

Quality of *Ginkgo* Preparations¹

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Abstract

A survey of known and of recently isolated constituents from *Ginkgo* leaves is given. The structures of flavonoids and terpene lactones which are considered to be the active compounds as well as their qualitative and quantitative determination in *Ginkgo* leaves and phytomedicines are presented. In the case of flavonoid analysis three selective methods worked out in our laboratories are described. The quality control of terpene lactones is discussed on the basis of a recently published paper. Finally, the standardization methods used for the quality control of *Ginkgo* preparations as well as the question as to whether or not phytomedicine generics – so called "phytogenics" – exist, is discussed.

Key words

Ginkgo biloba L., flavonoids, terpene lactones, ginkgolides, bilobalide, quality control, standardization, HPLC, phytomedicines, phytogenics.

Introduction

In Europe, mainly in Germany and France, but also in other countries of the EC and in countries of the EFTA, there is a large market for phytomedicines based on extracts from the leaves of *Ginkgo biloba* L. The *Ginkgo* market in Europe has a turnover of about 500 million US dollars. This figure emphasises the importance of the *Ginkgo* market. The market seems to be increasing. Looking at the population pyramid in Europe with more and more elderly people, this is not surprising. The indications for *Ginkgo* extracts are primarily related to diseases appearing with advanced age. Pharmacological and clinical tests applied on the extract EGb 761 have demonstrated that their main range of application is mainly peripheral circulatory insufficiency due to degenerative angiopathy and cerebrovascular insufficiency with the symptoms vertigo, tinnitus, headache, short-term memory, hearing loss, vigilance and mood disturbance (1).

The demonstrated importance of the *Ginkgo* market would theoretically suggest that there have been a large number of publications in the field of quality control. The contrary is true. For most of the various drugs listed in pharmacopoeias – even if their importance is only limited – there are far more papers. Up to now there exist no published general quality standards for *Ginkgo* leaves and *Ginkgo* phytomedicines, although laboratories in various universities are engaged in the analysis of *Ginkgo* constituents. The marketing strategy of most of the producers of *Ginkgo* preparations seems not to permit quality control standards elaborated by these companies to be published.

Constituents of *Ginkgo biloba* Leaves

Up to now a great number of apolar and polar compounds have been isolated from *Ginkgo* leaves: long-chain hydrocarbons and derivatives, alicyclic acids, cyclic compounds, carbohydrates and derivatives, flavonoids, isoprenoids (sterols, terpenoids), various compounds like (*Z,Z*)-4,4'-(1,4-pentadiene-1,5-diyl)diphenol, 6-hydroxykynurenic acid, cytokinins, β -lectins, carotenoids, and others. The *Ginkgo* extracts contain as active compounds flavonoids and terpene lactones (ginkgolides and bilobalide). They show effects on vascular and cerebral metabolic processes and inhibit platelet activating factor (PAF) (2, 3 and references cited therein).

Among the main known flavonoids (Fig. 1), a great variety of flavonol glycosides based on kaempferol and quercetin occur as mono-, di-, and triglycosides. Minor flavonoid compounds are derived from isorhamnetin, myricetin, and 3'-methylmyricetin. Structurally interesting compounds are flavonoid glycoside esters with coumaric acid. In addition, non-glycosidic biflavonoids (Fig. 2), catechins, and proanthocyanidins have been isolated.

The terpenoids (Fig. 3) are characteristic constituents of *Ginkgo* and have a unique diterpenoid structure for the five known ginkgolides, or a sesquiterpenoid structure in the case of bilobalide.

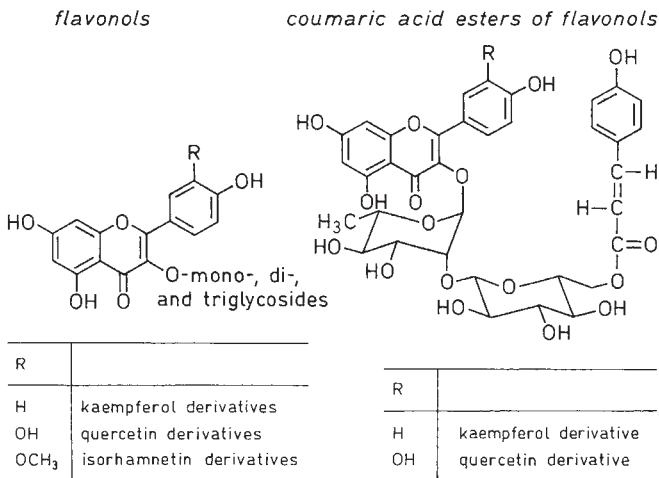


Fig. 1 Known flavonoid glycoside structures from leaves of *Ginkgo biloba*.

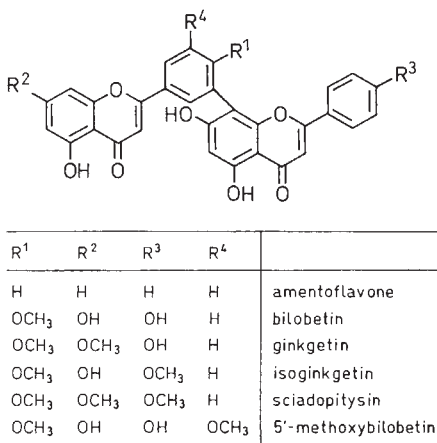


Fig. 2 Biflavones from leaves of *Ginkgo biloba*.

