

Comments on NTP TR 578

Peer Review Panel Meeting

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American Herbal Products Association

- AHPA is the national trade association and voice of the herbal products industry.
- AHPA is comprised of ~300 members domestic and foreign companies doing business as growers, processors, manufacturers and marketers of herbs and herbal products, and others providing support services.

Steven Dentali, Ph.D.

- Chief Science Officer at AHPA
- Former Chair of NCCAM's Product Integrity Working Group
- Current member of USP Nomenclature, Safety, & Labeling Expert Committee
- Trained Health Canada's Natural Health Products Directorate assessment officers regarding the definition and evaluation of herbal extracts

Today's Comments

- Focus on the identity of the botanical extract that was the subject of draft TR 578.
- Will be limited to the integrity of the test article.
- Support the written submission from AHPA that provide greater detail and include other considerations, including toxicological ones.

Two Major Points

- The unique *Ginkgo biloba* leaf extract discussed in TR-578 is not representative of other *Ginkgo biloba* leaf extracts marketed in the United States, and is almost certainly not sold in the United States.
- It is incorrect to represent it as similar to other *Ginkgo biloba* leaf extracts based on the dissimilarity of its chemical composition to that of other commercially available *Ginkgo biloba* leaf extracts.

The Supplier Intended to Make a Unique Extract

- Four U.S. patents for a ginkgo leaf extract described as a “new multicomponent drug.”
- For a “*highly concentrated effective content*” with about 20% to about 75% flavonol glycosides, 2.5% to 10% ginkgolides and 2.5% to 10% bilobalide.
- Described “*further removal of inactive substances*” to produce “*a different composition comprising new active components and combinations.*”
- Shanghai Xing Ling Science and Technology Pharmaceutical Company, Ltd. signed an agreement with a CRO for clinical trials on its extract to obtain FDA drug approval for the treatment of stable angina.

Availability of Extract in U.S. Marketplace

- AHPA contacted Shanghai Xing Ling via a Chinese speaking rep. of an AHPA member.
 - The representative was informed that Shanghai Xing Ling does not sell or market its own products that contain its proprietary ginkgo leaf extract in the United States.
 - AHPA has never found this proprietary ginkgo leaf extract offered for sale in the U.S. as an ingredient for use in ginkgo products.

Comparison to Published Analyses

Table 1 (Excerpted from TR-578 with information added)

Class	Identified Chemical Constituents	Target Specification in EGb 761® (range in other preparations)	TR-578 Test Article
Terpene Lactones	Ginkgolides A, B, C, and Bilobalide	6% (0.2%-11%)	15.4%
Flavonol Glycosides	Glycosides of Quercetin, Kaempferol, and Isorhamnetin	24% (24%-36%) [Only 3 of 50 products tested higher than 31.2%]	31.2%
All Others	Not Listed	70% (unknown)	53.4%

Comparison to Recognized Standards

	Flavonol Glycosides	Bilobalide	Ginkgolides A+B+C	Total Terpene Trilactones	Ginkgolic Acids
US Pharmacopeia	22.0-27.0%	2.6-5.8%	2.8-6.2%	5.4-12.0%	<5 ppm
European Pharmacopoeia	22.0-27.0%	2.6-3.2%	2.8-3.4%	5.4-6.6%	<5 ppm
German Commission E	22-27%	2.6-3.2%	2.8-3.4%	5-7%	<5 ppm
American Herbal Pharmacopoeia	22-27%	-	-	5-7%	-
Health Canada	22-27%	-	-	5-7%	-
TR-578 Test Article	31.2%	6.94%	8.42%	15.4%	10.45 ppm

NCCAM Test Article Requirements

- Detailed information relevant to the manufacturing process is missing.
 - details of the extraction such as solvent(s) used, ratio of dried plant to solvent, extraction time and temperature, pathogens, mycotoxins, pesticides, etc.
- No analysis of solvent residues, heavy metals, pesticides, microbial load, etc.

Recommended Changes

- Title the report “Toxicology and Carcinogenesis Studies of a Specific *Ginkgo biloba* Leaf Extract”
- State that it is unknown if this ingredient is now or has ever been sold or offered for sale in the United States.
- State that the test article is unlike most common commercially available products and its ratio of active constituents exceeds the specifications of the standardized ginkgo leaf extract known as EGb 761[®].

Use of CAS # is Inaccurate

- CAS No. 90045-36-6 is defined as
 - “Extractives and their physically modified derivatives such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues, etc., obtained from *Ginkgo biloba*, Ginkgoaceae.”
 - Use of it could have the effect of implying that the results of these studies are relevant to any and all extractives and derivatives obtained from any part of the ginkgo tree.
 - This term should be removed from any future revisions to Draft TR 578.

Nomenclature Confusion

- The scientific and common names of the *Ginkgo biloba* tree are not synonyms of *Ginkgo biloba* leaf extract.
- Using the “botanical name” of *Ginkgo biloba* for the test article, an extract, is inaccurate.
- Common name synonyms for the *Ginkgo biloba* tree should not be used as synonyms for the ginkgo extract used in the study