinting: unique species identifiers



Ginkgo biloba

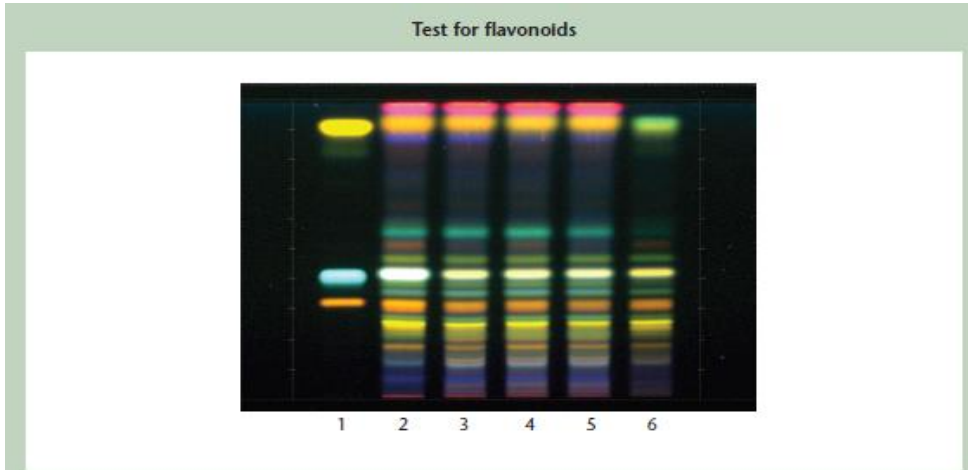


Fig. 5 Typical HPTLC chromatograms

Track assignment: 1) USP Rutin RS 0.6 mg/mL, USP Chlorogenic RS 0.2 mg/mL, and USP Quercetin RS (with increasing R_f); 2) ginkgo leaves (commercial sample); 3) ginkgo leaves (wild crafted); 4) ginkgo leaves, powder (commercial sample A); 5) ginkgo leaves, powder (commercial sample B); 6) ginkgo leaves, tincture (commercial sample)

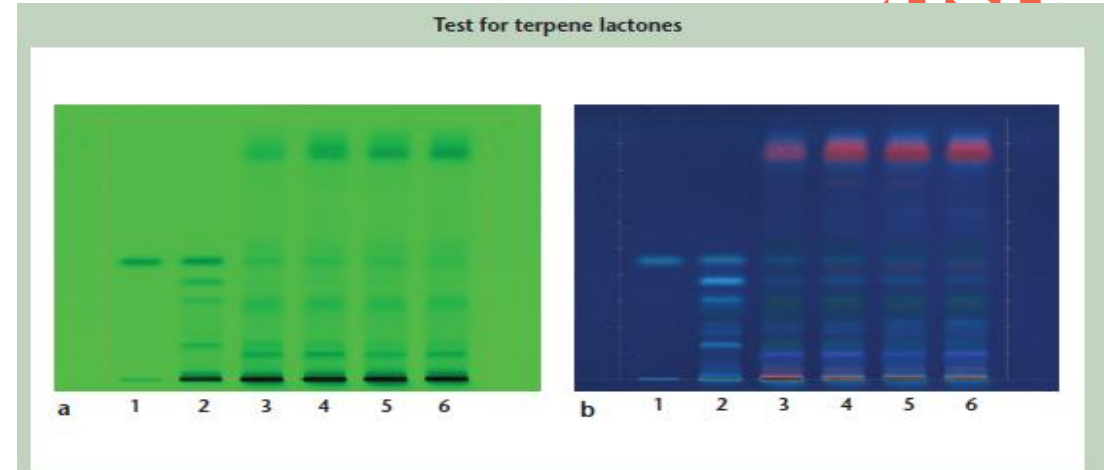


Fig. 6 Typical HPTLC chromatograms

Track assignment: 1) bilobalide (commercial sample), 1 mg/mL; 2) USP Ginkgo Terpene Lactones RS, 10 mg/mL; 3) ginkgo leaves (commercial sample); 4) ginkgo leaves (wild crafted); 5) ginkgo leaves, powder (commercial sample A); 6) ginkgo leaves, powder (commercial sample B)