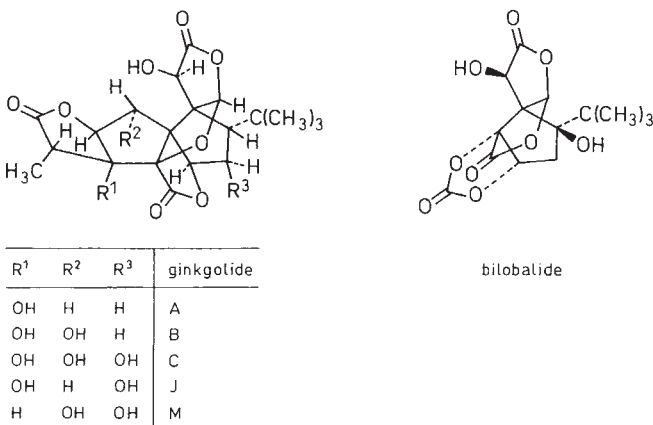


Fig. 3 Terpene lactones from leaves of *Ginkgo biloba*.

Isolation of Flavonoid Glycosides and Quantitation of Flavonoids and Terpene Lactones

The fact that no pharmacopoeial monograph entitled "Ginkgo folium" is in existence is indicative of the fact that no official standards have yet been set. The standardization of phytomedicines serves primarily as a precaution for the quality assurance of medicinal plant extracts. Up to now the most favorable standardization is performed on the active compounds which, in the case of Ginkgo leaves, would be their flavonoids and/or terpene lactones.

Isolation of flavonoid glycosides

In this connection, our primary aim was the development of a suitable method for quality control of the flavonoid glycosides occurring in *Ginkgo*. The development of such methods needs as a prerequisite reference compounds which are not usually commercially available. Therefore, our first step was to isolate the main *Ginkgo* flavonoid glycosides. We recently isolated twenty-one flavonoid glycosides (Table 1). Of these, three compounds were isolated for the first time from *Ginkgo biloba* namely apigenin 7-*O*-glucoside, luteolin 3'-*O*-glucoside, and myricetin 3-*O*-rutinoside. For two further flavonoids the structures had to be revised and five were new flavonol glycosides (3, 4).

The structures of all compounds were deduced from UV spectra, hydrolysis of the glycosides, and from other spectroscopic data. Acid hydrolysis gave the aglycone kaempferol in case of the new compound 1 and quercetin in case of 2 as well as the two sugars glucose and rhamnose (Fig. 4). Both compounds are substituted in position 3 as indicated by their UV spectra on addition of diagnostic shift reagents. Full structural assignments were made on the basis of the results of NMR spectroscopy. Thus, as a first step, proton and carbon resonances were unambiguously assigned using correlated 2D-NMR spectroscopy. Analysis of the chemical shifts and coupling constants then permitted us to determine the sugar linkages and the stereochemical aspects, e.g. compounds 1 and 2 could be shown to have 2'' → 1''' linkages as well as the β- and the α-configurations, respectively, of the glucose and rhamnose moieties.

Table 1 Flavonoids isolated from the leaves of *Ginkgo biloba* (3,4).

Isolated for the first time from *Ginkgo biloba*

- Apigenin 7-*O*-glucoside
- Luteolin 3'-*O*-glucoside
- Myricetin 3-*O*-rutinoside

Known flavonoids which required a structure revision

- Kaempferol 3-*O*-rha(2'' → 1''')glc(6''' → 1''')coumaroyl ester (3)
- Quercetin 3-*O*-rha(2'' → 1''')glc(6''' → 1''')coumaroyl ester (4)

New flavonoids

- Kaempferol 3-*O*-rha(2'' → 1''')glucoside (1)
- Quercetin 3-*O*-rha(2'' → 1''')glucoside (2)
- Kaempferol 3-*O*-rha(2'' → 1''')glc(6''' → 1''')coumaroyl(7'''' → 1''''')glucoside (5)
- Quercetin 3-*O*-rha(2'' → 1''')glc(6''' → 1''')coumaroyl(7'''' → 1''''')glucoside (6)
- Quercetin 3-*O*-rha(2'' → 1''')glc(6''' → 1''')coumaroyl-7-*O*-glucoside (7)

Based on the spectral data of flavonoids **1** and **2**, it was relatively easy to determine the structure of a series of similar acylated flavonoids: flavonoids **3** and **4** (Fig. 5) are identical with two flavonoids reported by Nasr et al. (5, 6). Unfortunately, these authors published a wrong inter-glycosidic linkage: 4'' → 1''' instead of 2'' → 1'''. Based on 2D-NMR experiments we could show that glucose is linked at the 2''-hydroxy group of rhamnose in the whole series of acylated *Ginkgo* flavonoids (3, 4). At the end of our studies the revision of the interglycosidic linkage of compounds **3** and **4** was also reported by Kang et al. (7). Alkaline hydrolyses of **3**, **4**, **5**, and **6** afforded products which were identical by TLC and HPLC with the previously discussed compounds **1** and **2**, respectively. Compound **7** gave, after alkaline hydrolysis, a degradation product whose chromatographic behaviour was characteristic of that of a flavonoid triglycoside. Therefore, **5** and **6**, but not **7**, had the third sugar unit attached to the acyl residue. The second glucose moiety in **7** is attached to the hydroxy group at C-7 which was shown by its UV spectrum on addition of diagnostic shift reagents and by NMR spectroscopy (3, 4).

