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ORIGINAL RESEARCH

# A New Ginkgo Fresh Plant Extract Increases Microcirculation and Radical Scavenging Activity in Elderly Patients

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## ABSTRACT

***Introduction:*** The authors investigated whether a new *ginkgo biloba* (ginkgo) fresh plant extract had a positive effect on microcirculation in the skin and liver of elderly individuals, and whether the extract had antioxidative properties *in vivo*. ***Methods:*** In a monocentric, controlled clinical trial with 32 elderly patients, 16 patients received three 90 mg ginkgo extract tablets twice daily for 30 days, and 16 patients acted as untreated controls. On days 0, 10, 20, and 30, microcirculatory parameters were measured using intravital microscopy in combination with reflection spectrometry, and the amount of reduced glutathione in the liver. ***Results:*** This new ginkgo fresh plant extract significantly increased the number of blood cell-perfused nodal points, the venular streaming flow, and the local hematocrit in treated participants compared to control participants and compared to values on day 0. The ginkgo preparation also increased microcirculation in the liver, and possessed antioxidative properties that resulted in significant increases in the amount of the radical scavenger glutathione in treated participants. ***Conclusion:*** The new ginkgo fresh plant extract increased the microcirculation significantly, and at the same time improved the radical scavenging capacity in elderly patients and was very well tolerated. This extract is an interesting adjuvant treatment option for patients suffering from impaired microcirculation and improves mechanisms which inhibit an accelerated expression of atherosclerosis.

**Keywords:** clinical trial; *ginkgo biloba;* ginkgoaceae; glutathione; liver; microcirculation

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## INTRODUCTION

Preparations of *ginkgo biloba* (ginkgo) are among the most widely researched and top-selling phytopharmaceuticals,[1] and are often used in elderly patients. Ginkgo has been investigated for the treatment of mild-to-moderate dementia symptoms, its ability to increase mental performance, and for cerebral insufficiency, tinnitus, vertigo, and peripheral

arterial occlusive disease.[2] The mode of action of ginkgo varies; in animal experiments, ginkgo preparations showed vasoregulatory activity,[3] leading to improved rheological properties in the blood. In humans, individuals with ginkgo had enhanced peripheral and coronary blood flow as a result of endothelium-dependent vasodilation.[4] Furthermore, more than 20 papers have described the *in vitro* antioxidative effects of gingko, which appears to protect endothelial cells.[5] However, ginkgo also inhibits platelet-activating factors, decreases the age-related loss of muscarinic cholinoreceptors, stimulates choline uptake in the hippocampus, and inhibits beta-amyloid deposition.[6]

Several studies have investigated the ability of ginkgo to increase the microcirculatory perfusion of blood vessels. In rats, cerebral microcirculation after subarachnoid hemorrhage,[7] as well as the hepatic microcirculation in warm ischemia,[8] was increased after intravenous or oral administration of ginkgo extract, and ginkgo may also have a protective effect on hepatic microcirculation in rats with induced liver injuries.[9]

Two clinical trials in elderly patients with either pathological viscoelasticity values[10] or poor cerebral circulation[11] showed that intravenous application of a ginkgo extract lead to a dose-dependent increase in microcirculation in the skin after acute application, or in the bulbar conjunctiva after 10-15 days. Two trials with orally administered ginkgo tablets in healthy volunteers showed an increase in cutaneous microcirculation after acute intake,[12] and an increase in forearm blood flow after 6 weeks.[13]

Currently, most studies use a single standardized ginkgo extract using acetone as an extractant (60%) and with a drug extraction ratio of 35-67:1. The authors developed a new ginkgo extract made from fresh leaves using a more traditional approach by using ethanol 65% as extractant and with a drug extraction ratio of 3-5:1. This extract was shown to have positive effects on retinal blood flow in healthy volunteers after acute application in a clinical pilot trial.[14] In the present clinical trial, the authors evaluated whether the new ginkgo extract would improve microcirculation in elderly individuals during a 30-day time period. To the authors knowledge, this is the first trial on ginkgo to assess not only changes in the microcirculation of the gingiva or skin in response to ginkgo, but also in a large inner organ such as the liver. Moreover, the authors believe that this is also the first investigation of whether the antioxidant activity of ginkgo observed *in vitro* can be demonstrated *in vivo* by measuring the amount of reduced glutathione.

