

Prevention of Arteriosclerosis and Promotion of Well-Aging

A Phytochemical Approach with Ginkgo biloba (EGb 761)

Zum ersten Mal publiziert «phytotherapie» einen englischen Artikel. Dies geschieht auf Wunsch des (deutschsprachigen) Hauptautors. Damit leitet die Redaktion von «phytotherapie» nicht etwa einen Wechsel zu nur noch englisch verfassten Beiträgen ein, es ist ganz einfach eine Anpassung an die Realität. Und heute darf man davon ausgehen, dass ein auf Englisch verfasster Artikel allen an Phytotherapie interessierten Personen zugänglich ist.

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Zusammenfassung

Die Vorbeugung oder Verzögerung der Arterioskleroseentstehung ist eine der bedeutsamsten Well-Aging-Massnahmen, da dies eine Möglichkeit zur Vermeidung von Myokardinfarkt und Schlaganfall ist. Zur Erreichung dieses prophylaktischen Ziels kann möglicherweise eine phytochemische Behandlung dienen, die der Peroxidation von Blutlipiden aufgrund ihrer Radikalfängereigenschaften für reaktive Sauerstoffspezies (ROS) entgegenwirkt. So sind zum Beispiel oxidierte LDL-Partikel hochatherogen. Auf diesem Hintergrund erforschten wir in einer Pilotstudie die Wirkung von Ginkgo biloba – dessen Fängereigenschaften freier Sauerstoffradikale ausführlich dokumentiert sind – auf die arteriosklerotische Nanoplaquebildung bei kardiovaskulären Hochrisikopatienten.

Nach Beschichtung einer Silikatoberfläche mit dem isolierten Lipoproteinrezeptor Proteoglykan (HS-PG) aus arteriellem Endothel und der Gefäßmatrix konnten wir die allerersten Stufen der arteriosklerotischen Plaqueentstehung mit ellipsometrischer Technik beobachten (Patent EP 0 946 876). Diese sogenannte Nanoplaquebildung wird durch den ternären Aggregationskomplex aus HS-PG-Rezeptor, Lipoproteinpartikeln und Kalziumionen repräsentiert. Dieses Modell wurde in mehreren klinischen Studien mit kardiovaskulären Hochrisikopatienten bestätigt, wobei deren native Blutlipoproteinfraktionen zur Anwendung kamen.

Bei acht Patienten, die sich einer aortokoronaren Bypass-Operation unterziehen mussten, betrug die Reduktion der arteriosklerotischen Nanoplaquebildung nach einer zweimonatigen Therapie mit Ginkgo-biloba-Spezialextrakt (EGb 761, 2-mal 120 mg täglich, Rökan® novo, Spitzner Arzneimittel, Ettlingen, Deutschland) im Mittel $11,9 \pm 2,5$ Prozent ($p < 0,0078$) und der Nanoplaquegröße $24,4 \pm 8,1$ Prozent ($p < 0,0234$). Zusätzlich war die Superoxid-dismutase (SOD-)Aktivität um $15,7 \pm 7,0$ Prozent ($p < 0,0391$) aufreguliert, der Quotient oxLDL/LDL um $17,0 \pm 5,5$ Prozent ($p < 0,0234$) erniedrigt und die Lipoprotein(a)-Konzentration um $23,4 \pm 7,9$ Prozent ($p < 0,0234$) im Patientenblut nach der zweimonatigen Ginkgo-Einnahme vermindert. Die Konzentration der gefässerweiternden Substanzen cAMP und cGMP war um $37,5 \pm 9,1$ Prozent ($p < 0,0078$) beziehungsweise um $27,7 \pm 8,3$ Prozent ($p < 0,0156$) erhöht. Eine multimodale Regressionsanalyse ergab die Basis für eine mechanistische Erklärung der Nanoplaquereduktion unter Ginkgo-Behandlung. Der arteriosklerosehemmende Effekt ist der Aktivitätserhöhung der körpereigenen Radikalfängerenzyme zuzuschreiben sowie einer Beeinträchtigung der Risikofaktoren oxLDL/LDL und Lp(a). Weiterhin wurde das Offenhalten des Bypasses durch die signifikante Erhöhung

der gefässerweiternden cAMP- und cGMP-Konzentrationen kräftig unterstützt.