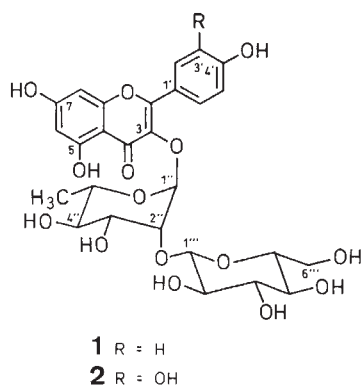
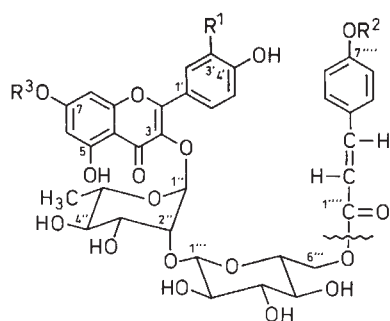


Fig. 4 New flavonoids from leaves of *Ginkgo biloba*.



	R ¹	R ²	R ³	Alkaline hydrolysis	→	
3	H	H	H	→		1
4	OH	H	H	→		2
5	H	glc	H	→		1
6	OH	glc	H	→		2
7	OH	H	glc	→		x

Fig. 5 Revision of flavonoid structures (**3**, **4**) and new flavonoids (**5–7**) from leaves of *Ginkgo biloba*.

Qualitative and quantitative determination of flavonoids

For the determination of the concentration levels of flavonoids in a plant extract, hydrolysis of the glycosides and their spectrophotometric detection as an aluminium chloride chelate complex is the current method. This method, described in several pharmacopeias, is not very specific and permits only an approximate estimation of the total flavonoids in plants. A detailed determination of the qualitative and quantitative composition of the aglycones is not possible. In the case of *Ginkgo* leaves, this method was not reproducible (3), probably due to the high amount of disturbing proanthocyanidins. On the other hand, reversed-phase high-performance liquid chromatography (RP-HPLC) and subsequent diode-array detection allows a selective analysis of the *Ginkgo* flavonoids.

Up to now there exist only a few investigations in the field of separation and quantitative determination of *Ginkgo* flavonoids. Briançon-Scheid et al. (8, 9), Song (10), and Pietta et al. (11) reported HPLC separations of biflavones. According to present knowledge the biflavones represent characteristic markers for the identification of *Ginkgo* leaves, but they do not show the desired activities and are therefore not suitable for a standardization. Therefore, we have worked out three selective HPLC methods which allow the analysis of flavonoids in *Ginkgo* leaves, extracts, and phytomedicines.

To begin with, we elaborated an HPLC method which requires the hydrolysis of the flavonoid glycosides (Fig. 6) (3, 12). This hydrolysis step was considered necessary due to the great number of flavonoid glycosides occurring in this plant. As a result we have proposed a simple, rapid, and good reproducible method which allows one to quantify the three aglycones kaempferol, quercetin, and isorhamnetin. The work-up procedure basically consists of two steps: extraction and hydrolysis of the glycosides, and sample clean-up. Extraction and hydrolysis are performed by refluxing the pulverized plant material or plant extract with 10 ml hydrochloric acid (25%) in 70 ml methanol for 60 min, while sample clean-up is carried out using C₁₈ solid-phase extraction cartridges. An aliquot of the resultant final solution is then injected into the HPLC system. The flavonoid aglycones can easily be analysed by RP-HPLC using a methanol-water gradient with 0.5% v/v orthophosphoric acid and UV detection at 370 nm. This efficient chromatographic procedure is advantageous compared to a similar method described by Wagner et al. (13), especially for serial analyses in quality control and stability tests of phytomedicines. The reduction of the genuine compounds by hydrolysis was already established in the quality control of other phytomedicines, e.g. for the standardization of willow preparations (14).

In the standardization of phytomedicines, a direct quantification of the naturally occurring active principles would be desirable. Often this is not possible because most reference compounds are not commercially available and, in addition in the case of *Ginkgo*, the flavonoid profile is very complex so that analysis during pharmaceutical quality control is rather tedious. However, the obtained aglycone content (Fig. 7) can be correlated with their total

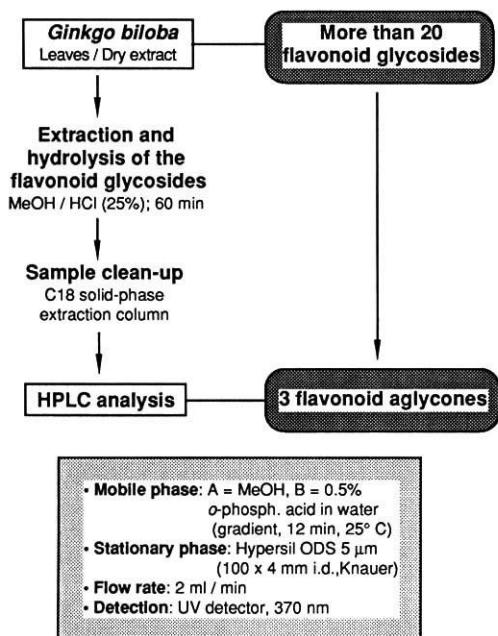


Fig. 6 Work-up procedure and HPLC determination of flavonoid aglycones.