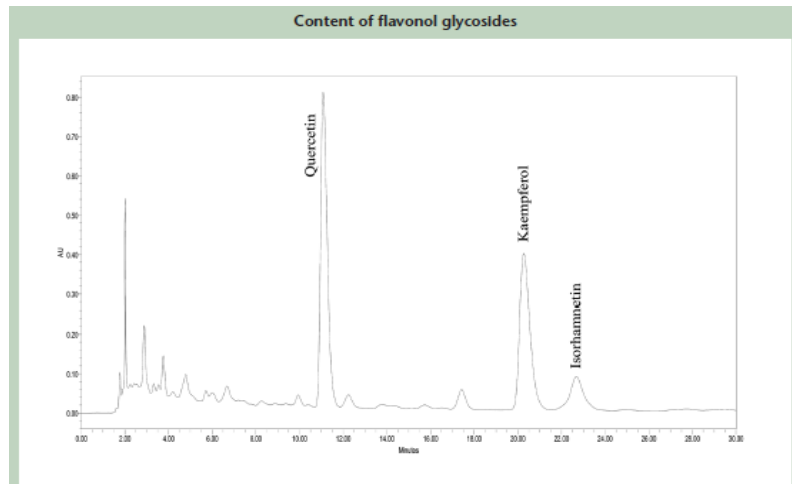


Fig. 8 Typical chromatogram of Sample solution

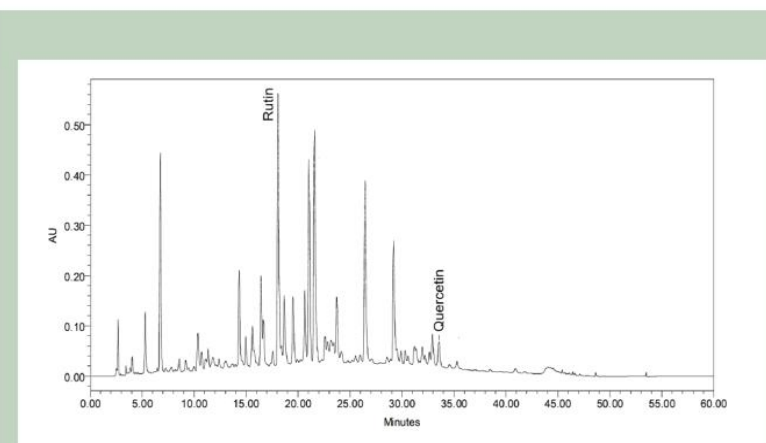


Fig. 12 Typical chromatogram of Sample solution

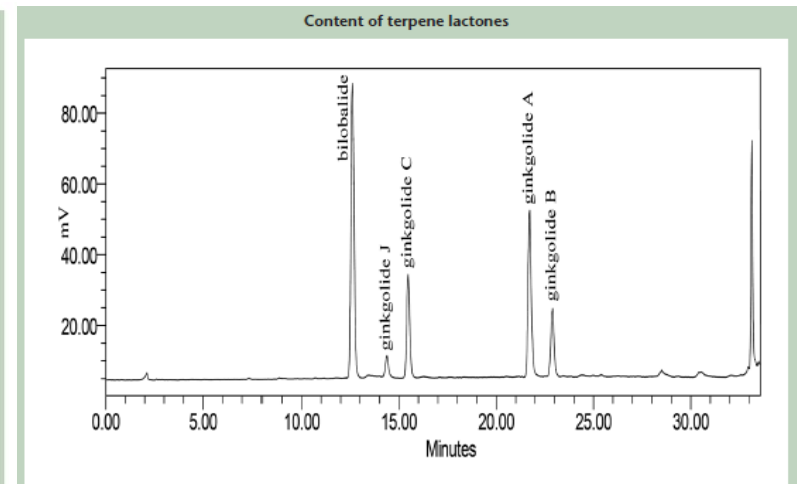


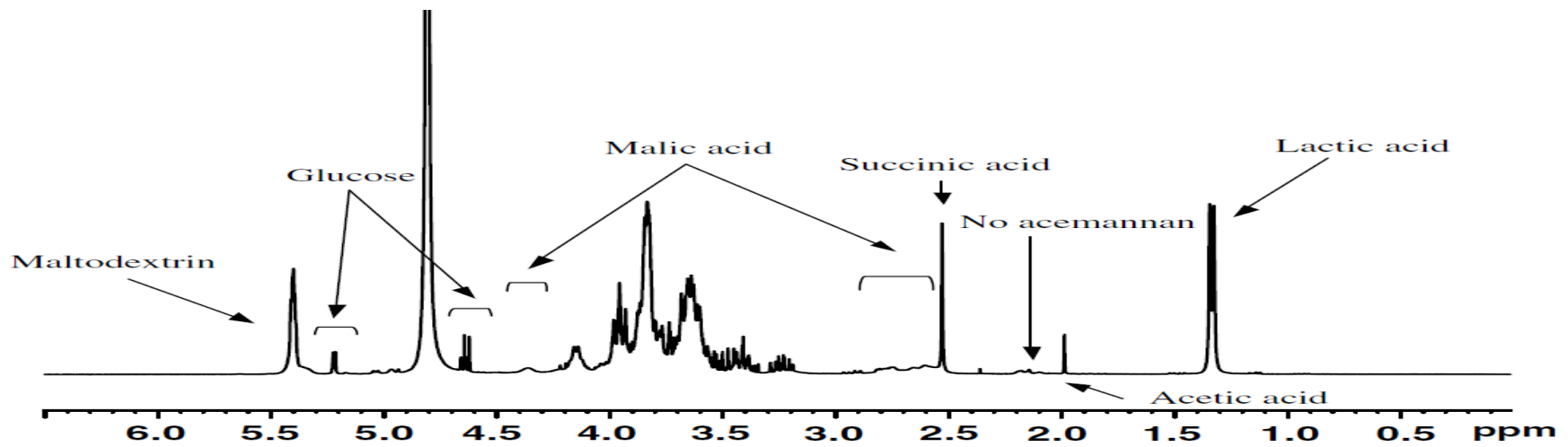
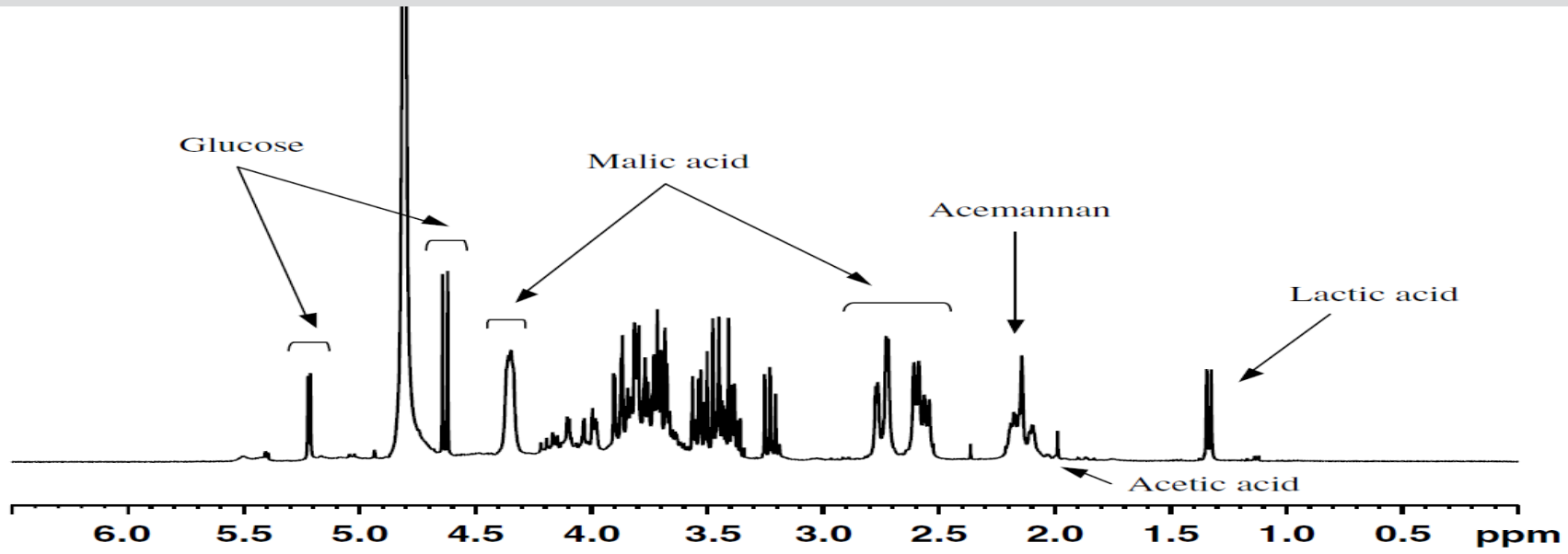
Fig. 9 Typical chromatogram of USP Ginkgo Terpene Lactones RS

NMR: Identity and quantitation in one analysis



- ▶ Potential for identity, purity and content all in one test!
 - Spectral fingerprints allow use as identification test
 - Chemometric approaches are needed for compendial application
 - Potential for quantitative analysis and impurity analysis at the same time

NMR Fingerprint: Aloe juice/gel example



DNA-BASED METHODS FOR AUTHENTICATION OF ARTICLES OF BOTANICAL ORIGIN

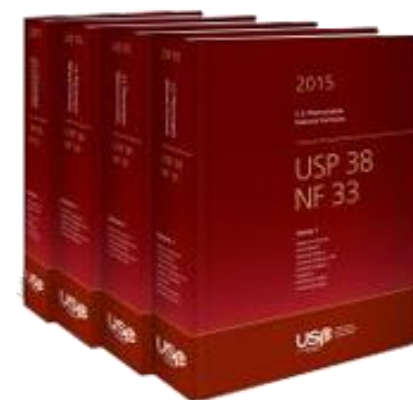
Because morphological identification often is not possible when the original plant material consists of dried, cut and shifted, or processed plant parts or when the material consists only of a whole, single plant part containing no taxonomic characters, additional identification methods, such as DNA-based identification, often are required for these sample types. DNA-based methods have been shown to be efficient in distinguishing genuine plant materials from adulterants in complex botanical matrices and can complement traditional botanical identification methods that rely on morphological features or chemistry. In addition, DNA-based methods often are more reliable than traditional methods, especially when applied to single-organ specimens that lack diagnostic taxonomic characters, to powdered materials in which the distinguishing characteristics are no longer visible, or when it is difficult to distinguish among closely related or morphologically similar species.

