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Effects of a *Ginkgo biloba* extract on forearm haemodynamics in healthy volunteers

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Summary

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The aim was to validate possible vasodilating effects of a *Ginkgo biloba* extract with a secondary aim of finding a pharmacodynamic signal relating to the active component of these extracts. We studied the effect of *G. biloba* extract on forearm haemodynamics in 16 healthy subjects (nine females, seven males) with a median age of 32 years (range: 21–47). The study was conducted as a randomized, double-blinded cross-over design using oral treatment with *G. biloba* extract (Gibidyl Forte® t.i.d. or placebo for 6 weeks. Forearm blood flow and venous capacity were measured by strain-gauge plethysmography. Blood pressure was measured by standard sphygmomanometry, and forearm vascular resistance (FVR) was derived. Measurements were made at baseline and after 3, 6, 9 and 12 weeks of treatment. Forearm blood flow was significantly higher during active treatment after 3 and 6 weeks as compared with placebo treatment for 3 and 6 weeks ($P<0{\cdot}05$). Mean arterial blood pressure was unchanged, making the calculated FVR significantly lower during active treatment ($P<0{\cdot}02$). It is concluded that oral treatment with a *G. biloba* extract (Gibidyl Forte®) is able to dilate forearm blood vessels causing increments in regional blood flow without changing blood pressure levels in healthy subjects. The increments in blood flow may be used as a biological signal for pharmacokinetic studies.

Introduction

The use of leaves or fruits of the *Ginkgo biloba* tree for medicinal purposes dates back to a Chinese pharmacopoeia of the late sixteenth century (Read, 1911). In the course of time, the use of the fruit has been abandoned, and in the modern literature reference is only made to use of leaf extracts. Several different extracts are available on the market, all containing flavonoids as their principal component and terpenes in a smaller amount. The group of terpenes seems to be unique for the leaves of *G. biloba*, and the same holds true for some of the members of the flavonoid group (Sticher *et al.*, 1991). A number of publications have addressed the possible effects of *G. biloba* extracts in various conditions, but by far the largest number have focused on the effects on cognitive functions in elderly subject and on patients with intermittent claudication. The possible beneficial effects of *G. biloba* extracts on intermittent claudication were first reported by Krammer (1966), who found an improvement in the walking distances. These results have been supported by a recent meta-analysis (Schneider, 1992). A study made by our group was not able to substantiate the beneficial effects in these patients (Drabaek *et al.*, 1996). The main obstacle, when evaluating the studies on *G. biloba*, is the abundance of different extracts with possible quantitative and qualitative differences in the content of flavonoids and terpenes. Another source of confusion is the various regimens with respect to the applied doses, probably reflecting the fact that pharmacokinetic studies are hampered by the lack of knowledge as to the active ingredient(s). If a valid biological signal could be found, then some of these sources of confusion could be settled. It has been hypothesized that the extracts possess a vasodilating effect on the basis of sporadic reports, claiming that *G. biloba* extracts are able to reduce blood pressure and stimulate hair growth (Kobayashi *et al.*, 1993) in line with the effects of the vasodilating substance, minoxidil (Fiedler-Weiss, 1987).

The present study was undertaken to validate the claimed vasodilating effects of a *G. biloba* extract in healthy adults with a secondary aim of finding a possible biological signal relating to the active component of these extracts.

Subjects and methods

The study included 16 healthy subjects (nine females and seven males) with a median age of 32 years (range: 21–47 years).

Seven subjects were smokers. None of the subjects had a previous history of neurological, cardiovascular, pulmonary, gastrointestinal, hepatic, or renal disease and they were all normotensive at the time of investigation. The participants received verbal and written information on the purpose of the study and written consent was obtained. The local ethics committee approved the study protocol.

The study was designed as a double-blinded, placebo-controlled cross-over protocol, in which the subjects were allocated to two groups of equal size on the basis of computer-generated random numbers. According to the outcome of randomization the subjects were given either active or placebo treatment for 6 weeks and were then crossed over to placebo or active treatment for another 6 weeks. Active treatment (Gibidyl Forte®, Ferrosam A/S, Copenhagen, Denmark) containing 9·6 mg ginkgoflavonglucoside and 2·4 mg terpenlactones per tablet was administered orally three times daily. The placebo and active tablets were identical in appearance, taste, and smell and were packed in identical containers consecutively numbered according to the randomization protocol. The observers were unaware of the results of randomization.