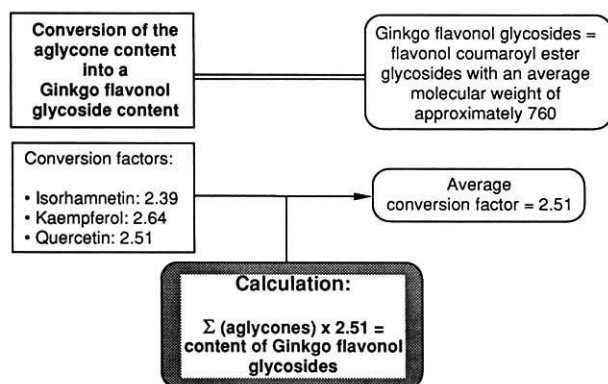


Fig. 7 Calculation of the *Ginkgo* flavonol glycoside content.

flavonoid glycoside content. This is done in accordance with the practice in the pharmaceutical industry, although no published data are available. The producers of *Ginkgo* preparations convert the obtained aglycone content into a "*Ginkgo* flavone" glycoside content, due to marketing considerations. As "*Ginkgo* flavone" glycosides, flavonol coumaroyl ester glycosides with an average molecular weight of approximately 760 are documented. Thus, the final flavonoid content is once again higher. A standardization based on these compounds is acceptable from a pharmaceutical viewpoint because they are lead substances in *Ginkgo* leaves and extracts.

The HPLC analysis of a hydrolyzed *Ginkgo* extract is shown in a typical chromatogram (Fig. 8). Kaempferol and quercetin are the main peaks which correspond in peak height intensity. The concentration of isorhamnetin is approximately five times lower. The very small minor peaks represent further aglycones, e.g. apigenin and

luteolin. They could also be analysed if they occurred at higher concentration levels. Our investigations have shown that dried *Ginkgo* leaves obtained from the commercial market contain an aglycone content of 0.2 to 0.4% w/w, corresponding to a calculated *Ginkgo* flavonol glycoside content of 0.5 to 1% w/w. Green leaves are considered to have a better quality. However, with reference to the flavonoid content we could not see any significant differences in our ontogenetic studies between June and November (Fig. 9).

The second method we worked out (MeOH-THF gradient with 0.5% orthophosphoric acid) allows, beside the quantitative determination of the flavonoid aglycones, a qualitative determination of the biflavones in the same run (Fig. 10) (for details, see 3, 15). This analysis method ensures that authentic *Ginkgo* leaves have been used as starting material for extraction. The ubiquitous aglycones alone are not specific enough to identify *Ginkgo biloba* leaves or *Ginkgo* full extracts. This method cannot be used in the case of some extracts like EGb 761 where the biflavonoids have been removed – as it will be shown later.

The third method (isopropanol/THF (25:65) – acetonitrile gradient with 0.5% orthophosphoric acid) allows a fingerprint analysis of all naturally occurring *Ginkgo* flavonoids in one HPLC run within 30 min (Fig. 11) (for details, see 3, 15). With this analytical method it is possible to identify twenty-two flavonoid glycosides, six flavonoid aglycones, and five biflavones by elution order and UV spectra. Due to the complex mixture of very polar, polar, and apolar flavonoids, the separation requires a sophisticated HPLC apparatus inclusive of a three-pump system and a diode-array detector. The fingerprint analysis is especially useful in performing stability tests. It could be shown that the flavonoid glycosides and the biflavones are stable, and that the ratios of the compounds do not change. An increase of the aglycones and a decrease of the glycosides would indicate an undesired degradation process in the extract. The fingerprint analysis especially allows one

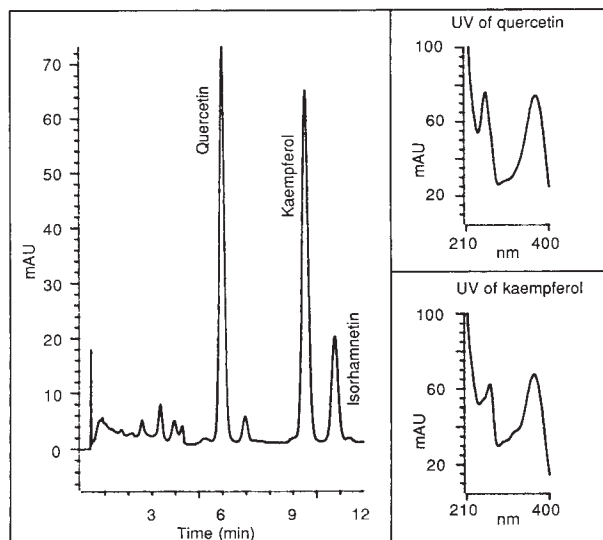


Fig. 8 HPLC chromatogram of a *Ginkgo* leaf extract after hydrolysis of the flavonoid glycosides.