## MATERIALS AND METHODS

### Patients

Inclusion criteria were ambulant geriatric patients of both genders, White, aged 60-70 years with no acute pathological conditions; concomitant treatments of the usual clinical categories for multi-morbid patients were permitted (eg, heart glycosides, antihypertensive agents, and diabetes medication). Other inclusion criteria were chronic disorders that were only slightly or moderately severe in character, no pathological acute diagnosis, free of common colds for 4 weeks, no physical or mental disabilities, adherence to study protocol, balanced character, and written informed consent.

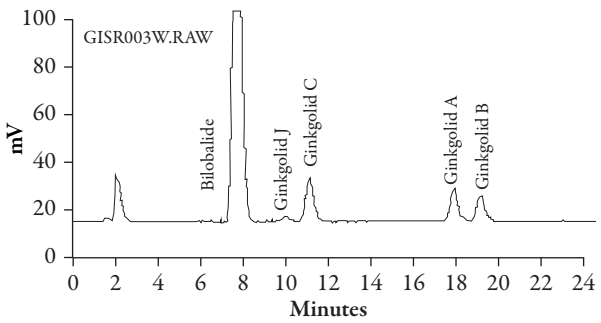
Exclusion criteria were heavy smoking (>10-15 cigarettes/day), alcohol and drug abuse, participation in another clinical trial in the previous 90 days, concomitant participation in another clinical trial, psychiatric diseases, epilepsy, suicidal tendencies, blood donation or blood loss >500 mL within the last

6 months, body weight not within ± 10% of the corresponding height, sex, and body type as described in the Metropolitan Life Insurance Company Tables 1983 or Broca index >150%, or overweight (>20% of normal weight), consumption of unusually large amounts of coffee or tea (more than 1 liter/day), according to the judgment of the investigator, individuals on weight-loss diets or with unbalanced diets, defined as diets which may lead to health hazards (ie, junk food, etc); chronic liver disease (two-fold normal value of transaminases), renal disorders (increase in serum creatinine >1.2 mg or creatinine clearance <50 mL/minute), number of leukocytes <3500/µL, number of thrombocytes <100,000/µL, suspected severe intestinal, pulmonary, or bronchial disorders; and severe parodontopathies. Patients with any other severe diseases were also excluded.

## Study Medication

Patients were issued one bottle with 180 tablets and told to take three tablets with water twice daily; once in the morning and once in the evening. Each tablet contained 90 mg of native extract (Batch No. 011301, Drug Extraction Ratio 3-5:1 calculated from the dried plant; extractant 65% ethanol V/V) of fresh ginkgo biloba leaves from a certified cultivation in France (batch number 009396) (A. Vogel Bioforce AG, Roggwil, Switzerland). The cultivation complies with the standards of Good Agricultural Practice (GAP); no voucher specimen has been kept. The extract contained <100 ppm ginkgolic acid and one tablet of 90 mg had 2.1% flavonol glycosides, 494 µg bilobalide, 220 µg ginkgolide A and 131 µg ginkgolide B. The fingerprint from the high-performance liquid chromatography (HPLC) analysis is given in Figure 1.

**Figure 1.** High-performance liquid chromatography (HPLC) fingerprint of ginkgolides and bilobalide from the ginkgo fresh plant extract.




## Study Conduct, Measurements, and Parameters

This was a controlled, nonblinded, parallel-group, monocentric clinical trial. The study included 32 participants; 16 participants received the test medication, and 16 participants acted as untreated controls. The study center was the Institute for Microcirculation in Berlin, Germany, and the trial was carried out in July and August 2004 in accordance with the guidelines of good clinical practice and the ethical obligations of the Declaration of Helsinki.

Eligible participants were investigated at day 0 which served as the baseline value, and at days 10, 20, and 30. Two hours prior to the investigation, participants were not allowed to drink alcohol, coffee, tea, or caffeinated carbonated beverages, they were to have had at least 6 hours of sleep the previous night, and sufficient acclimatization and rest (normal blood pressure, respiratory rate, and heart frequency). The measurements were taken while the participants were seated.

