Adulteration Stifles the *Ginkgo Biloba* Market

by Steve Myers

The ginkgo tree is one of the oldest on earth, dating back more than 225 million years, and its leaves are among the most unique in appearance. As an herbal remedy, *Ginkgo biloba* extract is extremely popular, repeatedly making top-selling lists in both the United States and Europe. The standardized extract of ginkgo leaves is also among the most established; however, it has become among the most adulterated.

Ginkgo has many uses in human health. *The ABC Clinical Guide to Herbs*, published by the American Botanical Council (ABC) and its founder Mark Blumenthal, cites cerebral insufficiency, vertigo/tinnitus and peripheral vascular disease as the primary uses of ginkgo, with other potential uses, including acute altitude sickness, hypoxia, acute cochlear deafness and sexual dysfunction associated with the use of SSRIs (selective serotonin reuptake inhibitors). Despite this long list of benefits, ginkgo has made its name in the natural remedies arena as a memory enhancer.

Ginkgo achieves these results by improving blood flow to tissues, including the brain, and by enhancing cellular metabolism. The root of these mechanisms is in the flavonoids and terpene lactones found in ginkgo leaves. The primary flavonol glycones in ginkgo are quercetin, kaempferol and isorhamnetin; the terpenes include ginkgolides (A through J) and bilobalides.

The flavanols handle ginkgo's antioxidant actions, including free radical scavenging. They also increase serotonin release and reuptake, stimulate choline uptake in the brain (hippocampus) and inhibit nitric oxide (NO) formation. For their part, ginkgolides support endothelium relaxation and inhibit platelet activating factor (PAF), which is involved in platelet aggregation, blood vessel constriction, neuronal plasticity and neuronal inflammation response. Bilobalides enhance cognition by affecting GABA receptors in the brain, and protect against ischemic injury and neuronal death via antioxidant and gene-protective mechanisms.

Based on these active constituents, the first standardized extract of ginkgo leaves by German company Dr. Willmar Schwabe GmbH was created around 1965 and focused on flavonol glycone and terpene lactone content. Dr. Schwabe and company developed an extract standardized to 24 percent flavonol glycosides and 6 percent terpene lactones. The first extract was based on a 10:1 ratio of leaves to final extract, but the eventual standard became an average 50:1—"This means that from 100 kg of dried ginkgo leaves, only 2 kg of the extract are obtained," explained Jochen Muelhoff, Ph.D., Schwabe. Actual acceptable ratios on the market range from 35 to 67 leaves per pound of extract, according to Blumenthal.

In its early years, this standardized *Ginkgo biloba* extract (GBE) targeted cerebral and peripheral blood flow and won approval from the German government as a pharmaceutical for the treatment of cerebral insufficiency—memory loss related to dementia or degenerative neurological diseases such as Alzheimer's disease. Germany also approved GBE for the treatment of tinnitus, vertigo and claudication (poor circulation in the legs). GBEs in Europe have since been required to adhere to the 24/6 (really within the range of 22-27/5-7) standardization, and must also contain less than 5 ppm (parts per million) of ginkolic acid, a toxic compound found in lesser amounts in ginkgo leaves than in seeds. The German Commission E monograph, which guides herbal medicines in Germany, also stipulates exact content of the terpenes ginkgolide A, B and C (2.8 percent to 3.4 percent) and bilobalide (2.6 to 3.2 percent).

The Germans and Schwabe literally set the standard for standardized GBE, as 24/6 extracts became the prevailing therapeutic ginkgo product on the market. However, regulations in the rest of the world, including the United States, have not quite caught up to the detailed level of the Germans and European Union on constituent content. Of course, this level of GBE is sold as a medicine in Germany, but as a dietary supplement in the United States.

The main U.S. regulation relative to the 24/6 ratio or specific content levels of key flavonoids and terpenoids is that a finished product must be labeled correctly relative to its contents. Thus, if a product claims to be standardized to certain constituents, it must clearly label the amounts of those compounds, as well as the source, if it is different from the primary ingredient (i.e., gingko leaves). If the contents don't match the label, the product is misbranded; if there are extra ingredients in the product that are not listed on the label, the product is also adulterated.

History of Ginkgo Adulteration

GBE started picking up steam in the late '90s supplement market, and the concept of 24/6 standardization stuck in the marketplace, which was increasingly eager for scientifically backed herbal extracts, especially ginkgo. Since independent testing organization ConsumerLab.com had a business model of gravitating to the supplements most popular with consumers, notably its own client base, ginkgo was one of the first herbs the group tested for quality and safety.

In 1999, ConsumerLab held finished ginkgo products to the German standards, testing them for flavonol glycoside and terpene lactone content. Of the 32 ginkgo products, selected based on sales and availability, 25 passed the content test. At almost 75 percent, the pass rate was considered pretty good, especially for an emerging supplement market segment. However, a follow-up round of ginkgo testing conducted in 2003 by ConsumerLab generated the opposite result—about 75 percent failed.