Measurements of systemic blood pressure and forearm haemodynamics were performed at the time of inclusion and following 3, 6, 9 and 12 weeks of treatment. All measurements were taken following 30 min of rest in the supine position. The measurements obtained at the time of inclusion served as a habituation procedure, and the results were not used for subsequent analysis. Forearm blood flow (FBF) was measured by the venous occlusion technique using strain-gauge plethysmography (Medimatic Plethysmograph SP2, Copenhagen, Denmark) with encapsulated sensors. Sensitivity and paper speed was adjusted to approximate a 45° slope of the initial deflection of the volume curve. The mean value of 10 consecutive measurements was used to calculate the FBF in each session, and between each of the 10 measurements, sufficient time was allowed for the volume curve to return to baseline. The forearm venous capacity (FVC) values were obtained as a single measurement in each session after venous occlusion for 5 min with a cuff-pressure of 40 mmHg. The volume of the forearm veins will increase with increasing external counter pressure and thus it is important to ensure a comparable and constant cuff-pressure. It has previously been shown that the venous volume attains a steady-state level within 4 min of occlusion (Sejersen *et al.*, 1981). Systemic blood pressure was obtained by the standard auscultatory method using the Korotkoff sounds corresponding to phase 1 and 5 for systolic and diastolic pressures, respectively. FBF was expressed in millilitre per minute per 100 g of tissue and FVC was expressed in millilitre per 100 g of tissue through the use of the internal calibration signal of the plethysmograph. Mean arterial blood pressure (MAP) was calculated as the diastolic pressure plus one-third of the difference between the systolic and diastolic blood pressure. Forearm vascular resistance (FVR) was derived by dividing MAP by FBF and expressed in arbitrary units.

The data were fed into the computer before breaking the randomization code and were analysed using a non-parametric two-way ANOVA evaluating the time course, the effect of treatment, and the interaction between time course and treatment. A two-sided 5% level of significance was used. Data are given as median values with 95% confidence limits in brackets.

Table 1 Forearm blood flow during treatment with *Ginkgo biloba* extract.

		Mean	SD
Run-in		2·32	1·40
Active	3 weeks	3·15*	1·25
	6 weeks	3·09*	1·68
Placebo	3 weeks	2·53	0·50
	6 weeks	2·77	1·49

Forearm blood flow measured by venous occlusion plethysmography in 16 healthy volunteers during treatment with *Gingko biloba* extract either as active drug or placebo.
Asterisk (*) denotes statistical significance compared with run-in values ($P<0·05$).

Results

All subjects complied with the study protocol, and except for two subjects, who complained of slight sleeping problems during active treatment, no side-effects were registered.

Systolic blood pressure was 119 mmHg (100–137) and 117 mmHg (100–135) after 3 weeks of active or placebo treatment, respectively, and 117 mmHg (104–139) and 117 mmHg (104–131) after 6 weeks of active or placebo treatment. Diastolic blood pressure was 69 mmHg (59–83) and 69 mmHg (54–87) after 3 weeks of active or placebo treatment, respectively, and 70 mmHg (58–81) and 70 mmHg (60–84) after 6 weeks of active or placebo treatment. Values of systolic and diastolic blood pressure did not change significantly in either group.

Forearm blood flow (Table 1) was within the expected range and the median values are shown in Fig. 1. FBF was significantly higher ($P < 0·05$) during active treatment after 3 and 6 weeks [3·2 ml min^{-1} $100g^{-1}$ tissue (1·6–4·4) and 3·3 ml min^{-1} $100g^{-1}$ tissue (1·4–5·6)] than after 3 [2·2 ml min^{-1} $100g^{-1}$ tissue (1·1–3·0)] and 6 weeks [2·8 ml min^{-1} $100g^{-1}$ tissue (1·4–4·9)] of placebo treatment. Two-way ANOVA showed significant interaction between time and treatment ($P<0·02$) with respect to FBF.

The changes in FBF were closely reflected in the FVR as neither active nor placebo treatment had any effect on systemic blood pressure. FVR was significantly lower ($P<0·02$) during active treatment after 3 and 6 weeks [33 units (18–54) and 33 units (15–48)] than after 3 [45 (24–89)] and 6 weeks [40 (16–72)] of placebo treatment. Two-way ANOVA showed significant interaction between time and treatment ($P<0·01$) with respect to FVR.