The applied investigative method was intravital microscopy in combination with reflexion spectrometry. The intravital microscopy investigation unit used a combined illuminating and radiating process with selective filtering and computer-aided image processing

(Zeiss and Nikon microscopes with a Kontron system [manufactured by Kontron, Eching, Germany]). The reflexion spectrometric investigations were carried out with the Spex System (Spex Industries, Edison, New Jersey, USA). Microphotography up to 1/8,000 s, super-Home Video System (S-VHS), and U-matic and cinema film with image frequencies up to 120 images/s (ARRI [Arnold & Richter Cine Technik, München, Germany] system) supported the documentation. A more detailed description of the instruments, methods, and technologies that were used in this study can be found in other papers.[15,16]

The target tissue was either a defined region of the subcutis of the lower left arm or of the oral mucosa (gingiva) with a volume of about 1200 µm$^3$. The authors assessed connected and complete microvascular networks that were perfused and had a defined target volume of about 1 mm$^3$ with 60 Kirchoff junctions (nodal points [$n_{NP}$]) and with an average microvessel diameter of >40 µm.

The authors assessed the following parameters by vital microscopy as microcirculatory parameters: 1) number of blood cell-perfused $n_{NP}$ in a defined network unit; 2) venular streaming flow ($Q_{ven}$); and 3) microcirculation hematocrit ($Hk_{MZ}$). To assess if ginkgo had an influence on the number of leukocytes which could be found in a defined region, the authors also measured the number of adhering white blood cells on a defined inner venule wall ($n_{WBC/A}$), and the relative concentration of intercellular adhesion molecule in the white blood cells ($C_{ICAM-1}$).

For a subgroup of 24 randomly selected participants (12 treated and 12 untreated; each group contained six men and six women), the following measurements were also made in the liver parenchyma (lower right costal arch, defined tissue volume unit V = 1200 µm$^3$): current flow in the sinusoids ($Q_{sin}$) (absolute amounts), and total cross section of the sinusoidal channel ($A_{sin}$). To assess whether ginkgo had antioxidative properties *in vivo*, the local amount of reduced and oxydated glutathione ($C_{GI\text{-}red}$) in the liver was measured. It is particularly rich in glutathione which acts as one of the strongest antioxidants in the human body.

At the end of the treatment period, the participants were assessed to determine if their condition had improved, remained the same, or worsened. In addition, participants reported any adverse events at each visit.

### Statistical Analysis

The authors determined the differences within both groups between the different time points (10, 20, and 30 days) and the baseline values at day 0. The differences between the treatment and control groups at each of the time points with the Wilcoxon rank sum test were also determined. Tests were carried out with a significance level of $\alpha$=0.05 (two-sided), and the critical values for *t* were taken from Ferguson.[17]

## RESULTS

### Demographic Data

The demographic data of the study population are listed in Table 1. The treatment and control groups were similar in age, height, weight, body mass index, and gender distribution, and were therefore comparable. All of the participants came to all of the study visits, and in the treatment group they were fully compliant regarding intake of the study medication.

### Efficacy and Safety Parameters

The mean number of blood cell-perfused $n_{NP}$ increased in the ginkgo group from 60 to 64.3 ± 2.5 in the defined network unit after 30 days of

treatment ($P$<0.05), while the values in the control group remained almost stable (from 60 to 58.4 ± 2.9 $n_{NP}$). From day 10 onward, the values in the ginkgo group compared to the control group were statistically significantly different ($P$<0.05) (Figure 2).

From day 20 of treatment onward, the $Q_{ven}$ in the ginkgo group was significantly greater compared to day 0 ($P$<0.05), and also compared to the control group ($P$<0.05) (Figure 3).

The $Hk_{MZ}$ remained almost stable in the control group, but it had decreased by 5.4% in the ginkgo group by day 30. In comparison to the control group, decreases in the $Hk_{MZ}$ in the ginkgo group were statistically significant from day 10 onward ($P$<0.05).