For products claiming to be standardized to 24/6, 25-percent success is abysmal. "In 1999, looking at proportions of flavonol glycosides and terpene lactones, they were pretty good," said William Obermeyer, former FDA natural products chemist and co-founder of ConsumerLab.com, noting what was tested in '99 was probably good ginkgo, relative to the materials that were used in clinical trials. "As we were going along, our 2003 test showed 77-percent failure, and our 2007 tests revealed 41-percent failure."

The 2007 tests also looked at lead levels, and although a few products contained some lead, none even remotely reached the level of safety concern. However, as a self-anointed watchdog for consumers, Obermeyer and ConsumerLab contend when faced with two otherwise identical standardized GBEs, would a consumer choose the one with lead or without lead content? "Heavy metals for Alzheimer's and brain health is counterproductive," he pointed out.

Overall, what the testing revealed was not a safety concern, but one of truth in labeling and product integrity. Obermeyer explained adding extra material to a GBE, to boost its constituent content and reach 24/6 status, causes a few problems. For one, if the added material is ginkgo leaves, the possibility of increased lead content goes up—the extraction process rids the GBE of lead, so adding in non-extracted leaf material brings in the lead naturally found in the plant. And for products claiming 24/6 standardization, adding in extra flavonoids from non-ginkgo sources, the most common adulteration in this market, is a mere trick of the testing for overall flavonoid and terpenoids content, but is not true to the material used in clinical trials for memory and other benefits.

"Even if the product does not claim to be 24/6 standardized, any use of structure-function claims relative to the research done on GBE extract would require substantiation relative to the materials used in those trials," Obermeyer added.

ConsumerLab used the same test each time, one based on the Official Methods of Analysis (OMA) method from AOAC, which basically mirrors the U.S. Pharmacopeia (USP)

method. This means the lower limit for quercetin and kaempferol was about 10 percent, and for isorhamnetin, about 2 to 3 percent. For terpenes, bilobalide and ginkoglides A, B and C lower limits were set at about 3 percent. In the absence of specific FDA lead limits for dietary supplements, the lab used California Proposition 65 regulations, which set the upper limit for lead intake from foods and supplements at 0.5 mcg/d. Obermeyer noted a fourth round of ginkgo testing is due out toward the end of November 2008.

The adulteration of 24/6 GBE is in the flavonol glycosides, not the terpene content. Ginkgo leaves naturally contain more terpenes than flavonol glycosides, so there is rarely a problem reaching the 6 percent terpenoids needed for the 24/6 standard. However, in order to meet the 24 percent glycosides, more leaves are required. This naturally increases costs, the primary driver of adulteration.

The flavonol glycosides can be separated from the terpenes during production, which makes it easier for unscrupulous companies to simply control the terpenes to 6 percent while boosting the glycosides to 24 by adding rutin or another cheap source of quercetin. The root of adulterants is rutin because it contains 98 percent quercetin and is cheaply sourced from buckwheat—about $10 per kilo, far below the cost of true ginkgo materials.

While added rutin/quercetin can raise the total level of flavonol glycosides to about 24 percent, a closer analysis of each glycoside can indicate potential adulteration.

In ginkgo testing over the years, Obermeyer has kept track of the ratio of quercetin to kaempferol (Q:K), which has become a definitive indicator of probable adulteration. He does not necessarily report these findings to consumers, as they are already bogged down with 24/6 standardization concept, but tracking these ratios allows the longtime lab hound to gauge the direction of quality in the ginkgo market. “I’m just continuing to see the spiral downward of these products,” he said.

Rutin out Adulterated Ginkgo

Turns out, the Q:K data for the standardized GBE created by Schwabe (called EGB 761) and others used in clinical research consistently tested for a tight ratio range, 1.25 to 1.65. Moreover, the GBE standard produces a ratio of three main glycosides, Q:K:I, at about 5:5:1.

Roy Upton, American Herbal Pharmacopeia (AHP), explained there are many factors that influence the ratios and total yields of both the terpenes and flavonoids—geographical, climate, time of harvest (especially), processing, etc. “This is the Achilles heel of any standard,” he said. “When establishing pass and fail criteria, you have to make sure that natural variations are accounted for; we did our best to take into consideration the natural variation of pure ginkgo leaves by looking at ratios that occurred in multiple leaves harvested from multiple areas, including the United States, Germany, France and China, as well as referring to the published literature and discussions with AHP advisors, who include some of the most renowned natural product chemists in the world.” Based on the naturally occurring profiles reflected in their analyses, the analyses of others, as well as the published literature, AHP felt safe proposing the 4:4:1 to 6:5:1 ratios. “These are actually broader than the Schwabe standards which were at 5:5:1,” he noted.

In 2006, GBE supplier Ethical Naturals contracted Eurofins, an FDA-certified, independent testing laboratory, to analyze 17 finished ginkgo products pulled from the market, as well as five powdered GBEs as controls. Eurofins tested each sample for total flavonglycosides (FGs) and each individual level for quercetin, kaempferol and isorhamnetin; likewise, total terpene lactones (TLs) were tested, as were individual levels of bilobalide, and ginkgolides A, B, C and J. Additional data were collected for lead levels in each product. While Eurofins generated the data, AHP was brought in to review the results and provide expert opinion on whether adulteration could be determined from the test data, which included Q:K and Q:K:I ratios.

