Label Claim and Adulteration Testing for Dietary Supplements

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Director of Scientific Affairs

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Eurofins Group Overview

Eurofins for unbiasis the **global leader in biological testing** with an unrivaled reputationed analysis

200,000 reliable analytical methods for characterizing the safety, identity, purity, composition, authenticity, and origin of products

Our **diverse laboratories** navigate seamlessly through a dynamic and ever-changing global marketplace

55K+ EMPLOYEES

900+ LABORATORIES

50 COUNTRIES

450M+ TESTS ANNUALLY

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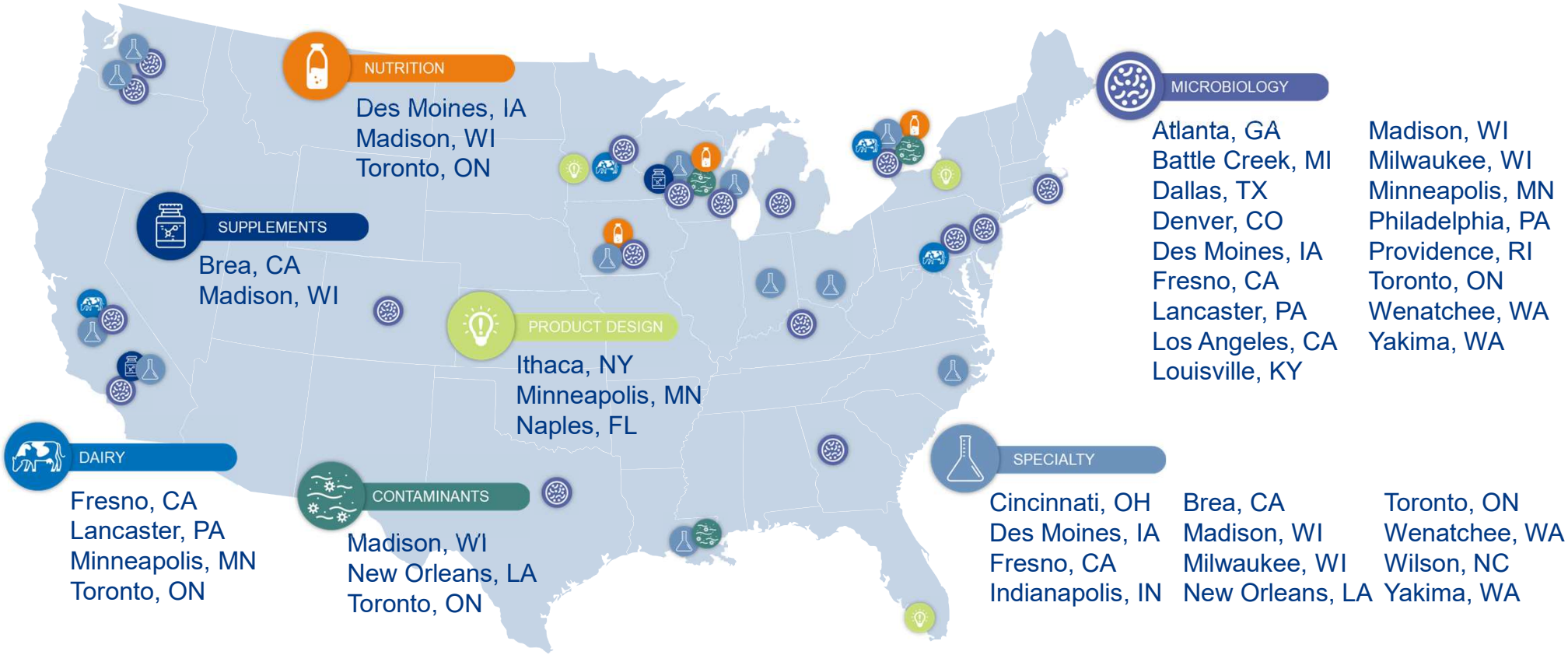
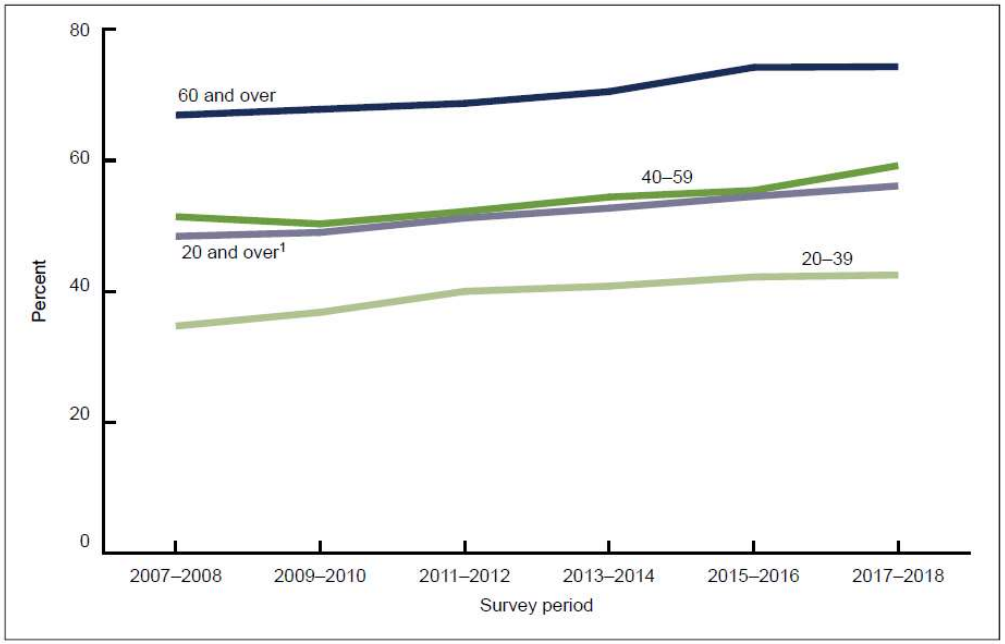
Eurofins US Food Footprint

