Valerian *Valeriana officinalis*
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The Undisclosed Presence of Excipients and Diluents in Botanical Extracts

High levels of undisclosed excipients and diluents may give buyers and consumers a misleading sense of botanical extracts' strength and composition

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This article discusses the composition and labeling of botanical extracts, with particular focus on the sale of botanical dietary ingredients and dietary and food supplement products. Published literature and reports from analysts suggest that some commercial extracts in the dietary and food supplement supply chain may contain little or none of the declared plant or plant extract. Experts in dietary supplement analysis have determined that this occurs mainly because of two schemes used by deceptive suppliers. First, certain suppliers excessively dilute native plant extracts with undeclared amounts of excipients and are ambiguous in disclosing the plant-to-extract ratio. Second, whole herbs are extracted to obtain specific fractions or compounds that are considered to be therapeutically beneficial and are provided to select markets. The marc (leftover or spent biomass) may then be re-sold without disclosure that it is pre-extracted material.

This article also discusses the undeclared addition of large amounts of diluents to botanical extracts in the context of US dietary supplement labeling regulations. Due to lack of specificity in US regulations, manufacturers and suppliers can take different approaches to labeling extracts, particularly when declaring plant-to-extract ratios, which are also known as drug-to-extract ratios (DERs) in the European Union (EU) and elsewhere, where the term "drug" refers to the original meaning of the term (i.e., dried plant material intended for use in or as medicine).

In addition, voluntary industry guidelines may unintentionally support excessively diluted or spent materials being sold under the pretense of an ingredient or product of specified quality. At the source of production, these practices of excessive dilution represent fraudulent attempts to deceive the industry buyer (e.g., a dietary or food supplement manufacturer) and finished product consumer. While not a safety concern, receiving and processing substandard ingredients as raw materials results in a finished product that may not meet regulatory requirements and will not deliver the benefits that are associated with the botanical extract.

Independent Lab Reports

Members from contract analytical laboratories have raised the issue of excessively diluted ingredients and products for a while. Bryan Fine from the contract analytical laboratory Alkemist Labs (Garden Grove, California) described one example during an informal conversation at

the 2023 annual conference of the Natural Health Product Research Society of Canada. Alkemist Labs was contracted to authenticate a valerian (*Valeriana officinalis*, Caprifoliaceae) root/rhizome extract by high-performance thin-layer chromatography (HPTLC). The result was a blank lane — hence, the ingredient failed the authentication criteria based on the absence of any characteristic valerian metabolites.

The manufacturer that requested the testing of the valerian extract was puzzled by the test results and queried the ingredient's supplier about the lack of valerian in the material. The supplier did not have the knowledge to respond (despite this being required by regulation), and the manufacturer was referred to several more ingredient suppliers further back in the value chain until the company that produced the extract eventually was identified. Upon asking the initial production company about the composition of the valerian extract, a company representative reportedly stated that the extract contained 0.25% valerian extract and 99.75% maltodextrin* and claimed that this dilution was the only way to produce a "valerian extract" that met the customer's price demands (B. Fine oral communication to S. Gafner, June 21, 2023).

This is an extreme example in which price, and not authenticity and activity, drove the botanical ingredient's composition. As the example also shows, such diluted ingredients are readily detected by routine identity tests, will not meet established specifications, and will be rejected by any dietary supplement or food supplement manufacturers that comply with current regulations related to identity testing of ingredients.

Manipulation and mislabeling of concentrations and dilutions of extracts are a big problem, according to an author of this article (JK). Many of these x:y extracts at claimed concentration ratios of 4:1, 10:1, or 20:1 seem to be more characteristic of 1:20. A lot of these inferior extracts are "phytochemical shadows" of the native botanical, the author explained.

There is also the potential for these already highly diluted extracts to be further diluted by the addition of more maltodextrin, a plant-derived filler or carrier commonly used, in appropriate amounts, for its functional benefits (e.g., enhanced stability, flavor, etc.) in the extract industry. According to author JK, this is very common and can often be seen by microscopy and FTIR (Fourier transform infrared microspectroscopy).

