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Substantial Differences in Proanthocyanidin Contents among *Ginkgo biloba* Leaf Extracts in Herbal Medicinal Products Obtained from the German Market

Authors

Stefan Germer[1], Thomas Ritter[1], Mario Wurglics[2]

Affiliations

1 Department of Analytical Development, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany

2 Institute for Pharmaceutical Chemistry, Goethe University, Frankfurt/Main, Germany

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Dr. Stefan Germer
Department of Analytical Development,
Dr. Willmar Schwabe GmbH & Co. KG
Willmar-Schwabe-Straße 4, 76227 Karlsruhe, Germany
Phone: + 49 72 14 00 54 45
stefan.germer@schwabe.de

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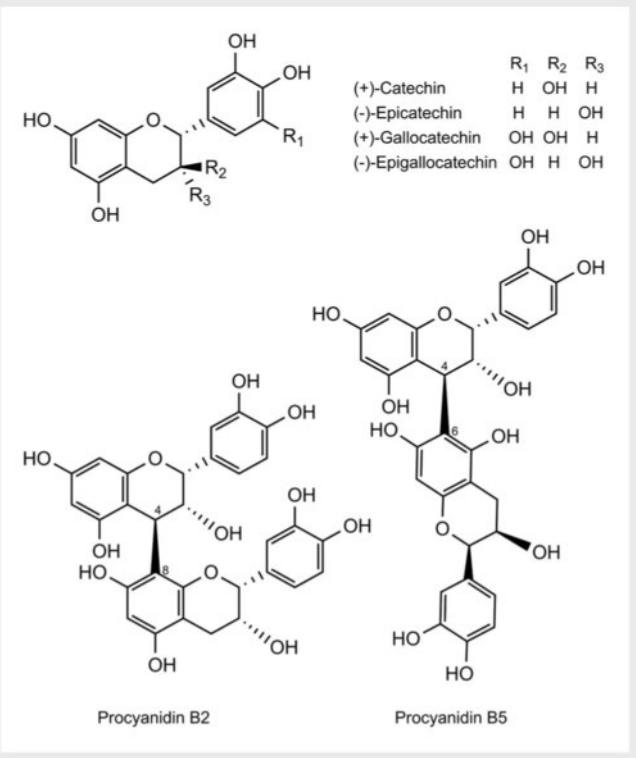
ABSTRACT

Pharmacologic activity of proanthocyanidins in *Ginkgo biloba* leaf extract has recently been reported. The objective of the present study was to screen proanthocyanidin contents in herbal medicinal products containing *Ginkgo* extracts. A recently published HPLC method for quantification of proanthocyanidins in *G. biloba* leaf extract EGb 761 was adopted to also be suitable for finished herbal medicinal products. The method was applied to 14 products from the German market. For each product, a set of three individual batches was purchased and analyzed. Substantial differences in proanthocyanidins contents were found among distinct products, ranging from 0.30 to 5.86%. The batch-to-batch variability within each product was low. The highest concentrations are in a similar range as, for example, the amount of *Ginkgo* terpene trilactones specified in the monograph for *G. biloba* leaf extract in the European Pharmacopeia. Although it has not yet been established whether and to what extent proanthocyanidins contribute to the overall pharmacological or clinical efficacy of *Ginkgo* extracts, a potential impact on the purported benefits of different contents in proanthocyanidins cannot be ruled out. Quality assessment of different *Ginkgo* extracts in the future may include proanthocyanidins.

Introduction

Ginkgo biloba L. (Ginkgoaceae) leaf dry extracts are active pharmaceutical ingredients in herbal medicinal products in many regions around the globe. Main indications include the improvement of (age-associated) cognitive impairment and quality of life in patients with mild dementia [1–3], tinnitus [4], and vertigo [5].