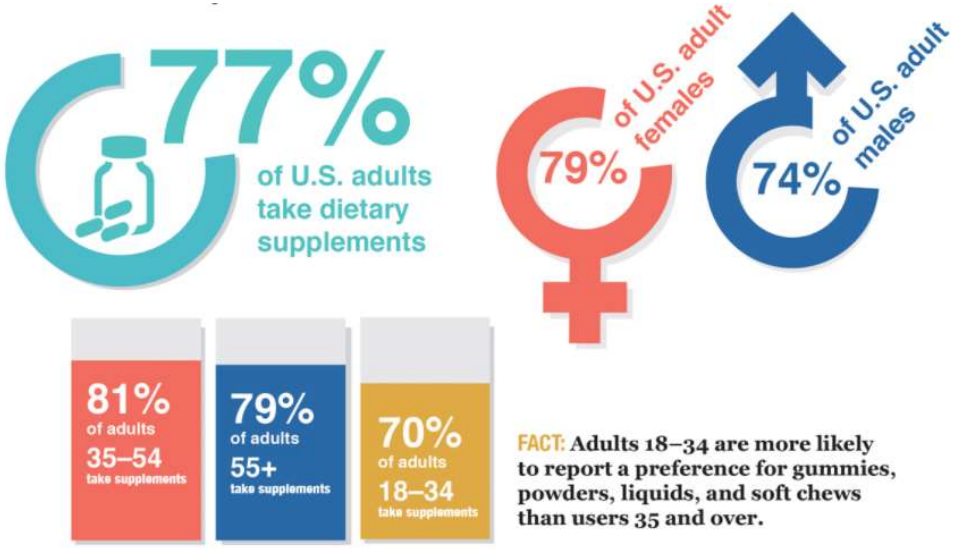


Trends in the use of dietary supplements

Figure 4. Trends in age-adjusted percentage of adults aged 20 and over who used any dietary supplement: United States, 2007–2008 through 2017–2018



[1]Estimates were age adjusted by the direct method to the 2000 U.S. Census population using age groups 20–39, 40–59, and 60 and over.
NOTES: Significant linear increasing trend for all groups. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db399-tables-508.pdf#4.
SOURCE: National Center for Health Statistics, National Health and Nutrition Examination Survey, 2007–2018.



https://www.crnusa.org/

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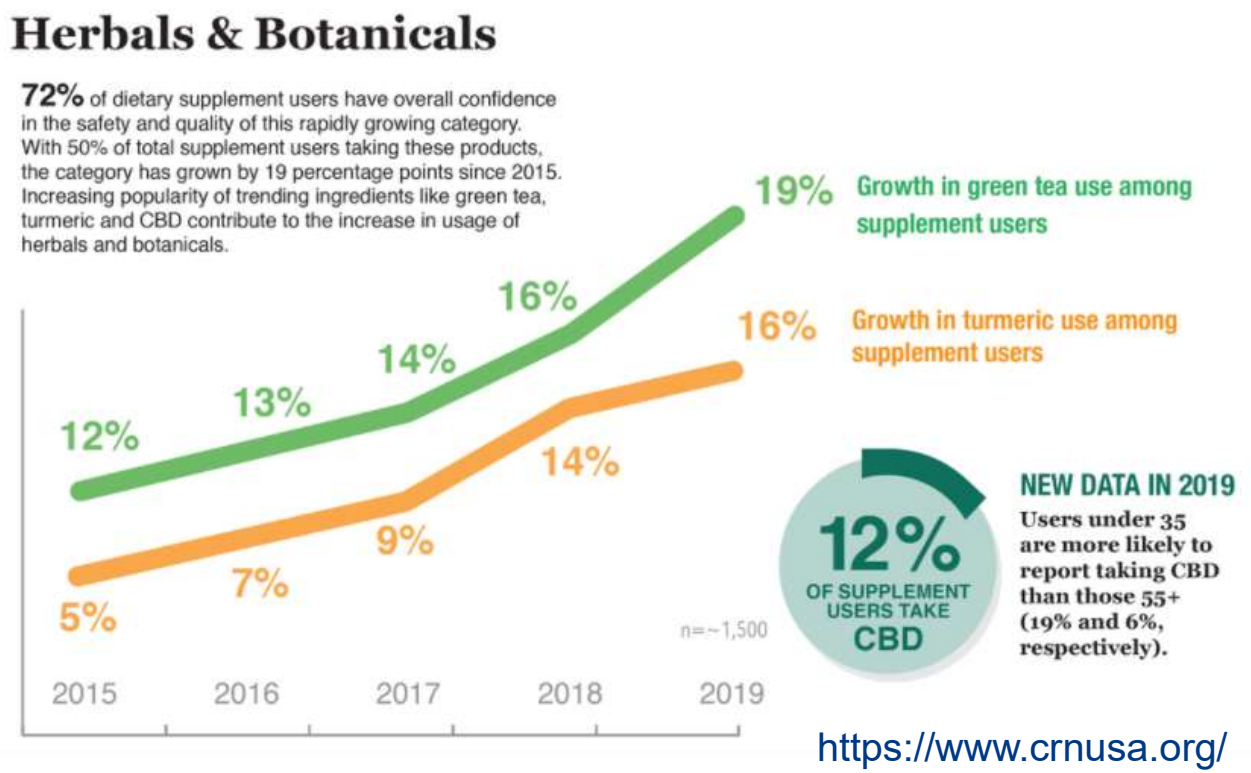
Trends in the use of dietary supplements



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Different terms in the US

- **Dietary ingredients** - The Federal Food, Drug, and Cosmetic Act defines a dietary ingredient as a vitamin; mineral; amino acid; herb or other botanical; dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of the preceding substances.
- **Dietary supplements** - Dietary supplements include dietary ingredients such as vitamins, minerals, herbs, amino acids, and enzymes. Dietary supplements are marketed in forms such as tablets, capsules, softgels, gelcaps, powders, and liquids. FDA regulates dietary supplements under a special category of food
- **Nutraceuticals** - There is no “nutraceutical” defined by the US federal law. It often appears on product labels from foreign countries or the FDA website in the names of companies that have received warning letters for violating the FDA regulations.
- **Functional foods -** The existing regulatory framework for functional foods is the same basic framework that applies to foods in general. This means the ingredients used in functional foods, including the dietary ingredients, must either be used in accordance with a food additive regulation issued by FDA or must qualify as "generally recognized as safe" (GRAS).

https://www.vectorstock.com/royalty-free-vector/cute-happy-funny-ginger-root-with-question-vector-31728216

Code of Federal Regulations for Dietary Supplements

- The production of dietary supplement follows 21 CFR 111 cGMP regulation

```
[Code of Federal Regulations]
[Title 21, Volume 2]
[CITE: 21CFR111]

                              TITLE 21--FOOD AND DRUGS
                            CHAPTER I--FOOD AND DRUG ADMINISTRATION
                            DEPARTMENT OF HEALTH AND HUMAN SERVICES
                           SUBCHAPTER B - FOOD FOR HUMAN CONSUMPTION
                  PART 111  CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING,
                            PACKAGING, LABELING, OR HOLDING OPERATIONS FOR DIETARY
                            SUPPLEMENTS
```

- The labeling rules of dietary supplement follow 21 CFR 101 Food Labeling regulation

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[Code of Federal Regulations]
[Title 21, Volume 2]
[CITE: 21CFR101]