To measure if the ginkgo treatment had an influence on the number of leukocytes in a vessel, the number of adhering white blood cells in a defined inner venule wall were counted. The $n_{WBC/A}$ had increased significantly after 20 days in the ginkgo group ($P$<0.05); furthermore, the $C_{ICAM-1}$ was significantly higher compared to both the baseline value and to the

**Table 1.** Demographic data.

| | Control | Ginkgo |
|---|---|---|
| Number of patients | 16 | 16 |
| Number of men/women | 8/8 | 8/8 |
| Average age (mean ± SD) | 65.4 ± 2.7 | 65.5 ± 2.76 |
| Body weight (mean ± SD) | 75.6 ± 3.03 | 75.0 ± 3.18 |
| Height (mean ± SD) | 172.3 ± 2.35 | 172.3 ± 2.33 |
| BMI men (mean ± SD) | 25.56 ± 1.31 | 25.5 ± 0.96 |
| BMI women (mean ± SD) | 25.34 ± 1.32 | 25.07 ± 1.21 |

BMI=body mass index.

**Figure 2.** Number of blood perfused nodal points ($n_{NP}$) in a defined network unit during the treatment period of 30 days in participants taking ginkgo tablets ($n$=16) and in untreated controls ($n$=16). *A statistically significant difference between the ginkgo and control group ($P$<0.05).

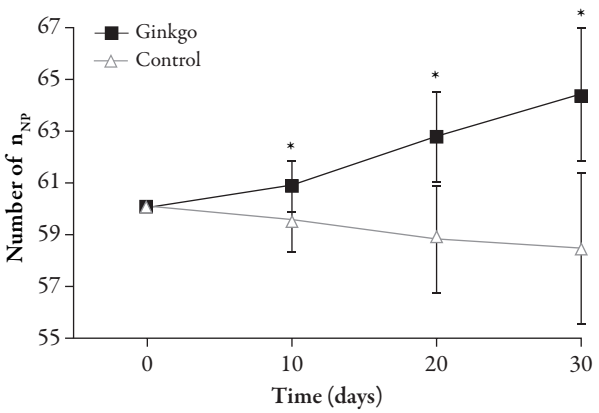



**Figure 3.** Venular streaming flow ($Q_{ven}$) in a defined network unit during the 30-day treatment period in participants taking ginkgo tablets ($n$=16) and in untreated controls ($n$=16). *A statistically significant difference between the ginkgo and control group ($P$<0.05).

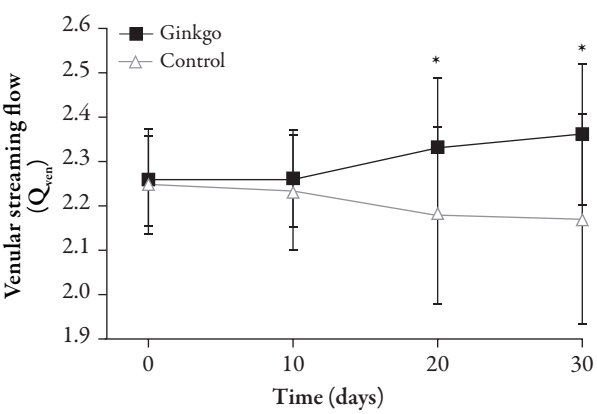
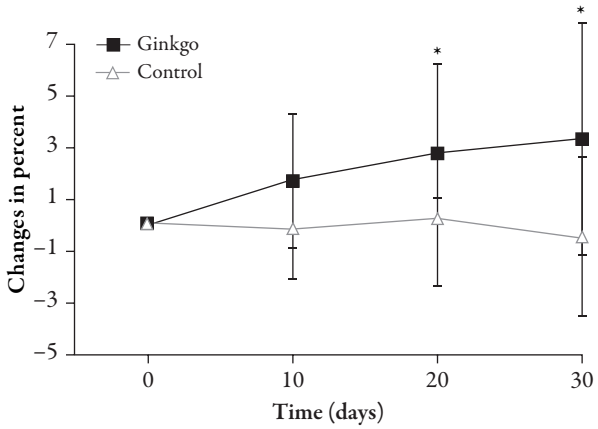


