

**The influence of Ginkgo  
special extract EGb 761<sup>®1</sup>  
on the performance  
of healthy subjects  
at computer workstations  
- open-label clinical study  
in pre-post design with  
a control group -**

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**[German title: Einfluss von Ginkgo-Spezialextrakt EGb 761<sup>®\*</sup> auf die Leistungs-  
fähigkeit bei gesunden Probanden am Bildschirmarbeitsplatz – Offene klinische  
Studie im Prä-Post-Design mit Kontrollgruppe ]**

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<sup>1</sup> Ginkgo special extract EGb 761<sup>®</sup> (Tebonin<sup>®</sup> intens 120 mg) Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe

## **SUMMARY**

**Background:** Lack of concentration, restlessness and stress, as well as sleeplessness and irritability are common ailments ascribed to computer work. Several clinical trials have revealed improvements in cognitive performance and stress tolerance of healthy volunteers with Ginkgo biloba extract EGb 761<sup>®</sup>, a drug usually used for the treatment of dementia. To investigate the effects of EGb 761<sup>®</sup> on cognitive performance in healthy volunteers exposed to computer work, a controlled, open-label, monocentric clinical trial using a pre-post-design was conducted in 2005.

**Methods:** 104 healthy volunteers, aged 45 years or above, spending at least 50% of their working hours in front of computer screens were enrolled in this study. They were assigned either to the Ginkgo group or the untreated control group in accordance with their personal preference. The approved dose of 120 mg twice a day of the special extract EGb 761<sup>®</sup> was taken by the participants of the Ginkgo group for 8 weeks. Before and after the 8-week treatment period, they underwent two computer tests measuring sustained attention and multi-modal reactivity as well as a visual test of spatial contrast sensitivity. Moreover, subjectively perceived stress during the test procedures, the subjects' health-related quality of life and the incidence of adverse events were documented. A training session preceded the baseline measurements to familiarize the subjects with the test procedures.

**Results:** After the 8-week treatment period, the test of sustained attention revealed a significant decrease by 30% in the number of errors committed by subjects of the EGb 761<sup>®</sup> group compared to a 6% decrease for participants of the control group ( $p=0.035$ , two-tailed t-test). The perceived stress level was significantly reduced by EGb 761<sup>®</sup> ( $p=0.007$ , two-tailed t-test) compared to the control group. The »vitality« factor of health-related quality of life was improved in female subjects treated with EGb 761<sup>®</sup> ( $p=0.04$ ). No difference between treatment groups was found for multi-modal reactivity or spatial contrast sensitivity.

**Conclusion:** The results indicate that improvements relevant to everyday functioning at work can be attained with EGb 761<sup>®</sup> treatment, along with an increase in stress tolerance and quality of life.

**Keywords:** Ginkgo biloba special extract, EGb 761<sup>®</sup>, controlled clinical trial, computer workstations, cognitive performance, stress perception, quality of life

Ginkgo biloba special extract EGb 761<sup>®</sup> is distinguished by a specific patented manufacturing procedure that ensures a consistent composition and concentration of active substances. The effect of EGb 761<sup>®</sup> on brain function, particularly in healthy subjects, but also in dementia patients, can be explained by the stabilisation of mitochondrial function [3, 18] and specific action at the neurotransmitter level [7, 12]. Furthermore, EGb 761<sup>®</sup> protects against hypoxia, possesses neuroprotective characteristics [17] and improves blood flow properties [4, 11].

Several studies indicate that favourable effects on cognitive performance and emotional stability (stress tolerance) can also be achieved with EGb 761<sup>®</sup> in subjects without cognitive disorders. Ginkgo biloba reduced the increase in blood pressure found in healthy subjects when subjected to the stressful conditions of cognitive testing, for example. Depending on the time of day, the stress-induced increase in salivary cortisol was also prevented in male subjects. These results suggest that Ginkgo biloba attenuates the physiological stress reaction and improves cognitive performance as a result [8].

Controlled double-blind studies with EGb 761<sup>®</sup> over a period of 4–6 weeks involving subjects without cognitive disorders showed an improvement in coping with stress [14], brain function, emotional stability [2] and cognitive performance (verbal and visual memory) [16], perceptual and mental capacity and attention [15].