                              TITLE 21--FOOD AND DRUGS
                            CHAPTER I--FOOD AND DRUG ADMINISTRATION
                            DEPARTMENT OF HEALTH AND HUMAN SERVICES
                           SUBCHAPTER B - FOOD FOR HUMAN CONSUMPTION
                                    PART 101  FOOD LABELING
```

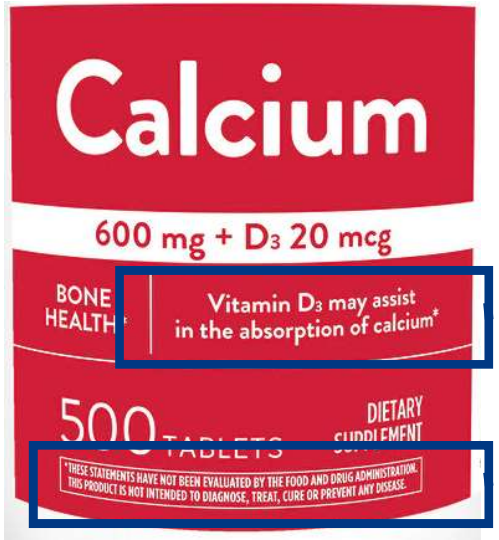
Dietary Supplement Label Claims

- Dietary supplements are not intended to treat, diagnose, cure, or alleviate the effects of diseases.
- US laws have strict requirements on what type of claims that can be used on dietary supplement labels.
- There are three categories of food and dietary supplement claims that are defined by FDA regulations:
  - Health claims
  - Structure/function claims
  - Nutrient content claims

Health Claims and Structure/Function Claims

- **Health claims** describe a relationship between a food substance or dietary supplement ingredient and reduced risk of a disease or health-related condition. **A health claim requires FDA evaluation and authorization prior to its use. - 21 CFR 101.14**

- **Structure/function claims** describe the role of a nutrient or dietary ingredient intended to affect the structure or function in humans or that characterize the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function. **Structure/function claims do not require preapproval by FDA but they require to include a disclaimer. - 21 CFR 101.93**



Nutrient Content Claims

Nutrient Content Claim characterizes the level of a nutrient in a dietary supplement and describes the level of a nutrient in the product, using terms such as:

- “free”, “high”, and “low” - 21 CFR 101.54(b), 101.60
- “high potency” - 21 CFR 101.54(f)
- “antioxidant” - 21 CFR 101.54(g)

A "Supplement Facts" panel is required if you make a nutrient content claim - 21 CFR 101.13(n)

21 CFR 101 requirements for label statements

Five statements are required on the containers and packages of dietary supplements:

1. The statement of identity (name of the dietary supplement) - 21 CFR 101.3(a)
2. The net quantity of contents statement (amount of the dietary supplement) - 21 CFR 101.105(a)
3. **The nutrition labeling - 21 CFR 101.36**
4. **The ingredient list - 21 CFR 101.4(a)(1)**
5. The name and place of business of the manufacturer, packer, or distributor - 21 CFR 101.5

The nutrition label for a dietary supplement is called a "Supplement Facts" panel - 21 CFR 101.36(b)(1)(i)

Supplement Facts

Serving Size 1 Capsule
Servings Per Container 100

Amount Per Capsule	% Daily Value
Calories 20	
Total Fat 2 g	3%*
Saturated Fat 0.5 g	3%*
Polyunsaturated Fat 1 g	†
Monounsaturated Fat 0.5 g	†
Vitamin A 765 mcg	85%
Vitamin D 21 mcg	105%
Omega-3 fatty acids 0.5 g	†

* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

Ingredients: Cod liver oil, gelatin, water, and glycerin.

Quality Regulation of Dietary Supplements

- 21 CFR 111.70 asks to
  - (b) establish specifications for each component used in dietary supplement manufacture for their (1) **identity**, (2) **purity**, **strength**, **composition**, and (3) **limits on contamination** that may adulterate or may lead to adulteration of the finished batch of the dietary supplement.
  - (d) establish specifications for dietary supplement labels (**label specifications**)

- 21 CFR 111.73: You must determine whether the 111.70 specifications are met.

- 21 CFR 111.75: What must you do to determine whether specifications are met?
  - (a)(1)(i) Conduct at least one appropriate test or examination to **verify the identity of dietary ingredient**