Introduction

In westernized societies, the epidemic atherosclerosis and its clinical sequelae heart disease and stroke are the underlying cause of about 50 percent of all deaths. Thus, the prevention or deceleration of atherogenesis is one of the most significant anti-aging objectives since this is a matter of avoidance of myocardial and cerebral infarction. Epidemiological studies have revealed several important environmental and genetic risk factors associated with atherosclerosis. Therefore, it is badly indicated that long-term changes in life style and prophylactic measures to reduce cardiovascular risk factors, solid diagnostic examinations before and during medicinal treatment, and profound and safe course controls are applied. Central to disease diagnosis and therapy is a clear understanding of the underlying biophysicochemical alterations and abnormalities.

The oxidation of LDL and other lipoproteins is an essential step in the pathogenesis of atherosclerosis, so the 'oxidative modification hypothesis' [50]. Many studies in animal models and clinical trials in humans pointed to the importance of oxidized LDL (oxLDL) [22]. Despite of epidemiologic data in humans supporting a protective role for antioxidant supplementation [17], prospective clinical trials

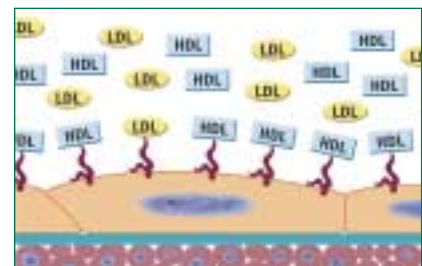


Figure 1: Cholesterol receptor (proteoglycan sulfate) with bound high-density lipoprotein HDL (normocholesterinaemic condition).

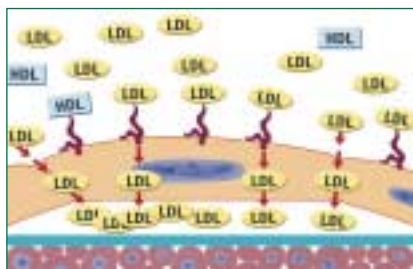


Figure 2: Cholesterol receptor (proteoglycan sulfate) with bound low-density lipoprotein LDL (hypercholesterinaemic condition). LDL is also located in the subendothelial space.

with antioxidant vitamins, such as vitamin E and β -carotene, in patients with preexisting atherosclerosis have thus far been disappointing [52]. This, however, is not necessarily in contradiction to the oxidative modification hypothesis, especially because antioxidants may have a beneficial effect on the long-term outcome only in the early stages of atherosclerosis. Furthermore, it is possible that these studies with antioxidants have not yet led to convincing results in favour of the oxidative modification hypothesis only because of methodologic difficulties [50]. Thus, pinpointing the molecular mechanisms responsible for LDL oxidation in vivo and defining the most susceptible patient populations will be necessary for the development of specific and efficacious approaches to antioxidant therapy.

The present communication elucidates results from a clinical trial which led to the discovery of a further pleiotropic Ginkgo biloba effect, that is the immediate intervention into plaque formation at the very earliest stages in atherogenesis before any cellular reactions. Nanoplaque build-up and estimate of its size could be pursued by ellipsometric techniques using an established molecular model for atherosclerosis [40], that was tested in a biosensor application with the lipid fractions of ginkgo-treated patients. Since the initial lipid deposition steps in atherogenesis are surface-related phenomena at endothelial cells and vascular matrices, we carried out this investigation on the adsorption of lipoproteins in order to learn more about their interfacial behaviour. Hydrophobic silica surfaces were modified through adsorption of heparan sulfate proteoglycan (HS-PG), the latter substrate both mimicking the surface receptors exposed to lipoproteins in the blood stream or on their paracellular

pathway [38,41]. In order to obtain information of some biological relevance, an important aspect of the present investigations was to perform these experiments at close to in vivo conditions. In the present study, the results of a long-term intervention of ginkgo, independent of any change in lipid concentrations, into atherosclerotic nanoplaque build-up using the plasma of eight cardiovascular high-risk patients after aortocoronary bypass operation are discussed and mechanistically interpreted.