The herbal drug "*Ginkgo* leaf" is described in the monograph of the Ph. Eur. [6] together with the monograph "*Ginkgo* dry extract, refined and quantified" [7]. The Committee on Herbal Medicinal Products of the European Medicines Agency publishes monographs as a basis for harmonized safety and efficacy assessment of national regulatory authorities in Europe. Such a monograph was published on *G. biloba* L., folium [8], summarizing the current knowledge about the clinical application of herbal medicinal



▶ **Fig. 1** Chemical basic structures of catechin monomers and proanthocyanidins.

products containing *Ginkgo* extracts complying with the Ph. Eur. The concept for classification of extracts in Europe is laid down in the monograph "Herbal Drug Extracts" of the Ph. Eur. [9]. According to the monograph "*Ginkgo* dry extract, refined and quantified" [7] of the Ph. Eur., *Ginkgo* extract is classified as a so-called quantified extract where some compounds are acknowledged to contribute to the clinical efficacy of the respective medicinal products and are thus used as active markers for quality control. The clinical efficacy and safety of the extract, which is the actual active ingredient, relies on the overall composition of the extract and consequentially on the particular manufacturing process.

For the quantified *Ginkgo* extract, the active markers specified in the monographs are the flavonol glycosides (specified at 22.0 to 27.0%) and terpene trilactones (specified at 2.6 to 3.2% for bilobalide and 2.8 to 3.4% for ginkgolides A, B, and C). However, both groups of compounds add up to only approximately 30% of the extract mass balance, whereas the remaining 70% of the compounds are either unspecified or even unknown. According to the concept of the monograph "Herbal Drug Extracts" of the Ph. Eur. in case of quantified extracts, it is implied that additional compounds are relevant for clinical efficacy.

Recently, we published a new method with the objective to enable quantification of an additional group of compounds called proanthocyanidins (PACs), with a remarkable phytochemical complexity in *Ginkgo* extract [10]. PACs belong to the flavonoid family and are composed of polymerized flavan-3-ol units. These units, also known as catechins, are linked either by carbon-carbon bonds in B-type PACs or with an additional ether bond in A-type PACs. The degree of polymerization of proanthocyanidins can vary, resulting in different molecular weights and chain lengths. The predominant PACs found in *G. biloba* include B-type proanthocyanidins, which are primarily composed of (epi-)gallocatechin and (epi-)catechin units linked through carbon-carbon bonds at positions 4$\beta \rightarrow$ 6 and 4$\beta \rightarrow$ 8 [10, 11] (see ▶ **Fig. 1**).

Phytochemical properties of PACs were reported in detail [10] for the proprietary *Ginkgo* leaf extract EGb 761 [12], which is one of the herbal active ingredients most intensely investigated in clinical studies and can thus be regarded as a benchmark for evidence-based herbal medicinal products. A consistent quantity of approximately 7% PACs was found in *Ginkgo* extract EGb 761 [10]. This portion can be considered as relevant in the mass balance of the extract since it is in the same percentage range compared to, e.g., the specified terpene trilactones. Preclinical studies conducted on PACs from *G. biloba* [13–16] reported pharmacological activities such as neuroprotection or antiamnesic activity, with potential relevance for the treatment of neurological disorders, suggesting that PACs might contribute to the overall efficacy profile.

In contrast to the well-controlled quantified markers flavonol glycosides and terpene trilactones, which are part of *Ginkgo* leaf extract specifications in herbal medicinal products, there is scarce knowledge concerning the contents of PACs in different *G. biloba* leaf extracts and no systematic comparisons have been reported so far. Given the potential contribution of PACs to the pharmacological activity of *Ginkgo* extracts, we were interested in assessing the levels of PACs in different herbal medicinal products containing *G. biloba* leaf extracts in the market. For this reason, a HPLC method for PACs in *G. biloba* leaf extract was applied after suitable sample preparation to several herbal medicinal products containing *G. biloba* leaf extracts. Choosing Germany as a benchmark market was due to the high level of regulation for *Ginkgo* extracts and a number of *Ginkgo* herbal medicinal products available from a range of marketing authorization holders. All 14 chosen *Ginkgo* products were purchased in Germany. All these products received marketing authorization as herbal medicinal products by the German authority BfArM [17]. The *Ginkgo* extracts contained in these products must comply with the monograph "*Ginkgo* dry extract, refined and quantified" [7], with mandatory specifications on flavonol glycosides and terpene trilactones. Hence, these parameters were not considered in our assessment, and the focus was solely on the PACs.