  - (c) **Verify** that **the finished batch of the dietary supplement** meets product specifications via tests and examinations

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Specification example

Product name	Tongkat Ali Extract Powder	Part Used	Root
Latin Name	*Eurycoma Longifolia Jack*	Extract Solvent	Pure water
Batch NO.	EE180327	Manufacturing Date	Mar,27th.2018
Batch Quantity	552Kgs	Expiration Date	Mar,26th.2020

Item	Specification	Result	Test Method
Assay(Eurycomanone)	NLT 2.0%	2.10%	HPLC
Identification	Conforms to Standard	Conforms	HPTLC
Appearance	Beige to yellow brown powder	Yellow brown	Visual
Odor	Characteristic	Conforms	Smell
Loss on Drying	≤ 10.0%	1.01 %	5g/105℃/2hrs
Total Heavy metals	≤ 20 ppm	Conforms	USP
Lead (Pb)	≤ 1.0 ppm	< 1.0 ppm	ICP-MS
Microbe Tests			
Total Plate Count	< 10,000 CFU/g	< 1,000 CFU/g	USP
Total Yeast & Mold	< 500 CFU/g	< 100 CFU/g	USP
Total Coliforms	< 10 CFU/g	< 10 CFU/g	USP
E.Coli	Absent	Absent	USP
Salmonella	Absent	Absent	USP
staphylococcus aureus	Absent	Absent	USP
Storage: Cool & dry place. Do not freeze. Keep away from straight light and heat. 2 Years when properly stored.			

https://www.everforeverbio.com/tongkat-ali-extract/

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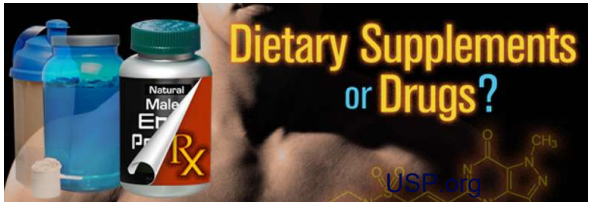
ADULTERATION

- FDA definition of adulteration
  - Under section 402(g)(1) of the Act [21 U.S.C. § 342(g)(1)], a dietary supplement shall be deemed to be adulterated if it has been prepared, packed, or held under conditions that do not meet cGMP regulations for dietary supplements.
- Economically motivated adulteration (different than FDA adulteration)
  - Substitute ingredients
  - Diluted ingredients
  - Adding API for product enhancement (weight loss, sexual enhancement)
- Unintentional and accidental adulteration
  - Issues with cross contamination (allergens, pesticides)
  - Microbiology
  - GMO
  - Active compounds degradation and interaction (vitamin B12 with dibasic calcium phosphate tableting agent; amino acid ingredient in gummy supplement)



- Your products are **adulterated** if they don't meet your finished product, ingredient, or label specifications.

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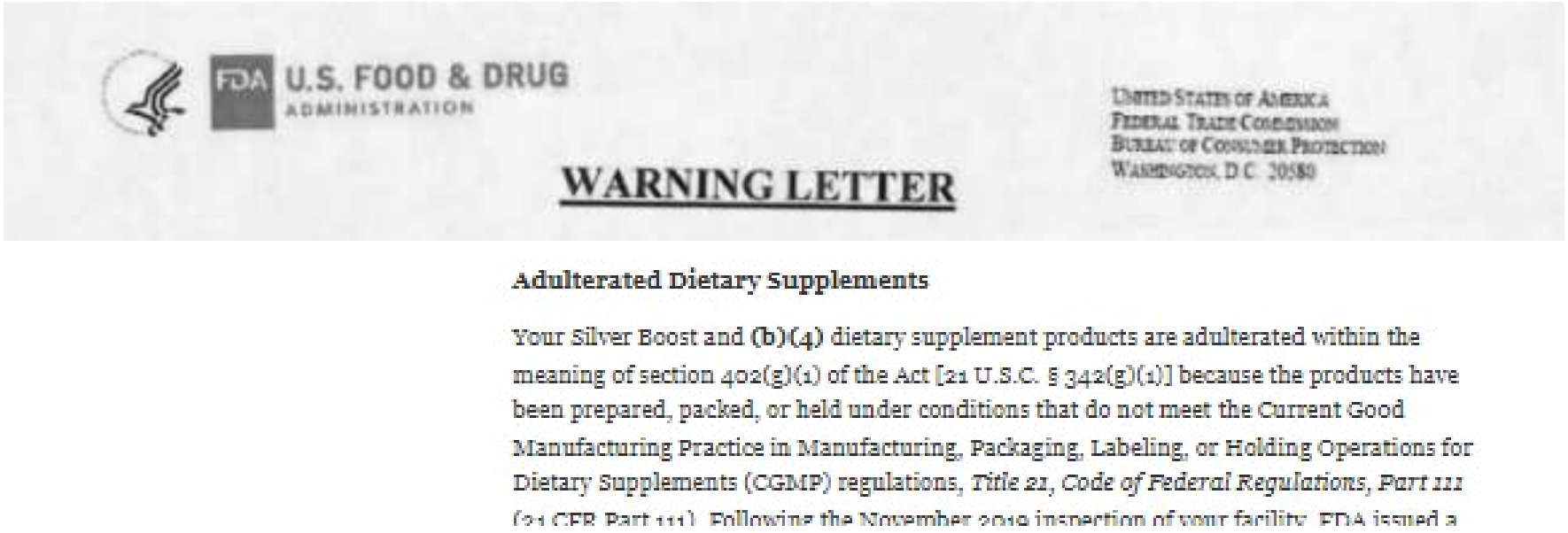
ADULTERATION

- The top two 21 CFR 111 violations are **specifications** and **testing** (more than 50%) for the last ten years.



U.S. FOOD & DRUG ADMINISTRATION

UNITED STATES OF AMERICA
FEDERAL TRADE COMMISSION
BUREAU OF CONSUMER PROTECTION
WASHINGTON, D.C. 20580

WARNING LETTER

Adulterated Dietary Supplements

Your Silver Boost and (b)(4) dietary supplement products are adulterated within the meaning of section 402(g)(1) of the Act [21 U.S.C. § 342(g)(1)] because the products have been prepared, packed, or held under conditions that do not meet the Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements (CGMP) regulations, *Title 21, Code of Federal Regulations, Part 111* (21 CFR Part 111). Following the November 2016 inspection of your facility, FDA issued a

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Testing method development in industrial settings

- 21 CFR Part 111 – Subpart E - 111.75

  (h)(1) “You must ensure that the tests and examinations that you use to determine whether the specifications are met are appropriate, **scientifically valid methods**.”

- 21 CFR Part 111 – Subpart J - 111.320

  (a) “You must verify that the laboratory examination and testing methodologies are appropriate for their intended use.”