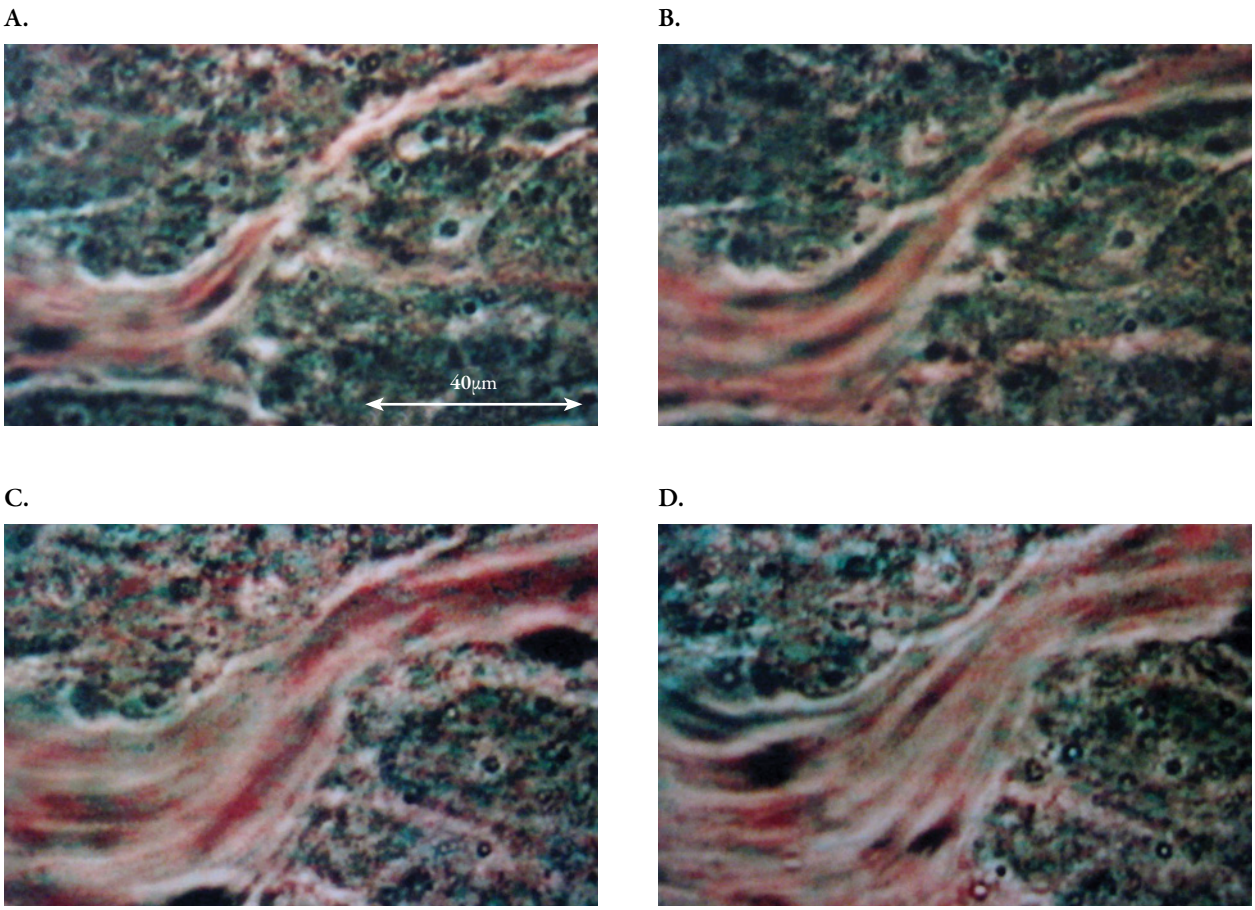
**Figure 4.** Relative changes in current flow in the sinusoids ($Q_{sin}$) in the liver in a defined network unit during the treatment period of 30 days in participants taking ginkgo tablets ($n$=16) and in untreated controls ($n$=16). *A statistically significant difference between the ginkgo and control group ($P$<0.05).




control group ($P$<0.05), which corresponded well with the $n_{WBC/A}$ number of artering leukocytes.