Forearm venous capacity was significantly higher ($P<0·05$) after 3 weeks of active treatment [1·2 ml $100g^{-1}$ (0·6–2·2)]

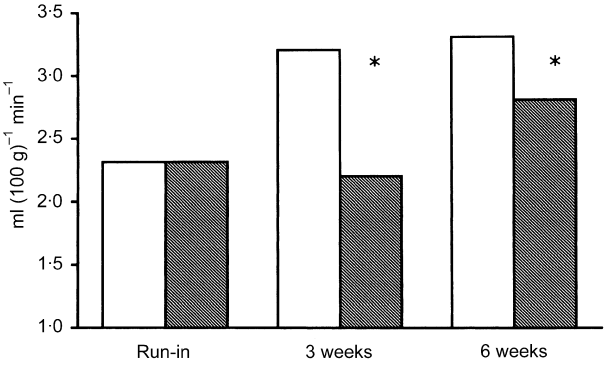

Figure 1 Forearm blood flow during treatment with *Ginkgo biloba* extract (Gibidyl Forte®) t.i.d. (open bars) or placebo (hatched bars). Measurement with strain-gauge plethysmography was performed after 3 and 6 weeks. Two-way ANOVA demonstrated significant differences as shown by asterisk (*) ($P<0.05$).

compared with 3 [0·8 ml $100g^{-1}$ (0·4–1·3)] and 6 weeks [0·8 ml $100g^{-1}$ (0·4–1·3)] of placebo treatment. The value of FVC after 6 weeks of active treatment [1·0 ml $100g^{-1}$ (0·6–1·2)] was not significantly different from any of the other recording sessions.

Discussion

This study has shown that an extract from the leaves of the *G. biloba* tree is capable of increasing FBF in healthy volunteers by reducing the local vascular resistance. The study has also pointed to a possible effect of the same preparation on FVC.

Forearm blood flow measured by venous occlusion technique reflects both muscular, dermal, skeletal and subcutaneous blood flows, but is dominated by the two first-mentioned regions. The changes in blood flow could be the result of a direct vasodilating effect of *G. biloba* extract on the regional resistance vessels or it could be caused by the initiation of central reflexes, either directly at the brain stem level or indirectly through the baroreflex control mechanisms. The fact that blood pressure levels did not differ between active and placebo treatment periods points to central mechanisms, but does not rule out the possibility of increments in cardiac output being counteracted through reductions in peripheral vascular resistance in order to leave blood pressure unchanged. However, the concurrent increment in venous capacity – although small – makes it more likely that the extract has a direct effect on vascular smooth muscles. The use of a relative high venous occlusion pressure during the study of venous capacity rules out that changes in this parameter was evoked by precapillary vasodilatation causing increments in the postcapillary venous pressure.

Two previous studies have demonstrated increments in dermal blood flow both after single oral dosing (Jung *et al.*, 1990) and after sequential intravenous administration for 4 days (Költringer *et al.*, 1989). In both studies significant rheologic changes were found to account for some of the effect seen on blood flow. The extracts in these studies were from different sources and also differed from that used in the present investigation.

The possible active substance or substances evoking the effect on blood flow could be found either in the group of flavonoids making up 26% of the extract or in the 6% occupied by the group of terpenes. The main obstacle in the search for one or more active components is the fact that the group of flavonoids comprises up to 40 different forms, of which eight are unique to the *G. biloba* leaves. To complicate matters further in this respect, the group of terpenes comprises six different forms, all of which are characteristic for the *G. biloba* species. The present finding of a biological response to oral dosing of a *G. biloba* extract could help in the search the active ingredient(s). The same response may prove useful in selecting the optimal dosing regimens amongst the many suggested in the literature.

The interest in finding the optimal dosing and active components of the *G. biloba* extracts is stimulated by the findings of beneficial effects of these remedies in patients with vascular disorders as documented by a meta-analysis of studies investigating patients with intermittent claudication (Schneider, 1992). The effects seen on walking distance in this disorder could be caused by the vasodilating properties of the extracts possibly easing the formation of collateral blood vessels.

In conclusion, our study has confirmed the claimed vasodilating effect of *G. biloba* extract on peripheral vessels preferentially on the arterial/arteriolar level. Whether this effect is caused by central or peripheral mechanisms cannot be answered, although the latter is more likely. The vasodilating and/or haemorheologic effects of *G. biloba* extracts may help explain previous findings of beneficial effects of the remedy in intermittent claudication. The vasodilating effect may also serve a possible biological signal useable for pharmacokinetic studies.

Acknowledgments

Gibidyl Forte® is a registered trademark, Ferrosan A/S, Denmark.

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