Four examples of very diluted botanical ingredients analyzed by HPTLC are shown in Figure 1.

The dilution of botanical extracts is not a new issue. In 1998, 18 commercially available aloe vera (*Aloe vera*, Asphodelaceae) products, including one dietary supplement, obtained from the US marketplace were analyzed using size-exclusion chromatography with refractive index detec-

* Maltodextrin is a short polymer of 3-17 glucose units obtained after partial hydrolysis from various carbohydrate sources such as corn (*Zea mays*, Poaceae), potato (*Solanum tuberosum*, Solanaceae), or tapioca (*Manihot esculenta*, Euphorbiaceae) starch. It is used as an excipient or filler in botanical extracts and other commercial formulations.

Figure 1. HPTLC Analysis of Four Diluted Botanical Ingredients

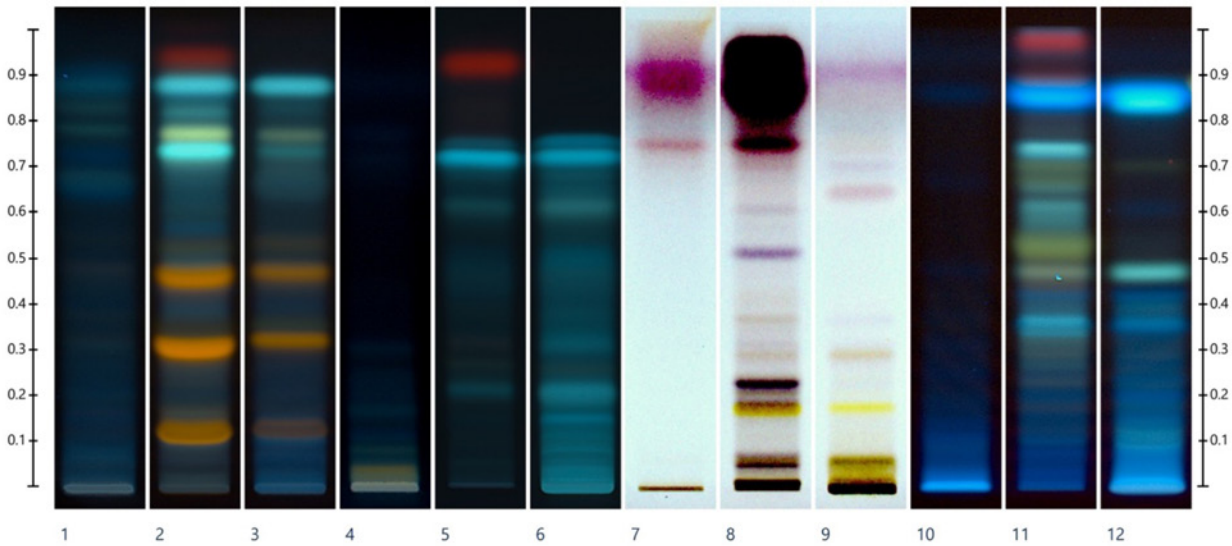

Image provided by Stacy Wise and James Kababick at Flora Research Laboratories, LLC.

Lanes 1-3: Peppermint (*Mentha* × *piperita*, Lamiaceae) leaf
Lanes 4-6: Lemon balm (*Melissa officinalis*, Lamiaceae) leaf
Lanes 7-9: Nettle (*Urtica dioica*, Urticaceae) leaf
Lanes 10-12: Chamomile (*Matricaria chamomilla*, Asteraceae) flower

Lanes 1, 4, 7, and 10: Commercial hot water extracts
Lanes 2, 5, 8, and 11: Botanical reference (methanol extracts)
Lanes 3, 6, 9, and 12: Botanical reference (water extracts)

Ginkgo *Ginkgo biloba*
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tion. The supplement product did not contain detectable amounts of the main polysaccharide in aloe vera.[1] In a separate summary of HPTLC reports of various aloe materials submitted for analysis between 2015 and 2017, Alkemist Labs indicated that it has "failed" aloe samples because they contained an excessively high content of maltodextrin.[2]

The presence at trace levels or absence of characteristic marker constituents (so-called "fairy-dusting") in botanical extracts is documented in the peer-reviewed literature and in unpublished reports. While the absence of chemical marker compounds does not always mean that an ingredient is not present in a formulation, it raises questions about the basis of any stated or implied structure-function claims or potential health benefits of the herbal dietary supplement.