Overall, the results of the Eurofins tests showed substantial adulteration and other quality control problems, relative to the control samples and established standards, including monographs. “The Ginkgo Quality Control Report (2006), tested 21 samples of raw material and finished product that were randomly chosen, and about half of the products tested showed adulteration with added flavonoids (based upon flavonoid ratios),” noted Cal Bewicke, Ethical Naturals. “Other products in the test were low in total flavonoids or terpene lactones, and four were high in lead.”

In its review of the data, AHP made a few key points. To more definitively determine adulteration, such testing should use at least two labs and a validated method from OMA, USP, AHP or similar, all which would be ideally harmonized. However, given the data from Eurofins, AHP concluded it is clear spiking with pure flavonoid compounds can be suspected for samples with Q:K ratios higher than 2.00, with the higher values more likely adulterated. In fact, some Q:K levels found in the testing were as high as 4.6 and 6.1.

“You clearly detect adulteration in this case, unless someone comes up with a genetic strain that preferentially concentrates quercetin ratios that are magnitudes higher than what is found in typical ginkgo leaves,” Upton confirmed.

In addition to rutin and quercetin, kaempferol is sometimes the target of ginkgo adulteration. Xianguo He, Ph.D., one of the earliest scientists to develop standardized extracts from botanicals in the United States, reported Chinese herbal extract of *Fructus sophorae* contains 10 times more kaempferol than in ginkgo leaves.

Using HPLC, the test used to detail rutin in ginkgo, a fingerprint analysis of the ginkgo extract can help expose adulteration of non-ginkgo kaempferol, such as from *Fructus sophorae*. Xianguo explained the HPLC chromatogram of a pure GBE shows three major peaks (quercetin, kaempferol and isorhamnetin) after hydrolyzation. An adulterated extract will show other small flavonoid peaks. He further suggested comparing Q:K and I:Q ratio peak areas for abnormal results, as well as a careful comparison of the HPLC fingerprint of a given commercial GBE with that of authentic extract by USP.

In addition to USP, the National Institute of Standards and Technology (NIST) issued a group of Standard Reference Materials (SRMs) for *Ginkgo biloba* in mid-2007 to help validate test methods for ginkgo and its constituents, good or bad. The reference materials include ginkgo leaves, powdered extract and ginkgo-containing tablets. These materials all have certified values for five terpene lactones, three flavone glycosides and four potentially toxic trace elements—arsenic, cadmium, lead and mercury.

Scope of Adulteration

Adulteration of GBE has been rumored for a while—the ConsumerLab.com tests seem to indicate the late '90s as a period of rising adulteration—but it only became an officially recognized problem in recent years. "I don't know when AHPA first became aware of reports of adulteration of ginkgo extract with added rutin," said Steven Dentali, Ph.D., chief scientific officer for AHPA (American Herbal Products Association). "However, it became an official AHPA-known adulterant in March of 2006, at the latest."

Likewise, coming up with a definitive percentage of the industry adulterating ginkgo extracts is a tough chore, according to Bewicke; but, given the testing done on GBE samples and finished products, it is safe to suspect a substantial portion of the market is spiking flavonoid content. "I believe that most manufacturers are now much more careful about the raw material they use; the knowledge of how to test for these adulterants has become more widespread, and widely used, than it was only a few years ago," he said. "However, some companies do turn a blind eye for the sake of the cheap cost of the materials."

"The vast majority of the prices we're up against in the U.S. market do not even support the cost of the raw materials used to manufacture a high quality ginkgo extract," said Jay Lee, Ph.D., president of Beijing Ginkgo Group. "Most contract manufacturers tell us they are simply meeting their customer's specifications, so if the customer simply states 24/6, then the contract manufacturer will seek the lowest cost 24/6." Lee added the rogue GBE suppliers are parasites that feed off of the success of others' investments in a quality product. "They have little investment in the cultivation of the trees, plant and equipment, hiring knowledgeable employees, promoting the science behind the product nor the education of the industry or consumers," he said. "If sales go down due to bad press, then the rogue suppliers simply move on to the next host."

Muelhoff called the adulteration of GBE a global problem, though he noted it is less of a problem in Europe, definitely a problem in the United States, and even more pronounced in some Asian countries. "People who deliberately spike ginkgo extracts with rutin are using some inferior material and make it up to the generally accepted specification," he added. "We consider this as fraud, as this material is definitely less effective and, depending on what else might be added, it could also be less safe."

What to do about it is another hard-to-answer question. "By the letter of the law, not disclosing the addition of an ingredient is illegal and an adulteration," Upton noted.

However, Muelhoff pointed out regulation is only one side of the medal and law enforcement is the other. "Even in high regulated countries, adulteration can be seen, if it has no consequences not to follow the rules (this factor plays a role especially in Asia)," he said.

Bewicke agreed the issue is too complex for government to police. "Self-regulation seems to be the way," he said. "As the knowledge of these problems becomes more widespread, along with the knowledge of the testing required to detect them, ethical manufacturers and suppliers can work together to address the problem." ❑

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