A study by the Federal Institute for Health and Safety at Work (Bundesanstalt für Arbeitsschutz) in 1997 showed that health disorders such as fatigue, lack of concentration, restlessness and tension, sleep disorders or irritability occur to an increasing degree in association with today's wide-spread use of computer workstations [1]. Everyday problems in using computers, such as system crashes or software errors, and the frequent pressure of deadlines have a stressful effect and can lead to mental stress at work.

The influence of drugs on such impairments has not been investigated to date, so that there is little experience with regard to appropriate study designs or outcome measures. The present study should therefore be regarded as an exploratory model, which aims to provide results about suitable testing procedures and test variables. However, as this investigation involves healthy subjects, any pharmacological intervention must be coupled with good tolerability. This prerequisite is fulfilled by the active substance EGb 761<sup>®</sup>. The study therefore investigated whether the Ginkgo extract had a direct effect on parameters relevant to a common and mentally stressful job such as working at a computer, whether effects could also be demonstrated in subjects below retirement age and the magnitude of the effects in healthy subjects.

In order to investigate the effect of Ginkgo special extract EGb761<sup>®</sup> (Tebonin<sup>®</sup> intens 120 mg, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe) on the performance of healthy subjects at computer workstations, a clinical study with employed persons who spent at least 50% of their working time in front of a computer screen was undertaken in 2005.

## **Methods**

### ***Study objective:***

The aim of the clinical study was to investigate the influence of EGb 761<sup>®</sup> on the performance of healthy subjects at workstations and to identify suitable tests to demonstrate these effects. The outcome measures included multi-modal reactivity (reactive stress tolerance), sustained attention and spatial contrast sensitivity of the subjects. Furthermore, the influence of the special extract on participant quality of life and perception of stress was to be monitored and its tolerability assessed.

**Test procedure:**

Reactive stress tolerance was measured using the Vienna Determination Test; a test procedure performed at the workstation to monitor reaction capacity. It requires continuous and, as far as possible, sustained rapid and varied reactions to rapidly changing visual and acoustic signals [19]. The test persons are shown spots of four different colours in different sequences and are required to press the keyboard button with the same colour when a spot appears. Furthermore, two acoustic signals are given, which have to be “suppressed” by activating the corresponding button. The third component is a visual signal at the right or left edge of the screen that requires operating the foot pedal on the same side. Stimulus presentation in this study was carried out in an adaptive mode, in which the presentation speed was adapted to the performance of the test person. The short form with a test phase of 4 minutes was used.

The sustained attention test was used to measure long-term concentration [20]. In this test, a row of 7 triangles with tips pointing upwards or downwards is continuously shown on the monitor over a period of 30 minutes. When the tips of three triangles point downwards, the test person is required to press a button. The computer registers the number of correct and incorrect responses. The simple but effective design of the test enables the measurement of individual long-term attention without making too many demands on subjects who perform less well [20].

The measurement of spatial contrast sensitivity was undertaken with charts (eyesight test). Both eyes were tested individually at a distance of 46 centimetres from the chart.

The quality of life was assessed using the German version of the Short Form (SF) 36 Health Survey. This comprises 8 domains »physical functioning«, »role-physical «, »bodily pain«, »general health«, »vitality«, »social functioning«, »role-emotional « and »mental health« [9].

Stress perception was documented using the visual analogue scale. This is a scale from 0 (= no stress) to 100 (= greatest imaginable stress), on which the test person was required to enter his/her perceived stress immediately after completing the two computer tests.

Tolerability was assessed on the basis of the adverse events occurring over the study period.

**Subject population:**

104 working male and female subjects aged  $\geq 45$  who spent at least 50% of their working day at a computer were enrolled in this study.

**Test medication:**

The dosage given during the study was two film-coated tablets EGb 761<sup>®</sup> per day corresponding to the dosage approved for the preparation. One film-coated tablet contains 120 mg dry extract of *Ginkgo biloba* leaves (35–67 : 1), extraction agent 60% acetone (w/w). The extract is adjusted

to 26.4–32.4 mg flavonoids, calculated as flavonoid glycosides, and 6.0–8.4 mg terpene lactones, comprising 3.36–4.08 mg ginkgolides A, B and C and 3.12–3.84 mg bilobalide, and contains less than 0.6 µg ginkgolic acids per film-coated tablet. The test medication was taken for 8 weeks.