Flora Research Laboratories (Grants Pass, Oregon) has reported suspected instances of spent biomass being re-distributed in the dietary supplement supply chain. After analyzing water extracts of saw palmetto (*Serenoa repens*, Arecaceae) fruit and valerian root, the independent lab found some of these extracts to be mainly composed of sugars and devoid of any of the characteristic saw palmetto fatty acids or typical valerenic acids. While the absence of these constituents can be explained by the polar extraction solvent (although the valerenic acids should be present in trace amounts), no known pharmacological or human clinical research supports any potential health benefits of such extracts.

Author JK suspects that these extracts may have been made from spent plant materials, such as fruits or roots that previously were solvent-extracted to obtain the valuable constituents, which were then sold at higher prices to the pharmaceutical industry or dietary supplement manufacturers, while the leftover spent material was re-extracted and the resulting extract sold as a low-cost dietary supplement ingredient (oral communication to S. Gafner, December 1, 2023). In most cases, absence of characteristic marker compounds associated with a particular botanical is indicative of a poor-quality material.

This was emphasized by Karl-Werner Quirin, managing director of Flavex Naturextrakte GmbH (Rehlingen-Siersburg, Germany), a manufacturer of supercritical botanical extracts. "The important active and marker constituents of botanicals used in dietary supplements are well known," he wrote (email to S. Gafner, March 5, 2024). "Serious extraction companies choose a solvent which is best suited for these substances which finally constitute the value of the extract. The companies add a qualified and batch-related CoA [certificate of analysis] to each product."

Published Literature

In a report on ginkgo (*Ginkgo biloba*, Ginkgoaceae) leaf extract food supplement† quality, Czigle et al[3] described a product with 0.49% flavonol glycoside and 0.03% terpene lactone content and concluded that this product contained "just traces of the [ginkgo] extract together with excipients of the dosage formulation."

Collins et al[4] also presented data about "ginkgo" dietary supplements with very low or no ginkgo constituents. A total of 20 bulk ginkgo leaf extracts from 15 suppliers to the US market were analyzed qualitatively by HPTLC, and quantitatively by nuclear magnetic resonance (NMR) and high-performance liquid chromatography (HPLC) with ultraviolet/visible detection (HPLC-UV/Vis) for flavonol glycosides and HPLC with evaporative light-scattering detection (HPLC-ELSD) for terpene lactones. One sample contained no flavonol glycosides or terpene lactones, while another sample contained trace amounts of terpene lactones but no flavonol glycosides when assayed by HPLC-ELSD and no measurable amounts of any characteristic ginkgo metabolites when NMR was used for the analyses. One bulk extract was devoid of any triterpene lactones but contained traces of flavonoids, and three others were composed solely of rutin and quercetin.[4] Similar results were reported in an investigation of ginkgo products combining HPTLC and NMR.[5]

Frommenwiler et al[6] published data on their HPTLC analyses of black cohosh (*Actaea racemosa*, Ranunculaceae) root and rhizome, echinacea (*Echinacea* spp., Asteraceae) root and/or aerial parts, and milk thistle (*Silybum marianum*,

† In the United States most botanical products for internal use are termed and regulated as "dietary supplements." In the EU and elsewhere they are termed and regulated as "food supplements."