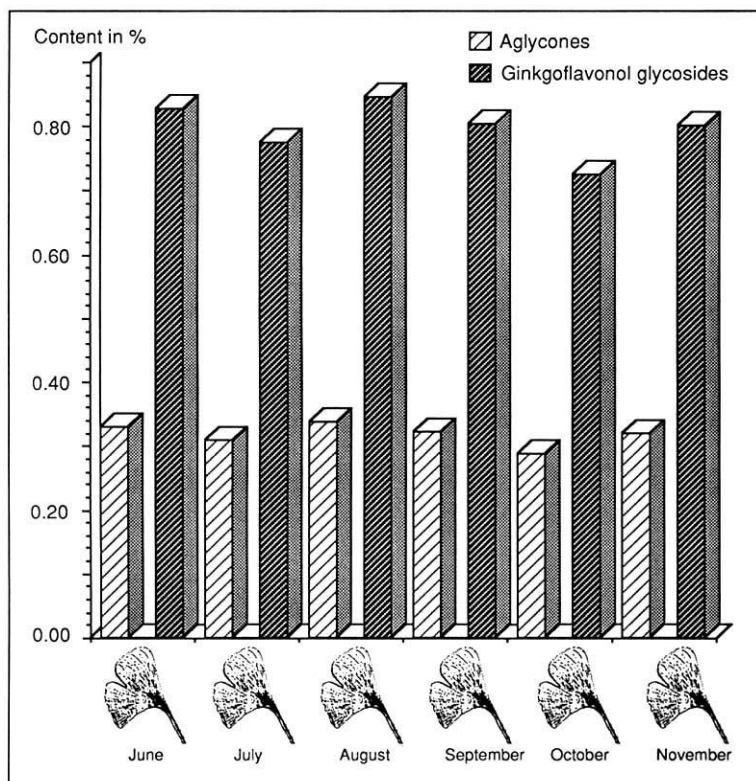


Fig. 9 Concentration of flavonoid aglycones and *Ginkgo* flavonol glycosides in dependence of the harvest [leaves of a female *Ginkgo* tree; In reference (2) erroneously leaves of a male *Ginkgo* tree were recorded].

to identify the very typical flavonol coumaroyl ester glycosides 21 [quercetin 3-*O*-rha(2''→1''')glc(6'''→1''')coumaroyl ester] and 22 [kaempferol 3-*O*-rha(2''→1''')glc(6'''→1''')coumaroyl ester]. Both are well separated from each other and from other compounds.

In 1989, a fingerprint HPLC separation of flavonoids from *Ginkgo* leaves was described by Wagner et al. (13). In this study twenty peaks were detected within 55 min but only two flavonoids (rutin, astragalol) and the four biflavones (bilobetin, ginkgetin/isoginkgetin, and sciadopitysin), ginkgol, shikimic acid, and 6-hydroxykynurenic acid could be assigned. Recently, Pietta et al.* (16) reported an HPLC method for the separation of fifteen known *Ginkgo* flavonoids within 50 min. The assignment was done with reference compounds for six flavonoids. The other flavonoid glycosides were assigned by their UV/Vis spectra using a diode-array detector, though their absorptions were less than ten milliabsorption units (mAU). Such assignments, without any other investigations, are very speculative. In both papers (13, 16), the separation and the identification of the flavonoids are not very developed and not complete. Lobstein et al.* (17) used gradient elution with acetonitrile and 0.1 N phosphoric acid to separate flavonoids and biflavones within 50 min. No diode-array detector was coupled to the HPLC system. Additionally, the lack of reference compounds prevented complete peak assignment. Kaempferol and quercetin 3-*O*-coumaroyl glucorhamnosides and the biflavones in leaves were quantified. A small study about the seasonal variation resulted.

Qualitative and quantitative determination of terpene lactones

The analysis of the terpene lactones was until recently much more difficult due to their low concentration in the leaves – according to van Beek et al. (18) very often below 0.1% w/w. Furthermore, these compounds show very poor UV characteristics and have to be extracted first from a highly complex matrix, e.g. no suitable sample clean-up for HPLC analysis has been described in the literature. A promising clean-up procedure, detection and determination method was presented by van Beek et al. (18). Prior methods published between 1981 and 1990 (19–23) give either unsatisfactory results, or are otherwise inadequate, and could not be reproduced because important experimental data were lacking.

In the following we refer to the publication of van Beek et al. (18) and to personal communications with van Beek. Selective extraction of *Ginkgo* leaves (Fig. 12) with methanol-water (10:90), or of phytomedicines with water, followed by a sample clean-up with polyamide and C₁₈ solid-phase extraction columns in series, gives extracts that can be readily analysed by RP-HPLC with water-methanol (67:33) as mobile phase and RI detection. Boiling water with a few percent of methanol has been found to be a selective primary extraction solvent for the ginkgolides. However, many interfering compounds are co-extracted, but these can be removed using the sample clean-up procedure shown. The polyamide column removes most of the phenolics. The terpene lactones are retained by the C₁₈ purification column by eluting with a low methanol content. By increasing the methanol content the terpene lac-

* Papers were published after the Saarbrücken symposium.