### ***Study design:***

The clinical study was carried out in 2005 as an explorative, open-label, monocentric study in pre-post design with a control group (without administration of a test medication). The allocation to active substance or control groups took place at the first appointment (time point 0) and could be chosen freely by the test persons. At time point 0, test training with the two computer tests was performed for all participants in order to acquaint the subjects with the workstation testing procedure. After a subsequent two-week run-in-period, baseline testing (time point 1) and issue of test medication were carried out. After an eight-week treatment period (time point 2), the subjects repeated the two computer tests. At time points 1 and 2, spatial contrast sensitivity was also tested. In addition, stress perception after performing the computer tests and quality of life were recorded. The occurrence of adverse events during the study period was also documented.

### ***Sample size calculation and statistical analysis:***

It was estimated that a sample of 80 subjects (EGb 761<sup>®</sup>: n=50, control group: n=30) would be needed to demonstrate a standardised effect with a power of 80% and a type 1 error of  $\alpha = 0.05$ . With an expected dropout rate of 20%, it was therefore necessary to recruit 100 subjects. The Wilcoxon test, the non-parametric Mann-Whitney rank-sum test for independent samples and the t-test for independent samples were used for the statistical analysis. 95% confidence intervals were calculated. An exploratory analysis of the data was performed in order to generate one or more hypotheses for the outcome measures. The analysis of the Per-Protocol (PP) subjects was of primary interest in this exploratory model.

## **Results**

The analysis of the efficacy variables is based on the data from all subjects for whom at least one of the efficacy parameters was measured at time point 2 (Full-Analysis-Set, FA-Set), and all subjects who completed the study according to protocol (Per-Protocol-Set, PP-Set). Of 104 subjects who completed the test training at time point 0, 101 could be analysed. Two subjects did not appear for the last test session and one subject had to be excluded from the study at time point 1 because of taking psychotropic substances. In total, 84 subjects completed the study according to protocol. In addition, a safety analysis was performed with all subjects (Safety-Population) who were still participating in the study at time point 1 (103 subjects).

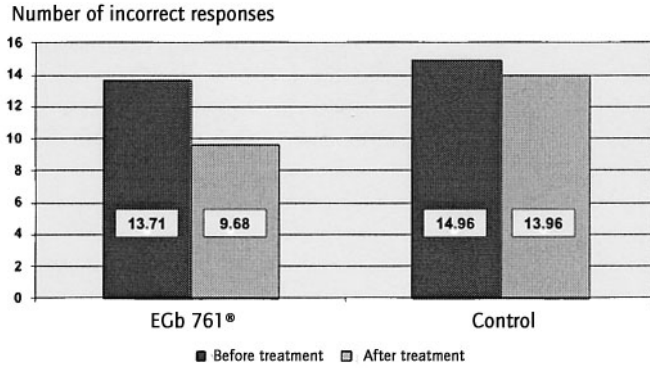
***Subjects and demographic parameters:***

In the PP-Set, 56 subjects (66.7%) were in the Ginkgo group and 28 subjects (33.3%) in the control group. In both groups, 60.7% of the participants were female. The average age of the subjects was essentially the same in both groups, with a mean of 51.6 years (51.3 years in the Ginkgo group and 52.2 years in the control group). Significant differences were not observed in these or in other demographic data, or in the baseline values of the target parameters.

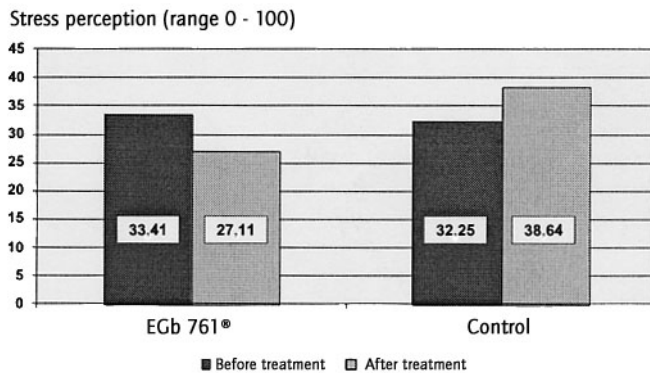
***Effects:***

In the sustained attention test, the number of errors by subjects treated with EGb 761<sup>®</sup> dropped significantly between the second and third time points compared to the control group ( $p=0.035$ , two-tailed t-test). In the Ginkgo group, incorrect responses were reduced by 30%, in the control group by only 6% (Fig. 1).

