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REVIEW ARTICLE

Ginkgo biloba Extracts: A Review of the Pharmacokinetics of the Active Ingredients

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Abstract *Ginkgo biloba* is among the most favourite and best explored herbal drugs. Standardized extracts of *Ginkgo biloba* represent the only herbal alternative to synthetic antidementia drugs in the therapy of cognitive decline and Alzheimer's diseases. The clinical efficiency of such standardized *Ginkgo biloba* extracts (GBE) is still controversial, but authors of numerous international clinical studies recommended the use of GBE in the described therapies.

Extracts of *Ginkgo biloba* are a mixture of substances with a wide variety of physical and chemical properties and activities. Numerous pharmacological investigations lead to the conclusion that the terpene trilactones (TTL) and the flavonoids of GBE are responsible for the main pharmacological effects of the extract in the therapy of cognitive decline. Therefore, the quality of GBE products must be oriented on a defined quantity of TTL and flavonoids. Furthermore, because of their toxic potential the amount of ginkgolic acid should be less than 5 ppm.

However, data on pharmacokinetics and bioavailability, especially related to the central nervous system (CNS), which is the target tissue, are relatively rare. A few investigations characterize the TTL and flavonoids of *Ginkgo biloba* pharmacokinetically in plasma and in the brain. Recent investigations show that significant levels of TTL and *Ginkgo biloba* flavonoids cross the blood–brain barrier and enter the CNS of rats after oral application of GBE. Knowledge about the pharmacokinetic behaviour of these substances is necessary to discuss the pharmacological results on a more realistic basis.

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1 Introduction

Ginkgo biloba (Ginkgoaceae) is regarded to be the only surviving tree species of the order Ginkgoales. It has been around for about 280 million years [1, 2] and has been used for pharmaceutical and medical purposes in China for several hundred years to treat various diseases. This use, however, has not been based on any scientific background. Today, extracts of *Ginkgo biloba* have become one of the most common and best explored herbal medicinal products (HMP).

It is important to stress that *Ginkgo biloba* products are currently one of the most widely sold and studied medicinal plant preparations. The actual extent of the market for HMP in the USA is difficult to assess, because the products are sold mostly in health food stores, by mail order, or by multi-level marketing organizations, for which accurate statistics are not available [3]. In conclusion, there are no recent accurate global sales figures available, but van Beek and Montoro [4] cited an indicative figure of one billion US dollars. In addition a drastic increase has been reported in the use of *Ginkgo biloba* leaf phytomedicines in China in recent years, rising sharply from Chinese yuan 600 million (US dollars 75 million) in 2000 to Chinese yuan 1.7 billion (US dollars 212.5 million) in 2004 [5]. In 2008, in Germany 7.4 million defined daily doses of GBE were dispensed at the expense of the statutory health insurance system [6]. But the actual use of GBE is probably much higher because GBE can also be bought without a prescription in Germany. Accurate statistics of the over the counter use of GBE in Germany are not available either.

Ginkgo biloba products are offered today in many different preparations sometimes without any kind of scientific background and control. However, in evidence-based medicine and all clinical investigations and treatments *Ginkgo biloba* should only be used in the form of standardized *Ginkgo biloba* extracts (GBE; e.g. EGb 761®, LI 1370®) defined by a special composition and manufacturing process. A description of the variety of commercial extracts and the regulatory background is given later (see Sect. 2). GBE are widely used to ameliorate the symptoms of age-related cognitive decline in conditions ranging from mild memory impairment and cerebral insufficiency to dementia including Alzheimer's disease (AD). GBE is consequently used in modern phytotherapy as a herbal alternative to classic antidementia drugs. In addition, recent in vitro pharmacological investigations lead to the hypothesis that different ingredients of *Ginkgo biloba* [bilobalide (Bb)] can protect against neuronal degeneration resulting from ischaemic events [7, 8].

A decrease in mitochondrial function is known to play a key role in the aging process of the brain and age-related diseases such as AD [9, 10]. In addition, oxidative stress, the direct result of the imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), as well as intracellular antioxidant defences, are invariably involved in the onset of neurological pathologies such as AD [11–13]. In 2009 the German Institute for Quality and Efficiency in Health Care (IQWiG [14]) published an extensive meta-analysis of clinical studies which investigated the effects and benefits of EGb 761®. In conclusion this meta-analysis indicates a positive effect, especially in relation to daily life activity and cognitive efficiency, and moreover showed that the GBE EGb 761® has only few side effects and is well accepted by patients [15]. In addition, numerous further clinical studies also illustrated benefits for patients with age-related cognitive decline after taking standardized GBE [16–18]. However, other clinical studies on EGb 761® challenged the effects and benefits of the use of EGb 761® [19, 20]. The Cochrane systematic review by Kasper and Schubert [21] discusses the relevant differences between the two reviews by the IQWIG [15] and by Birks and Grimley Evans [20]. In contrast to the review by the IQWiG [15], Birks et al. [20] also included studies carried out with GBE products of poor quality. Furthermore, some studies also included people with age-related cognitive problems instead of dementia. These facts could explain why Birks et al. concluded that GBE products have no effects for patients with dementia compared to placebo.

The current review summarizes the pharmacokinetic data available of *Ginkgo biloba* TTL and flavonoids and compares the concentrations used in the in vitro pharmacological studies with determined maximal plasma and brain concentrations of the active ingredients. It is based on a systematic literature search in the database Pubmed (using the keywords "ginkgo", "ginkgo flavonoids", "ginkgo terpenelactones", "ginkgolides", "bilobalide", "ginkgo pharmacokinetics").

2 Regulatory Background of Herbal Medicines

Herbal medicines have been used in healthcare worldwide since the earliest days of humankind. Even in developed countries, patients rely on medicinal plants and herbal medicines in their primary care. Recognition of their clinical, pharmaceutical and economic value is still growing, although this varies widely among countries and is in most cases linked to the legal position of these herbal preparations. In some countries, phytomedicines are well established, whereas in others they are sold as dietary supplements. In the USA, most herbal products are regulated as foodstuff, food supplements or dietary supplements, even though many are used as folk remedies by consumers. In Germany, HMP can be offered as "rational" medicines (§21, §105 AMG) licensed to a defined medical indication, as "traditional use" (i.e. products based on §39a AMG), dietary supplements, as food or as homoeopathic products [22].

Irrespective of any regulatory issues, plants or parts of plants should only be used in the form of standardized extracts in evidence-based medicine. Theses standardized extracts are defined by the quality of their raw plant material and the manufacturing process. Thus this combination leads to a defined composition of ingredients in each extract. The USP 32 (United States Pharmacopeia 32) and the European Pharmacopoeia 6.1 published monographs for GBE and GBE formulations. USP 32 contains monographs on Ginkgo, powdered Ginkgo extract, Ginkgo capsules and Ginkgo tablets. The European Pharmacopoeia 6.1 contains a monograph on *Ginkgo biloba* extract. Both pharmacopeias refer to the standardized dry extract (produced with acetone 60 %, drug/extract ratio (DER) 35–37:1; e.g. EGb 761®, Li 1370®) with a defined composition (5–7 % TTL, 22–27 % flavonoids, <5 ppm ginkgolic acids, see also part IV) which is also preferred by the German Federal Health Agency (Commission E [23]). The Commission E and the IQWiG recommended 120–240 mg of this dry extract a day for a 'symptomatic treatment of disturbed performance in organic brain syndrome within the regimen of a therapeutic concept in cases of demential syndromes such as Alzheimer's disease' and pointed out that the patients experience a benefit after taking e.g. 240 mg EGb 761® per day [15, 24]. The World Health Organization (WHO) has accepted the aforementioned standardized extract as an antidementia drug on the basis of pharmacological in vitro and in vivo studies as well as numerous clinical studies supporting the

efficacy of EGb 761® in the CNS with a daily dose of 240 mg EGb 761® [15, 25, 26]. Moreover, GBE has been listed in the Anatomical Therapeutic Chemical (ATC) Classification Index since 2000. The safety of GBE has been documented for several years [27, 28]. Today, EGb 761® is the best explored standardized extract in terms of clinical efficiency, in vivo and in vitro pharmacology and pharmacokinetics.

The following review focuses mainly on GBE that conform with the monograph of the USP 32, the European Pharmacopoeia 6.1 and the German Commission E. The brand name and its composition will be bookmarked individually (see Table 1) if important aspects refer to other *Ginkgo biloba* extracts. This review also contains human and animal data from different studies. The implementation of animal data in the review is necessary because of the lack of human data, especially regarding the CNS availability of the ginkgolides and flavonoids.

3 Compounds and Pharmacology

Ginkgo biloba contains different components such as flavonoids, terpene trilactones, proanthocyanidines, ginkgolic acids, biflavone, polyflavones and ginkgotoxins [29, 30]. Variations in the amount of the different components in the plant are primarily related to harvesting periods, drying process and storage. However, as discussed before, in case of evidence-based medicine, the standardized GBE (e.g. EGb 761® and LI 1370®) represents the pharmaceutically used and recommended form of *Ginkgo biloba*.

The standardized GBE consists, among others, of two major fractions with specific pharmacological profiles: the terpene trilactones (TTL) (ginkgolide A (GKA), B (GKB), C (GKC), J (GKJ) and bilobalide (Bb) (see Fig. 1a and 1b) in a concentration of 5.4–6.6 % (GKA, GKB and GKC together 2.8–3.4 % and Bb 2.6–3.2 %), and the flavonoids, comprising 22–27 % of the extract. The flavonoid fraction is composed mainly of three flavonols, namely quercetin, kaempferol and isorhamnetin (see Fig. 1c), which are combined with at least one sugar moiety (see Fig. 1d). The amount of ginkgolic acids (see Fig. 1e) in GBE must be less than 5 ppm. It is undisputed today that the pharmacologically active compounds of GBE are the TTL and the flavonoids [9, 31].

3.1 Terpene Trilactones

The TTL compound class is very rare in the plant kingdom; it has only been found in *Ginkgo biloba* so far. Detailed structures of the TTL are shown in Fig. 1a. Ginkgolides, which are C_{20} diterpenes, consist of six five-membered rings, that is a spiro[4,4]nonane carbocylic ring, three lactones and a tetrahydrofuran, whereas Bb is a sesquiterpene. They are the only known natural products possessing a *tert*-butyl group [32].

It was shown that EGb 761® protects mitochondria from age-related damage and improves mitochondrial function and energy metabolism; this action is mainly due to the ginkgolides and Bb. In recent times, this hypothesis has been discussed as a predominant mechanism of EGb 761® action, because it is well established that the decreased mitochondrial function plays a major role in the pathophysiology of AD [9, 10, 33–36]. A concentration of 10 µg/mL EGb 761®, containing approx. 300 ng/mL Bb and 300 ng/mL ginkgolides, protected PC12 cells against H_2O_2 in vitro [35]. The same concentration protected the complexes of the mitochondrial respiratory chain in PC12 cells against thenoyltrifluoroacetone (TTFA), NaN_3 (10 mmol/L) and oligomycin (10 µmol/L) [9]. In addition, low concentrations of EGb 761® (10 µg/mL) were able to reduce sodium nitroprusside (SNP)-induced mitochondrial membrane potential changes; ATP levels could be stabilized at concentrations as low as 5 µg/mL EGb 761® [36]. Two possible molecular mechanisms for the mitochondrial protection by EGb 761® are discussed [37]: (i) platelet activating factor (PAF, 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) receptor antagonism [38] and (ii) an interaction with chloride channels [7, 39].

(i) The TTL inhibit the effect of PAF at the PAF receptor. GKB is the strongest PAF antagonist in comparison to the other TTL; GKB is 25 times stronger than, for example, GKC [40]. A further study showed that the PAF antagonism was effective in the submicromolar range (GKA, half maximal inhibitory concentration [IC_{50}] = 0.74 µmol/L; GKB, IC_{50} = 0.25 µmol/L) [41, 42]. PAF is a potent phospholipid mediator of leukocyte functions, platelet aggregation and pro-inflammatory signalling. Since TTL act as antagonists of PAF, they are able to improve blood circulation. Excessive PAF promotes neuronal damage; and inhibition of this process plays a critical role in neuronal survival and prevention of ischaemic brain injury [31, 38, 43–47].

(ii) TTL also act as selective use-dependent blockers of glycine-activated chloride channels in the hippocampal neurones of the rat. The IC_{50} values for saturating blocking action of GKB and GKC are 0.273 and 0.267 µmol/L, respectively, whereas GKA and GKJ are less effective (IC_{50} values 1.97 and 2.0 µmol/L) [39, 48]. Kondratskaya et al. pointed out that GKB inhibits glycine currents in a non-competitive manner. Furthermore, GKB has an increased sensitivity for inhibitory glycine receptors if the receptor contains a β-subunit. In this case, the IC_{50} value decreases to the nanomolar range [49].