Our interest was to get an idea to what extent a so far little noticed group of compounds like PACs are present in the products, and to assess batch-to-batch consistency. Therefore, for each product, three batches were analyzed for PACs, covering a period of several years during which these herbal medicinal products were marketed.

Finally, we transferred the analytical method to a third-party laboratory to show suitability of the method for industrial analytical purposes.

▶ **Table 1** Results for PACs expressed as % values calculated in respect to the declared amount of *Ginkgo* extract in a single dose of each product; 14 herbal medicinal products with *Ginkgo* extract and 3 individual batches each. Laboratory 1 is Dr. Willmar Schwabe GmbH & Co. KG and laboratory 2 is the Central Laboratory of German Pharmacists e. V. (Zentrallaboratorium Deutscher Apotheker e. V.).

No	Product	Company*	Batch	Lab. 1	Lab. 2	PACs [%] single	PACs [%] mean
1	Gingonin	TAD Pharma GmbH, Cuxhaven	SC5122	x		0.86	0.66
			SD5445	x		0.80	
			SH9656		x	0.31	
2	Ginkgo-Maren	HERMES Arzneimittel GmbH, Großhessenlohe	92102C	x		0.34	0.42
			00901A	x		0.60	
			10702A		x	0.32	
3	Ginkgovital Heumann	Heumann Pharma GmbH & Co. KG, Nürnberg	1183020700	x		0.83	0.58
			1362720500		x	0.27	
			1425210500	x		0.65	
4	Kaveri	KSK-Pharma Vertriebs AG, Berghausen	173084	x		0.63	0.49
			181120	x		0.44	
			192057	x		0.40	
5	Gingobeta	betapharm Arzneimittel GmbH, Augsburg	1324390100	x		1.00	0.69
			1324390300		x	0.37	
			1394210200	x		0.70	
6	Doppelherz Ginkgo	Queisser Pharma GmbH & Co. KG, Flensburg	3001079	x		0.59	0.60
			50129		x	0.55	
			010031	x		0.65	
7	Binko	Klinge Pharma GmbH, Bad Ems	1290980700		x	0.43	0.47
			1290980600	x		0.48	
			1290980500	x		0.50	
8	Ginkgo AL	Aliud Pharma GmbH, Laichingen	91232	x		0.62	0.61
			93440		x	0.40	
			145223E	x		0.81	

continued next page

▶ **Table 1** *Continued*

No	Product	Company*	Batch	Lab. 1	Lab. 2	PACs [%] single	PACs [%] mean
9	Ginkgo-ADGC	KSK-Pharma Vertriebs AG, Berghausen	181122	x		0.32	0.30
			192081	x		0.36	
			132105		x	0.21	
10	Ginkgo AbZ	AbZ Pharma GmbH, Ulm	138415A		x	0.31	0.66
			143481B	x		0.55	
			144046A	x		1.13	
11	Ginkgo 1 A Pharma	1 A Pharma GmbH, Holzkirchen	KF8018		x	0.38	0.70
			LP5482-AA	x		0.98	
			LW8733	x		0.74	
12	Ginkobil	Ratiopharm GmbH, Ulm	2440220	x		4.80	4.50
			2740622		x	4.21	
			2750622		x	4.48	
13	Gingium	Hexal AG, Holzkirchen	LP6994		x	0.95	1.29
			LP7481		x	1.09	
			LV9288	x		1.84	
14	Tebonin	Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe	0300421		x	6.17	5.86
			0480122		x	5.77	
			0490322		x	5.64	

* The term company refers to the entity responsible for placing the respective product on the market according to the valid marketing authorization

Results and Discussion

The results obtained by HPLC for PAC contents in the 14 herbal medicinal products are summarized in ▶ **Table 1**. Results obtained by us, and results obtained by the third-party laboratory are indicated.