The change in stress perception was significantly better in the subjects treated with Ginkgo, who showed a highly significant decrease in perceived stress ( $p=0.007$ , two-tailed t-test). This effect was found to the same extent in both male and female subjects and was not observed in the control group (Fig. 2).



**Figure 1:** Change in number of incorrect responses in the sustained attention test ( $p = 0.035$  for treatment group difference, two-tailed  $t$ -test)



**Figure 2:** Change in perceived stress ( $p = 0.007$  for treatment group difference, two-tailed  $t$ -test)

An improvement in the quality of life domain »vitality« was found in the group treated with Ginkgo, while a deterioration was found in the control group ( $p=0.004$ , two-tailed  $t$ -test). This effect was confirmed for female subjects in the gender-specific analysis.

The results of the spatial contrast sensitivity measurements showed improvements in some of the participants. However, no significant differences were found between the two groups. The tests on reactive stress tolerance showed no difference between the Ginkgo group and the control group (Vienna Determination Test).

Corresponding results were found in the analogous analysis of the FA-Set data.

**Tolerability:**

Altogether 13 adverse events (AEs) were observed in 10 subjects in the Ginkgo group (15.4%) during the course of the study (Safety-Population). Three of the AEs occurred between time point 0 and time point 1 prior to taking the test preparation. In the control group, 4 AEs were found in 4 subjects (10.5%). These all occurred during the test phase. None of the events was serious. The most frequent adverse events found (Ginkgo: 5, control group: 3) were within the System-Organ-Classes »Infections and infestations« and »Gastrointestinal disorders« (4 listings in the Ginkgo group). A causal relationship with the study medication was excluded in 94% of cases. Altogether, the tolerability of Ginkgo special extract EGb 761<sup>®</sup> was assessed as good.

**Discussion**

Earlier studies showed that an improvement in memory, ability to concentrate and mental balance (emotional stability) could be achieved in elderly persons with cerebral disorders or dementia following a daily dosage of 120–240 mg Ginkgo special extract EGb 761<sup>®</sup> [5, 6, 10, 13]. These effects may be ascribed to the neurotropic properties of the flavone glycosides and terpene lactones contained in the extract. An improvement in mitochondrial function probably represents a central mechanism of action [3, 18].

The objective of the present study was to investigate whether improvements in cognitive performance could also be demonstrated in a common activity such as working at a computer monitor and whether the results could also be shown in persons below retirement age. The study was designed to help develop test parameters that could be used in more extensive investigations with confirmatory paradigms. The results showed a significant improvement in concentration at a computer workstation after eight-week administration of 240 mg EGb 761<sup>®</sup> per day: In the sustained attention test, the number of errors dropped by almost one third. Furthermore, the personal perception of stress was lowered significantly on taking EGb 761<sup>®</sup>. The Ginkgo extract was also shown to be well tolerated.

A stress-reducing action of EGb 761<sup>®</sup> and a positive effect on cognitive performance has also been demonstrated in other investigations. The results of these studies with healthy subjects without cognitive disorders were similar to those found in the present study [8, 15, 16].

These results are of particular significance for the over 45 age group, where working at a computer is often felt to be mentally stressful. The results indicate that long-term improvements in concentration relevant to everyday activities and working situations combined with an increase in stress tolerance and a consequent improvement in quality of life can be achieved with special extract EGb 761<sup>®</sup>. The specific effects on the two subjective assessment scales argue against the assumption that persons only assessed themselves to be better because they knew that they had been taking Ginkgo. Moreover, the noticeably lower number of errors in the objective



sustained attention test cannot be explained by non-specific factors, such as the knowledge of not being in the control group.

Clear subjective and objective improvements in favour of EGb 761<sup>®</sup> were evident in pre-post and between-group comparisons. For the majority of participants, this was associated with the wish to continue taking EGb 761<sup>®</sup> during subsequent self-medication. A more extensive double-blind investigation would appear appropriate from a methodological viewpoint.