Table 1 Detailed overview on used *Ginkgo biloba* extracts and products

Extract	Composition	Comment	References
EGb 761® (Tebonin®) (Dr. W. Schwabe GmbH, Karlsruhe, Germany)	Ginkgolide A, B, C, J and bilobalide in a concentration of 5–7 %, and the flavonoids, making up 22–27 % of the extract	Conforms with USP and Pharm. Eur.	[3, 80, 100, 109, 110, 127, 144, 147–150]
LI 1370® (Kaveri®) (Lichtwer Pharma GmbH, Berlin, Germany)	Ginkgolide A, B, C, J and bilobalide in a concentration of 5–7 %, and the flavonoids, making up 22–27 % of the extract	Conforms with USP and Pharm. Eur.	[143]
Ginkgo biloba leaf extract (Istituto Biochimico Pavese, Pavia, Italy)	No details	No evaluation possible	[139, 141]
Ginkgo biloba extract (Obsidian, Port Talbot, UK)	The tablet was stated to contain 28.8 mg flavonoids and 7.2 mg terpene lactones	No evaluation possible	[121]
Ginkgo biloba tablets (purchased from Boots Glasgow, UK)	Tablets had a stated content of 28.8 mg of total flavonoid glycosides	No evaluation possible	[138]
TianBaoNing® capsules (a commercially available *Ginkgo biloba* leaf extract product)	Standardized to contain 9.6 mg of flavonol glycosides and 2.4 mg of terpenes per capsule	No evaluation possible	[5]
Gineton®	No detailed description	No evaluation possible	[142]
Ginkgo biloba extract tablets (obtained from Zhejiang CONBA Pharmaceutical Manufacturing Company, Ltd., Hangzhou, China)	Containing 1.134 mg Q, 1.223 mg K	Does not conform with USP and Pharm. Eur.	[119, 151]
GBE supplied by Tama Seikagaku-Kogyo Co. (Tokyo, Japan)	Containing 24.9 % flavonoids, 10.6 % TTL (2.9 % ginkgolide A, 1.4 % ginkgolide B, 2.1 % ginkgolide C and 4.2 % bilobalide)	Conforms with USP and Pharm. Eur.	[76, 77]
GBE purchased from Zhejiang Comba Pharmaceutical Co., Ltd (Lanxi, Zhejiang, China)	Containing 26.1 % flavonols, 8.9 % TTL (2.3 % ginkgolide A, 1.5 % ginkgolide B, 1.1 % ginkgolide C and 4.4 % bilobalide)	Conforms with USP and Pharm. Eur.	[152]
Powder of GBE Tama Biochemical Co., Ltd. (Tokyo, Japan)	Containing 24.2 % flavonoids and 9.4 % terpenes	Conforms with USP and Pharm. Eur.	[153]
GBE dry powder (Indena S.A., Milan, Italy)	Containing 6.2–7.1 % TTL and 21–24.4 % flavonoids	Conforms with USP and Pharm. Eur.	[154]
GBE (Hong Kong, Herbs Product Ltd., Kowloon, Hong Kong)	22.9 % flavonol glycosides, 6.8 % TTL	Conforms with USP and Pharm. Eur.	[155]
Ginkgolon-24 provided by Tokiwa Phytochemical Co., Ltd. (Chiba, Japan)	Over 24 % flavonoid glycosides and 6 % terpene lactones and <1 ppm ginkgolic acids	Conforms with USP and Pharm. Eur.	[156, 157]
Centrum Herbals (distributed by Whitehall-Robins Healthcare, Madison, USA)	24 % flavonoid glycosides and 6 % terpene lactone	Conforms with USP and Pharm. Eur.	[3]
Geriaforce™ tincture (fresh plant tincture)	1 mL contains the equivalent of 920 mg *Ginkgo biloba* leaves as active ingredients; DER = 1:9, 65 % (v/v) ethanol is used for extraction (containing 236.97 μg/mL Bb; 109.21 μg/mL GA; 54.01 μg/mL GB)	Does not conform with USP and Pharm. Eur.	[127]
Ginkgo fresh plant extract tablet	90 mg of Ginkgo fresh plant extract (DER = 3–5:1; extracted with 67 % ethanol v/v) (1 tablet contains 493.74 μg Bb; 220.38 μg GA; 131.14 μg GB)	Does not conform with USP and Pharm. Eur.	[127]

DER drug/extract ratio, *GA* ginkgolide A, *GB* ginkgolide B, *Q* quercetin, *K* kaempferol, *TTL* terpene trilactone, *USP* United States Pharmacopeia, *Pharm. Eur.* European Pharmacopoeia

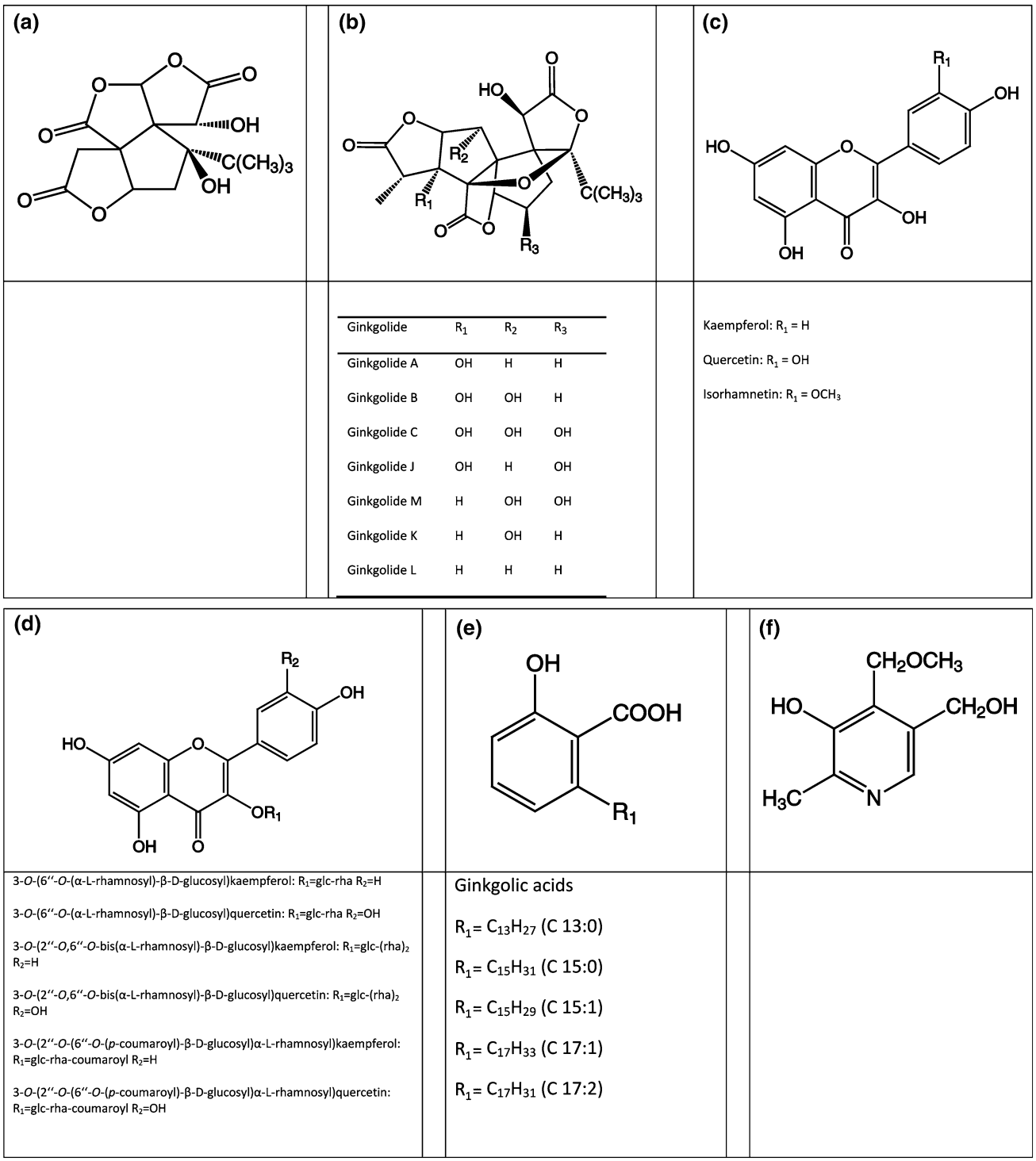

Fig. 1 Chemical structures of *Ginkgo biloba* terpene trilactones (**a** bilobalide, **b** ginkgolide), *Ginkgo biloba* flavonoids (**c**, **d**), ginkgolic acids (**e**), ginkgotoxin (**f**) [29, 30, 40, 160]

Furthermore the influence of EGb 761® on the gene expression [50] and metabolism of amyloid precursor protein (APP) in order to prevent Aβ fibrillogenesis is discussed [31, 51–54]. Pretreatment with GKA and GKB (ED_{50} values GKA, 40 nM; GKB, 10 nM) protects cortical neurons against $A\beta_{1-42}$-induced synapse damage [52]. But there are indications that early and possibly intraneuronal accumulation of Aβ, rather than its late extracellular deposits, is responsible for neuronal dysfunction and degeneration [55].

Treatment of rats and adrenocortical cells with GKB reduces the mRNA, protein and ligand-binding levels of the adrenal peripheral-type benzodiazepine receptor, a mitochondrial cholesterol binding protein, which leads to decreased corticosteroid synthesis [56]. EGb 761®, especially GKB, decreases stress-induced elevations of serum corticosterone without affecting physiological basal levels [57].

Bb is also involved in protection of mitochondria and in vitro shows a dose-dependent increase in the respiratory control ratio, owing to lower oxygen consumption during state 4. By protecting complex I and III activities, Bb allows mitochondria to maintain their respiratory activity under ischaemic conditions as some oxygen is present, thereby delaying the onset of ischaemia-induced damage. In addition, Bb has a protective effect on cellular ATP content [58, 59].

Furthermore, Tchantchou et al. [60] were able to demonstrate that EGb 761® enhances adult hippocampal neurogenesis and phosphorylation of CREB in a transgenic mouse model of AD as well as a stimulation of neurogenesis and synaptogenesis by Bb and quercetin via a common final pathway in hippocampal neurons [61].

Bb is also able to reduce triethyltin-induced cerebral edema as well as damage from cerebral ischaemia and decrease cortical infarct volume in certain stroke models [43, 62, 63]. The Klein group also investigated the effects of Bb in stroke models and cerebral edema. In an experimental model of hypoxia-induced phospholipid breakdown, it was found that Bb was the active constituent of the extract [64] acting in the submicromolar range (IC_{50} 0.38 μmol/L). Furthermore, Weichel et al. [65] described antagonistic effects of Bb on NMDA receptor-induced choline release from hippocampal slices (IC_{50} 2.3 μmol/L). Recently it was shown that Bb inhibits the release of glycine under ischaemic conditions, but not under basal conditions [7, 8, 66, 67]. The neuroprotective properties of Bb have been reviewed previously [68, 69].

Adverse effects of HMP as a result of herb–drug interactions have recently received a great deal of attention. The questions of whether GBE influences the bleeding characteristics in humans or interacts with antiplatelet agents such as ticlopidine have been discussed controversially in the past few years [70]. Theoretically, the PAF antagonism could be one possible pharmacodynamic mechanism. However, Koch has shown that the necessary concentrations of TTL would never be reached using the recommended dose of GBE [71]. Kloft et al. reviewed 18, out of 280, clinical trials related to this issue. However, as the data of the published clinical investigations are very inhomogeneous at present, a final recommendation is not possible [72].

The effect of *Ginkgo biloba* components on cytochrome P-450 (CYP) enzymes is still subject to highly controversial discussion today [73–76]. Umegaki et al. [76] and Shinozuka et al. [77] showed that GBE fed to rats significantly increased the concentration of hepatic CYP, the expression of various CYP RNA and the activity of some enzymes. Furthermore, Izzo and Ernst [73] reviewed numerous investigations evaluating the interaction of GBE components and CYP450. The clinical trials used alprazolam, midazolam, nifedipine (CYP3A4), caffeine (CYP1A2), chlorzoxazone (CYP2E1), debrisoquine (CYP2D6), tolbutamide, diclofenac, flurbiprofen (CYP2C9) and omeprazole (CYP2C19) as probe drugs in animals and humans [73]. The results are, however, not consistent; an effect on CYP enzymes by GBE and its compounds therefore seems unlikely. A clinical study observed that after 2 weeks of GBE exposure, the area under the concentration–time curve (AUC) and maximum plasma concentration (C_{max}) of midazolam, a known CYP3A4 substrate, were reduced by 34 and 31 %, respectively [78]. In contrast, Gurley et al. [79] reported that the midazolam metabolism in 12 volunteers did not change after 28 days of GBE application. Overall, current studies regarding GBE induction of CYPs contain contradictory results and are far from conclusive. Using published data, it is not possible to assess whether the interactions of GBE compounds and CYP-450 enzymes exhibit clinical relevance for humans. Chatterjee et al. [80] suggest that the effects of EGb 761® on drug-metabolising enzymes are specific for rats and may not be extrapolated to man. In conclusion, further investigations in humans are necessary.

3.2 Flavonoids

Flavonols are a large family of polyphenolic compounds occurring ubiquitously in the plant kingdom and are thus taken in by humans and animals with their regular diet. In this section, we focus on the numerous flavonol glycosides which have been identified as derivatives of the aglycones quercetin, kaempferol and isorhamnetin which are present in *Ginkgo biloba* [4, 22]. More than 30 genuine flavonoids are known in *Ginkgo biloba*. The diversity of different flavonoids does not result from the variability of the 2-phenylchromane framework but from the different glycosides found in *Ginkgo biloba*. The sugar moiety consists of glucose and/or rhamnose in various of mono-, di- or triglycosides with different binding patterns [29] (see Fig. 1d).

Some epidemiological data suggest a preventive effect on cardiovascular diseases by high intake of flavonoids [81, 82]. In addition, the flavonoid glycosides are also considered to be effective in the treatment of chronic venous insufficiency [22]. The positive protective effects are thought to be due to antioxidative and radical scavenger effects of the flavonoids.

It is undisputed that oxidative stress is one of the major risk factors in development and progression of AD. Post-mortem analyses showed increased lipid peroxidation, protein oxidation and nucleic acid oxidation in the CNS of AD patients [83]. In preclinical studies flavonoids appeared to be potent antioxidants and radical scavengers leading to a decrease of reactive oxygen species (ROS) tissue levels and inhibition of membrane lipid oxidation. Furthermore, flavonoids chelate pro-oxidant transitional metal ions and modify the expression of antioxidants. The flavonoid fraction of EGb 761® has higher radical scavenger potency than the TTL. In cellular systems, the flavone glycosides scavenge superoxide anions, hydroxyl radicals and peroxyl radicals, and prevent lipid peroxidation. Quercetin and myricetin in particular bring about a substantially reduced oxidation of *tert*-butylhydroperoxide [31, 43, 69, 84–86].

Beside the radical scavenger effect, some flavonoids appear to promote the loss of innate immune cell functions [87], a reduction of inflammatory cytokine production, especially TNF-α, IL-1β, prostaglandin E2 [88], and a decrease in NFκB signalling [89–91]. These anti-inflammatory effects, shown for different flavonoids, may also be part of the mode of action of Ginkgo flavonoids and reduce the progression of AD.

EGb 761® influences the neuroaminergic neurotransmission which could explain the positive effect on cognition in mice or human volunteers. Fehske et al. [37, 92] showed that the flavonoid fraction of EGb 761® leads to inhibition of the norepinephrine uptake and therefore to a cognition-enhancing and mood-elevating effect. Treatment with EGb 761® and its main constituent flavonoids during 14 days increased the dopamine concentration in the extracellular fluid of the prefrontal cortex of awake rats in a dose-dependent manner [93]. These results partly explain the increased learning performance of gerbils treated with EGb 761® recently published by Moeller et al. [94].

3.3 Ginkgolic Acids

Ginkgolic acids are a mixture of structurally related *n*-alkyl phenolic acid compounds of *Ginkgo biloba* (see Fig. 1e). They are strong allergens with the ability to cause severe allergic reactions. In addition to their allergic property, they possess possible cytotoxic, mutagenic, carcinogenic and genotoxic properties [95]. The amount of ginkgolic acids in GBE must be less than 5 ppm because of the described side effects [96–99].