Twelve of the fourteen products consistently showed very low PAC contents of approximately 1%, calculated on the basis of the labelled extract quantity, whereas the product with EGb 761 contributed approximately 6% PACs. One product was found to have PAC contents at a level in-between.

Three batches of a product were analyzed, and the mean value is reported. Except for product number 4, which is no longer available on the German market, at least one batch of each product was tested in the third-party laboratory as indicated in the table. For product number 14, only results of this laboratory are reported.

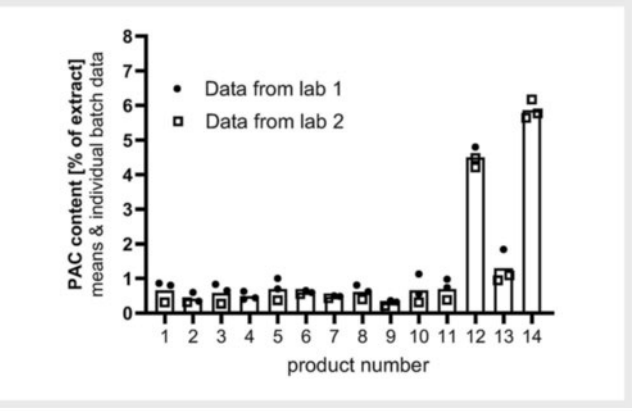
The results from ▶ **Table 1** are visualized in ▶ **Fig. 2**, indicating the origin of each individual data point.

Differences are also obvious in exemplary chromatograms of the 14 products as shown in ▶ **Fig. 3**. In all samples, peaks for delphinidin and cyanidin are detectable. Intensities of the peaks correlate to the calculated quantities of PACs. Only product number 14 shows relevant areas, as indicated by the dark-labelled peaks on the top of the figure.

The majority of randomized placebo-controlled clinical trials on *G. biloba* leaf extracts have been conducted with EGb 761 [18, 19]. The results of these studies have considerably contributed to the HMPC assessment report and monograph, which is a reference for marketing authorizations in the European Union and other countries. The HMPC monograph includes the same quality parameters as the monograph in the Ph. Eur., in which, however, only approximately one-third of the *Ginkgo* extract composition is described and specified. Accordingly, the vast majority of the extract components are defined neither in quality nor in quantity. However, it is to be expected that constituents other than the flavonol glycosides and terpene trilactones may also be of importance for the efficacy and safety of *G. biloba* leaf extracts.

The manufacturing process of the *Ginkgo* extract EGb 761 has been published in detail [20]. In the course of the last few years, more and more companies have applied for a certificate of suitability (CEP) for their *G. biloba* leaf extracts to confirm compliance with the monographs of the Ph. Eur. and many certificates have been granted [21]. The parameters relating to the requirements of the Ph. Eur. can be considered compliant in this case. However, the knowledge about other quality aspects is unknown to the public. Therefore, we started a product screening for the quantification of PACs. This was the first time the previously published HPLC method for *Ginkgo* PACs was used to analyze herbal medicinal products containing *Ginkgo* leaf extract at the finished product level.

The results for PACs reported in this study show very low amounts in some products and quantitatively relevant amounts on the other side of the spectrum (▶ **Table 1**). In the case of the products with low amounts of PACs, it can be assumed that additional compounds are present to account for the unknown portion in the extract composition.



▶ **Fig. 2** Results for products numbers 1 to 14 as summarized in ▶ **Table 1**. Mean values are indicated by the bars, while the corresponding individual results of single batches are indicated by dots (laboratory 1) or squares (laboratory 2), respectively. Laboratory 1 is Dr. Willmar Schwabe GmbH & Co. KG and laboratory 2 is the Central Laboratory of German Pharmacists e. V. (Zentrallaboratorium Deutscher Apotheker e. V.).