Asteraceae) seed commercial dietary and food supplements and bulk ingredients. Dietary and food supplement samples consisted of extracts (n = 57), powdered plant (n = 15), mixtures of extracts and powdered plant (n = 6), or liquid extracts (n = 9). All bulk ingredients (seven extracts and 20 whole, cut, or powdered roots) were labeled to contain black cohosh. In total, 60 black cohosh, 23 echinacea, and 31 milk thistle samples were analyzed. Three black cohosh, two echinacea, and two milk thistle samples did not show any bands characteristic of the labeled plants and no or only very weak signals beyond the application point. Overall, 11 milk thistle samples, three echinacea samples, and 33 black cohosh samples were considered to be of questionable quality. Similarly, in a report on HPTLC analyses of 73 commercial elder (*Sambucus nigra*, Viburnaceae) berry preparations, three products essentially had a blank lane, indicative of a lack of any plant metabolites, with several others having bands unrelated to elder berry at a very low concentration.[7]

Analyses by HPTLC of 47 commercial St. John's wort (*Hypericum perforatum*, Hypericaceae) aerial part dietary supplements sourced from the United Kingdom, Germany, and the United States showed a number of products providing a "weak" fingerprint (i.e., low contents of marker constituents). Ten samples were categorized as having a faint flavonoid fingerprint, with six of them exhibiting spots of undeclared food dyes.[8]

Also using HPTLC, data from an unpublished investigation on the authenticity of aerial parts of single-ingredient eyebright (*Euphrasia officinalis*, Orobanchaceae) dietary supplements showed four out of 10 products with a weak fingerprint or no detectable eyebright at all (Figure 2, lanes 14-17), while the product in lane 13 was determined to be made from an unidentified *Odontites* (Orobanchaceae) species (Figure 2).

Brusač et al[9] also reported products with undetectable or trace levels of marker constituents. Of the 35 dietary supplements analyzed by HPLC-UV/Vis, two single-ingredient products purchased online — one labeled to contain andrographis (*Andrographis paniculata*, Acanthaceae) aerial parts and one labeled as boswellia (*Boswellia serrata*, Burseraceae) oleogum resin — were considered by the authors to be of no therapeutic value due to low contents or absence of constituents.** Three additional products containing either boswellia or combinations of boswellia and turmeric (*Curcuma longa*, Zingiberaceae) rhizome with or without andrographis had only trace levels of the typical marker constituents. However, these supplements also were labeled to contain glucosamine with or without chondroitin and other ingredients. Hence, it is possible that these products were predominantly made of either of both of these non-botanical ingredients.

Case Study: Berry Extracts

Another possible source of diluted or manipulated extracts originates from manufacturers that repurpose byproducts or waste products of other industries to make a dietary ingredient (i.e., an ingredient for use in a finished dietary supplement). While some of these byproducts may contain constituents with valuable medicinal properties, the benefits of such ingredients should be determined in appropriate studies.

** Constituents included andrographolide, neoandrographolide, or 14-deoxy-11,12-didehydroandrographolide for andrographis, and 11-keto-β-boswellic acid, 3-*O*-acetyl-11-keto-β-boswellic acid, α-boswellic acid, β-boswellic acid, 3-*O*-acetyl-α-boswellic acid, or 3-*O*-acetyl-β-boswellic acid for boswellia.

Figure 2. HPTLC Analysis of Authenticated *Euphrasia* Species and 10 Dietary Supplements Sold in the United States