## Acknowledgements

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### ZUSAMMENFASSUNG

**Hintergrund:** Im Zusammenhang mit Computer-Bildschirmarbeit treten häufig gesundheitliche Beschwerden wie Konzentrationsstörungen, innere Unruhe und Anspannung sowie Schlafstörungen und Reizbarkeit auf. Verschiedene kontrollierte Studien deuten darauf hin, dass mit dem zur symptomatischen Behandlung der Demenz eingesetzten Trockenextrakt aus Ginkgo biloba EGb 761<sup>®</sup> auch bei Personen ohne Hirnleistungsstörungen Verbesserungen der kognitiven Leistungsfähigkeit und der emotionalen Belastbarkeit erzielt werden können. Die vorliegende Untersuchung wurde als offene, monozentrische klinische Studie im Prä-Post-Design mit Kontrollgruppe durchgeführt, um den Einfluss des Extraktes auf die Leistungsfähigkeit von gesunden Probanden am Bildschirmarbeitsplatz zu untersuchen und erste Erfahrungen auf diesem Feld der arbeitsnahen Ergebnisforschung zu sammeln.

**Methodik:** In die Studie wurden 104 gesunde, berufstätige Probanden im Alter von  $\geq 45$  Jahren aufgenommen, die mindestens 50% ihrer Arbeitszeit am Computer-Bildschirm verbrachten. Die Teilnehmer wurden nach ihrem persönlichen Wunsch entweder der Ginkgo- oder der unbehandelten Kontrollgruppe zugeteilt. Der Ginkgo-Spezialextrakt EGb 761<sup>®</sup> wurde in der zugelassenen Dosierung von täglich 2 x 120 mg über 8 Wochen von den Teilnehmern der Ginkgo-Gruppe eingenommen. Jeweils vor und nach der achtwöchigen Untersuchungsphase absolvierten die Probanden 2 Computertests zur Messung der dauerhaften Konzentrationsfähigkeit (Daueraufmerksamkeit) und der reaktiven Belastbarkeit (Reaktionsvermögen) sowie eine Testung der räumlichen Kontrastsensitivität (Sehtest). Außerdem wurde die gesundheitsbezogene Lebensqualität der Teilnehmer erhoben, das persönliche Stressempfinden nach Durchführung der Computertests mittels Analogskala erfasst und das Auftreten unerwünschter Ereignisse dokumentiert. Um die Probanden mit dem Verfahren der Computertests vertraut zu machen, wurde vor Beginn der Untersuchungsphase ein Testtraining durchgeführt.

**Ergebnisse:** Im Daueraufmerksamkeitstest sank die Anzahl der Fehler der mit Ginkgo behandelten Probanden zwischen Beginn und Ende der Studie im Vergleich zur Kontrollgruppe signifikant ( $p=0,035$ , zweiseitiger t-Test). So konnte in der Ginkgo-Gruppe ein Rückgang der falschen Angaben um 30% verzeichnet werden (Kontrollgruppe: 6%). Das Stressempfinden entwickelte sich signifikant besser bei den mit Ginkgo behandelten Probanden ( $p=0,007$ , zweiseitiger t-Test). Bei der Lebensqualität der Probanden zeigte sich im Bereich »Vitalität« für die weiblichen Probanden eine Verbesserung zugunsten der mit Ginkgo Behandelten ( $p=0,04$ ). Bei der reaktiven Belastbarkeit sowie der räumlichen Kontrastsensitivität konnten keine Unterschiede zwischen der Ginkgo- und der Kontrollgruppe nachgewiesen werden.

**Schlussfolgerung:** Die Ergebnisse weisen darauf hin, dass mit dem Ginkgo-Extrakt EGb 761<sup>®</sup> alltags- und arbeitsrelevante Verbesserungen der Konzentrationsfähigkeit, verbunden mit einer Steigerung der Stresstoleranz und der Lebensqualität, erzielt werden können.

**Schlüsselwörter:** Ginkgo-Spezialextrakt, EGb 761<sup>®</sup>, kontrollierte klinische Studie, Bildschirmarbeit, kognitive Leistungsfähigkeit, Stressempfinden, Lebensqualität

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