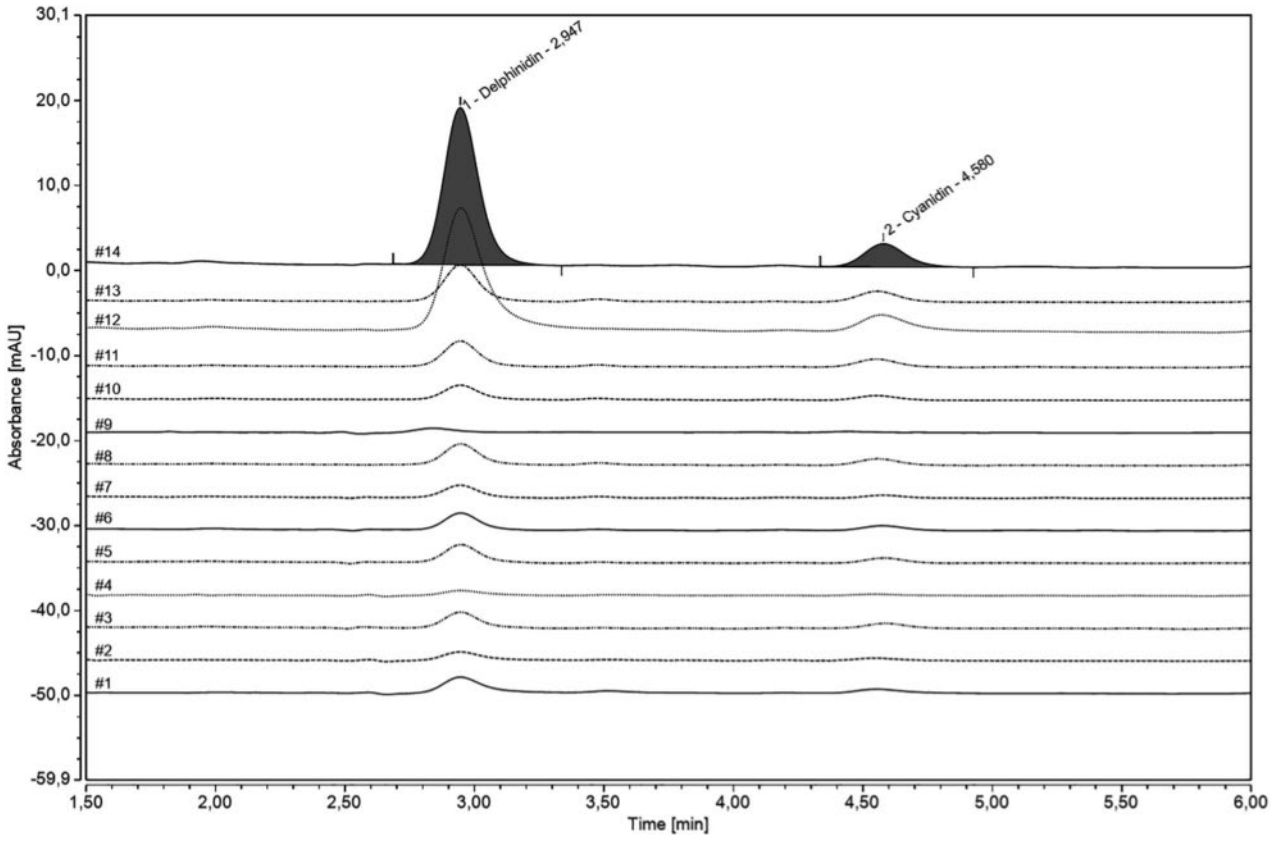
Most of the products show PAC contents below 1%, whereas product number 14 has a content of approximately 6% and product number 12 is between 1 and 6%. The individual results are consistent for each product. The results obtained by laboratory 1 and laboratory 2 are comparable, which confirms suitability of this methodology and transferability between different laboratories.