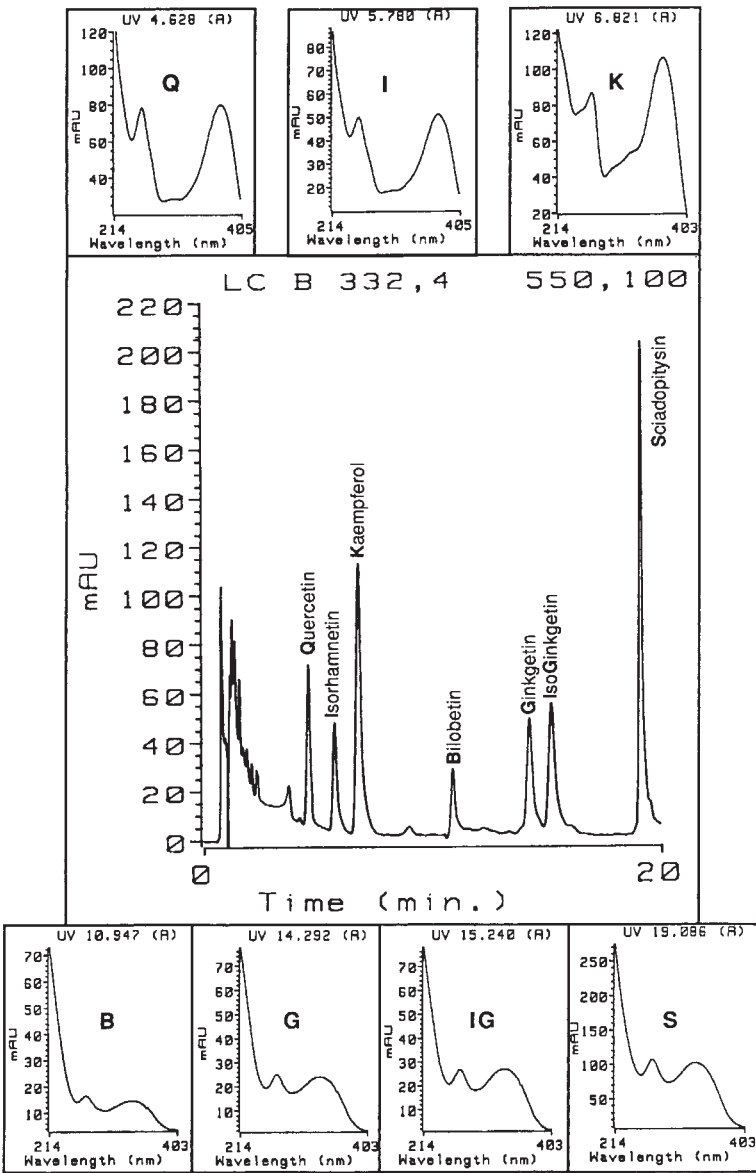


Fig. 10 HPLC chromatogram and UV spectra of the aglycones and biflavones of a *Ginkgo* leaf extract after hydrolysis of the flavonoid glycosides.

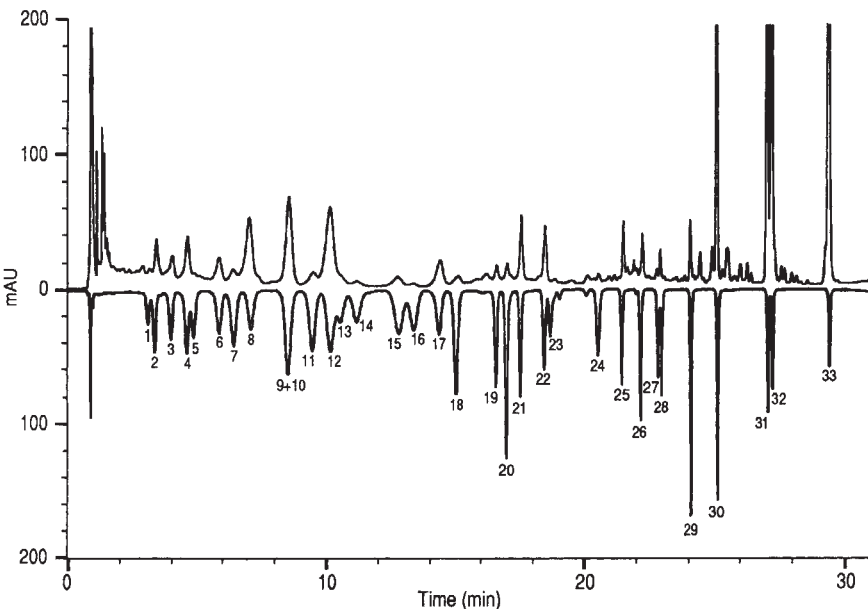


Fig. 11 Fingerprint chromatogram of an ethanolic leaf extract of *Ginkgo biloba* (upper chromatogram) and of isolated flavonoids and reference compounds (lower chromatogram).

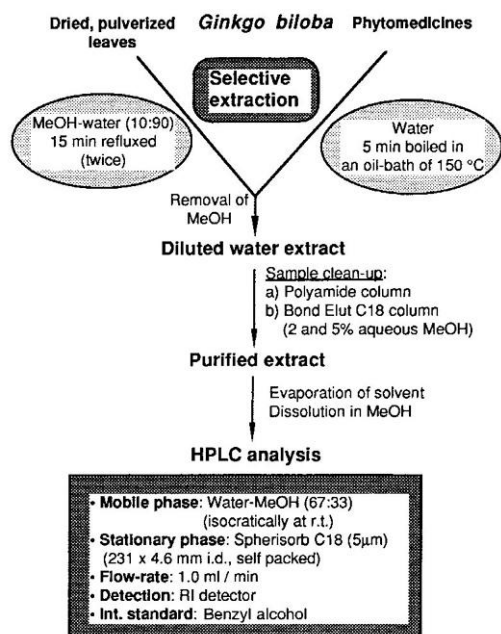


Fig. 12 Work-up procedure and HPLC determination of terpene lactones according to van Beek et al. (18).

tones can be removed from the column. This clean-up procedure allows analysis of the terpene lactones if RI detection is used instead of the usual UV detection.

All the leaves and phytomedicines investigated were found to contain bilobalide and ginkgolides, although large differences between different leaf batches or *Ginkgo* preparations from different manufacturers were observed. The leaves investigated were from seven different sources (Fig. 13). Leaves obtained from France contained the highest amount of total terpene lactones whereas all the others contained much less. The total concentration of such terpenes was found to vary by a factor of 40. In all of the investigated samples the bilobalide content was equal to or higher than that of the total ginkgolides.