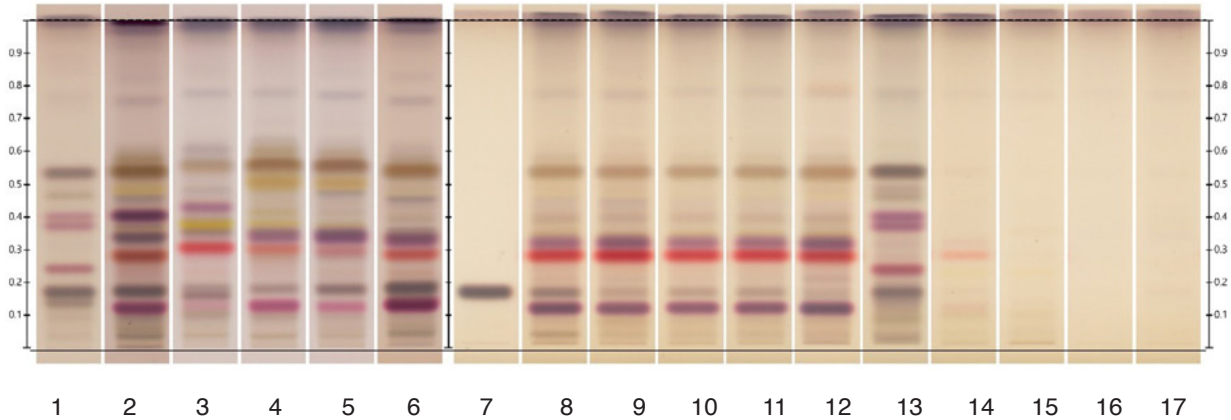


Image provided by Camag, AG.

Lane 1: *Odontites luteus*
Lanes 2 and 4: *Euphrasia rostkoviana*
Lane 3: *Euphrasia picta*
Lanes 5-6: *Euphrasia stricta*
Lane 7: Aucubin (1 mg/mL)
Lanes 8-17: Commercial dietary supplements labeled to contain *Euphrasia officinalis* or eyebright herb

For example, it has become somewhat common for some suppliers to take the leftover marc from cranberry (*Vaccinium macrocarpon*, Ericaceae) fruit juice production and use these "press cakes" for solvent extraction. Cranberry is commonly used as a dietary supplement ingredient to support urinary tract health and cranberry juice is frequently served in assisted living facilities for elders to help prevent urinary tract infections. The urinary tract health benefits are due at least partly to water-soluble proanthocyanidins (PACs) present in cranberry juice.[10,11] However, these occur predominantly in the juice, and only traces remain in the skin and seeds (press cakes), which are characterized by the presence of insoluble PACs (i.e., PACs that are bound to the plant's cellulose fibers). While some benefit is associated with insoluble PACs, no known credible published evidence supports their use for maintaining a healthy urinary tract.[12]

This example of cranberry illustrates the complexity of the diluted extract market. When extracts obtained from spent botanical materials are traded, they may not be clearly labeled as missing some of the plant part's putative beneficial compounds. They often are presented as if they are whole-herb extracts that contain a broad spectrum of constituents in appreciable amounts. Manufacturers may purchase these in good faith, believing they will deliver the benefits expected from the botanical ingredient. In a finished product, a consumer seldom knows the difference among the various ingredients derived from the same plant, but products made from waste ingredients will always cost less than those made from herbs containing the full spectrum of phytochemicals, thus presenting an economic advantage (to the seller) for the sale of potentially ineffective products. The same practice has been shown to occur with other fruit extracts, most notably elder berry[13] and bilberry (*Vaccinium myrtillus*, Ericaceae) extracts.[14]

Labeling Dietary Supplements/Botanical Extracts in the United States

Highly diluted herbal extracts or spent plant materials sold as dietary ingredients and dietary supplements are not considered a safety risk, as the diluents typically represent materials that are generally recognized as safe (GRAS). However, selling herbal extracts that do not deliver the expected benefits does a disservice to public health, is a violation of public trust in herbal products, and, depending on the label claims, may violate federally mandated current Good Manufacturing Practices (cGMPs), which require herbal products to be accurately labeled.

Current requirements for nutrition labeling are codified in section 21 of the *United States Code of Federal Regulations* (specifically CFR 101.36). In section 21 CFR 101.36(b)(3)(ii)(C), the regulation stipulates that "For a dietary ingredient that is an extract from which the solvent has been removed, the weight of the ingredient shall be the weight of the dried extract."[15] The term "extract," however, is not defined in CRF 101.36.

Clarification is provided in the American Herbal Products Association's (AHPA's) guidance policy for "Retail Labeling of Dietary Supplements Containing Soft or Powdered Botanical Extracts," which was published in 2000.[16] This document defines extracts as a combination of the native extract[††] *and* any added carrier and excipient, since this is often the form in which bulk extracts are sold worldwide. While this pragmatic definition likely was based on the idea that small amounts of carriers and excipients are sometimes an essential part of the manufacturing of extracts (to prevent clumping or increase the flow characteristics of a powder, for example), an unintended consequence is that it has left the door open for some producers to sell highly diluted extracts while still complying with AHPA's guidance.