Results and Discussion

Development of Atherosclerosis

To begin with, the formation and development of an atherosclerotic plaque and of a thrombus, as they occur in the peripheral large and small arteries, shall be called back to mind very briefly. The primary lesion (fatty streak) proceeds over months and years to a calcified atheroma with fibrous cap which can disrupt at the shoulder in the case of a vulnerable plaque [22,50]. The injury is occluded by wound healing processes (finally thrombus formation), which may have fatal consequences imperative to prevent. Looking at blood vessels in a longitudinal section, the vascular smooth muscle cells are found crossways. In the endothelial cell membrane, the molecular cholesterol receptors (heparan sulfate proteoglycan, HS-PG), the size of which is in the nanodimension scale, are represented. Physiologically, these cholesterol docking sites are occupied by high-density lipoprotein (HDL), because HDL has a fourfold higher affinity constant to HS-PG as compared to LDL [1] (Figure 1).

This means that a person with a blood concentration of 50 mg/dL HDL can afford a 200 mg/dL LDL concentration without being cardiovascularly endangered if otherwise no further risk factors (e.g. smoking, hypertension etc.) exist. Thus, HDL bound to the HS-PG receptor does not only control the cholesterol back transport (lipid exit) from the cells to the liver, but also, in a feedforward circuit, the entire transmembrane and paracellular lipid entry into the vessel wall [1,39]. Thus, for diagnostics at least the LDL/HDL quotient has to be measured in order to obtain a first insight into the lipid status of a person.

If the LDL cholesterol concentration in the plasma of a patient is strongly in-

creased, his HDL concentration is diminished or if both are the case, the lipoprotein receptors are occupied by LDL (Figure 2). An interaction can easily occur between HS-PG receptors, LDL and the Ca^{2+} ions in the blood, ternary aggregational complexes can be formed, atherosclerotic nanoplaques have developed, the very first stages of atherosclerotic plaques before any cellular response.

At present, these nanoplaques cannot be detected by laboratory chemical procedures nor can they be depicted by NMR imaging or spiral-computer tomography. The chemical analysis of fully blown atherosclerotic plaques yielded heparan sulfate proteoglycan receptors, lipoproteins and calcium as main components, i.e. the same constituents as in the atherosclerotic nanoplaque on the molecular level. When a high concentration of reactive oxygen species (ROS) occurs in the blood and/or tissue, as, for example, in the case of smoking or after extensive exposure to sunlight, LDL particles, cell membranes or even DNA can be oxidatively attacked [50]. By lipid peroxidation, LDL is transformed to the even more aggressive oxLDL (an oxygen radical itself), which does not only create nanoplaques very easily, but, being no longer recognized as endogenous, is taken up by attracted macrophages finally changing to foam cells. Now a stage of atherosclerosis is reached, in which cellular reactions promote plaque formation progressively [35].

Preventive Effects of Ginkgo Extract on Nanoplaque Formation

The cell surface membrane uptake of lipoproteins in general is carried out by the LDL receptor, lipoprotein related peptide (LRP) [20] and HS-PG pathways [3]. As just elaborated, in the arterial vascular wall, where atherosclerotic plaques develop, HS-PG sequestration plays the major role [18]. In our atherosclerosis model, a hydrophobic methylated silica surface is coated by a monomolecular layer of isolated proteoglycan sulfate depositing through its transmembrane hydrophobic core domain (patent EP 0 946 876) [40] (Figure 3). The glycosaminoglycan (GAG) side chains are stretched out into the blood substitute solution because of their negative fixed charges giving rise to electrostatic repulsion [23,42,43].