  (b) “You must identify and use an appropriate **scientifically valid method** for each established specification for which testing or examination is required to determine whether the specification is met”

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Testing method development in industrial settings

- Full Method Validation
  - Specificity
  - System Suitability
  - Linearity
  - Accuracy
  - Precision
  - Quantification limit
  - Detection limit
  - Ruggedness
  - Forced Degradation
  - Sample and standard stability
  - Multi-lab

- Scientifically-Valid Method Verification
  - Specificity
  - System Suitability
  - Linearity
  - Accuracy
  - Precision
  - Quantification limit
  - Detection limit
  - Ruggedness
  - Forced Degradation
  - Sample and standard stability
  - Multi-lab

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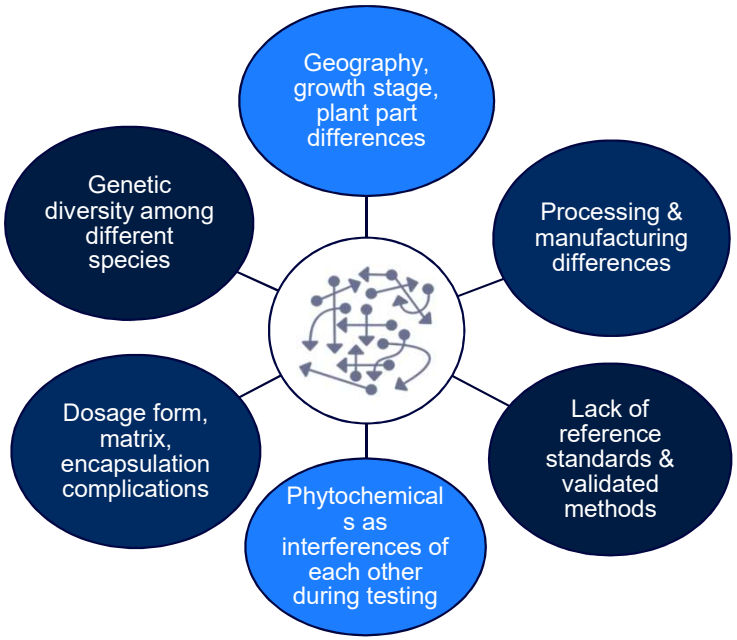
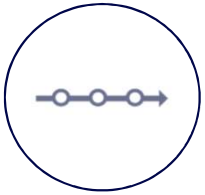
Naturally-derived, botanical dietary supplements are highly complex



Botanical Supplement Testing

VS



Active Pharmaceutical Ingredient (API) Testing

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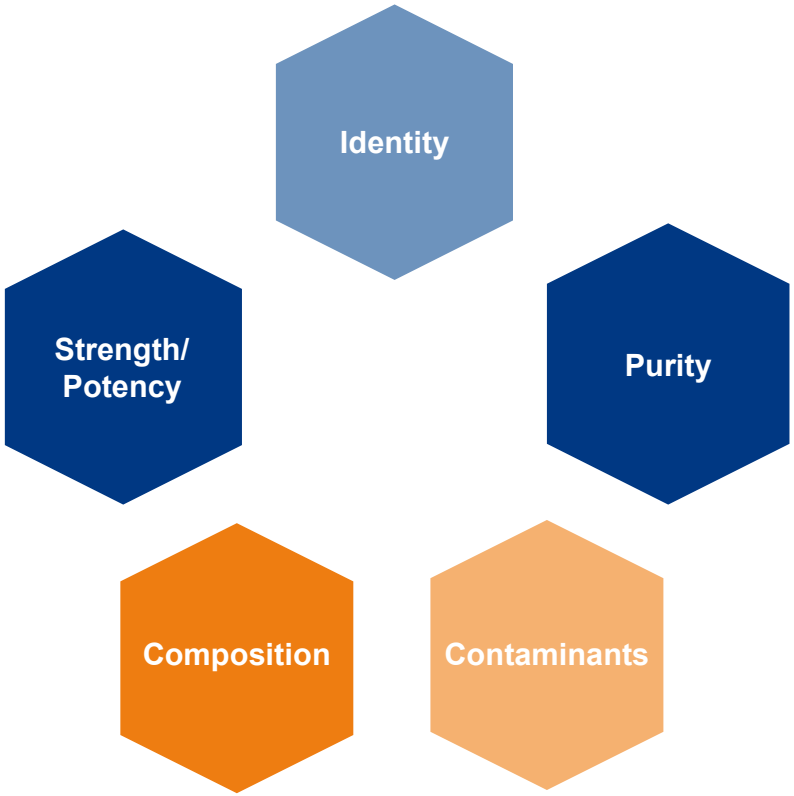
What do you test?



Identity

- Is your green tea extract ingredient a green tea extract?
- The identity tests may include:
  - Organoleptic (color, taste, odor): sensory method
  - Appearance: visual inspections, macroscopic, microscopic
  - Physical: Melting-point, Density
  - Chemical: Wet Chemistry (Titrimetric, colorimetric, precipitation); Spectroscopy (UV/VIS, FL, FTIR, NMR); Thin Layer Chromatography (TLC or HPTLC); Liquid Chromatography (HPLC, UPLC); Gas Chromatography (GC); Mass Spec (LC-MS/MS, GC-MS/MS, HRMS, MALTI-TOF, DART-MS, AMS);
  - Molecular: DNA barcoding, next-generation sequencing (NGS)
  - Microbiological: Agar media-based or turbudity microbiological methods
  - Biological: Enzyme-Linked ImmunoSorbent Assay (ELISA)

Multiple tests to determine Botanical Identification as an “orthogonal” approach

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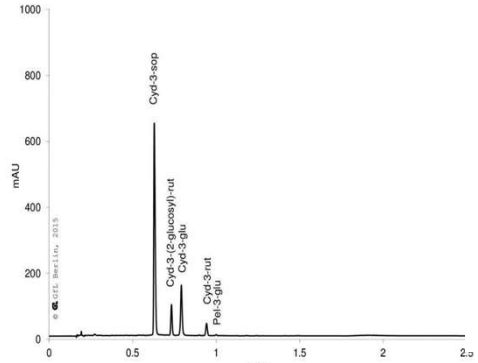
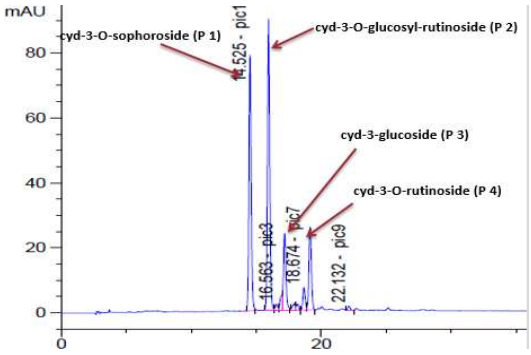
Identity - Botanical economically motivated adulteration



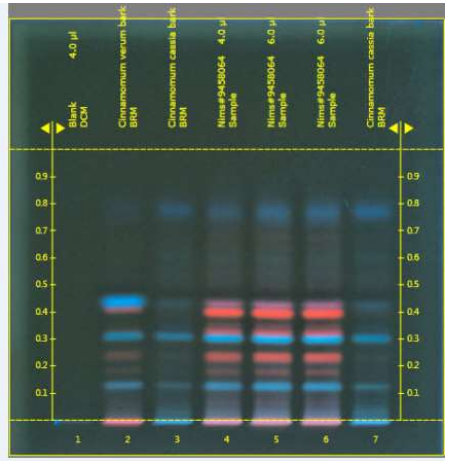
Raspberry (*Rubus idaeus*)

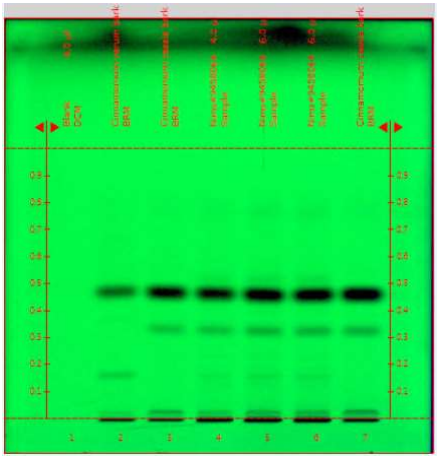


Maravilla Raspberry

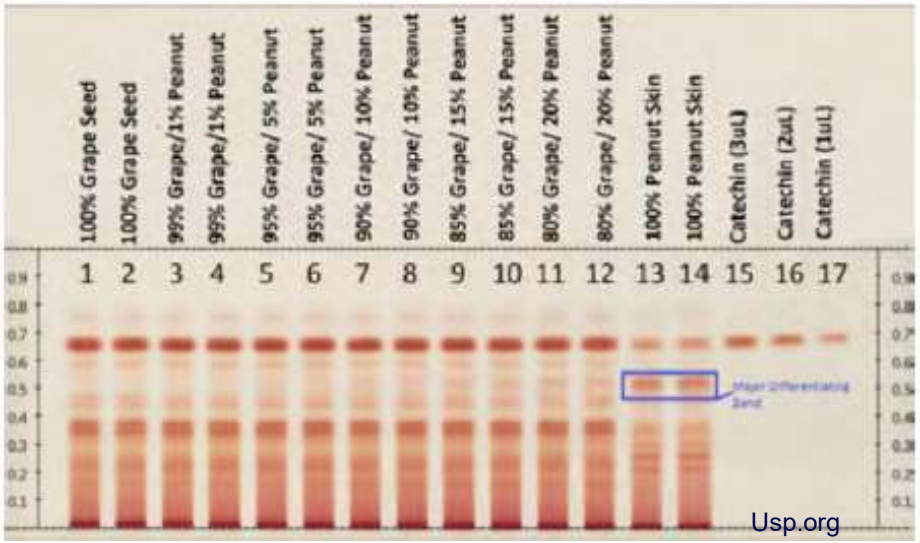
HPLC to distinguish Maravilla Raspberry from common raspberry: Anthocyanin profile for Maravilla showing higher levels of cyanidin-3-glucosyl-rutinoside and cyaniding-3-rutinoside.

HPTLC to distinguish true cinnamon, Cinnamomum verum vs. other cinnamon: Client samples from lane 4-6 showed the presence of the adulterant Cinnamomum cassia under the short wave UV light (254 nm).





Identity - Botanical economically motivated adulteration



Adulteration of Grape Seed Extract with Peanut Skin Extract tested by Thin Layer Chromatography

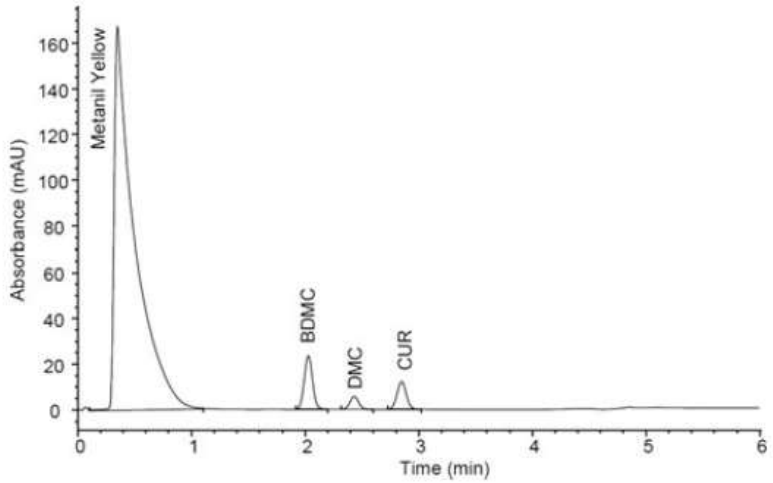


Fig. 4 Chromatographic separation of curcuminoid standards containing metanil yellow as an adulterant

Mudge et.al. Food Anal. Methods, 2016

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Tales from the Elder: Adulteration Issues of Elder Berry

A review of analytical laboratory evidence documenting adulteration and fraud in the international market for elder berry ingredients

By Stefan Gafner, PhD[a]; Travis Borchardt[b]; Melanie Bush[c]; Sidney Sudberg[d]; Nicolas G. Feuillère, PhD[e]; Mathieu Y.R. Tenon[e]; Justine H. Jolibois[e]; Pascale J.N. Bellenger[e]; Hong You, PhD[f]; Rebecca E. Adams[g]; Jeremy Stewart, PhD[h]; Ido Dagan[h]; Timothy Murray, PhD[h]; and David L. Erickson, PhD[i]