The reasons for these differences in the composition of the extracts may be due to differences concerning the drug material used or due to details of the extraction process of the different manufacturers, which are, however, not disclosed to the public in all cases.

The slightly lower content of 6% of product number 14 in comparison to the quantity published before for the corresponding *Ginkgo* extract EGb 761 [10] is believed to be correlated to the complex sample preparation caused by matrix effects in the herbal medicinal product consisting of a variety of pharmaceutical excipients.

Our analytical comparison demonstrates that in some of the herbal medicinal products containing *G. biloba* leaf extracts, the contents of PACs is quite significant, up to 6%, and thus in the same quantitative range as the Ph. Eur. specified amount of *Ginkgo* terpene trilactones (5.4 to 6.6%). At the same time, PACs have been reported to exert various pharmacological effects, such as antioxidant or anti-inflammatory activities. Although it has not yet been established whether and to what extent PACs contribute to the overall pharmacological or clinical efficacy of *Ginkgo* extracts, a potential impact of different contents in PACs cannot be ruled out [22].

Our findings lead us to the conclusion that the phytochemical composition of *Ginkgo* herbal medicinal products available on the German market differs substantially. Such differences should also be considered when the clinical evidence generated with one product is transferred to products with an obviously different phytochemical composition, which can be distinguished by a closer



▶ **Fig. 3** Overlay of exemplary chromatograms received by reversed-phase C18 HPLC at 530 nm for the 14 herbal medicinal products. After acidic hydrolysis of the PACs in the samples, the anthocyanidins delphinidin and cyanidin were detectable and could be used for quantification. The assignment of products numbers 1 to 14 corresponds to ▶ **Table 1**.

look at their phytochemistry. Therefore, we suggest to further characterize the composition of *G. biloba* leaf dry extracts in general in order to support a serious discussion on whether extracts or their effects can be compared or not. It is in the realm of possibility that many extracts considered "bioequivalent" based on today's requirements of the Ph. Eur. are actually quite different in their composition, and thus may differ in their clinical efficacy and safety.

Materials and Methods

Test samples

Fourteen products containing *Ginkgo* extracts available in German pharmacies were selected. Thirteen were film-coated tablets that contained either 120 or 240 mg *Ginkgo* extract as single-dose active pharmaceutical ingredient as indicated on the label and in the package leaflet. One product was a hard gelatin capsule with 120 mg *Ginkgo* extract. All of them were authorized as herbal medicinal products in Germany by the Federal Institute for Drug and Medical Devices. From each product, three individual batches were purchased in German pharmacies. Among the products, only product number 14 (Tebonin) contained *Ginkgo* extract EGb 761 [12], the material used in the recently reported development of a new HPLC method for quantification of PACs in *Ginkgo* extract [10]. Voucher specimens of all products are deposited in the archive of Dr. Willmar Schwabe GmbH & Co. KG.

Solvents, reagents, and chemicals

Methanol (p.a.), o-phosphoric acid, and hydrochloric acid were purchased from Merck. Deionized water was obtained by a water purification system (Evoqua, Water Technologies). For the preparation of the hydrolysis solution, 1 part methanol and 1 part 1.5 M hydrochloric acid were mixed (v/v). The hydrolysis solution must be prepared fresh for each analysis.

Reference standard

Two sources for the reference standard were used: procyanidin B2 with a purity ≥ 98 % was purchased from Cayman Chemical Company. Additionally, procyanidin B2 was purchased with a purity of 93 % from Phytolab. The reference standard procyanidin B2 was hydrolyzed in the reference solution to form the reference peak cyanidin *in situ* (see below).