Lipoprotein particles or cations may interact with the GAG chains, for exam-

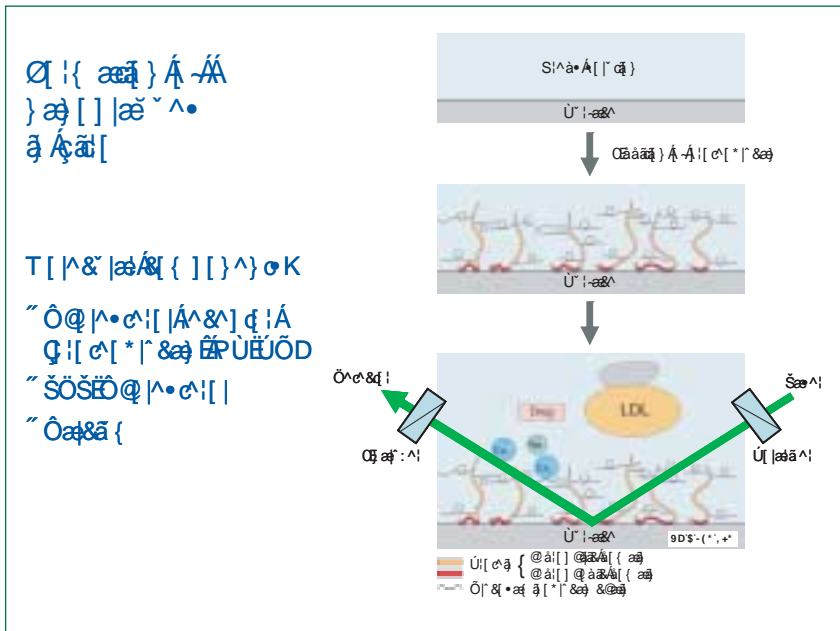


Figure 3: Monomolecular coating of a methylated silica surface with proteoglycan sulfate molecules and their interaction both with Ca^{2+} and Na^{+} ions and lipoprotein particles in blood substitute solution (not to scale). Furthermore, the influence also of pharmaceuticals can be tested in this laser-based biosensor model (EP 0 946 876).

Problem Formulation

- Is it possible in high-risk patients to reduce atherosclerotic nanoplaque formation with the special Ginkgo extract EGb 761?
- What is the underlying mechanism?

Figure 4: Problem Formulation

ple, on occasion of their positive amino acid residues or simply their positive charges. Thus, the situation reflects physiological conditions, since, for example, in the endothelial cell membrane, the scenario differs only in one respect, that the short hydrophilic intracellular core domain is located in the cell interior. In this sense, the hydrophobic silica surface simulates the cell membrane overlaid with the glycolyx quite perfectly.

With the following pilot study we wanted to evaluate the applicability of the molecular model for nanoplaque formation in the clinical situation (Figure 4).

The study «Klinische Studie zur arteriosklerotischen Nanoplaquebildung an Bypass-Patienten unter dem Einfluss von Ginkgoextrakt Rökan® (EGb 761)» was conducted at the Heart Center Brandenburg, Clinic for Cardiac Surgery, Bernau, Germany, according to good clinical practice and ethical principles of the Declaration of Helsinki. All patients gave

their written informed consent prior to their inclusion in the study. The local Ethics Committee of the Landesärztekammer Brandenburg, Cottbus, Germany, approved the study (S10/2004). Within this clinical trial investigating the effectiveness of ginkgo extract on lipoprotein subfractions in cardiovascular high-risk patients after aortocoronary bypass operation, the blood of the patients was taken before and after two months therapy with 2 x 120 mg ginkgo daily (Figure 5), and the in vivo-concentration of the VLDL/IDL/LDL-fraction applied in our assay [3,9].

The atherosclerotic nanoplaque as represented by the ternary complex of the HS-PG receptor, lipoprotein particles and calcium ions was then pursued through increasing the Ca^{2+} concentration (Figure 6). This ternary aggregational formation on endothelial cell membranes and vascular matrices may mimic the ‘primary lesion’ with its endothelial dysfunction, the very earliest stages in atherogenesis on a molecular level [39].