All of the parameters described above were assessed in the subcutis; by measuring immediately under the right costal arch, the authors were also able to investigate microcirculation in the liver. There was a significant difference in the $Q_{sin}$ in the ginkgo and the control groups from day 20 onward ($P$<0.05) (Figure 4). An example of the change in $Q_{sin}$ for a participant in the treatment group is illustrated in Figure 5. For the cross section of the Asin sinusoidal channel, no significant differences in characteristics between the ginkgo and control groups occurred. However, within

**Figure 5.** Vital microscopic examples of the functional condition of hepatic microcirculation; ie, diameter of the sinusoid and streaming flow in a participant before and after application of the ginkgo extract. A) day 0; B) day 10; C) day 20; D) day 30.



the ginkgo group there were significant changes between day 0 and day 10 onward ($P$<0.05). To assess changes in antioxidative properties, the authors measured the amount of reduced hepatic glutathione $C_{GI\text{-}red}$. Ginkgo appeared to improve the antioxidative capacity of the body: after 10 days, there was an increase in the $C_{GI\text{-}red}$, which continued to increase up to day 30, and was significantly different from the baseline value and the control group from day 20 onwards ($P$<0.05) (Figure 6).

Of the 16 patients in the control group at the end of the treatment, 11 described their state of health as unchanged, four described it as worse, and one described it as improved. In the ginkgo group, five participants described their state as unchanged, two described it as worse, and nine described it as improved. The tablets were well tolerated and no side effects were reported during the treatment period.

## DISCUSSION

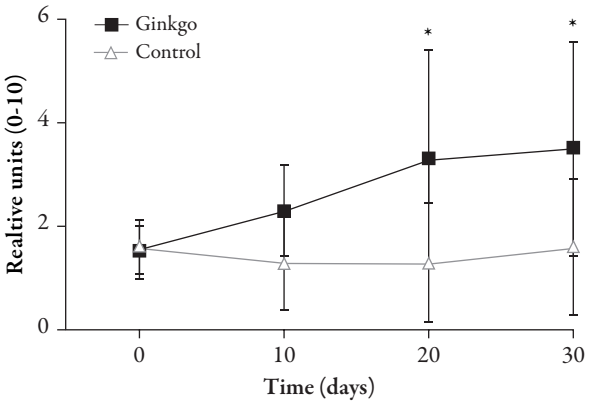
Although previous trials have shown that intravenously or orally administered ginkgo preparations have a positive effect, particularly on dermal microcirculation,[11-13] to the authors knowledge, this was the first trial to find improvement in a variety of microcirculation parameters in the skin and gingiva. The number of perfused $n_{NP}$ rose, and the venular streaming flow and hematocrit of microcirculation increased significantly compared to baseline and control values, generally after 10-20 days of taking the ginkgo fresh plant tablets.

In addition, this study demonstrated for the first time that a ginkgo preparation enhanced the microcirculation of the liver, an example of a large inner organ. This suggests that microcirculation in the entire body may be augmented. The authors also found that in the ginkgo treatment group, the amount of reduced glutathione in the liver was doubled, suggesting an increase in antioxidative action.

Nevertheless, the trial also has several limitations. The patient population was rather small and restricted to elderly patients and the treatment duration was, at 30 days, quite short. A larger, longer lasting trial with a younger population would be warranted to show if a generally younger population would experience the same effects as in this trial, and if a longer treatment with the ginkgo fresh plant tablets would lead to even better results. The mode of action of increased microcirculation caused by ginkgo is not fully understood.

In rats, an increase in blood perfusion after ginkgo application was attributed to regulation of the precapillary sphincter and to dilation of perfusion capillaries,[18] and in the blood of eight patients taking a ginkgo preparation for 2 months, concentrations of the vasodilating molecules, cyclic adenosine monophosphate (cAMP), and cyclic guanosine monophosphate (cGMP) were significantly increased compared to baseline.[19] The extent to which inhibition of a platelet activating factor (PAF)[20] and the improved rheological properties of blood play