Often, diluents like maltodextrin are added to "comply" with drug-to-extract ratio (DER) requirements of a dietary supplement manufacturer. DERs represent the amount of material obtained after extraction from a plant material relative to the starting amount of biomass. As an example, if 100 kg of dried Asian ginseng (*Panax ginseng*, Araliaceae) root yields 20 kg of ginseng root extract, the DER is 5:1.[17] Since this is the native or genuine DER, this is referred to as $DER_{genuine}$ or native extract ratio (NER). If an excipient is added to the native extract, the resulting DER is called DER_{total} according to the European Medicines Agency.[18] It rarely happens that a specific amount of crude botanical material consistently yields exactly the same amount of extract, even when using the same solvent. This occurs because of the natural variation of the chemical constituents in the botanical material. Therefore, labels in some geographic regions (e.g., Europe and Australia) appropriately use ranges for the DER (e.g., 4-7:1 rather than 5:1).[17] In North America, the use of a single value DER on herbal dietary supplement labels is much more common. Two cases of how these DERs can be, and are, manipulated are outlined below.

The first case deals with a supplier that provided a milk thistle extract with a stated DER of 4:1. The COA indicated that the extract consisted of 5% milk thistle extract and 95% maltodextrin. The supplier justified this high amount of maltodextrin as being necessary to comply with the 4:1 DER request of the manufacturer and stated that the original milk thistle extract was an 80:1 native extract, hence this extract had to be diluted by a factor of 20 times to obtain the 4:1 extract requested. The supplier proposed to specify "180 mg of milk thistle extract (4:1)" on the label, even though the product contained only 9 mg (5%) of native milk thistle extract (80:1).

The second example is from a contract manufacturer commissioned to make an Asian ginseng root dietary supplement. In a statement to the company ordering the ginseng products, the contract manufacturer explained how the DER was calculated:

Ratio extracts are made from highly concentrated material and a carrier. The more concentrated the starting material, the more carrier is needed to obtain the final ratio.

[††] Native extract means the material that consists only of components present in the original plant or formed during the extraction process, excluding any excipients or other added substances.

There are countless combinations to end up at the desired ratio. Here are a few examples:

- 80% of 5:1 concentrate + 20% carrier = 4:1 final ratio
- 40% of 25:1 concentrate + 60% carrier = 10:1 final ratio
- 60% of 10:1 concentrate + 40% carrier = 6:1 final ratio
- 40% of 10:1 concentrate + 60% carrier = 4:1 final ratio

Sibyl Swift, PhD, chief science officer and vice president of regulatory affairs at cbdMD and former associate director for research and strategy at the US Food and Drug Administration (FDA), a position in which she directed the research agenda of the Office of Dietary Supplement Programs and worked closely on office policy and enforcement, wrote: "The FDA always interpreted the law on labeling of dry extracts from plants that any excipient has to be listed separately from the native dry extract, i.e., that the amount of labeled extract does not include any flow agents, anticaking agents, antistatic agents, lubricants, or whatever else companies may add to an extract to improve the ability to process it. And it certainly wouldn't include any fillers used to adjust the plant-to-extract ratio" (email to S. Gafner, April 4, 2024). This suggests that the current interpretation of the regulations as detailed in AHPA's aforementioned guidance document is not in agreement with the FDA's interpretation.