Summarizing, at an HS-PG-coated silica surface representing a receptor site for specific lipoprotein binding through basic amino acid-rich residues within their apolipoproteins, the binding process was studied by ellip-

sometric techniques [41]. HDL was found to exhibit a high binding affinity and a protective effect on interfacial HS-PG layers with respect to LDL and Ca^{2+} complexation. LDL proved to be deposited strongly at the proteoglycan-coated surface, particularly in the presence of Ca^{2+} , apparently through complex formation ‘lipoprotein receptor (HS-PG) – low-density lipoprotein – calcium’. This ternary complex build-up may be interpreted as atherosclerotic nanoplaque formation on the molecular level before any cellular reactivity, possibly responsible for the atherosclerotic primary lesion.

Although there was no change in lipid concentrations after ginkgo medication, it is demonstrated in Figure 7 how nanoplaque generation can be reduced.

Here, the results with the lipoprotein fraction of VLDL/IDL/LDL in its natural blood concentration of one of the patients are illustrated. It is impressively shown that the lipid docking mechanism to HS-PG fundamentally changed after drug treatment and that the first gradual and then steep increase in nanoplaque formation was largely blocked upon a two month medication with ginkgo. Since nanoplaque formation is a Ca^{2+} -driven process, a complete Ca^{2+} titration curve was measured. As one can easily see, the stepwise increase in adsorbed amount (nanoplaque build-up) upon Ca^{2+} additions of 10.08 and 17.64 mmol/L in the baseline measurement is no longer present after ginkgo treatment. Calculating the percent reduction in nanoplaque formation and size at each Ca^{2+} concentration used, the mean value of all experimental points during the Ca^{2+} period in question was related to the mean value of all experimental points during the VLDL/IDL/LDL binding period ($[Ca^{2+}] = 0$ mmol/L). The respective quotient for each Ca^{2+} period in the

Study design

- n = 8 Patients**
State after bypass operation upon high-grade coronary artery disease
- Therapy**
Standard therapy: ASA, beta-blocker, ACE inhibitor
+ 2 x 120 mg Ginkgo special extract EGb 761 over 2 months
No statins, no calcium antagonists, no nitrate compounds
- Experimental Parameters**
Nanoplaque formation and size (ellipsometry)
Changes in blood lipid concentrations
Activity of ROS scavenging enzymes and its consequences
Concentration of vasodilating substances (cAMP, cGMP)

Figure 5: Study design

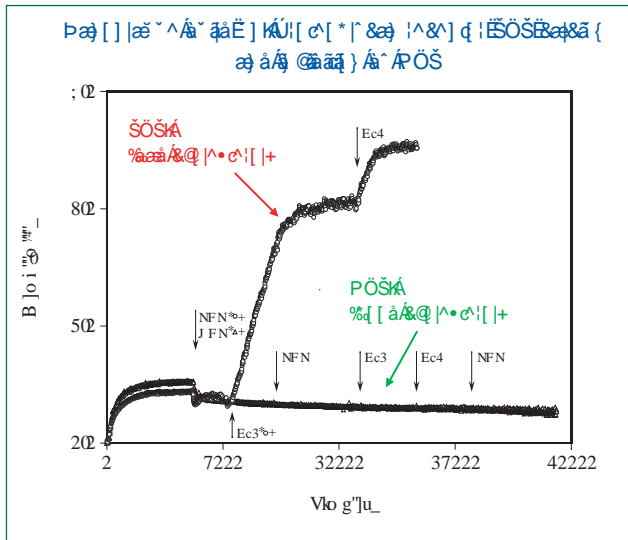


Figure 6: Comparison of the Ca²⁺-induced LDL deposition at methylated silica coated with heparan sulfate proteoglycan in the absence (circles) and presence (triangles) of HDL addition (0.75 mmol/L) prior to the LDL addition (1.5 mmol/L). At time zero, proteoheparan sulfate was adsorbed, whereas the other additions are indicated in the figure (Ca1: 2.52 mmol/L; Ca2: 10.08 mmol/L).