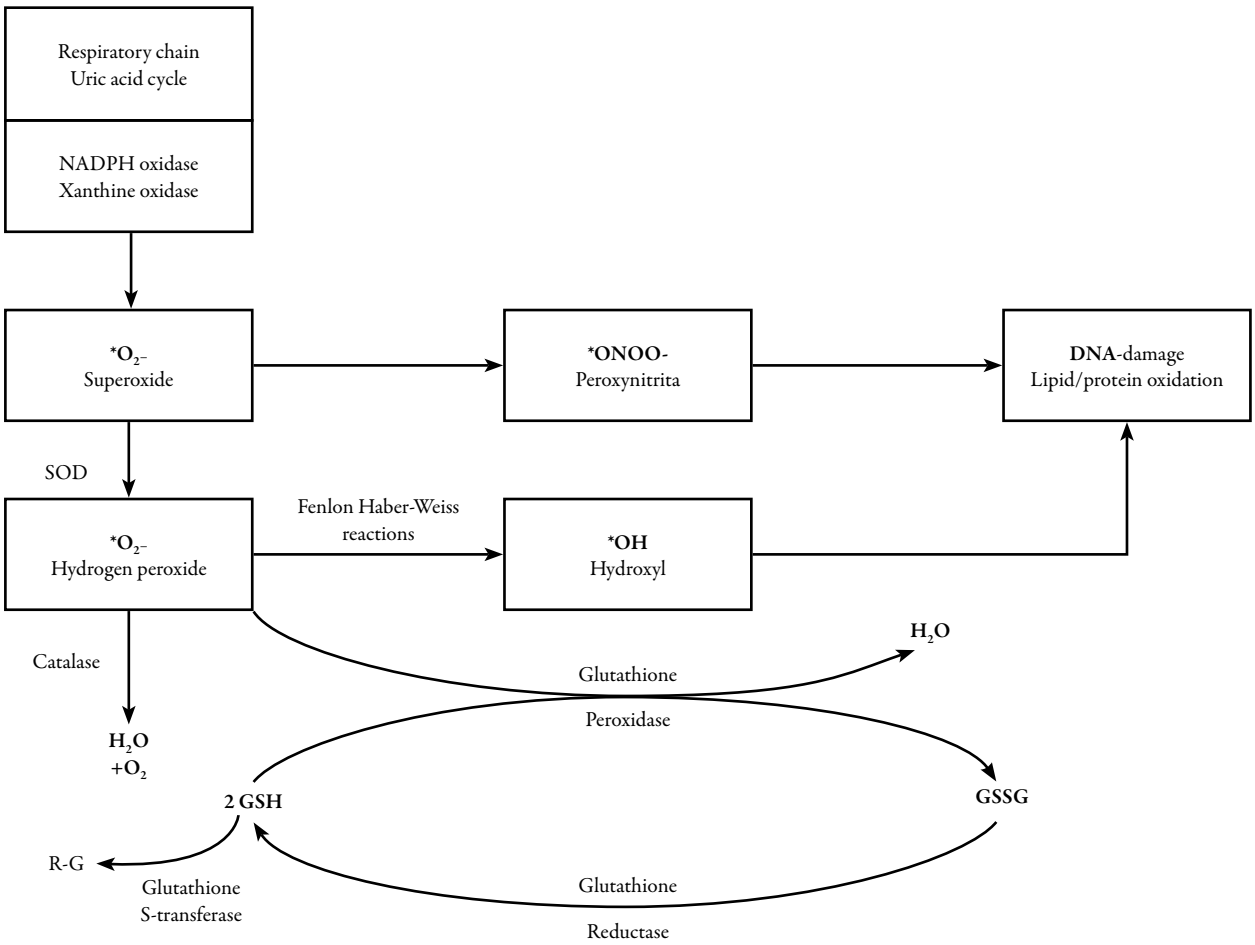
**Figure 6.** Amount of reduced glutathione measured in the liver in a defined network unit during the treatment period of 30 days in participants taking ginkgo tablets ($n$=16) and in untreated controls ($n$=16). *A statistically significant difference between the ginkgo and control group ($P$<0.05).



a role in improved microcirculation remains a topic of discussion.[5]

The active constituents of ginkgo that are responsible for its pharmacological effects are mostly flavonoids, terpenoids, such as ginkgolide A, B, and C, and bilobalides.[2] Although ginkgo was used traditionally as a tea,[21] alcoholic tincture,[22] or extract, just one extract has been used in most clinical trials and research: the standardized ginkgo special extract EGb761 (DER 35-67:1, producer Dr. Willmar Schwabe GmbH, Karlsruhe, Germany). In this trial, a new extract was used made from fresh leaves from ginkgo with ethanol as an extractant, which is a more traditional way to produce a herbal preparation. In a previous study, administration of this extract was associated with a significant improvement in the retinal capillary blood flow after 1 hour in eight healthy volunteers.[14] In a bioavailability trial, the extract displayed absorption kinetics for the active constituents