Preparation of standard solutions

The reference standard (procyanidin B2) was weighed exactly into appropriate volumetric flasks and dissolved in the hydrolysis solution to obtain a standard solution with 100 µg procyanidin B2/mL. For an example chromatogram, see **Fig. 1S**, Supporting Information. This standard solution was diluted with the hydrolysis solution to prepare an additional standard solution with 10 µg procyanidin B2/mL. For an example chromatogram, see **Fig. 2S**, Supporting Information. The standard solutions were hydrolyzed in parallel and in the same way as described for the sample solutions (see below). The standard solutions appeared clear after hydrolysis and were used directly for HPLC analysis without prior filtration.

Preparation of sample solutions

All products that presented as film-coated tablets were milled without removing the film coating at room temperature in a mixer mill (Retsch MM 400, 30 Hz, 1 min) resulting in a fine powder. For one product that presented as a hard gelatin capsule, the capsule was opened manually, and the filling powder was used directly. The weighed-in quantity for the obtained powder was calculated with reference to the labelled quantity of *Ginkgo* extract in the individual product. In all cases, quantities of the powder corresponding to 100 mg *Ginkgo* extract were weighed exactly into 25 mL volumetric flasks, filled up to volume with hydrolysis solution, and dissolved in an ultrasonic bath (SONOREX Super RK510, 160/320 W, 35 kHz, Company Bandelin) for 10 min at room temperature. The solution was stirred for additional 20 min followed by centrifugation (2900 *g*, 10 min). The obtained test solutions were hydrolyzed in a boiling water bath in tightly closed 10 mL hydrolysis tubes with screw caps remaining above the surface. The time of 45 min was determined to be the optimal duration to yield a complete hydrolysis. After hydrolysis, the closed tubes were cooled in an ice bath and stored at ambient conditions until they reached room temperature (23 °C). The sample solutions obtained were completely clear, and no additional filtration or centrifugation was applied. The sample solutions were transferred to HPLC vials and used directly for HPLC analysis. For chromatograms of product numbers 8 and 14, see **Figs. 3S** and **4S**, Supporting Information.

High-performance liquid chromatograpy analysis

The HPLC analysis was performed as previously described [10] on a Thermo UltiMate 3000 system with autosampler WPS-3000 TRS, pump LPG-3400 RS, detector MWD-3000 RS, and column oven TCC-3000 SD (Thermo) using a Kromasil C18 (5 µm, 4 × 125 mm) column (MZ-Analysentechnik) without a pre-column. The mobile phase consisted of water adjusted to pH 2.0 with o-phosphoric acid 85 % solution (phase A) and methanol (phase B). The following gradient was applied at a flow rate of 1.0 mL/min: isocratic from 0.00–1.00 min at 60 % eluent A, from 1.00–8.00 min linear from 60 % eluent A to 54.5 % eluent A following 8.00–9.00 min linear 0 % eluent A, 4 min column wash with 0 % eluent A, from 13.00–13.50 min to 60 % eluent A and 6.5 min equilibration period with 60 % eluent A, resulting in a total run time of 20.00 min. A visual light detection wavelength of 530 nm, a column temperature of 25 °C, and an injection volume of 10 µL were applied.

The retention time for delphinidin was approximately 2.9 min, for cyanidin 4.6 min, and for pelargonidin 6.3 min. Quantitation was done for the peaks of delphinidin and cyanidin individually using the standard solutions of hydrolyzed procyanidin B2 and both results were added for further calculation. Delphinidin was calculated as cyanidin. Smaller peaks like pelargonidin were not considered in the sample solutions for quantitation due to being off the dynamic detection range.

Since the PAC fraction purified from *Ginkgo* extract EGb 761 was set to be 100 % by convention as described in a previous publication [10], a conversion factor was needed to determine the contents of PACs using procyanidin B2. The applied HPLC assay correlates to a response factor of 2.12 for the water-free fraction of PACs. Results obtained as procyanidin B2 in the products were multiplied by 2.12 and these results are shown in ▶ **Table 1** for direct comparison.

Data analysis

Data processing and analysis was carried out using Chromeleon 7.2 SR5 software (Thermo). ▶ **Fig. 2** and **Fig. S5**, Supporting Information, was produced with GraphPad Prism, version 9.3.4, for Windows (GraphPad Software).