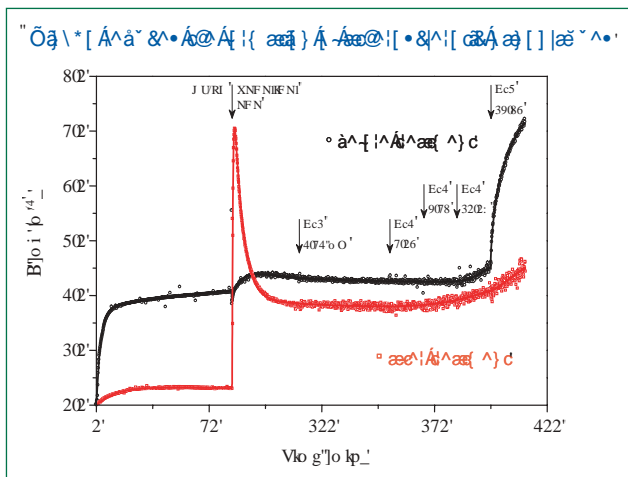


Figure 7: Total adsorbed amount versus time. At time zero, HS-PG (0.1 mg/ml) was adsorbed on hydrophobic silica from a Ca²⁺-free Krebs solution. The first arrow indicates the addition of the plasma VLDL/IDL/LDL fraction at its in vivo concentration from a cardiovascular high-risk patient either untreated (○, black curve) or after 2 months treatment with daily 2 x 120 mg Ginkgo biloba extract (□, red curve). Total Ca²⁺ concentrations in solution are indicated at the arrows. The thick, solid lines were computed by an iterative parameter fit of the nonlinear allosteric-cooperative, simple-saturative or exponential kinetics to the experimental points using an algorithm for least-squares estimates. The pH was 7.40 (○) and 7.24 (□), respectively.

control curves was set to 100 percent [cf. 39].

Figure 8 shows that beyond nanoplaque formation and deposition (A) also its dimensional build-up (B) is a Ca²⁺ driven process.

Adsorbed layer thickness which is related to the molecular size of the ternary aggregational complexes did not markedly increase upon Ca1, but pro-

minently upon Ca2 additions, in complete accordance with former experiments in the absence of proteoglycan coating of the silica surface [42] and with light scattering experiments [24], where the adsorbed amount and particle size, respectively, increased significantly with Ca2 incubation. The augmentation in adsorbed layer thickness with increasing Ca²⁺ concentration took a distinctly reduced course after 2 months of therapy as compared to the control curve. This applies particularly to Ca²⁺ concentrations up to 17.64 mmol/L.

These investigations with the atherogenic apoB100 lipoprotein fraction from eight high-risk patients emphasized that long-term treatment with ginkgo can partly prevent both the formation and the size development of ternary nanoplaques, and this even at high Ca²⁺ concentrations. Figure 9 illustrates the extent of inhibition. There arose a similar curve profile for both the reduction in adsorbed amount and in adsorbed layer thickness of ternary nanoplaques dependent on the Ca²⁺ concentration used.

The degree of inhibition varied between 11.9 and 44.5 percent for nanoplaque formation. Similar in shape, but more prominent results were found for the reduction in nanoplaque size ran-

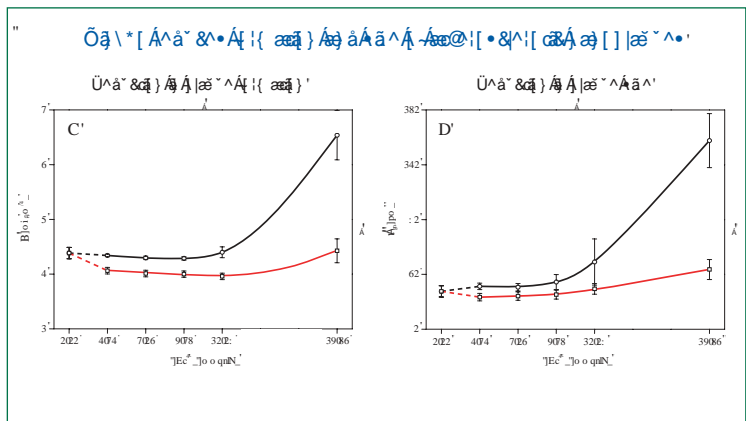


Figure 8: Total adsorbed amount (A) and adsorbed layer thickness (B) as derived from experiments as shown in Figure 10, dependent on the Ca²⁺ concentration of the Krebs solutions. Adsorbed amounts and layer thicknesses were normalized to a common mean value of the VLDL/IDL/LDL incubation periods (zero Ca²⁺ concentration). Symbols as indicated in Figure 10 (○, □) reflect the mean values of all experimental points during the Ca²⁺ period in question, averaged for 8 patients (A: p < 0.007 for all Ca²⁺ concentrations; B: p (*) < 0.016).