Van Beek et al. have shown (Fig. 14) that controlled, partially purified *Ginkgo* phytomedicines like Tebonin, Rökan, or Tanakan contain much higher concentrations of ginkgolides and bilobalide than other, especially Dutch preparations, which are prepared according to the homeopathic pharmacopoeia. One French preparation (Ginkgogink) was entirely different from all others. It contained high concentrations of all the ginkgolides, but bilobalide could not be detected. As bilobalide is the major terpenoid in all the leaves and other phytomedicines investigated, this suggests that bilobalide has been selectively removed during the manufacturing process. Additionally, in the chromatogram of this preparation some extra peaks could be observed, not present in any other sample of leaves or phytomedicines.

According to a private communication from van Beek, the presented method works well. However, the clean-up procedure is rather time-consuming and depends very much on the quality of commercially available C₁₈ purification columns. Therefore, we are hoping together

with van Beek that a much simplified one-column purification method will be available soon.

Ginkgo Extracts and Preparations

In summary, it follows that extract A is not identical with extract B, nor preparation A with preparation B. As in the case of other medicinal plants, there are existing *Ginkgo* "full extracts", also called "crude extracts or simple extracts" (Fig. 15). They contain most of the constituents in a similar ratio to the starting material. Such extracts are produced mainly using ethanol-water as extraction medium. The result is a complex mixture consisting of active principles, inert plant constituents, and in some cases constituents which may cause adverse side effects.

Ginkgo phytomedicines have been well-known in Europe in part due to an "enriched or special extract" named EGb 761, which was developed in the laboratories of Schwabe in Karlsruhe (FRG). This is obtained using a relatively tedious work-up and purification procedure which comprises various steps like liquid/liquid extraction, precipitation, and concentration. Therefore, high-molecular-weight constituents like tannins, proteins, and polysaccharides, in addition to other compounds like biflavones and ginkgolic acids, which are not desired because of complex formation with other compounds or because of allergenic properties, are removed or reduced. The desired active principles like flavonoid glycosides and terpene lactones are thus enriched.

Standardization

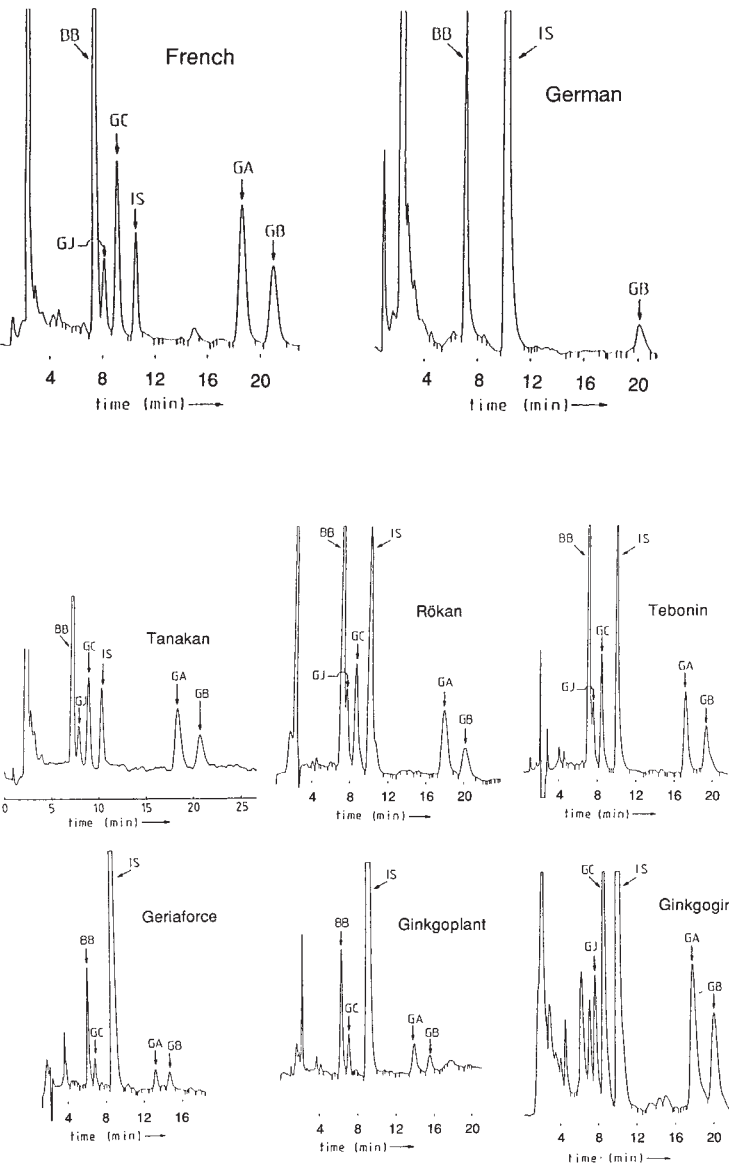
Until recently all commercially available *Ginkgo* preparations were standardized with a "*Ginkgo* flavone" glycoside content. The preparations based on the extract EGb 761 comprising e.g. Tebonin forte, Rökan, Tanakan, and Ginkobil are standardized with a "*Ginkgo* flavone" glycoside content of 24 % w/w. Lately, the extract EGb 761 has also been standardized on the basis of the presence of 6 % w/w terpene lactones (ginkgolides and bilobalide). This practice refers to the use of active constituents for the standardization and is a truly positive matter. Probably other companies will sooner or later follow this practice. Other preparations produced in the same way as EGb 761 or by applying similar manufacturing steps, like Kaveri, Gincosan, and Craton, are standardized with a "*Ginkgo* flavone" glycoside content of 16–25 % w/w, two further preparations, *Ginkgo* dragees Duopharm and Salus-Haus, of 7.4 % w/w. Certain preparations based on crude extracts, like Valverde Vital or Allium Plus, are usually standardized to a minimum flavonoid content of 2 % w/w, the French preparation Arkogelules *Ginkgo* to a minimum flavonoid content of 0.5 % w/w.