3.4 Ginkgotoxins

Ginkgotoxins (see Fig. 1f) are held responsible for side effects such as epileptiform seizures, unconsciousness and paralysis of the legs [30]. Still it must be kept in mind that ginkgotoxins are predominantly found in the seeds of *Ginkgo biloba* and not in the leaves which are used for producing GBE. The published data indicate that no toxic effects are expected after an application of GBE in the recommended dose.

4 Pharmacokinetics

As mentioned above, numerous investigations are published about the in vitro and in vivo pharmacological effects and mechanisms of GBE and its components. The extensive knowledge about the pharmacokinetic characteristics including absorption, excretion and metabolism of the pharmacodynamic active compounds, the TTL and the flavonoids of *Ginkgo biloba*, allows an evaluation and discussion of the pharmacological mechanisms. In 1986, Moreau et al. studied the absorption of a radiolabelled ^{14}C extract prepared from *Ginkgo biloba* leaves in rats. The pharmacokinetics of radiolabelled EGb 761® was characteristic for a two-compartment model, with an apparent first-order phase and a half-life of about 4–5 h. Absorption was at least 60 % and specific activity in blood peaked after 1–5 h. At 3 h, the highest values for specific radioactivity were measured in the stomach and small intestine, indicating that this may be the site of absorption. Glandular and neuronal tissues and eyes showed a high affinity for the labelled substance. After oral administration, exhaled $^{14}CO_2$ accounted for about 38 % of the administered dose after 72 h. After 72 h, 22 % was excreted in urine and 29 % in feces [100, 101].

Over the past 15 years, the analytical methods have shown a substantial improvement in terms of their lower limit of detection (LOD) and limit of quantification (LOQ) of TTL and flavonoids in biological matrices. Different analytical methods [e.g. gas chromatography (GC)/mass spectrometry (MS), liquid chromatography (LC)/MS (electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI)) and LC/fluorescence detector (FD)] have been published for the determination of *Ginkgo biloba* constituents in the leaves, extracts, pharmaceutical formulations and biological matrices (e.g. plasma, brain). For GC analytics a derivatization step with for example BSTFA (*N*,*O*-bis(trimethylsily)trifluoroacetamide) prior to analysis is necessary, whereby silylated compounds are generated [102–111]. A detailed summary of analytical methods and characteristics of *Ginkgo biloba* constituents is published by van Beek and Montoro [4].

The enhanced analytical possibilities have allowed the investigation of the pharmacokinetic behaviour of TTL and flavonoids in plasma of animals and humans [102, 106, 109, 110, 112–118]; determination of the components and their metabolites leads to a characterization of absorption

and excretion parameters [119–121]. So far, the undisputed target tissue of EGb 761® has been the CNS. Recent studies investigated the CNS bioavailability and tissue levels of TTL [105, 109, 122] and flavonoids [110] in rats which lead for the first time to a pharmacokinetic characterization at the target tissue.

The following part of the review will go into details of pharmacokinetic characteristics of the pharmacological active compounds, TTL and flavonoids, of *Ginkgo biloba* after administration of GBE or the pure substances (in relation to TTL).

4.1 Terpene Trilactones

As explained above, some important pharmacological effects of GBE are caused by the TTL. The fact that native GKA, GKB and Bb are detectable in human and animal plasma (for details, see below) following oral application of GBE leads to the hypothesis that these compounds do not undergo metabolism. In contrast, Wang et al. [123] described that GKB is metabolised to its hydroxyl metabolite in rats and that CYP2D6 is the major rat CYP enzyme responsible for the GKB metabolism in rat liver microsomes. Furthermore, Mauri et al. [103] suggest that GKC undergoes a rapid methylation following oral application. The majority of investigations could not detect native GKC in plasma [103, 109, 112]. Only Xie et al. [104] described pharmacokinetic characteristics of native GKC in rat plasma. But these investigations applied the substance intravenously. All these facts taken together lead to the hypothesis that TTL do not undergo metabolism with the sole exception of GKC following oral application. This hypothesis was proved by Fourtillan et al. who reported that a large amount of the given dose is excreted unchanged in urine (72.3 % GKA, 41.4 % GKB and 31.2 % Bb after oral administration) [102, 112]. Little information about the metabolism of these GBE compounds is available today; more detailed studies will therefore be necessary. Furthermore, a discussion has arisen as to whether GKB exists in two forms in the body because of the local pH value and metabolism. Suehiro et al. [124] suggest that the physiological pH value suffices to open one of the three lactone rings leading to an ionized form of GKB. A Caco-2 cell model study showed that passive membrane diffusion dominates the absorptive transport behaviour of GKB and the pH of the intestine is the critical factor for the absorption of GKB. The transport was enhanced at weakly acidic pH on the apical side. Lv et al. pointed out that no concentration dependence and saturation were observed for the absorptive transport of GKB at concentrations up to 50 µmol/L. In the in situ closed loop, the absorption of GKB was intestinal segment-selective: the absorption of GKB in the upper intestine was significantly higher than that in the lower intestine because of the different pH gradients in the intestine [125].

It is undisputed today that TTL (native GKA, GKB and Bb) of GBE are available in plasma of humans and animals after oral application of GBE or pure substances. Table 2 shows a detailed overview of the studies dealing with pharmacokinetic characteristics of the TTL. In the past 15 years, numerous pharmacokinetic studies have been carried out, following the first pharmacokinetic investigation of Moreau et al. [100] in 1986 as discussed above. Preclinical investigations with rats showed that TTL reached maximum plasma concentrations (t_{max}) very rapidly. t_{max} values ranging from 0.5 to 4 h have been found for the TTL (see Figs. 2, 3) [106, 109, 126]. GKB probably tends to reach t_{max} a little later than GKA and Bb. In addition, the investigations with human volunteers approve the short t_{max} value. Fourtillan et al.'s t_{max} values of 1–3 h for GKA, GKB and Bb are in accordance with those in studies by Woelkart et al. [127] and Kressmann et al. [3]. Furthermore Woelkart et al. compare three different Ginkgo preparations in relation to their pharmacokinetic profile (see Fig. 2). The comparison of oral application in fasting volunteers and after breakfast shows a short delay in t_{max} for the latter group [102]. Furthermore, Mauri et al. investigated whether TTL complexed with soy phospholipids lead to a better pharmacokinetic characteristic. t_{max} was reached more rapidly (GKB, 4–2 h; Bb, 1–0.5 h) and C_{max} was much higher (Bb, 533–1,001 ng/mL; GKB, 352–625 ng/mL), but GKB only showed a higher AUC value for the application of the soy preparation [126]. As shown in Table 2, the half-life ($t_{½}$) values of the TTL range from 1 to 11 h; in the majority of humans, the $t_{½}$ values are longer than those in animals, and the $t_{½}$ values of GKB are longer than those of GKA and Bb. The short $t_{½}$ of the TTL is an indicator of the lack of accumulation of TTL in humans or animals. This hypothesis was confirmed by the results reported by Biber [112]. Oral application of GBE for 8 days does not change t_{max}, C_{max} and the AUC value when comparing days 1 and 8.

The C_{max} values are also included in Table 2. The data illustrate that GKA, GKB and Bb lead to adequate plasma concentrations in humans and animals. Dose linearity is indefinable in regard to the C_{max} values. GKB usually shows lower C_{max} values than GKA and Bb resulting from the proportion of GBE.

Interestingly Ude et al. [109] were able to show that GKA and Bb lead to higher C_{max} and AUC values after oral application of GBE (EGb 761®) in comparison to an application of the pure substance in the same dose range. Comparable phenomena for hyperoside were published by Butterweck et al. [128].

However, the main effects of the TTL take place in the CNS, as described in Sect. 3. It is thus important whether

Table 2 Pharmacokinetic data of *Ginkgo biloba* terpene trilactones in plasma

References	Species	Analysed compound	Application form	Dosage	t_{max} (h)	C_{max} (ng/mL)	AUC ng·h/mL	$t_{½}$ (h)	V_d (L)	CL (L/h)
Human studies										
Fourtillan et al. [102]	Human (plasma)	GKA	Lyophilised GBE, i.v.	100 mg (GKA, 1.16 mg; GKB, 0.9 mg; Bb, 3 mg)	0.24	73.04	146.75	3.75	36.9	8.02
		GKB			0.26	42.42	111.84	5.23	53.6	8.27
		Bb			0.23	57.08	97.46	3.19	150.0	36.26
		GKA	GBE solution (fasting)	3 mL (GKA, 1.44 mg; GKB, 1.03 mg; Bb, 3.36 mg)	1.06	33.29	146.04	4.50	NA	7.20
		GKB			1.17	16.46	109.9	10.57	NA	3.86
		Bb			1.17	18.81	78.97	3.21	NA	15.78
		GKA	GBE solution (after breakfast)		2.04	21.14	159.40	3.95	NA	5.64
		GKB			2.50	11.48	112.33	9.47	NA	4.00
		Bb			2.87	11.84	77.03	4.26	NA	8.54
Mauri et al. [158]	Human (plasma)	Bb	p.o.	160 mg Ginkgoselect® (free formulation)/160 mg Ginkgoselect® Phytosome®	2/3	37.6/60.3	6,927.0/ 13,961.7	138.5 min/ 190.1 min	NA	NA
		GKA			2/4	41.8/108.1	8,434.1/ 28,361.1	158.1/113.1	NA	NA
		GKB			2/3	5.6/13.4	1,030.7/ 2,530.9	140.9/101.6	NA	NA
Drago et al. [145]	Human (plasma)	GKB	p.o.	80 mg/kg GBE once daily	2.25	12.62	187.85	11.64	NA	NA
				40 mg/kg twice daily	2.25	22.18	135.99	4.31	NA	NA
Kressmann et al. [3]	Human (plasma)	GKA	p.o.: capsules (Centrum Herbals)	120 mg (single dose)	2.21	9.43	83.92	4.99	NA	NA
			p.o.: tablets (EGb 761®)		1.17	22.22	121.35	3.93	NA	NA
		GKB	p.o.: capsules (Centrum Herbals)		2.21	1.31	18.90	9.91	NA	NA
			p.o.: tablets (EGb 761®)		1.54	8.27	59.88	6.04	NA	NA
		Bb	p.o.: capsules (Centrum Herbals)		2.08	33.11	191.56	3.52	NA	NA
			p.o.: tablets (EGb 761®)		1.21	54.42	217.24	3.19	NA	NA
Biber [112]	Human (plasma)	GKA	EGb 761® p.o. (single dose)	80/120/240 mg EGb 761® (GKA, 1.056/1.584/ 3.168 mg; GKB, 0.560/ 0.840/1.680 mg/ Bb, 2.280/ 3.420/6.840 mg)	0.61/0.60/0.75	15.2/25.3/ 42.9	69.9/103.2/ 211.1	4.5/4.5/5.1	NA	NA
		GKB			1.29/0.92/1.21	6.53/9.12/ 18.11	43.75/70.03/ 140.69	6.5/8.5/9.9	NA	NA
		Bb			0.86/0.67/0.72	30.2/35.2/ 58.6	114.7/128.1/ 247.1	5.5/4.0/4.9	NA	NA
		GKA	EGb 761® p.o. (after single and multiple dose)	Day 1/8	0.71/0.75	20.77/21.58	113.3[a]/113.1[b]	6.09/9.06	NA	7.1/NA
		GKB			1.04/1.29	8.54/10.73	70.81[a]/73.74[b]	9.78/12.53	NA	8.4/NA
		Bb			0.71/0.92	21.85/25.85	91.15[a]/105.0[b]	4.00/4.12	NA	20.1/NA
Ding et al. [121]	Human (urine)	Bb	p.o.	Tablet with GBE containing 7.2 mg terpene lactones	Sampling only after 4 h	1,556	NA	NA	NA	NA
		GKA				1,659	NA	NA	NA	NA
		GKB				652	NA	NA	NA	NA
		GKC				97	NA	NA	NA	NA

Table 2 continued

References	Species	Analysed compound	Application form	Dosage	t_{max} (h)	C_{max} (ng/mL)	AUC ng·h/mL	$t_{½}$ (h)	V_d (L)	CL (L/h)
Woelkart et al. [127]	Human (plasma)	GKA	p.o.	Geriaforce™	0.92	3.81	7.30	2.31	NA	NA
				Ginkgo biloba fresh plant extract tablets	0.80	7.27	16.57	2.66	NA	NA
				EGb 761®	0.93	16.97	42.25	3.60	NA	NA
		GKB		Geriaforce™	0.88	1.45	2.99	2.34	NA	NA
				Ginkgo biloba fresh plant extract tablets	2.35	4.61	15.45	4.01	NA	NA
				EGb 761®	2.00	10.90	37.54	3.94	NA	NA
		Bb		Geriaforce™	1.09	6.17	16.56	2.33	NA	NA
				Ginkgo biloba fresh plant extract tablets	0.88	11.16	29.38	2.52	NA	NA
				EGb 761®	1.06	29.87	76.38	2.08	NA	NA
Animal studies										
Biber and Koch [106]	Rat (plasma)	Bb	p.o.	30/55/100 mg/kg EGb 761®	1/0.5/0.5	159/275/398	496.9/887.0/1,998.1	2.2/1.7/3.0	NA	29.2/30.0/24.2
		GKA			0.5/0.5/0.5	68/147/301	220.7/389.6/778.8	1.7/2.0/1.8	NA	30.1/31.3/28.5
		GKB			1/1/1	40/69/103	143.2/254.1/368.3	2.0/2.5/2.0	NA	29.0/30.0/37.6
Mauri et al. [126]	Rat (plasma)	Bb	p.o. acute administration	Pure substances free/complexes with soy phospholipids	1/0.5	533/1,001	87,101/87,502	NA	NA	NA
		GKB			4/2	352/625	86,880/153,855	NA	NA	NA
Hua et al. [159]	Dog (plasma)	GKB	Intragastric administration	0.1 mg/kg	0.5	43.8	NA	2.85	NA	NA
Chen et al. [130]	Rat (plasma)	GKB	i.v. (single dose)	4 mg/kg	NA	NA	59.7[c] (μg·min/mL)	2.9	2.27 (L/kg)	0.07 (L/min/kg)
				12 mg/kg	NA	NA	170.5[c] (μg·min/mL)	6.1	3.27 (L/kg)	0.07 (L/min/kg)
				36 mg/kg	NA	NA	676.5[c] (μg·min/mL)	4.9	2.76 (L/kg)	0.05 (L/min/kg)
			i.v. (multiple dose)	12 mg/kg	NA	NA	155.49[c] (μg·min/mL)	3.42	2.14 (L/kg)	0.07 (L/min/kg)
Xie et al. [104]	Rat (plasma)	Bb	i.v. (tail vein)	8 mg/kg in saline (content of GKA was 303.2 μg, GKB 168.8 μg, GKC 100.3 and Bb 98.0 μg per dose)	NA	NA	39.06[c] (μg·h/L)	1.13	478.0 (L/kg)	301.1 (L/h/kg)
		GKA			NA	NA	258.6[c] (μg·h/L)	0.97	49.33 (L/kg)	36.82 (L/h/kg)
		GKB			NA	NA	157.6[c] (μg·h/L)	1.02	163.9 (L/kg)	112.1 (L/h/kg)
		GKC			NA	NA	115.3[c] (μg·h/L)	0.67	130.4 (L/kg)	136.8 (L/h/kg)