ging between 21.1 and 67.4 percent. Thus, the special ginkgo extract EGb 761 effectively diminished both atherosclerotic nanoplaque formation in high-risk patients and reduced nanoplaque size.

Mechanistic Explanation of Nanoplaque Reduction

Unlike statins, ginkgo is not an HMG-CoA reductase inhibitor and a lipid lowering drug. Therefore, it is not surprising that no correlations are seen between nanoplaque reduction on the one hand and variations in the lipid fractions VLDL, IDL and LDL applied in the experiment on the other hand (very low r-values). This result was to be expected. Since ginkgo has been well known for a long time as an oxygen free radical scavenging substance with high antioxidative capacity [14,16,44] as well as a potent vasodilator drug [4,10,12], we determined superoxide dismutase (SOD) activity, oxLDL/LDL ratio and cyclic nucleotide concentrations of cAMP and cGMP in the blood of the patients. In Figure 10, the results for both the SOD activities and oxLDL/LDL ratios before and after a 2-month ginkgo treatment are summarized.

While the oxLDL/LDL quotient was reduced by 17.0 percent (p < 0.0234), the SOD activity increased by 15.7 percent (p < 0.0391) on average. Obviously, the reactive oxygen species (ROS) scavenging properties of ginkgo diminished the share of oxidized LDL in total LDL-cholesterol and in this way relieved cytosolic SOD of the free radical burden. Alternatively, a direct stim-

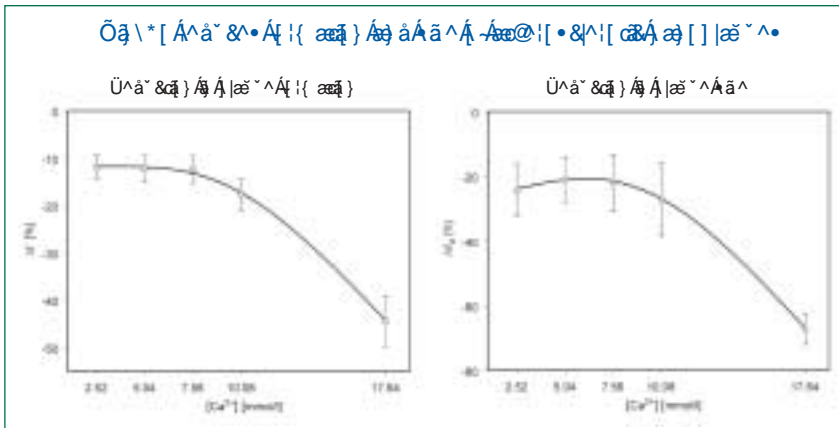


Figure 9: Reduction in Ca^{2+} -induced changes in adsorbed amount (A) and layer thickness (B) as derived from the curves in Figure 8. The reductions upon application of the VLDL/IDL/LDL fractions taken from 8 patients treated with 2 x 120 mg/d Ginkgo biloba for a 2-month intake were calculated as a ratio to the control values of the untreated patients.