Figure 1. US Sales of Elder Dietary Supplements from 2011 to 2019[43-51]

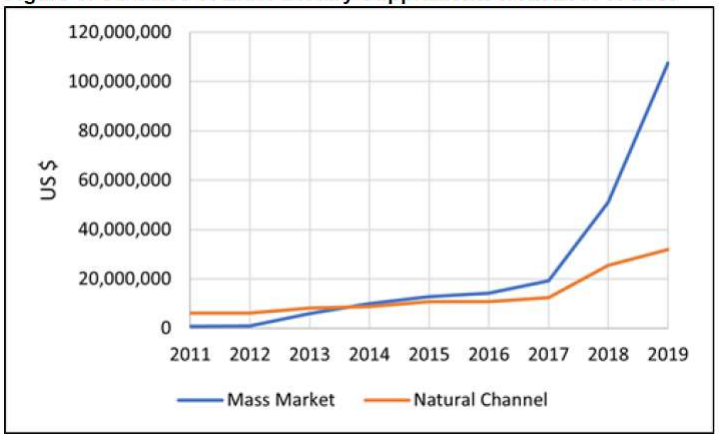


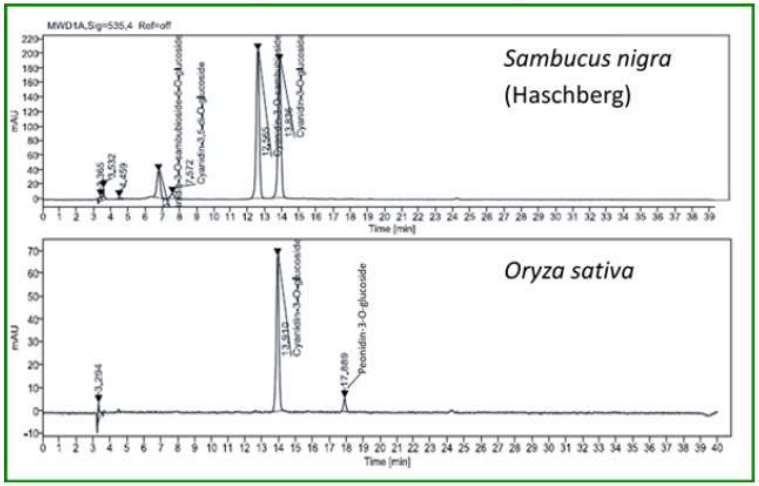
Table 2. Results of Elder Berry Product Testing

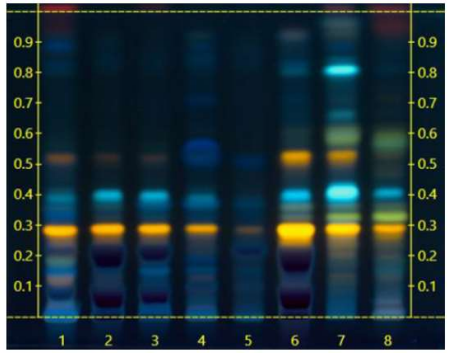
Company*	Method	Adulterated/ Failed Identity Test	Total
Alkemist Labs	HPTLC[b]	32	369
Artemis[a]	**HPTLC[b]/HPLC[c]**	**4**	**11**
DNA4 Technologies	WGS[b]	0	2
Eurofins	HPTLC[b]	2	55
Gaia Herbs	UV/Vis[b]	0	6
Nature's Way	**HPTLC[d]/HPLC[c]**	**16**	**33**
Naturex	**HPLC[b]**	**4**	**10**
NSF International	HPTLC[b]	0	46
Total		**58**	**532**

* Companies in bold included competitors' products in their analyses.

[a] Analysis performed by Alkemist Labs (HPTLC) and Complete Phytochemical Solutions (HPLC)
[b] Proprietary method
[c] United States Pharmacopeia (USP) European Elder berry dry extract monograph[66]
[d] Institute for Nutraceutical Advancement method

Figure 3. HPLC-Vis Chromatogram of Authentic Elder Berry Extract and a Bulk 'Elder Berry' Ingredient Containing Black Rice Extract





Lanes 1–2: Authentic European elder berry
Lane 3–6: Commercial elder berry products
Lane 7: Authentic European elder flower
Lane 8: Authentic blue elder berry

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AMERICAN BOTANICAL COUNCIL

Strength/Potency

- Strength/potency is the concentration of the ingredients. Each item should be listed on the label. When there are analytical methods available, you will be expected to use testing to verify your label. Occasionally, you can exempt testing requirement and justify the strength/potency level by input level.

Supplement Facts

Serving Size 1 Tablet
Servings Per Container 45

Amount Per Serving		% Daily Values for Children 1 through 3 Years of Age	% Daily Values for Adults and Children 4 or more Years of Age
Calories	10		
Total Carbohydrates	2 g	1%**	< 1%*
Total Sugars	2 g	†	†
Includes 2 g Added Sugars		8%**	4%*
Vitamin A	900 mcg	300%	100%
Vitamin C	90 mg	600%	100%
Zinc	11 mg	367%	100%
Herbal Blend Rose Hips, Echinacea Extract.	30 mg	†	†

* Percent Daily Values are based on a 2000 calorie diet
** Percent Daily Values are based on a 1000 calorie diet
† Daily Value not established

www.esha.com/products/supplements-analysis-labeling/us-supplement-label-formats/

Supplement Facts

Serving Size: 3 Liquid Soft-Gels
Servings per Container: 25

	Amount per Serving	%Daily Value
Calories	30	
Total Fat	2 g	2%**
Protein	3 g	
Chromium (as Chromium Picolinate) Chromax®	100 mcg	286%
Flaxseed Oil (seed)	1500 mg	†
L-Citrulline	750 mg	†
[illegible]	[illegible]	†
Green Tea extract (50% EGCG, 135 mg)(leaf)	270 mg	†
[illegible]	[illegible]	†
(50% Hydroxycitric acid, 50 mg)(fruit rind)		
Caffeine (from Coffee Bean) (*Coffea arabica*) (bean)	75 mg	†
BioPerine Complex	3 mg	†
BioPerine® Black Pepper extract (95% piperine)(fruit), Ginger extract (5% gingerols)(rhizome)		

**% Daily Value based on a 2,000 calorie diet
†Daily Value not established

Other Ingredients: Gelatin, purified water, glycerin, annatto (color), beeswax, soy lecithin and titanium dioxide (color).

Contains: Soy, Tree Nuts (coconut)

BioPerine® is a registered trademark of Sabinsa Corporation.
Chromax®, including Chromax® logo, is a registered trademark of Nutrition 21, LLC and is patent protected.

No preservatives added.

https://irwinnaturals.com/

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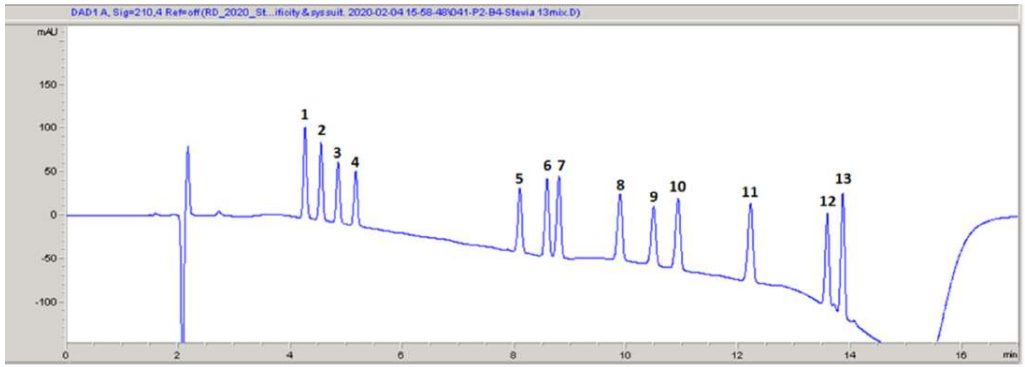