Table 2 continued

References	Species	Analysed compound	Application form	Dosage	t_{max} (h)	C_{max} (ng/mL)	AUC ng·h/mL	$t_{½}$ (h)	V_d (L)	CL (L/h)
Zhao et al. [142]	Dog (plasma)	Bb	p.o./i.v.	Gineton	Only a graphic summary without a table of data					
		GKA								
		GKB								
		GKC								
		GKJ								
Madgula et al. [131]	Rat (plasma)	Bb	Intra tail vein	8 mg/kg Bb	1 h	69.1 µg/mL	NA	NA	NA	NA
Ude et al. [109]	Rat (plasma)	Bb	p.o.	600 mg/kg EGb 761® (and pure substance same range)	0.5 (0.5)	2,860.2 (2,461.4)	18,513.7 (9,683.2)	NA	NA	NA
		GKA			0.5 (0.5)	1,006.5 (699.5)	6,300.0 (2,868.2)	NA	NA	NA
		GKB			2 (2)	388.3 (355.7)	4,001.0 (3,650.6)	NA	NA	NA
		GKC			Not detectable					

GBE Ginkgo biloba extract, *GKA* ginkgolide A, *GKB* ginkgolide B, *GKC* ginkgolide C, *NA* not available

[a] $AUC_{(\omega)}$

[b] $AUC_{(12)}$

[c] $AUC_{(\infty)}$

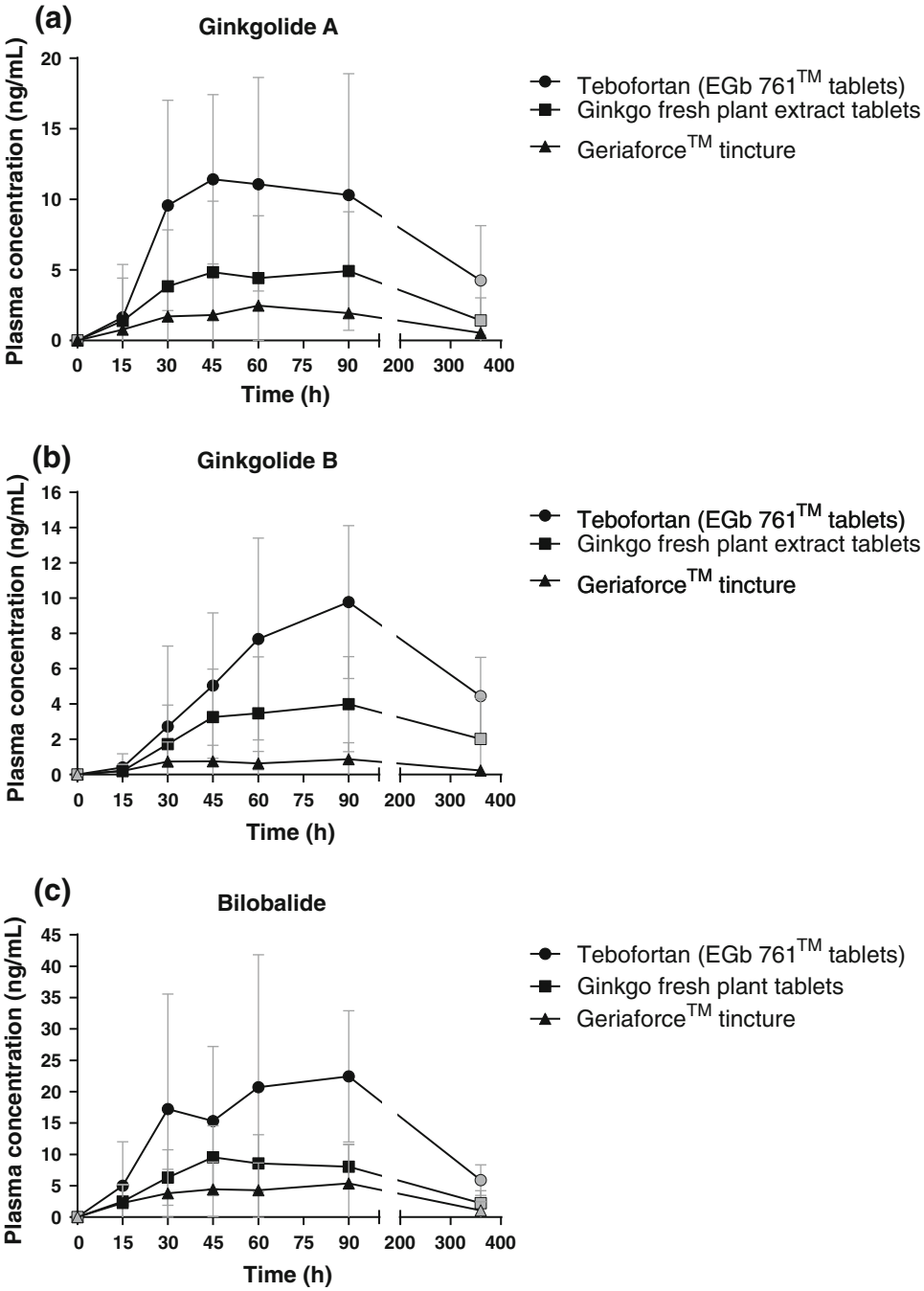

Fig. 2 Plasma concentration–time curve of ginkgolide A (**a**), ginkgolide B (**b**) and bilobalide (**c**) after administration of three different Ginkgo preparations in humans. *Error bars* represent the standard deviation [127]

these substances are able to cross the blood–brain barrier. Knowledge about the availability of GKA, GKB and Bb in target tissue of the CNS is of fundamental importance.

A recent study characterized GKA, GKB and Bb in the CNS of rats and presented a complete pharmacokinetic profile of TTL in the brain. After oral application of 600 mg/kg GBE (EGb 761®) to rats, GKA, GKB and Bb could be detected in sufficient concentrations to exert a pharmacological effect (for C_{max} values, see Table 3) in the brain tissue [109]. A fast and sensitive LC–MS method enables the authors to demonstrate that GKA, GKB and Bb reach the CNS rapidly with a t_{max} range of 1–2 h (see Fig. 4). After 24 h no TTL could be detected. In agreement with the known plasma data, native GKC was not available in the brain. Further investigation using a combination of microdialysis and LC–MS analytic methods established that Bb was present in defined regions of mouse brain [122]. First, the results of this study confirm the pharmacokinetic characteristics of Bb of the first study by Ude et al. (described above). Second, the investigation shows that Bb exists extracellularly in an unbound state and does not bind in membrane; and third, the experimental setup

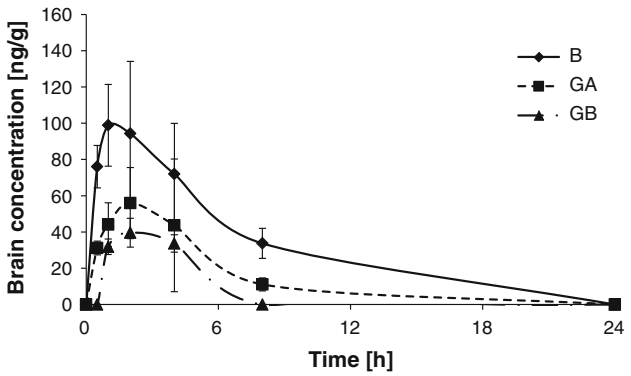

Fig. 3 Plasma concentration–time curves of ginkgolide A (GA), ginkgolide b (GB) and bilobalide (B) after per oral application of 600 mg/kg EGb 761® in rat (*error bars* represent standard deviation; all values obtained from a rat model) [109]

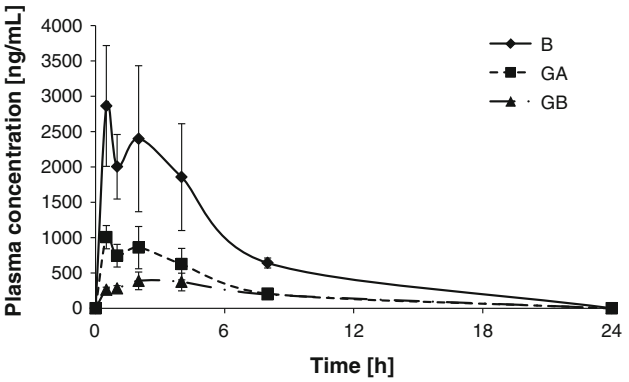

Fig. 4 Brain concentration–time curves of ginkgolide A (GA), ginkgolide b (GB) and bilobalide (B) after per oral application of 600 mg/kg EGb 761® in rat (*error bars* represent standard deviation; all values obtained from a rat model) [109]. Brain concentration of the respective compound relates to per gram of brain homogenate (for details, see [109, 111])

used allowed the characterization of the pharmacokinetics of Bb in relation to ischaemic events and stroke. If Bb was applied to the mice 1 h before stroke, the Bb level in the affected brain region did not decrease to the same extent as would have been the case without an ischaemic event, but the Bb concentration does not fall below the detection limit [122, 129].

In addition, a further study with brain data of Bb was published by Rossi et al. [105]. Although this study was well designed, it has some limitations in regard to daily practice, owing to use of the phospholipidic complex of the EGb 761®, which is not comparable to the capsule for daily use, and also the authors determined only the Bb concentration in plasma and the brain. The investigation finds a C_{max} of 3 µg at 0.5 h after application of the phospholipid complex; furthermore no Bb was found before and after C_{max}. The studies by Chen et al. [130] and Madgula et al. [131] provided isolated information about CNS availability. Chen et al. [130] reported GKB levels in different rat tissues in a table and for brain showed the value "148.9" but without a unit. Madgula et al. [131] applied 8 mg/kg Bb into rat tail veins and determined a C_{max} of 23.1 µg/mL after 2 h (t_{max}). Furthermore, an investigation into the in vivo biodistribution of GKB showed that (a) GKB crosses the blood–brain barrier because radioactivity was detectable in brain regions by microPET and (b) the brain distribution shows regional heterogeneity with the highest concentration in the olfactory bulbs and the hypothalamus [124].

Taken together, the studies of the past decade showed clearly that TTL from GBE are not metabolised, with the exception of GKC, and were absorbed in the systemic circulation after oral administration. Moreover, GKA, GKB and Bb are able to cross the blood–brain barrier and

Table 3 Pharmacokinetic data of *Ginkgo biloba* terpene trilactones in central nervous system and brain

References	Species	Analysed compound	Application form	Dose	t_{max} (h)	C_{max}
Chen et al. [130]	Rat	GB	i.v.	12 mg/kg	1	148.9[a]
Rossi et al. [105]	Rat	Bb	p.o.	20 mg/kg Bb as phospholipid complex	0.5	3 µg/g
Madgula et al. [131]	Rat	Bb	Intra tail vein	8 mg/kg Bb	2	23.1 µg/mL
Ude et al. [109]	Rat	Bb	p.o.	600 mg/kg EGb 761® (and pure substance same range)	1 (1)	98.2 ng/g (96.4 ng/g)
		GA			2 (4)	56.0 ng/g (54.7 ng/g)
		GB			2 (4)	39.6 ng/g (39.9 ng/g)
		GC			Not detectable	
Lang et al. [129]	Mice	Bb	i.p.	10 mg/kg	0.67	19 ng/mL

GBE Ginkgo biloba extract, *GA* ginkgolide A, *GB* ginkgolide B, *GC* ginkgolide C

[a] Without unit in original literature

significant concentrations are measurable in the CNS of rodents, although some of these investigations were performed with rather high doses of GBE.

4.2 Flavonoids

Flavonoids are polyphenolic compounds which are probably found in all green plants [29]. Aglycones like quercetin are rarely found in plants and extracts. In most cases, one or more sugar moieties are attached to the aglycone. These sugar moieties play an important role in determining the absorption characteristics. The absorption of flavonoids was significantly lower after oral intake of aglycones (e.g. quercetin) and monoglycosides (e.g. quercetin-3′-*O*-β-D-galactoside) compared to that after the intake of various monoglucosides (e.g. quercetin-3-glucoside). The bioavailability after ingestion of diglycosides (e.g. rutin) was about half of that after intake of monoglucosides [22, 115, 132, 133]. The absorption of aglycones is very limited, even though it seems that the absorption of kaempferol in man is more effective than that of quercetin at low doses [115]. Interindividual variations in absorption and excretion are low [134]. Furthermore, t_{max} of rutin was also significantly delayed (0.7 h for the monoglucosides versus 7 h for rutin), indicating an absorption in the terminal ileum after microbial degradation [114]. In contrast, the uptake of quercetin monoglucosides within 1 h suggests resorption in the upper small intestine. Therefore, two hypotheses have been proposed for this phenomenon: (i) carrier-mediated uptake of quercetin glucosides by the intestinal sodium-dependent glucose transporter SGLT1 [135]; and (ii) deglucosylation by the enzyme phloridzin hydrolase in the brush border membrane and penetration of the lipophilic aglycone through the enterocyte membrane by passive diffusion [22, 114].