Highly Diluted Botanical Extracts in the International Market

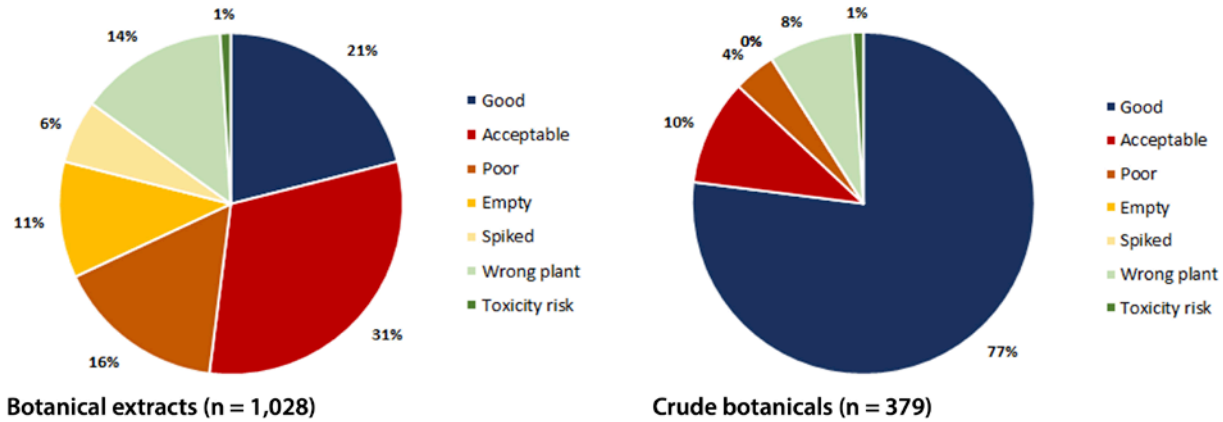
Based on the available information, it appears that the issue of highly diluted herbal dietary supplements is international in scope. Several of the published studies cited previously were carried out with samples obtained in Europe.[3,6,8] Absence or low levels of the typical chemical markers have been reported in bilberry fruit and broccoli (*Brassica oleracea*, Brassicaceae) food supplements purchased in Germany.[14,19] In a separate study of products purchased from different countries, very low concentrations of the typical flavonolignans were determined in four of 26 milk thistle dietary supplements by ultra high-performance liquid chromatography with mass spectrometric detection (UHPLC-MS). Two of the milk thistle products were from the United States, and the other two from the Czech Republic.[20]

The increased sale of highly diluted or "empty" extracts also has been noted at BotaniCERT, a contract analytical laboratory based in Grasse, France. A review of test results obtained by UHPLC with ultraviolet/visible detection (UHPLC-UV/Vis) over the period from 2017 to 2019 — conducted on 379 crude (whole, cut, or powdered) botanical ingredients and 1,028 extracts — showed no crude materials lacking the expected constituents, but 11% of the extracts were considered "empty" or devoid of any constituents characteristic for the labeled or any other botanical ingredient (Figure 3).

Based on the results obtained, crude botanicals, such as whole, cut, or powdered plant parts have a lower risk of being diluted or adulterated compared to extracts. Specific examples of a highly diluted and an acceptable extract based on the UHPLC-UV/Vis analyses are provided in Figure 4.

The use of highly diluted extracts appears to be a problem primarily in products sold as dietary or food supplements, in contrast to those regulated as herbal drugs in Europe or as traditional herbal medicines (e.g., traditional herbal medicinal products [THMPs] in the EU) throughout much

Figure 3. Review of Test Results on Botanical Extracts and Crude Botanicals by BotaniCERT*



* Samples were analyzed between 2017 and 2019 and were sourced in France (70%) or other countries in Europe (30%).

Good: Compliant with the label expectation/expected quality.
Acceptable: A little diluted (two-fold or more), but the concentration of chemical markers is acceptable.
Poor: Highly diluted (from five- to 100-fold or more) samples, but the typical chemical markers are detectable. The botanical ingredient concentration is low but high enough to confirm that it is the right species.
Empty: Unable to see any compounds, or only few chemical markers in trace amounts (close to a few µg/g for each compound) may be detectable but not at sufficiently high concentrations to confirm the identity of plant.
Spiked: Spiked by pure compounds not originating from the claimed sources, such as caffeine in guarana (*Paullinia cupana*, Sapindaceae) or vitamin C in acerola (*Malpighia emarginata*, Malpighiaceae).
Wrong plant: The labeled ingredient has been substituted to a large degree by another plant (not a simple contamination).
Toxicity risk: Presence of undeclared exogenous compounds (such as sildenafil, psilocin, etc.) or a toxic plant.

of the world. When regulated as traditional herbal medicines, individual botanical ingredients used in products must meet formal pharmacopeial specifications of the various countries. THMPs in the EU also are manufactured in a manner that requires in-depth characterization and control of raw materials and minimum quality standards according to pharmacopeial monographs, and the products must be supported by a detailed dossier outlining the herb's pharmacology and safety.