Strength/Potency - Rapid determination for stevia ingredients and products

- Rapid & Eco-friendly with 14 min separation time (compared to JECFA 2017's 80 min run time) and 11.9 mL/run mobile phase use.
- Robust on columns from 3 different manufactures.
- Cost effective and accurate – HPLC platform using authentic standards, not UPLC or Mass Spec.
- Excellent method specificity – peak resolution ≥ 1.5.



JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

pubs.acs.org/JAFC

Article

Rapid and Economic Determination of 13 Steviol Glycosides in Market-Available Food, Dietary Supplements, and Ingredients: Single-Laboratory Validation of an HPLC Method

Zhiyan Liu, Kangzi Ren, Ye Feng, Tommy Uong, Scott Krepich, and Hong You*

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www.just-drinks.com

www.foodbusinessnews.net

Strength/Potency - AOAC Official Method Final Action 2020.05: Cocoa Flavanols and Procyanidins

- Cocoa flavanol and procyanidin analysis in industry setting has always been challenging because of its chemical complexity.
- Eurofins contributed to the **AOAC 2020.05 final action official method** developed by MARS and has led to set up this method across multiple Eurofins labs in the US, Germany, and China.
- Co-study director of the **AOAC multi-lab study** that involves 13 laboratories across the world.

MARS Edge

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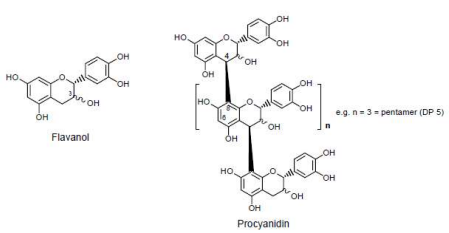
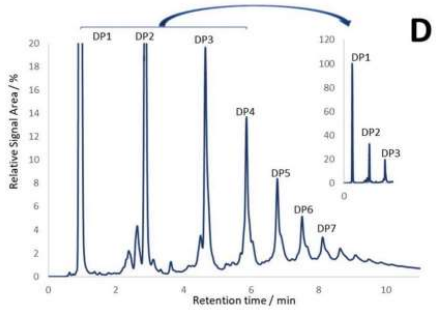


Figure 2012.24A. Chemical structures of flavanols and procyanidins. One example of degree of polymerization (DP) 5 is shown.



Purity

- The portion of percentage of a dietary supplement that represents the intended product.
  - Foreign or Unknown Materials
  - Chromatographic Purity
  - Microbiological Purity

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Composition

- Physical tests of the material or product
  - Powder – particle size
  - Tablets – weight variation, hardness, disintegration
  - Capsule – weight variation, dissolution/rupture
  - Liquids – pH, dissolved solids, viscosity, BRIX

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Limit of contaminates

- The FDA sets permissible levels of various contaminants and these levels cannot be exceeded in the dietary supplement.
  - Heavy Metals
  - Pesticides
  - Residual Solvents
  - Mycotoxins
  - Allergens
  - Active Pharmaceutical Ingredients (API)

amazon seller central

Dietary supplements

If you list products on Amazon, you must comply with all fede listings.

For **sexual enhancement and weight loss supplements**, the COA must include testing results for the specific compounds outlined below. The general COA requirements above still apply.

Category	Test for	Frequency of submission
Sexual enhancements	Sildenafil Tadalafil Vardenafi Sulfoaildenafil Desmethyl carbodenafil	Annually
Weight loss and weight management	Sibutramine Desmethylsibutramine Phenolphthalein Fluoxetine	Annually

https://sellercentral.amazon.com/gp/help/external/55N3JF2WQS7RVNE

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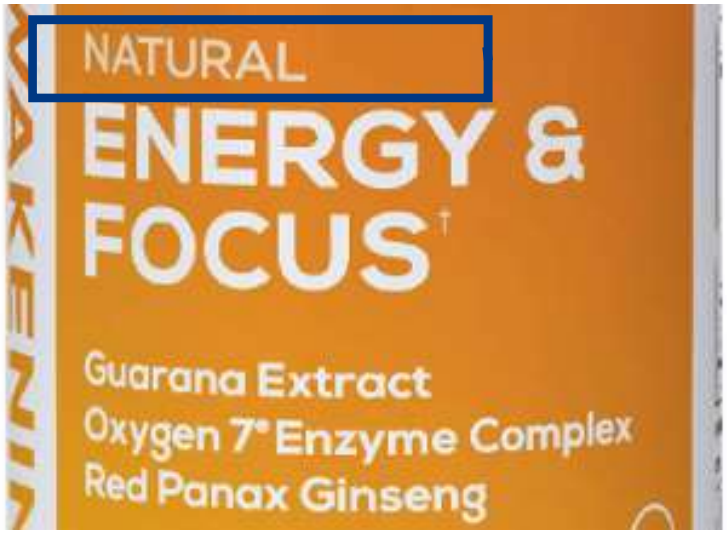
Other label claims

- Use of the Term “Organic”
- Use of the Term “Natural”
- Use of the Term “Healthy”



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Label Claims for Food & Dietary Supplements

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Among the claims that can be used on food and dietary supplement labels are three categories of claims that are defined by statute and/or FDA regulations: health claims, nutrient content claims, and structure/function claims. Learn more about these categories from *Label Claims for Conventional Foods and Dietary Supplements.*