Furthermore, flavonoids undergo extensive metabolism, so neither genuine flavonoid glucosides nor their corresponding aglycones can be detected in plasma; for example intact rutin and free quercetin are not present in human plasma. The investigation by Graefe et al. pointed out that instead of native rutin and the quercetin aglycone, four to five quercetin glucuronides were present in human plasma. Furthermore, only one phase I metabolite with an intact flavonoid moiety, isorhamnetin (3′-*O*-methylquercetin), was present in conjugated form in human plasma. The total concentrations of isorhamnetin conjugates were about one-tenth of total quercetin concentrations [136]. Day et al. identified seven different quercetin and 3′-methylquercetin conjugates in human plasma, after consumption of fried onions containing quercetin-3,4′-glucoside, quercetin-3-glucoside, quercetin-4′-glucoside and 3′-methylquercetin-4′-glucoside. Major circulating compounds were quercetin-3-glucuronide, 3′-methylquercetin-3-glucuronide and quercetin-3′-sulfate. A detailed observation showed that approximately 33 % of the absorbed quercetin was present as sulfate conjugates and one-fifth was methylated [137]. The characterization of the flavonoid metabolites in human and animal urine confirms the hypotheses of metabolism: A small “proof of concept study” with five volunteers determined the flavonoid metabolites in urine 4 h after oral application of GBE capsules [121]. In this study, flavonoid aglycone urine levels were lower than the limit of quantitation. But after treating the samples with β-glucuronidase, they could be readily identified and quantitated; however, only a small amount of the ingested flavonoids was present in the urine, which is in agreement with a previous report by Watson and Oliveira [138]. These results also confirm the hypotheses that after absorption through the intestinal wall the flavonoid aglycones are excreted in the urine not only as glucuronides (as suggested by Watson and Oliveira [138]) and sulfate conjugates, but also in hydro-, dihydro- or methylated form, which may account for the reduced excretion values [121]. A detailed description of the metabolism of the flavonoids is shown in Fig. 5.

In addition, Pietta et al. [139] investigated the flavonoid metabolites in rat urine samples after oral administration of an undefined GBE. No glycosides or aglycones could be detected in the urine but different degradation products such as benzoic, phenylacetic or 3-(phenyl)propionic acid were present. Obviously, a large proportion of the ingested flavonoids pass into the intestine without degradation and undergo colonic biotransformation by enzymes of the colonic microflora [140]. Similar observations were made for the administration of a GBE to healthy volunteers, but the metabolites of flavonoids in urine differed slightly from that detected in urine of rats. Only substituted benzoic acids [i.e. 4-hydroxybenzoic acid conjugate, 4-hydroxyhippuric acid, 3-methoxy-4-hydroxyhippuric acid, 3,4-dihydroxybenzoic acid, 4-hydroxybenzoic acid, hippuric acid and 3-methoxy-4-hydroxybenzoic acid (vanillic acid)], but no phenylacetic acid or phenylpropionic acid derivatives were found in human urine [141]. Pietta et al. conclude that in humans a more extensive metabolism takes place, but such differences might also be caused by the individual composition of the microflora The investigations by Pietta et al. should be viewed critically as to whether, in 1995, the analytical method (LC-DAD) may have lacked the ability to detect low concentrations of flavonoids.

Consequently, and in light of the metabolism of the flavonoids described above, it is obvious that not the genuine flavonoid glycosides nor their corresponding aglycones, but their metabolites are responsible for the pharmacological effects in each organism.

As mentioned above, the improvement of analytical techniques over the past 15 years has permitted

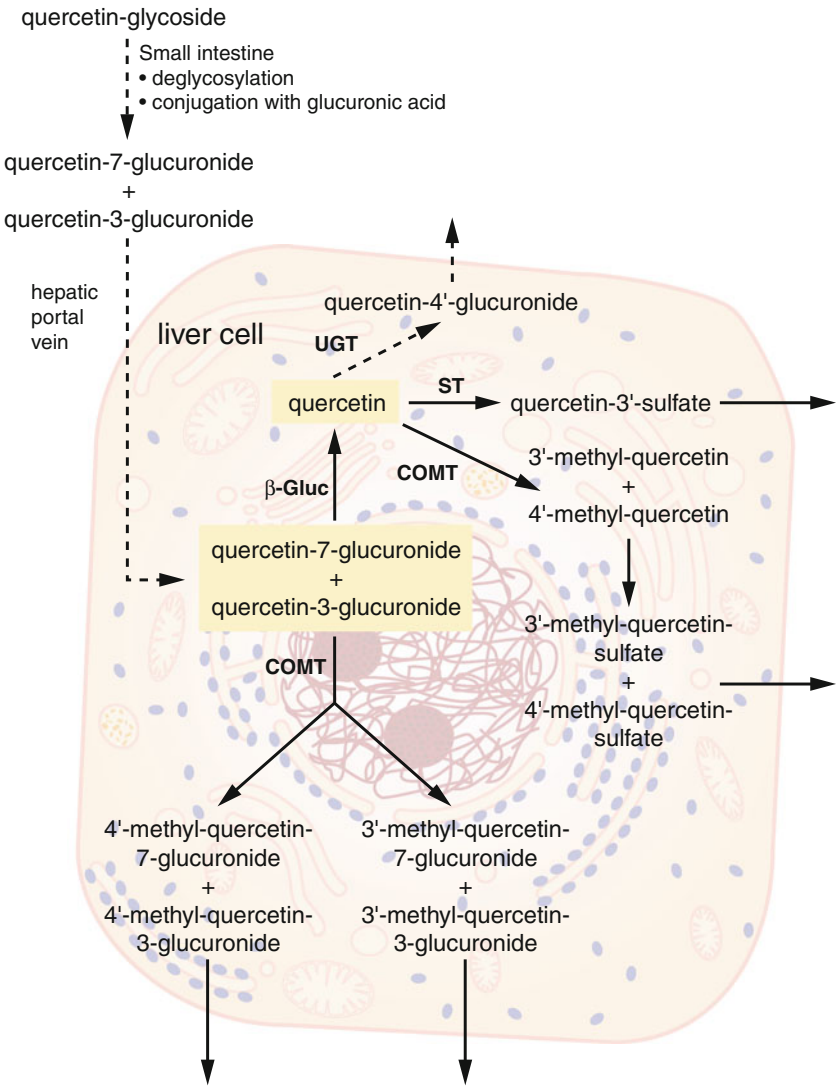

Fig. 5 Flavonoids metabolism in mammalian liver. *UGT* uridine diphosphate glucuronosyltransferase, *ST* sulfotransferase, *COMT* catechol-*O*-methyltransferase, *β-Gluc* β-glucoronidase [161–163]

investigations of the flavonoid aglycones in biomatrices such as urine, plasma and brain in more detail. In the past, many investigations dealt with the pharmacokinetic behaviour of flavonoids after application of several products, e.g. onions, St. John's wort, broccoli, and green tea; for a review, see Wurglics and Schubert-Zsilavecz [22]. The present review aims to discuss studies that investigated the plasma and brain levels of flavonoids after the application of GBE in humans and animals. Real pharmacokinetic studies of *Ginkgo biloba* flavonoids are rare. Several studies show kinetic data, but they give only a description of an analytical method or assay without any pharmacokinetic usable content [119, 121, 138, 142].

We identified four publications which appropriately describe the pharmacokinetics of *Ginkgo biloba* flavonoids (see Table 4). Zhao et al. presented pharmacokinetic profiles for all three investigated flavonoids (quercetin, kaempferol, isorhamnetin) after application of TianBaoNing® capsules in beagles. The three compounds were detectable in plasma up to 36 h post-dosing and exhibited two maximum concentrations (for detailed pharmacokinetic parameters, see Table 4) [5]. Furthermore in a second plasma pharmacokinetic study with beagles, Zhao et al. compared oral with intravenous application of GBE Gineton®. Regrettably the authors did not specify the GBE Gineton® and they described the pharmacokinetic study only in a very sketchy manner [142].

Furthermore, an early pilot study with two healthy volunteers published by Nieder investigated the plasma pharmacokinetics of *Ginkgo biloba* flavonoids after oral application of 50, 100 and 300 mg GBE Li1370® [143]. These results by Nieder lead to the conclusion that the flavonoids have a t_{max} of 2–2.5 h and an elimination half-life of 2–4 h; flavonoids were not detectable in human plasma after 24 h and a linear relationship between GBE doses and plasma concentrations was shown at low doses. This study has only very limited informative value, because of the low number of volunteers and the inadequate

Table 4 Pharmacokinetic data of *Ginkgo biloba* flavonoids in plasma

References	Species	Analysed compound	Application form	Dosage	t_{max} (h)	C_{max} (ng/mL)	AUC (ng·h/mL)	$t_{½}$ (h)	V_d (L)	CL (L/h)
Human studies										
Nieder [143]	Human (plasma)	Flavonols	p.o. (tablets)	50 mg, 100, 300 mg LI 1370® (tablets)	2–3	ca. 150/50/25	NA	2–4	NA	NA
Wójcicki et al. [144]	Human (plasma)	Quercetin	p.o. (single oral)	1	2.47	12.16	63.71	2.98	170.01	39.07
				2	2.00	13.79	64.66	NA	NA	NA
				3	2.00	13.45	60.15	NA	NA	NA
		Kaempferol		1	2.44	26.73	138.43	2.89	190.92	45.86
				2	2.03	30.02	138.08	NA	NA	NA
				3	2.03	28.94	130.37	NA	NA	NA
		Isorhamnetin		1	2.44	7.26	34.63	2.84	208.13	52.83
				2	2.03	9.62	39.99	NA	NA	NA
				3	2.03	7.81	31.55	NA	NA	NA
		In addition to Wójcicki et al.: Three different formulations (capsules (1), drops (2) from Agon Pharma; tablets (3) from Schwabe)								
Ding et al. [121]	Human (urine)	Quercetin	p.o.	Tablet with GBE containing 28.8 mg flavonoids	Sampling only after 4 h	35.8	NA	NA	NA	NA
		Kaempferol				53.6	NA	NA	NA	NA
		Isorhamnetin				23.5	NA	NA	NA	NA
Animal studies										
Zhao et al. [5]	Dog (plasma)	Quercetin	p.o. (capsules)	Single dose of three capsules (3× 9.6 mg flavonol glycosides and 2.4 mg terpenes)	1/11[a]	17.4/17.6[a]	304	NA	NA	NA
		Kaempferol			1/11[a]	9.37/6.83[a]	147	NA	NA	NA
		Isorhamnetin			1/11[a]	2.82/5.01[a]	62.2	NA	NA	NA
Zhao et al. [142]	Dog (plasma)	Quercetin	p.o./i.v.	Gineton	Only a graphic summary without a table of data					
		Kaempferol								
		Isorhamnetin								
Rangel-Ordóñez et al. [110]	Rat (plasma)	Quercetin	p.o. (extract-suspension)	Single dose of 600 mg/kg EGb 761®	8	176	11.285[b] 43.532[c]	NC[d]	0.058	0.0037 (mL/min)
		Kaempferol			8	341	19.947[b] 46.673[c]	NC[d]	0.015	0.0023 (mL/min)
		Isorhamnetin			8	183	5.734[b] 6.198[c]	19	0.008	0.0147 (mL/min)
		Quercetin	p.o. (extract-suspension)	Eight daily doses of 600 mg/kg EGb 761®	8	789	29.170[e] 32.668[f]	22	0.084	0.0436 (mL/min)
		Kaempferol			8	3.878	108.478[e] 116.354[f]	18	0.013	0.0082 (mL/min)
		Isorhamnetin			8	1.868	60.141[e] 70.402[f]	24	0.008	0.0036 (mL/min)

NA not available, *GBE Ginkgo biloba* extract, *NC* not calculated

[a] The ginkgo flavonols exhibit two peak concentrations (C_{max}) after a single dose

[b] $AUC_{(0–72)}$

[c] $AUC_{(0–\infty)}$

[d] $t_{½}$ could not be calculated because of a too high concentration after 71 h

[e] $AUC_{(0–72)}$

[f] $AUC_{(0–\infty)}$

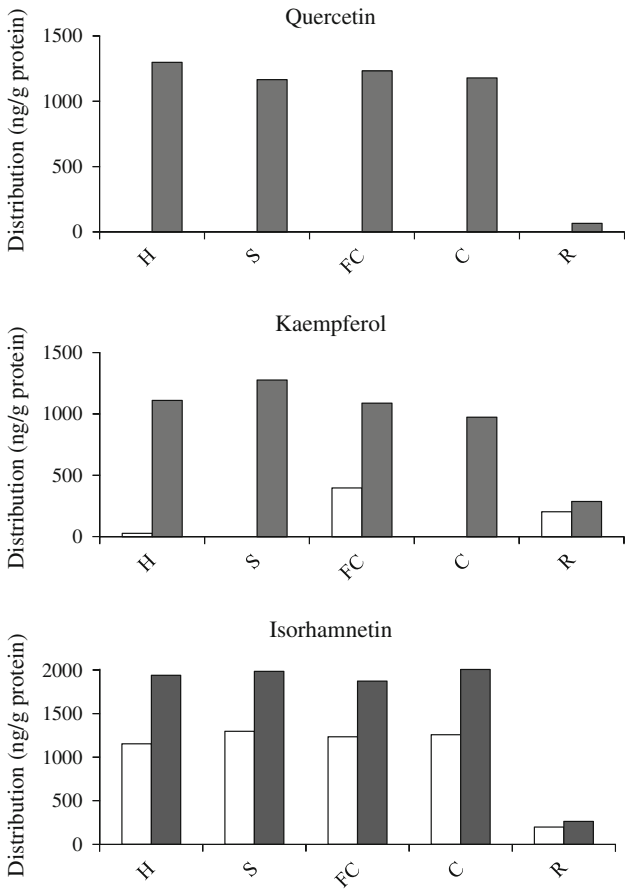

Fig. 6 Distribution of *Ginkgo biloba* flavonoid aglycones in the hippocampus (*H*), striatum (*S*), frontal cortex (*FC*), cerebellum (*C*) and rest (*R*) of the rat brain after eight daily doses of 600 and 100 mg/kg of EGb 761® [110]

analytical technique used. The analysis by Wójcicki et al. compared three different GBE formulations (drops, capsules and tablets) in relation to the oral bioavailability of *Ginkgo biloba* flavonoid glycosides. This study describes a one-compartment model with zero-order absorption without lag-time and a t_{max} of approximately 2 h for each of the flavonoids. The zero value was reached 24 h after the intake of a single dose of GBE. The authors suggested that the volume of distribution showed a moderately extensive penetration into the tissue. An elimination half-life of short duration (about 3 h) and total body clearance (ca. 39–53 L/h) pointed to a rapid elimination of theses flavonoids from the blood. Furthermore, the study concludes that the three different formulations of GBE used are bioequivalent. The conclusion is based on the demonstrated and comparable pharmacokinetic characteristics after oral intake [144].