**Figure 7.** Scheme of the production of free oxygen radicals and their elimination and detoxification by superoxide dismutase (SOD), catalase, and glutathione peroxidase. Increased amounts of reduced glutathione (two glutathione [GSH]) are mostly caused by SOD upregulation. GSSG=glutathione disulphide; NADPH=nicotinamide adenine dinucleotide phosphate; OH=hydroxide; ONOO=peroxynitrite. *Diagram adapted from Siegel et al.*[19] *with friendly permission of Springer Verlag, Vienna, which also owns the copyright for this figure.*



(bilobalide and ginkgolide A and B) that were similar to the standardized extract; these constituents may be the basis for the rapid increase in retinal blood flow.[23] In another trial in elderly patients with age-related non-Alzheimer mild cognitive impairment, daily intake of two tablets containing 90 mg each of the ginkgo fresh plant extract was associated with an improvement in the SF-12 quality-of-life mental health subscore. Furthermore, treated patients had decreased memory impairment and increased ability to concentrate; in this study, the extract was well tolerated.[24] The study on the retinal blood flow[14] showed a good efficacy between 90 and 270 mg extract, and the bioavailability trial showed a higher amount of active constituents in the blood than as if a patient would take a ginkgo tincture.[23] Thus, a dosage scheme of 2x 90 mg extract daily was chosen, which proved to be safe and effective in the above mentioned trial in elderly patients.[24]

An important finding of this study was that the ginkgo preparation used was associated with a two-fold increase in the amount of reduced gluthathione in the liver, indicating antioxidant activity. Glutathione is a specific, low molecular weight thiol (SH) group carrier; two molecules of glutathione become one double molecule linked by a disulfide bridge, by means of reversible oxidation. The unreduced and reduced forms of glutathione are an important cellular oxidation-reduction system, particularly in liver cells.[25] Details about the formation of glutathione are outlined in Figure 7.[19] The effect of the ginkgo extract on glutathione is in line with the findings of Rodriguez et al.,[26] who found that the activity of superoxide dismutase (SOD) was upregulated by 15.7% on average after a 2 month application of 240 mg of Egb761/day in eight patients, leading to a reduced ratio of oxidized low-density lipoprotein (LDL) to normal LDL, and a higher concentration of lipoprotein (a). Based on their results, Rodriguez et al. saw potential for ginkgo as an adjuvant treatment for atherosclerosis prevention in predisposed patients.

The improved microcirculation observed in the current study has several clinical implications: impaired microcirculation can be a precondition or manifestation of numerous pathologies, such as chronic venous insufficiency,[27] hypertension, insulin resistance, and sepsis,[28] and it is believed to play a role in metabolic syndrome,[29] Raynaud syndrome,[30] and erectile dysfunction.[31] Microcirculation is generally decreased in smokers,[32] and most likely also in patients with cognitive disorders.[33] Furthermore, as people age, perfusion decreases; thus, elderly persons in particular have impaired microcirculation.[34] Ginkgo has a very good safety record[2,21] and the good tolerability of this ginkgo extract has been seen in all the trials which have been carried out so far.[14,23,24] Thus, taking ginkgo to improve perfusion of the capillary networks in the entire body may be a good preventative measure or an adjuvant treatment option for people with impaired microcirculation.

## CONCLUSION

The authors found that a new ginkgo fresh plant extract improved microcirculation significantly, and increased the body's ability to scavenge free radicals. The treatment was well tolerated and accepted by the patients. This new ginkgo extract may be an interesting complementary treatment option in patients suffering from diseases in which decreased microcirculation plays a pivotal role. In addition, because it boosts the body's radical scavenging properties, it should be considered as an adjuvant preventative treatment for atherosclerosis.

## ACKNOWLEDGMENTS

A. Vogel Bioforce sponsored the trial. Dr. Klopp and Dr. Niemer carried out independently the whole trial and analyzed the data. A. Suter is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

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