External results (laboratory 2)

As already described in the Introduction, besides analysis in the laboratory of the authors, results from an external laboratory were also included in the study. Only in the case of product number 4 was this not possible, as this product was no longer available on the German market at the time the external analysis took place. For product number 14, only external results are reported. For analysis by a third-party laboratory, the method described above was transferred to the Central Laboratory of German Pharmacists e. V. (Zentrallaboratorium Deutscher Apotheker e. V., https://zentrallabor.com/). Comparability of the results of both laboratories was evaluated and the results were considered to be equivalent. The method was applied to challenge the validity of the method and exclude any result bias by independent external reproducibility. These external results are labelled in the table of the individual results (▶ **Table 1**). Variability of results are the consequence of the variability of the batches tested.

Validation data

The method was comprehensively validated addressing the parameters precision, intermediate precision, linearity, accuracy, selectivity, and robustness. As we found significantly different contents of PACs, validation of precision and intermediate precision was done on the 1 and 6 % levels, and we selected a representative product for the lower level (number 4) and for the higher level (number 14). The test for precision with n = 6 individual sample preparations showed a relative standard deviation of 8.48 % for the lower level and 7.14 % for the higher level. The test was repeated after 1 week for evaluation of intermediate precision with new sample preparation and new calibration and showed a relative standard deviation of 7.91 % for the lower level and 6.30 % for the higher level. Linearity of the method was already tested in a previous publication [10] by linear regression, with 12 concentrations between 0.602 µg procyanidin B2/mL to 120.400 µg pro-

cyanidin B2/mL. The correlation coefficient was 0.999 946 with a y-intercept of − 0.0181 area and a slope of 0.0353 area/µg/mL. As a real recovery rate of PACs for the evaluation of accuracy in the products cannot be tested directly due to the indirect principle of the method using the reference standard procyanidin B2, and because the scope of the study was a comparison of products, we also applied an indirect approach similar to the previous validation for the extract level [10]. As the reference substance cyanidin is formed *in situ* by the acidic hydrolysis of procyanidin B2, accuracy was addressed by the addition of several selected levels of procyanidin B2 to an accurately weighed quantity of the milled herbal medicinal products, which was done for all 14 herbal medicinal products individually. This was necessary, as except for product number 14, no samples of authentic excipient mixtures were available as well as no samples of the individual pure *Ginkgo* extracts without excipients. The quantity of the milled herbal medicinal products was half, as described in the test procedures, and was supplemented by the addition of procyanidin B2 at five concentration levels each. For the evaluation of accuracy, we focused on a graphical interpretation with a view on the linear relationship of the received peak areas and the x- and y-intercepts, respectively. **Fig. 5S** (Supporting Information) shows that the method is applicable for all 14 products, independent of the individual composition of pharmaceutical excipients, which offers direct comparability of the obtained results. Selectivity was shown with a view on the peak identification of delphinidin and cyanidin and their good chromatographic separation, as already described in a previous publication [10]. Robustness of the method was tested by variation of the method parameters described in the test procedures, such as column temperature and pH value of mobile phase A within relevant ranges, and was considered to be suitable. Also, the time required for an analysis series was suitable to guarantee stability of reference and sample solutions.

Supporting information

Chromatograms of standard solutions at different concentrations and different samples as well as a graphical figure of the standard addition results are available as Supporting Information.

Contributors' Statement

Sample preparation and analysis: T. Ritter; Design of the study: M. Wurglics, S. Germer; Interpretation of the data: M. Wurglics, S. Germer; Drafting the manuscript: S. Germer

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Conflict of Interest

The authors Stefan Germer and Thomas Ritter are employees of Dr. Willmar Schwabe GmbH & Co. KG. The author Mario Wurglics has received speaker's honoraria and research grants from Dr. Willmar Schwabe GmbH & Co. KG.

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