Rangel-Ordóñez et al. [110] showed in a recent rat study that flavonoids are bioavailable in plasma as well as in the brain after oral application of EGb 761®. The study in our laboratory included one investigation with a single oral administration of 600 mg/kg EGb 761® and repeated application of 100 and 600 mg/kg EGb 761® to rats for 8 days. A single dose of 600 mg/kg EGb 761® resulted in maximum plasma concentrations of 176, 341 and 183 ng/mL for quercetin, kaempferol, and isorhamnetin/tamarixetin, respectively. In comparison, the repeated administration of the same dose for 8 days led to an approximate 4.5-fold increase in the plasma concentration for quercetin, an 11.5-fold increase for kaempferol and a 10-fold increase for isorhamnetin/tamarixetin. The maximum concentration of 341 ng/mL after the single dose application was achieved after 8 h and remained constant for several hours before it slowly decreased after 24 h. The plasma level of quercetin metabolites increased rapidly and reached the maximum concentration of 176 ng/mL within 2 h after administration. The plasma concentration of quercetin decreased very slowly within the first 72 h; at the end of that period, 78 % of the maximum concentration could still be detected. The concentration level of isorhamnetin/tamarixetin increased within the first 8 h to approximately 183 ng/mL and then decreased continuously. After 72 h, 9.5 % of the maximum concentration was still detectable in plasma [110].

Moreover, the target tissue of GBE components is the CNS. Rangel-Ordóñez et al. showed for the first time that flavonoids reach the CNS and cross the blood–brain barrier after oral application of GBE, but only kaempferol and isorhamnetin/tamarixetin were detected in brain samples. A single dose of 600 mg/kg EGb 761® resulted in maximum brain concentrations of 291 ng/g protein for kaempferol and 161 ng/g protein for isorhamnetin/tamarixetin. A repeated administration of the same dose for 8 days led to an approximate twofold increase for the two components. Maximum brain concentrations, corresponding to approximately 293 and 161 ng/g of protein in the brain for kaempferol and isorhamnetin/tamarixetin, respectively, were measured 8 h after application. Even though the C_{max} of isorhamnetin/tamarixetin was lower than that of kaempferol, the former could be detected in the brain for longer [110].

In order to provide more details of brain tissue levels of the flavonoids of GBE, the distribution of the three analytes in rat brain was investigated after repeated dosing (8 days) of 100 or 600 mg/kg EGb 761®. Interestingly, besides kaempferol and isorhamnetin/tamarixetin, quercetin could also be determined when administering EGb 761® at a high dose (600 mg/kg). All three aglycones tended to be distributed in the brain with certain preference for the hippocampus, striatum, cerebellum and frontal cortex. Other brain areas contained only very small amounts of the aglycones. Kaempferol and isorhamnetin/tamarixetin could be quantified even after the administration of the lower dose (100 mg/kg). At this dose, kaempferol accumulated with a marked preference for the frontal cortex (about

65 %), whereas isorhamnetin/tamarixetin were found in hippocampus, striatum, frontal cortex and cerebellum in comparable concentrations. Figure 6 shows the distribution of *Ginkgo* flavonoid aglycones in the hippocampus, striatum, frontal cortex, cerebellum and rest of the rat brain after eight daily doses of 600 and 100 mg/kg of EGb 761® [110].

So far, only limited data on the bioavailability of GBE flavonoids in humans are available, but taken together with animal data it is obvious, that metabolites of the GBE flavonoids reach the circulation in significant concentrations. Furthermore, some metabolites may be able to cross the blood–brain barrier and reach the CNS.

5 Conclusion

Ginkgo biloba is among the most extensively used medicinal plants and its extracts are among the best explored HMP. However, numerous extracts with different compositions of *Ginkgo biloba* are available and used for clinical investigations and daily use. Only GBE which meet the demands of the USP 32 or the European Pharmacopoeia 6.1 are state-of-the-art today and should therefore be recommended in daily practice and used in all clinical investigations; EGb 761® is the best explored GBE.

As discussed in this review, the pharmacokinetic characteristics of TTL and flavonoids are known even if the number of pharmacokinetic investigations of *Ginkgo biloba* TTL and flavonoids is small.

These studies demonstrated that GKA, GKB and Bb as well as flavonoids reach the CNS and brain, the target tissue, after oral application of EGb 761® in adequate concentrations. The TTL are characterized by short $t_{½}$ which leads to zero levels 24 h after application in plasma as well as in the brain. The fact that the $t_{½}$ of TTL is relatively short also underlines the recommendation of an intake of GBE twice daily. The flavonoids show relatively long $t_{½}$. In humans $t_{½}$ of flavonoids is about 10–17 h, which also supports a twice-daily dosing [112, 145]. In the case of a high dose regime, an accumulation in rat plasma and brain could be observed. This effect may be caused by application of a high dose of GBE.

Knowledge of the pharmacokinetic characteristics of the active compounds is required for the interpretation of in vitro and in vivo pharmacological investigations.

A direct comparison of the concentrations used in the in vitro pharmacological studies and the determined maximal plasma and brain concentrations of the terpenoids after oral administration shows that the in vivo brain concentrations are not as high as the concentrations used for in vitro experiments but they are approximately in the same range. Additionally, it must be kept in mind that the concentrations of TTL in brain tissue determined by Ude et al. [109] represent the whole brain. Higher levels of terpenoids may be reached in certain brain areas as the distribution of radiolabelled GKB in the brain demonstrated by Suehiro et al. [124] and the distinct distribution of flavonoids in different brain areas, such as hippocampus, frontal cortex, cerebellum and striatum, after oral administration shown by Rangel-Ordóñez et al. [110] indicated but this needs to be further evaluated in future investigations. In conclusion, the data support the hypothesis of mitochondrial protection due to the aforementioned mechanisms, and the other pharmacological hypothesis discussed.

The notion of a link between GBE and CYP interactions and changes of bleeding time in humans has already been discussed. In both cases the published data and clinical trials are very inhomogeneous and inconsistent [72, 73]. After reviewing the published literature, we are not able to conclude that there is a special risk from taking GBE together with other drugs.

Summarizing the different aspects of GBE, we point out that GBE are well explored HMP. The pharmacodynamic characteristics are examined at length in a large number of studies. In addition, several pharmacokinetic studies have shown that the pharmacological active compounds of GBE are available in human and animal plasma after oral and i.v. application. Recent investigations characterize TTL and flavonoids of *Ginkgo biloba* in the CNS and moreover were able to demonstrate that these GBE ingredients cross the blood–brain barrier in adequate concentration. Although, *Gingko biloba* is one of the best investigated medicinal plants, there are still many open questions about the mode of action, the role of different ingredients and even the efficacy of GBE in the therapy of AD.

As described in Sect. 3.1, many in vitro and in vivo studies with terpene trilactones allow one to draw the conclusion that TTL play a major role in the antidementia effect of GBE, but until now a clear correlation of the clinical effect of the TTL and their concentration in the CNS tissue is still missing. Preliminary results by Ude et al. [109] show that TTL are able to cross the blood–brain barrier and significant concentrations of TTL are measurable in the brain. But the dosage used in this animal study was much higher than the recommended daily dose in humans. On the other hand, Ude et al. investigated only whole brain tissue homogenates, and did not differentiate among various brain regions. Interestingly, Rangel-Ordóñez et al. [110] found significant variations, when examining different brain regions according to the flavonoid concentration. In order to establish a correlation of brain tissue concentrations of TTL in various regions and the concentrations of these substances used in in vitro tests further studies are necessary.

Nevertheless, the presence of other ingredients such as flavonoids seems to be necessary for a sufficient antidementia activity of the extract.

The clinical efficacy is also a point of lively discussion. Whereas the Cochrane Collaboration conclude in their review that there is no benefit for patients taking GBE, the IQWiG review describes the GBE-containing products as an effective treatment of AD. For the future, clinical studies with GBE products that conform to the monographs of the USP or European Pharmacopoeia, in a sufficient dosage regime (240 mg extract per day), placebo controlled or against standard antidementia drugs are needed. However, the difficulty with the definition of realistic clinical endpoints in clinical trials related to GBE remains [146].

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References

1. DeFeudis FV. A brief history of EGb 761 and its therapeutic uses. Pharmacopsychiatry. 2003;36(Suppl 1):S2–7.
2. Gong W, Chen C, Dobes C, et al. Phylogeography of a living fossil: pleistocene glaciations forced *Ginkgo biloba* L. (Ginkgoaceae) into two refuge areas in China with limited subsequent postglacial expansion. Mol Phylogenet Evol. 2008;48(3):1094–105.
3. Kressmann S, Biber A, Wonnemann M, et al. Influence of pharmaceutical quality on the bioavailability of active components from *Ginkgo biloba* preparations. J Pharm Pharmacol. 2002;54(11):1507–14.
4. van Beek TA, Montoro P. Chemical analysis and quality control of *Ginkgo biloba* leaves, extracts, and phytopharmaceuticals. J Chromatogr A. 2009;1216(11):2002–32.
5. Zhao Y, Wang L, Bao Y, et al. A sensitive method for the detection and quantification of ginkgo flavonols from plasma. Rapid Commun Mass Spectr. 2007;21(6):971–81.
6. Schwabe U. Arzneiverordnungs-Report 2009: Aktuelle Daten, Kosten, Trends und Kommentare. 1. Aufl. Heidelberg Neckar. Springer, Berlin; 2009.
7. Klein J, Weichel O, Hilgert M, et al. Excitotoxic hippocampal membrane breakdown and its inhibition by bilobalide: role of chloride fluxes. Pharmacopsychiatry. 2003;36(Suppl 1):S78–83.
8. Mdzinarishvili A, Kiewert C, Kumar V, et al. Bilobalide prevents ischemia-induced edema formation in vitro and in vivo. Neuroscience. 2007;144(1):217–22.
9. Abdel-Kader R, Hauptmann S, Keil U, et al. Stabilization of mitochondrial function by *Ginkgo biloba* extract (EGb 761). Pharmacol Res. 2007;56(6):493–502.
10. Mancuso M, Coppedè F, Murri L, et al. Mitochondrial cascade hypothesis of Alzheimer's disease: myth or reality? Antioxid Redox Signal. 2007;9(10):1631–46.
11. Christen Y. Oxidative stress and Alzheimer disease. Am J Clin Nutr. 2000;71(2):621S–9S.
12. Reddy VP, Zhu X, Perry G, et al. Oxidative stress in diabetes and Alzheimer's disease. J Alzheimers Dis. 2009;16(4):763–74.
13. Reddy PH. Mitochondrial dysfunction in aging and Alzheimer's disease: strategies to protect neurons. Antioxid Redox Signal. 2007;9(10):1647–58.
14. Institute for Quality and Efficiency in Health Care. http://www.iqwig.de. Accessed 23 Aug 2012.
15. IQWIG. Abschlussbericht: Ginkgohaltige Präparate bei Alzheimer Demenz; 2008.
16. Ihl R, Bachinskaya N, Korczyn AD et al. Efficacy and safety of a once-daily formulation of *Ginkgo biloba* extract EGb 761 in dementia with neuropsychiatric features: a randomized controlled trial. Int J Geriatr Psychiatry 2010;26(11):1186–94.
17. Napryeyenko O, Sonnik G, Tartakovsky I. Efficacy and tolerability of *Ginkgo biloba* extract EGb 761 by type of dementia: analyses of a randomised controlled trial. J Neurol Sci. 2009;283(1–2):224–9.
18. Le Bars PL, Kieser M, Itil KZ. A 26-week analysis of a double-blind, placebo-controlled trial of the *Ginkgo biloba* extract EGb 761 in dementia. Dement Geriatr Cogn Disord. 2000;11(4):230–7.
19. Dekosky ST, Williamson JD, Fitzpatrick AL, et al. *Ginkgo biloba* for prevention of dementia: a randomized controlled trial. JAMA. 2008;300(19):2253–62.
20. Birks J, Grimley Evans J. *Ginkgo biloba* for cognitive impairment and dementia. Cochrane Database Syst Rev 2009;(1):CD003120.
21. Kasper S, Schubert H. *Ginkgo biloba* extract EGb 761® in the treatment of dementia: evidence of efficacy and tolerability. Fortschr Neurol Psychiatr 2009;77(9):494–506.
22. Wurglics M, Schubert-Zsilavecz M. Hypericum perforatum: a 'modern' herbal antidepressant: pharmacokinetics of active ingredients. Clin Pharmacokinet. 2006;45(5):449–68.
23. Federal Institute for Drugs and Medical Devices of Germany. http://www.bfarm.de. Accessed 3 Jul 2012.
24. Kommission E. Monographie: Trockenextrakt (35-67:1) aus Ginkgo Blättern. Bundesanzeiger 1994;Nr. 133.
25. DeFeudis FV, Drieu K. *Ginkgo biloba* extract (EGb 761) and CNS functions: basic studies and clinical applications. Curr Drug Targets. 2000;1(1):25–58.
26. Blecharz-Klin K, Piechal A, Joniec I, et al. Pharmacological and biochemical effects of *Ginkgo biloba* extract on learning, memory consolidation and motor activity in old rats. Acta Neurobiol Exp (Wars). 2009;69(2):217–31.
27. Oken BS, Storzbach DM, Kaye JA. The efficacy of *Ginkgo biloba* on cognitive function in Alzheimer disease. Arch Neurol. 1998;55(11):1409–15.
28. Zimmermann M, Colciaghi F, Cattabeni F, et al. *Ginkgo biloba* extract: from molecular mechanisms to the treatment of Alzheimer's disease. Cell Mol Biol (Noisy-le-grand). 2002;48(6):613–23.
29. Singh B, Kaur P, Gopichand, et al. Biology and chemistry of *Ginkgo biloba*. Fitoterapia. 2008;79(6):401–18.
30. Leistner E, Drewke C. *Ginkgo biloba* and ginkgotoxin. J Nat Prod. 2009;73(1):86–92.
31. Ramassamy C, Longpre F, Christen Y. *Ginkgo biloba* extract (EGb 761) in Alzheimer's disease: is there any evidence? Curr Alzheimer Res. 2007;4(3):253–62.
32. van Beek TA. Chemical analysis of *Ginkgo biloba* leaves and extracts. J Chromatogr A. 2002;967(1):21–55.
33. Leuner K, Hauptmann S, Abdel-Kader R, et al. Mitochondrial dysfunction: the first domino in brain aging and Alzheimer's disease? Antioxid Redox Signal. 2007;9(10):1659–75.
34. Leuner K, Pantel J, Frey C, et al. Enhanced apoptosis, oxidative stress and mitochondrial dysfunction in lymphocytes as potential biomarkers for Alzheimer's disease. J Neural Transm Suppl. 2007;72:207–15.
35. Eckert A, Keil U, Kressmann S, et al. Effects of EGb 761 *Ginkgo biloba* extract on mitochondrial function and oxidative stress. Pharmacopsychiatry. 2003;36(Suppl 1):S15–23.
36. Eckert A, Keil U, Scherping I, et al. Stabilization of mitochondrial membrane potential and improvement of neuronal