With reference to the standardization of the preparations, one has to remark that the declared 24 % w/w "*Ginkgo* flavone" glycosides and the 6 % w/w terpene lactones, respectively, are related to the extract employed in therapy. For the production of phytomedicines only an aliquot quantity is used, e.g. in the case of Tebonin forte solution 4 g of extract in 100 ml solution. That means the content of the active principles in the phytomedicine is reduced by a factor 25.

Ginkgolide and bilobalide concentration in leaves

Origin of leaves	Content (%)
Chinese	0.134
Dutch	0.037
Dutch (1989)	0.196
Dutch	0.006
French	0.266
French	0.252
German	0.032

The total concentration of terpenoids varied by a factor 40.



Total terpene lactone concentration in phytomedicines

Phytomedicine	Content (%)
Tanakan (F)	0.220
Rökan (D)	0.192
Tebonin (D)	0.213

Geriaforce (NL)	0.017
Ginkgoplant (NL)	0.013
Naphyto DØ (NL)	0.012
Ginkgogink (F)	0.111

The total concentration of terpenoids varied by a factor 18.

Fig. 13 HPLC determination of ginkgolides and of bilobalide in leaves from *Ginkgo biloba* according to van Beek et al. (18).

Fig. 14 HPLC determination of ginkgolides and of bilobalide in *Ginkgo* phytomedicines according to van Beek et al. (18).

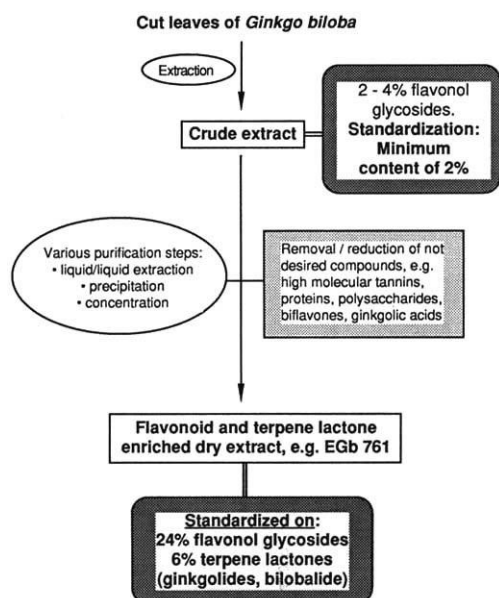


Fig. 15 Extraction procedure for *Ginkgo* preparations.

Generics in the Case of Phytomedicines – “Phytogenerics”

Since the expiration of the patent for the extract EGb 761, the question as to whether or not phytomedicine generics – so called “phytogenics” – exist has been discussed vehemently, probably due to marketing considerations. Certainly it can be stated – as it was said before – that one extract is not equal to another. The production of an enriched extract like EGb 761 results from – as we have seen – a series of purification steps which are not likely to be reproducible when carried out by another pharmaceutical company. Therefore, the composition of extract constituents and thus efficacy may be different. This point is especially of importance in the case of plant extracts containing not only one active principle but a complex mixture (24, 25). The above-mentioned facts, however, do not imply that generics are not really possible in the area of phytomedicines. If this were to be the case, phytomedicines would need in future standards for their registration which even well-documented extracts might hardly satisfy. It is also a fact that differences may exist between generics of synthetically produced substances and the corresponding original medicament, e.g. as a result of variations in galenical formulation. For generic monosubstances, methods for the comparison of the bioavailability exist. Such methods are not yet available in the case of phytomedicines. Therefore, their comparable evaluation is much more difficult to perform. In case of phytomedicines a valuation is only possible with comparable proof of efficacy. In this point lies the major difficulty in the evaluation of phytomedicines. For *Ginkgo*, no pharmacological and clinical procedures are yet available for leaf extracts. So far, almost all investigations were made with the standardized extract EGb 761 and the preparations based on this extract. Even though other available preparations use different extraction and manufacturing procedures, they still refer to the above-mentioned pharma-

cological and clinical investigations. This is, of course, in no way justified.

Ginkgo preparations with a low flavonoid and terpene lactone content are permitted in various countries for self-medication. Indications for such preparations are e.g. in Switzerland: reduced mental and physical efficiency, loss of concentration, memory and impulsion, vertigo, and other similar symptoms. In connection with the treatment of these primary symptoms of an initial cerebrovascular insufficiency, the question arises as to whether an enriched extract with a high flavonoid and terpene lactone content or a full extract is needed. Full extracts are more common in phytotherapy and are used for other flavonoid- and proanthocyanidin-containing medicinal plants, e.g. in the case of *Crataegus*. Investigations in relation to dose-dependent activity are not available yet. Some practical knowledge shows that full *Ginkgo* extracts improve vigilance and mental efficiency in older people. Carefully performed psychometric and analogous studies have to confirm this. Therefore, I would like to urge the manufacturers of *Ginkgo* products other than EGb 761 to prove the efficacy and safety of their extracts and preparations.

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