FDA encourages that petitions and notifications be submitted in electronic form. See *How to Submit Label Claim Petitions & Notifications: Electronic Submission of Health Claim Petitions and Notifications* for more information.

Types of Claims

Definitions, Guidance, Regulatory Information, and Permitted Claims

- FDA Modernization Act of 1997 (FDAMA) Health and Nutrient Content Claims
- Health Claims That Meet Significant Scientific Agreement (SSA)
- Qualified Health Claims
- Nutrient Content Claims
- Structure/Function Claims for Dietary Supplements and Conventional Foods

Related Topics

- Organic on Food Labels
- Use of the Term Natural on Food Labeling
- Use of the Term Healthy on Food Labeling

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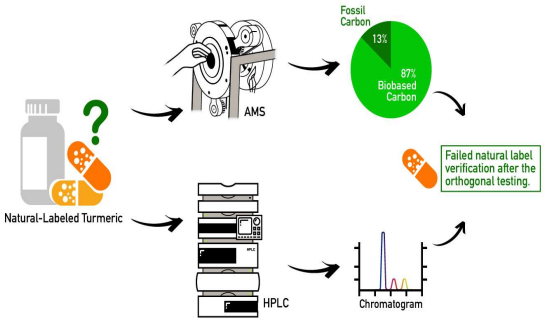
Test for “Natural” claim – Confirming botanical origin

- The FDA has considered the term "natural" to mean that nothing artificial or synthetic (including all color additives regardless of source) has been included in, or has been added to, a food that would not normally be expected to be in that food.
- Commercial dietary supplements containing turmeric ingredients were tested for synthetic curcumin adulteration.
- Using only the carbon-14 **Accelerator Mass Spectrometry** method cannot determine which constituent(s) contain synthetic compound that was derived from petroleum-based materials, whereas using a method with an **HPLC** alone can only provide indirect evidence of curcuminoids’ natural origin



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Food Chemistry

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In Press, Journal Pre-proof

Analytical strategies to determine the labelling accuracy and economically-motivated adulteration of “natural” dietary supplements in the marketplace: turmeric case study

Hong You [a, 1], Haley Gershon [b, 1], Florencia Goren [b], Fei Xue [c], Traci Kantowski [d], Len Monheit [d]

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Test for “Natural” claim – Confirming botanical origin

- Only 4 out of the 14 samples analyzed supported authentic label claims. And a significant correlation between the percentage of curcumin-to-curcuminoids and % biobased carbon (Pearson’s r = -0.875, p = 0.000) indicated that synthetic curcumin was greatly attributed to determined synthetic ingredients.

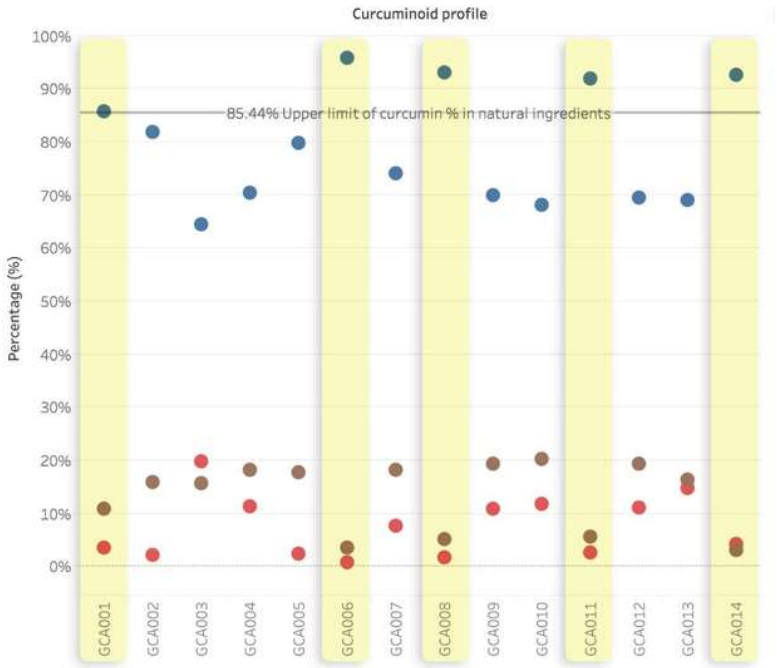

Figure 2. Curcuminoids profile of study samples (HPLC results). Blue dots indicate curcumin-to-total c
Brown dots indicate desmethoxycurcumin-to-total curcuminoids ratio values. Red dots indicate bisdesm
curcuminoids ratio values. Samples were highlighted by yellow color shadow when their percentages of
curcuminoids (relative curcumin value) were found to be more than 85.44%

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Take home messages

- Dietary supplement is regulated in a special category of Food and follows the food labeling rules
- Specification violation is the top reason for dietary supplement adulteration. And testing is necessary to verify the specifications.
- It is important to use scientifically-valid analytical methods to test the identity, strength, purity, composition, and contaminants of dietary supplements

Thank You!

For Q&A, please contact me at hongyou@eurofinsus.com

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