energy metabolism by *Ginkgo biloba* extract EGb 761. Ann N Y Acad Sci. 2005;1056:474–85.
37. Müller WE, Abdel-Kader R, Fehske CJ, et al. Grundlagen der therapeutischen Anwendung von EGb 761®: Wirkung auf die Kraftwerke der Zellen. Pharmazie in unserer Zeit. 2009;38(5): 408–16.
38. Belayev L, Khoutorova L, Atkins K, et al. LAU-0901, a novel platelet-activating factor antagonist, is highly neuroprotective in cerebral ischemia. Exp Neurol. 2008;214(2):253–8.
39. Chatterjee SS, Kondratskaya EL, Krishtal OA. Structure-activity studies with *Ginkgo biloba* extract constituents as receptor-gated chloride channel blockers and modulators. Pharmacopsychiatry. 2003;36(Suppl 1):S68–77.
40. Nakanishi K. Terpene trilactones from *Ginkgo biloba*: from ancient times to the 21st century. Bioorg Med Chem. 2005;13(17):4987–5000.
41. Bate C, Kempster S, Williams A. Platelet-activating factor antagonists protect amyloid-beta damaged neurons from microglia-mediated death. Neuropharmacology. 2006;51(2):173–81.
42. Stromgaard K, Nakanishi K. Chemistry and biology of terpene trilactones from *Ginkgo biloba*. Angew Chem Int Ed Engl. 2004;43(13):1640–58.
43. Smith JV, Luo Y. Studies on molecular mechanisms of *Ginkgo biloba* extract. Appl Microbiol Biotechnol. 2004;64(4):465–72.
44. Smith PF, Maclennan K, Darlington CL. The neuroprotective properties of the *Ginkgo biloba* leaf: a review of the possible relationship to platelet-activating factor (PAF). J Ethnopharmacol. 1996;50(3):131–9.
45. Braquet P. Proofs of involvement of PAF-acether in various immune disorders using BN 52021 (ginkgolide B): a powerful PAF-acether antagonist isolated from *Ginkgo biloba* L. Adv Prostaglandin Thromboxane Leukot Res. 1986;16:179–98.
46. Mukherjee PK, DeCoster MA, Campbell FZ, et al. Glutamate receptor signaling interplay modulates stress-sensitive mitogen-activated protein kinases and neuronal cell death. J Biol Chem. 1999;274(10):6493–8.
47. Chen C, Bazan NG. Lipid signaling: sleep, synaptic plasticity, and neuroprotection. Prostaglandins Other Lipid Mediat. 2005;77(1–4):65–76.
48. Kondratskaya EL, Fisyunov AI, Chatterjee SS, et al. Ginkgolide B preferentially blocks chloride channels formed by heteromeric glycine receptors in hippocampal pyramidal neurons of rat. Brain Res Bull. 2004;63(4):309–14.
49. Kondratskaya EL, Betz H, Krishtal OA, et al. The beta subunit increases the ginkgolide B sensitivity of inhibitory glycine receptors. Neuropharmacology. 2005;49(6):945–51.
50. Rimbach G, Wolffram S, Watanabe C, et al. Effect of *Ginkgo biloba* (EGb 761) on differential gene expression. Pharmacopsychiatry. 2003;36(Suppl 1):S95–9.
51. Yao Z, Drieu K, Papadopoulos V. The *Ginkgo biloba* extract EGb 761 rescues the PC12 neuronal cells from beta-amyloid-induced cell death by inhibiting the formation of beta-amyloid-derived diffusible neurotoxic ligands. Brain Res. 2001;889(1–2): 181–90.
52. Bate C, Tayebi M, Williams A. Ginkgolides protect against amyloid-beta1-42-mediated synapse damage in vitro. Mol Neurodegener. 2008;3:1.
53. Augustin S, Rimbach G, Augustin K, et al. Effect of a short- and long-term treatment with *Ginkgo biloba* extract on amyloid precursor protein levels in a transgenic mouse model relevant to Alzheimer's disease. Arch Biochem Biophys. 2009;481(2):177–82.
54. Longpré F, Garneau P, Christen Y, et al. Protection by EGb 761 against beta-amyloid-induced neurotoxicity: involvement of NF-kappaB, SIRT1, and MAPKs pathways and inhibition of amyloid fibril formation. Free Radic Biol Med. 2006;41(12): 1781–94.
55. Hauptmann S, Scherping I, Dröse S, et al. Mitochondrial dysfunction: an early event in Alzheimer pathology accumulates with age in AD transgenic mice. Neurobiol Aging. 2008;30(10): 1574–86.
56. Amri H, Drieu K, Papadopoulos V. Transcriptional suppression of the adrenal cortical peripheral-type benzodiazepine receptor gene and inhibition of steroid synthesis by ginkgolide B. Biochem Pharmacol. 2003;65(5):717–29.
57. Amri H, Li W, Drieu K, et al. Identification of the adrenocorticotropin and ginkgolide B-regulated 90-kilodalton protein (p90) in adrenocortical cells as a serotransferrin precursor protein homolog (adrenotransferrin). Endocrinology. 2004;145(4): 1802–9.
58. Janssens D, Michiels C, Delaive E, et al. Protection of hypoxia-induced ATP decrease in endothelial cells by *Ginkgo biloba* extract and bilobalide. Biochem Pharmacol. 1995;50(7):991–9.
59. Janssens D, Remacle J, Drieu K, et al. Protection of mitochondrial respiration activity by bilobalide. Biochem Pharmacol. 1999;58(1):109–19.
60. Tchantchou F, Xu Y, Wu Y, et al. EGb 761 enhances adult hippocampal neurogenesis and phosphorylation of CREB in transgenic mouse model of Alzheimer's disease. FASEB J. 2007;21(10):2400–8.
61. Tchantchou F, Lacor PN, Cao Z, et al. Stimulation of neurogenesis and synaptogenesis by bilobalide and quercetin via common final pathway in hippocampal neurons. J Alzheimers Dis. 2009;18(4):787–98.
62. Chandrasekaran K, Mehrabian Z, Spinnewyn B, et al. Bilobalide, a component of the *Ginkgo biloba* extract (EGb 761), protects against neuronal death in global brain ischemia and in glutamate-induced excitotoxicity. Cell Mol Biol (Noisy-le-grand). 2002;48(6):663–9.
63. Chandrasekaran K, Mehrabian Z, Spinnewyn B, et al. Neuroprotective effects of bilobalide, a component of *Ginkgo biloba* extract (EGb 761) in global brain ischemia and in excitotoxicity-induced neuronal death. Pharmacopsychiatry. 2003;36(Suppl 1):S89–94.
64. Klein J, Chatterjee SS, Loffelholz K. Phospholipid breakdown and choline release under hypoxic conditions: inhibition by bilobalide, a constituent of *Ginkgo biloba*. Brain Res. 1997;755(2): 347–50.
65. Weichel O, Hilgert M, Chatterjee SS, et al. Bilobalide, a constituent of *Ginkgo biloba*, inhibits NMDA-induced phospholipase A2 activation and phospholipid breakdown in rat hippocampus. Naunyn Schmiedebergs Arch Pharmacol. 1999;360(6):609–15.
66. Kiewert C, Kumar V, Hildmann O, et al. Role of GABAergic antagonism in the neuroprotective effects of bilobalide. Brain Res. 2007;1128(1):70–8.
67. Kiewert C, Kumar V, Hildmann O, et al. Role of glycine receptors and glycine release for the neuroprotective activity of bilobalide. Brain Res. 2008;1201:143–50.
68. DeFeudis FV. Bilobalide and neuroprotection. Pharmacol Res. 2002;46(6):565–8.
69. Ahlemeyer B, Krieglstein J. Neuroprotective effects of *Ginkgo biloba* extract. Cell Mol Life Sci. 2003;60(9):1779–92.
70. Kim B, Kim K, Lim KS, et al. Influence of *Ginkgo biloba* extract on the pharmacodynamic effects and pharmacokinetic properties of ticlopidine: an open-label, randomized, two-period, two-treatment, two-sequence, single-dose crossover study in healthy Korean male volunteers. Clin Ther. 2010;32(2):380–90.
71. Koch E. Inhibition of platelet activating factor (PAF)-induced aggregation of human thrombocytes by ginkgolides: considerations on possible bleeding complications after oral intake of *Ginkgo biloba* extracts. Phytomedicine. 2005;12(1–2):10–6.
72. Kloft C, Kellermann A. Blutungsneigung durch Ginkgo-biloba-Extrakt? Kontroverse Diskussion. Pharmazie in unserer Zeit. 2009;38(5):440–6.

73. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. Drugs. 2009;69(13):1777–98.
74. Deng Y, Bi H, Zhao L, et al. Induction of cytochrome P450s by terpene trilactones and flavonoids of the *Ginkgo biloba* extract EGb 761 in rats. Xenobiotica. 2008;38(5):465–81.
75. Deng Y, Bi H, Zhao L, et al. Induction of cytochrome P450 3A by the *Ginkgo biloba* extract and bilobalides in human and rat primary hepatocytes. Drug Metab Lett. 2008;2(1):60–6.
76. Umegaki K, Taki Y, Endoh K, et al. Bilobalide in *Ginkgo biloba* extract is a major substance inducing hepatic CYPs. J Pharm Pharmacol. 2007;59(6):871–7.
77. Shinozuka K, Umegaki K, Kubota Y, et al. Feeding of *Ginkgo biloba* extract (GBE) enhances gene expression of hepatic cytochrome P-450 and attenuates the hypotensive effect of nicardipine in rats. Life Sci. 2002;70(23):2783–92.
78. Robertson SM, Davey RT, Voell J, et al. Effect of *Ginkgo biloba* extract on lopinavir, midazolam and fexofenadine pharmacokinetics in healthy subjects. Curr Med Res Opin. 2008;24(2):591–9.
79. Gurley BJ, Gardner SF, Hubbard MA, et al. Cytochrome P450 phenotypic ratios for predicting herb–drug interactions in humans. Clin Pharmacol Ther. 2002;72(3):276–87.
80. Chatterjee SS, Doelman CJ, Noldner M, et al. Influence of the Ginkgo extract EGb 761 on rat liver cytochrome P450 and steroid metabolism and excretion in rats and man. J Pharm Pharmacol. 2005;57(5):641–50.
81. Hertog MG, Feskens EJ, Kromhout D. Antioxidant flavonols and coronary heart disease risk. Lancet. 1997;349(9053):699.
82. Yochum L, Kushi LH, Meyer K, et al. Dietary flavonoid intake and risk of cardiovascular disease in postmenopausal women. Am J Epidemiol. 1999;149(10):943–9.
83. Markesbery WR, Lovell M. Damage to lipids, proteins, DNA, and RNA in mild cognitive impairment. Arch Neurol. 2007;64(7):954–6.
84. Ahlemeyer B, Krieglstein J. Pharmacological studies supporting the therapeutic use of *Ginkgo biloba* extract for Alzheimer's disease. Pharmacopsychiatry. 2003;36(Suppl 1):S8–14.
85. Smith JV, Luo Y. Elevation of oxidative free radicals in Alzheimer's disease models can be attenuated by *Ginkgo biloba* extract EGb 761. J Alzheimers Dis. 2003;5(4):287–300.
86. Kaschel R. *Ginkgo biloba*: specificity of neuropsychological improvement—a selective review in search of differential effects. Hum Psychopharmacol. 2009;24(5):345–70.
87. Rubio-Perez JM, Morillas-Ruiz JM. A review: inflammatory process in Alzheimer's disease, role of cytokines. ScientificWorldJournal. 2012;2012:756357.
88. Zheng LT, Ock J, Kwon B, et al. Suppressive effects of flavonoid fisetin on lipopolysaccharide-induced microglial activation and neurotoxicity. Int Immunopharmacol. 2008;8(3):484–94.
89. Kim J, Kina T, Iwanaga Y, et al. Tea polyphenol inhibits allostimulation in mixed lymphocyte culture. Cell Transpl. 2007;16(1):75–83.
90. Kang TH, Lee JH, Song CK, et al. Epigallocatechin-3-gallate enhances CD8+ T cell-mediated antitumor immunity induced by DNA vaccination. Cancer Res. 2007;67(2):802–11.
91. Min K, Yoon W, Kim SK, et al. Immunosuppressive effect of silibinin in experimental autoimmune encephalomyelitis. Arch Pharm Res. 2007;30(10):1265–72.
92. Fehske CJ, Leuner K, Muller WE. *Ginkgo biloba* extract (EGb761) influences monoaminergic neurotransmission via inhibition of NE uptake, but not MAO activity after chronic treatment. Pharmacol Res. 2009;60(1):68–73.
93. Yoshitake T, Yoshitake S, Kehr J. The *Ginkgo biloba* extract EGb 761® and its main constituent flavonoids and ginkgolides increase extracellular dopamine levels in the rat prefrontal cortex. Brit J Pharmacol. 2010;159(3):659–68.
94. Moeller CK, Kurt S, Scheich H, et al. Improvement of auditory discrimination learning by *Ginkgo biloba* extract EGb 761. Neurosci Lett. 2009;463(3):219–22.
95. Liu ZH, Zeng S. Cytotoxicity of ginkgolic acid in HepG2 cells and primary rat hepatocytes. Toxicol Lett. 2009;187(3):131–6.
96. Ahlemeyer B, Selke D, Schaper C, et al. Ginkgolic acids induce neuronal death and activate protein phosphatase type-2C. Eur J Pharmacol. 2001;430(1):1–7.
97. Hausen BM. The sensitizing capacity of ginkgolic acids in guinea pigs. Am J Contact Dermat. 1998;9(3):146–8.
98. Baron-Ruppert G, Luepke NP. Evidence for toxic effects of alkylphenols from *Ginkgo biloba* in the hen's egg test (HET). Phytomedicine. 2001;8(2):133–8.
99. Hecker H, Johannisson R, Koch E, et al. In vitro evaluation of the cytotoxic potential of alkylphenols from *Ginkgo biloba* L. Toxicology. 2002;177(2–3):167–77.
100. Moreau JP, Eck CR, McCabe J, et al. Absorption, distribution and elimination of a labelled extract of *Ginkgo biloba* leaves in the rat. Presse Med. 1986;15(31):1458–61.
101. Kleijnen J, Knipschild P. *Ginkgo biloba*. Lancet. 1992;340(8828):1136–9.
102. Fourtillan JB, Brisson AM, Girault J, et al. Pharmacokinetic properties of bilobalide and ginkgolides A and B in healthy subjects after intravenous and oral administration of *Ginkgo biloba* extract (EGb 761). Therapie. 1995;50(2):137–44.
103. Mauri P, de Palma A, Pozzi F, et al. LC-MS characterization of terpene lactones in plasma of experimental animals treated with *Ginkgo biloba* extracts correlation with pharmacological activity. J Pharm Biomed Anal. 2006;40(3):763–8.
104. Xie J, Ding C, Ge Q, et al. Simultaneous determination of ginkgolides A, B, C and bilobalide in plasma by LC–MS/MS and its application to the pharmacokinetic study of *Ginkgo biloba* extract in rats. J Chromatogr B Analyt Technol Biomed Life Sci. 2008;864(1–2):87–94.
105. Rossi R, Basilico F, Rossoni G, et al. Liquid chromatography/atmospheric pressure chemical ionization ion trap mass spectrometry of bilobalide in plasma and brain of rats after oral administration of its phospholipidic complex. J Pharm Biomed Anal. 2009;50(2):224–7.
106. Biber A, Koch E. Bioavailability of ginkgolides and bilobalide from extracts of *Ginkgo biloba* using GC/MS. Planta Med. 1999;65(2):192–3.
107. Ding S. Fingerprint profil of *Ginkgo biloba* nutritional supplements by LC/ESI–MS/MS. Phytochemistry. 2008;69:1555–64.
108. Sora DI, Stefanescu V, David V, et al. Validation of an LC-MS/MS assay of terpene trilactones in *Ginkgo biloba* extracts and pharmaceutical formulations through standard addition method. J Pharm Biomed Anal. 2009;50(3):459–68.
109. Ude C, Paulke A, Nöldner M et al. Plasma and brain levels of terpene trilactones in rats after an oral single dose of standardized *Ginkgo biloba* extract EGb 761®. Planta Medica 2011;77(3):259–64.
110. Rangel-Ordóñez L, Nöldner M, Schubert-Zsilavecz M et al. Plasma levels and distribution of flavonoids in rat brain after single and repeated doses of standardized *Ginkgo biloba* extract EGb 761®. Planta Medica 2010;76(15):1683–90.
111. Paulke A, Schubert-Zsilavecz M, Wurglics M. Determination of St. John's wort flavonoid-metabolites in rat brain through high performance liquid chromatography coupled with fluorescence detection. J Chromatogr B Analyt Technol Biomed Life Sci. 2006;832(1):109–13.
112. Biber A. Pharmacokinetics of *Ginkgo biloba* extracts. Pharmacopsychiatry. 2003;36(Suppl 1):S32–7.