Conclusion

There are many high-quality botanical dietary and food supplements available worldwide. These products are produced by reputable manufacturers and undergo stringent identity and strength testing, often involving third party analysis or pharmacopeial methods to ensure purity and potency. However, scientific publications and data from contract analytical laboratories provide evidence that some so-called botanical extracts mainly consist of carriers and excipients. The presence of such highly diluted herbal extracts sold as dietary supplements is not considered a safety risk, as the diluents (e.g., maltodextrin, lactose, various types of starch, etc.) are GRAS materials.

However, selling herbal extracts in very low concentrations to consumers or health professionals is misleading, as they pay for inferior products that do not provide the expected (or claimed) health benefits. Using ineffective products also harms the herbal dietary supplement industry, as it lowers consumer confidence in the benefits of using such products. It can also negatively impact the reputation of the industry when products fail to meet their claimed or implied benefits and the media reports information about low-quality products.

While current US regulations do not stipulate that herbal extracts cannot be sold in minute quantities, the law requires the labeled amount of the botanical ingredient to be accurate. Nevertheless, additional regulatory clarity regarding the labeling of dried botanical extracts and — specifically — further clarification of the meaning of an extract in 21 CFR 101.36(b)(3)(ii)(C) would be useful for the botanical dietary supplement industry. Finally, the inclusion of high amounts of carriers, diluents, and excipients as part of the labeled herbal ingredient concentration is a practice that certain companies in the herbal dietary supplement industry should reconsider. HG

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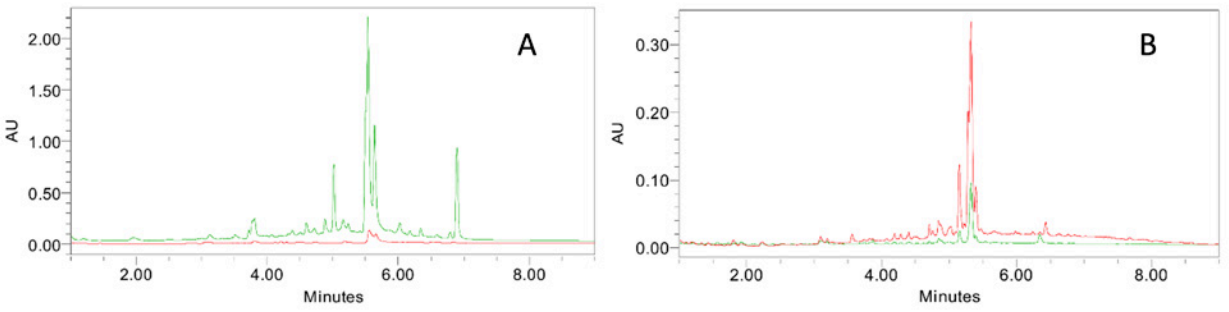
Figure 4. UHPLC Analyses of (A) Lady's Mantle and (B) Tick Trefoil



Chromatogram A shows the profile of 30% aqueous ethanol extract of authentic lady's mantle (*Alchemilla vulgaris*, Rosaceae) leaf (green) versus a commercial 30% aqueous ethanol extract of lady's mantle leaf with a specified DER of 5:1 (red). The quantitative data reveal that the commercial extract is approximately 80-fold more diluted than the specification (5:1). The calculated DER_{total} is approximately 0.06:1.

The UHPLC-DAD chromatogram B shows the profile of water extract of reference of tick trefoil (*Grona adscendens*, Fabaceae) (green) versus a commercial dried water extract with a specified DER of 2:1 (red). Quantitative analysis reveals the commercial extract is approximately 60% more concentrated than the specification; hence the DER_{total} is approximately 3.2:1. According to the result, this commercial dried extract is compliant with the specified DER.

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Bilberry *Vaccinium myrtillus*
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