DNA Barcoding

DNA barcoding is a particular type of DNA sequence-based identification method that uses short sequences of specific nuclear or plastid DNA loci for identification of plant species. The assays rely on comparison of nucleotide sequences from a specific stretch of DNA (DNA sequences or DNA barcode) to perform DNA sequence-based identification. Further, DNA-based methods, such as next-generation sequencing (NGS) technologies, are able to identify multiple species in a mixture, including expected and unexpected species.

Botanical Identification Using DNA (Sanger) Sequencing

The process for botanical identification using DNA (Sanger) sequencing includes marker selection, DNA extraction, polymerase chain reaction (PCR) primers and amplification, DNA sequencing, and comparison with reference materials, as described in the following sections. See *Nucleic Acid-Based Techniques—Extraction, Detection, and Sequencing* 〈1126〉, *Nucleic Acid-Based Techniques—Amplification* 〈1127〉, and *Nucleic Acid-Based Techniques—Genotyping* 〈1129〉 for additional information.



Considerations for DNA-based identification



- ▶ DNA-based methods are useful for botanical ingredient ID
 - High degree of specificity and sensitivity
 - Can distinguish closely related or morphologically similar species
- ▶ DNA-based methods are not suitable as the sole basis for ID
 - May not be suitable for botanical extracts, unless validated
 - False negative results from processed ingredients or due to interferences from the matrix
 - False positive results from foreign organic matter naturally occurring in the plant material at low but allowable levels (NMT 2%)
 - May be fooled by deliberate addition of small amounts of raw material
- ▶ **Suitable as an orthogonal test which measures a unique attribute**

USP General Chapter <2251>



The chapter currently addresses only one segment of adulteration:

- **Sexual enhancement:**

Also referred to as the Erectile Dysfunction category, this encompasses a functionally coherent group of adulterants, including several approved drugs (e.g. sildenafil), their numerous approved and unapproved analogues, synthetic intermediates, and derivatives. Their functionality is manifested by selective inhibition of phosphodiesterase type 5 enzyme (PDE5).

- **Weight loss:**

This category comprises a functionally and chemically diverse compounds that include stimulants, laxatives, diuretics, anorexiant, and psychoactive drugs. Although stimulants constitute an important segment of weight loss adulterants, the oral anorexiant sibutramine dominates this category, frequently in combination with phenolphthalein, a banned laxative.

- **Sports performance enhancement:**

Professional and amateur athletes are targeted with designer anabolic steroids and stimulants, many of which are banned by the World Anti-Doping Agency (WADA). These DS are customarily formulated in protein- and fat-rich matrices, thereby further complicating detection.

USP General Chapter <2251>



- Appendix A of the chapter details six general screening methods:
 - LC-UV
 - LC-MSn
 - NMR
 - HPTLC – visual, UV densitometry, MS
 - API-MS (DART)
 - Bioassay
- Two informational tables: 64 known adulterants, chromatographic data for 34 compounds, mass-spectral data with fragmentation, chemical structures.
- UV spectra acquired under experimental conditions specified in the chapter.

Emerging Technologies



- DNA-based ID
- NMR
- Chemometrics
- Digital standards and Databases
- Non-targeted methods
- Metabolomics

Value of public standards in DS&HM



Industry

Dietary supplement and ingredient manufacturers produce quality products



Practitioner/Patient

Uphold practitioner and patient confidence in the quality of their supplements



Government

Regulators ensure quality products reach consumers



USP
NF

USP–NF General Notices Section 5.80

USP Reference Standards are authentic specimens that have been approved as suitable for use as comparison standards in USP or NF tests and assays. (See USP Reference Standards 11.)

Where *USP* or *NF* tests or assays call for the use of a USP Reference Standard, only those results obtained using the specified USP Reference Standard are conclusive. Where a procedure calls for the use of a compendial article rather than for a USP Reference Standard as a material standard of reference, a substance meeting all of the compendial monograph requirements for that article shall be used. If any new *USP* or *NF* standard requires the use of a new USP Reference Standard that is not yet available, that portion of the standard containing the requirement shall not be official until the specified USP reference material is available.

Where *USP* or *NF* tests or assays call for the use of a USP Reference Standard, only those results obtained using the specified USP Reference Standard are conclusive.

Questions?



Thank You