113. Manach C, Morand C, Crespy V, et al. Quercetin is recovered in human plasma as conjugated derivatives which retain antioxidant properties. FEBS Lett. 1998;426(3):331–6.
114. Cermak R, Landgraf S, Wolffram S. The bioavailability of quercetin in pigs depends on the glycoside moiety and on dietary factors. J Nutr. 2003;133(9):2802–7.
115. Hollman PC, van Trijp JM, Buysman MN, et al. Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man. FEBS Lett. 1997;418(1–2):152–6.
116. Erlund I, Kosonen T, Alfthan G, et al. Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. Eur J Clin Pharmacol. 2000;56(8):545–53.
117. Williamson G, Manach C. Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. Am J Clin Nutr. 2005;81(1 Suppl):243S–55S.
118. Paulke A, Noldner M, Schubert-Zsilavecz M, et al. St. John's wort flavonoids and their metabolites show antidepressant activity and accumulate in brain after multiple oral doses. Pharmazie. 2008;63(4):296–302.
119. Wang FM, Yao TW, Zeng S. Determination of quercetin and kaempferol in human urine after orally administrated tablet of *Ginkgo biloba* extract by HPLC. J Pharm Biomed Anal. 2003;33(2):317–21.
120. Watson DG, Pitt AR. Analysis of flavonoids in tablets and urine by gas chromatography/mass spectrometry and liquid chromatography/mass spectrometry. Rapid Commun Mass Spectr. 1998;12(4):153–6.
121. Ding S, Dudley E, Chen L, et al. Determination of active components of *Ginkgo biloba* in human urine by capillary high-performance liquid chromatography/mass spectrometry with on-line column-switching purification. Rapid Commun Mass Spectr. 2006;20(24):3619–24.
122. Ude C. Pharmakokinetische Charakterisierung der Terpenlaktone aus *Ginkgo biloba* im ZNS am Tiermodell [Dissertation zur Erlangung des Doktorgrades der Naturwissenschaften]. Frankfurt am Main: Goethe Universität Frankfurt am Main; 2010.
123. Wang DL, Liang Y, Chen WD, et al. Identification of ginkgolide B metabolites in urine and rat liver cytochrome P450 enzymes responsible for their formation in vitro. Acta Pharmacol Sin. 2008;29(3):376–84.
124. Suehiro M, Simpson NR, Underwood MD, et al. In vivo biodistribution of ginkgolide B, a constituent of *Ginkgo biloba*, visualized by MicroPET. Planta Medica. 2005;71(7):622–7.
125. Lv H, Wang G, Wu X, et al. Transport characteristics of ginkgolide B by Caco-2 cells and examination of ginkgolide B oral absorption potential using rat in situ intestinal loop method. Int J Pharm. 2008;351(1–2):31–5.
126. Mauri P, Minoggio M, Iemoli L, et al. Liquid chromatography/atmospheric pressure chemical ionization ion trap mass spectrometry of terpene lactones in plasma of animals. J Pharm Biomed Anal. 2003;32(4–5):633–9.
127. Woelkart K, Feizlmayr E, Dittrich P, et al. Pharmacokinetics of bilobalide, ginkgolide A and B after administration of three different *Ginkgo biloba* L. preparations in humans. Phytother Res PTR. 2010;24(3):445–50.
128. Butterweck V, Liefländer-Wulf U, Winterhoff H, et al. Plasma levels of hypericin in presence of procyanidin B2 and hyperoside: a pharmacokinetic study in rats. Planta Medica. 2003;69(3):189–92.
129. Lang D, Ude C, Wurglics M, et al. Brain permeability of bilobalide as probed by microdialysis before and after middle cerebral artery occlusion in mice. J Pharm Pharm Sci. 2010;13(4):607–14.
130. Chen WD, Liang Y, Xie L, et al. Pharmacokintics of the ginkgo B following intravenous administration of ginkgo B emulsion in rats. Biol Pharm Bull. 2007;30(1):1–5.
131. Madgula VLM, Avula B, Yu Y, et al. Intestinal and blood–brain barrier permeability of ginkgolides and bilobalide: in vitro and in vivo approaches. Planta Medica. 2010;76:599–606.
132. Hollman PC, Bijsman MN, van Gameren Y, et al. The sugar moiety is a major determinant of the absorption of dietary flavonoid glycosides in man. Free Radic Res. 1999;31(6):569–73.
133. Hollman PC, de Vries JH, van Leeuwen SD, et al. Absorption of dietary quercetin glycosides and quercetin in healthy ileostomy volunteers. Am J Clin Nutr. 1995;62(6):1276–82.
134. DuPont MS, Day AJ, Bennett RN, et al. Absorption of kaempferol from endive, a source of kaempferol-3-glucuronide, in humans. Eur J Clin Nutr. 2004;58(6):947–54.
135. Wolffram S, Blöck M, Ader P. Quercetin-3-glucoside is transported by the glucose carrier SGLT1 across the brush border membrane of rat small intestine. J Nutr. 2002;132(4):630–5.
136. Graefe EU, Wittig J, Mueller S, et al. Pharmacokinetics and bioavailability of quercetin glycosides in humans. J Clin Pharmacol. 2001;41(5):492–9.
137. Day AJ, Mellon F, Barron D, et al. Human metabolism of dietary flavonoids: identification of plasma metabolites of quercetin. Free Radic Res. 2001;35(6):941–52.
138. Watson DG, Oliveira EJ. Solid-phase extraction and gas chromatography–mass spectrometry determination of kaempferol and quercetin in human urine after consumption of *Ginkgo biloba* tablets. J Chromatogr B Biomed Sci Appl. 1999;723(1–2):203–10.
139. Pietta PG, Gardana C, Mauri PL, et al. Identification of flavonoid metabolites after oral administration to rats of a *Ginkgo biloba* extract. J Chromatogr B Biomed Appl. 1995;673(1):75–80.
140. Rechner AR, Smith MA, Kuhnle G, et al. Colonic metabolism of dietary polyphenols: influence of structure on microbial fermentation products. Free Radic Biol Med. 2004;36(2):212–25.
141. Pietta PG, Gardana C, Mauri PL. Identification of *Ginkgo biloba* flavonol metabolites after oral administration to humans. J Chromatogr B Biomed Sci Appl. 1997;693(1):249–55.
142. Zhao Y, Sun Y, Li C. Simultaneous determination of ginkgo flavonoids and terpenoids in plasma: ammonium formate in LC mobile phase enhancing electrospray ionization efficiency and capacity. J Am Soc Mass Spectr. 2008;19(3):445–9.
143. Nieder M. Pharmakokinetik der Ginkgo Flavonole im Plasma. Müncher Medizinische Wochenschrift. 1991;133:61–2.
144. Wójcicki J, Gawrońska-Szklarz B, Bieganowski W, et al. Comparative pharmacokinetics and bioavailability of flavonoid glycosides of *Ginkgo biloba* after a single oral administration of three formulations to healthy volunteers. Mater Med Pol. 1995;27(4):141–6.
145. Drago F, Floriddia ML, Cro M, et al. Pharmacokinetics and bioavailability of a *Ginkgo biloba* extract. J Ocul Pharmacol Ther. 2002;18(2):197–202.
146. Kaschel R. Ginkgo-Extrakt bei Personen mit nachlassender mentaler Leistungsfähigkeit. Studienergebnisse differenziert betrachten. Pharmazie in unserer Zeit. 2009;38(5):432–9.
147. Greenblatt DJ, von Moltke LL, Luo Y, et al. *Ginkgo biloba* does not alter clearance of flurbiprofen, a cytochrome P450–2C9 substrate. J Clin Pharmacol. 2006;46(2):214–21.
148. Jiang X, Williams KM, Liauw WS, et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol. 2005;59(4):425–32.
149. Uchida S, Yamada H, Li XD, et al. Effects of *Ginkgo biloba* extract on pharmacokinetics and pharmacodynamics of tolbutamide and midazolam in healthy volunteers. J Clin Pharmacol. 2006;46(11):1290–8.
150. Markowitz JS, Donovan JL, Lindsay DeVane C, et al. Multiple-dose administration of *Ginkgo biloba* did not affect cytochrome

P-450 2D6 or 3A4 activity in normal volunteers. J Clin Psychopharmacol. 2003;23(6):576–81.
151. Wang FM, Yao TW, Zeng S. Disposition of quercetin and kaempferol in human following an oral administration of *Ginkgo biloba* extract tablets. Eur J Drug Metab Pharmacokinet. 2003;28(3):173–7.
152. Tang J, Sun J, Zhang Y, et al. Herb–drug interactions: effect of *Ginkgo biloba* extract on the pharmacokinetics of theophylline in rats. Food Chem Toxicol. 2007;45(12):2441–5.
153. Kubota Y, Kobayashi K, Tanaka N, et al. Pretreatment with *Ginkgo biloba* extract weakens the hypnosis action of phenobarbital and its plasma concentration in rats. J Pharm Pharmacol. 2004;56(3):401–5.
154. Lau AJ, Chang TK. Inhibition of human CYP2B6-catalyzed bupropion hydroxylation by *Ginkgo biloba* extract: effect of terpene trilactones and flavonols. Drug Metab Dispos 2009;37(9):1931–7.
155. Yin OQP, Tomlinson B, Waye MMY, et al. Pharmacogenetics and herb–drug interactions: experience with *Ginkgo biloba* and omeprazole. Pharmacogenetics. 2004;14(12):841–50.
156. Yoshioka M, Ohnishi N, Koishi T, et al. Studies on interactions between functional foods or dietary supplements and medicines. IV. Effects of *Ginkgo biloba* leaf extract on the pharmacokinetics and pharmacodynamics of nifedipine in healthy volunteers. Biol Pharm Bull. 2004;27(12):2006–9.
157. Yoshioka M, Ohnishi N, Sone N, et al. Studies on interactions between functional foods or dietary supplements and medicines. III. Effects of *Ginkgo biloba* leaf extract on the pharmacokinetics of nifedipine in rats. Biol Pharm Bull. 2004;27(12):2042–5.
158. Mauri P, Simonetti P, Gardana C, et al. Liquid chromatography/atmospheric pressure chemical ionization mass spectrometry of terpene lactones in plasma of volunteers dosed with *Ginkgo biloba* L. extracts. Rapid Commun Mass Spectr. 2001;15(12):929–34.
159. Hua L, Guangji W, Hao L, et al. Sensitive and selective liquid chromatography–electrospray ionization mass spectrometry analysis of ginkgolide B in dog plasma. J Pharm Biomed Anal. 2006;40(1):88–94.
160. Schötz K. Quantification of allergenic urushiols in extracts of *Ginkgo biloba* leaves, in simple one-step extracts and refined manufactured material (EGb 761). Phytochem Anal PCA. 2004;15(1):1–8.
161. Paulke A. Untersuchungen zur ZNS-Bioverfügbarkeit wirksamkeitsbestimmender Inhaltsstoffe von Johanniskraut [Dissertation]. Frankfurt am Main: Goethe Universität Frankfurt am Main; 2007.
162. Ude C, Paulke A, Schubert-Zsilavecz M, et al. Chemie, Pharmakokinetik und Metabolismus von Ginkgo-Extrakt. Eines der bestuntersuchten Phytopharmaka. Pharmazie in unserer Zeit. 2009;38(5):418–23.
163. O'Leary KA, Day AJ, Needs PW, et al. Metabolism of quercetin-7- and quercetin-3-glucuronides by an in vitro hepatic model: the role of human beta-glucuronidase, sulfotransferase, catechol-*O*-methyltransferase and multi-resistant protein 2 (MRP2) in flavonoid metabolism. Biochem Pharmacol. 2003;65(3):479–91.