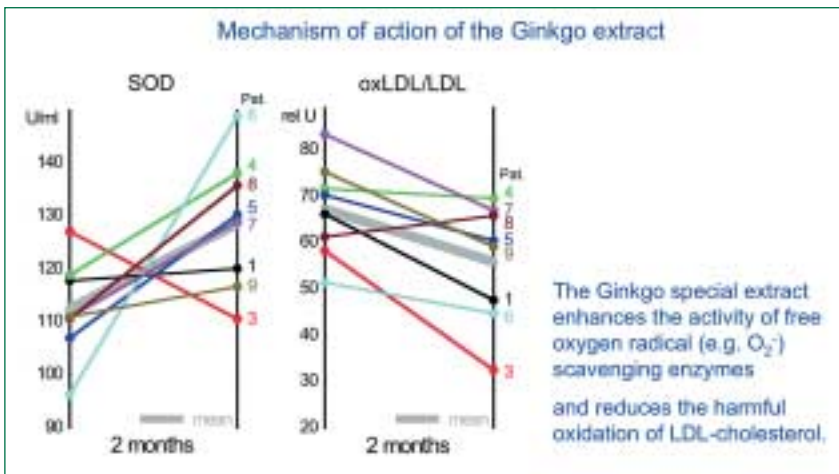


Figure 10: Superoxide dismutase activity (SOD) and oxLDL/LDL ratios in the blood of 8 cardiovascular high-risk patients before and after a 2-month ginkgo therapy. Mean time courses are given by the thick grey lines.

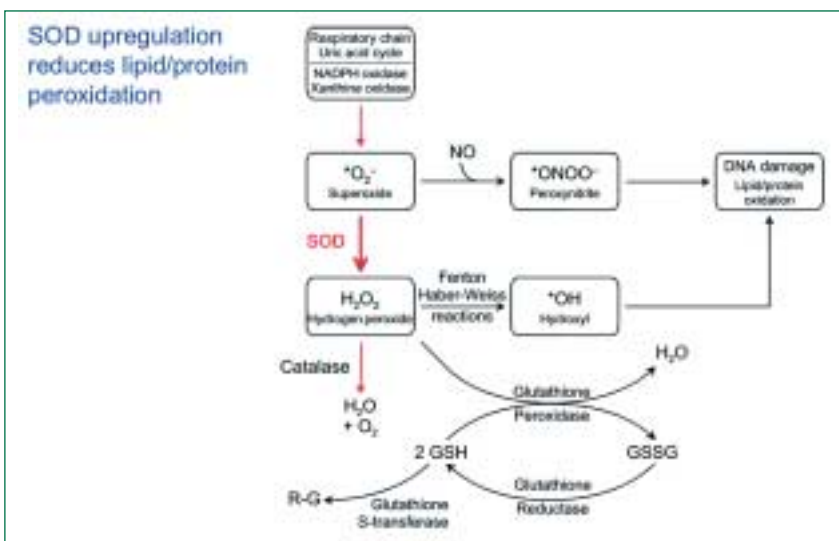


Figure 11: Production of free oxygen radicals in the respiratory chain and the uric acid cycle and their elimination and detoxification by superoxide dismutase (SOD), catalase and glutathione peroxidase. The SOD upregulation by ginkgo extract attenuates the lipid/protein oxidation.

ulation of SOD by ginkgo has been described [7,29].

As a powerful antioxidant, ginkgo diminishes oxidative stress by its high content in flavonoid constituents [6,21, 33,48]. These phenylbenzopyrones are free radical scavengers and thus decrease ROS [cf. 30]. Superoxide anion radicals generated in the respiratory chain and the uric acid cycle are dismuted by SOD to hydrogen peroxide and oxygen. Under physiological conditions, the conjugation of catalase to SOD ensures that as soon as a superoxide dismutation reaction occurs, the resultant H_2O_2 is removed by the immediate proximity of the catalase molecule [27]. Thus, catalase conjugated to SOD and additionally the redox function of glutathione minimize the conversion of hydrogen peroxide to hydroxyl radicals by the Fenton reaction. These highly aggressive and toxic hydroxyl radicals can attack lipids, proteins or DNA to acquire the missing electron (Figure 11).

We have seen that the conversion of H_2O_2 to H_2O and O_2 is multiply safeguarded and normally not the rate limiting step. Under ginkgo therapy, the SOD activity was upregulated, either because SOD was relieved through the radical scavenging properties of ginkgo or directly stimulated by ginkgo. Thereby, the reaction $^*\text{O}_2^- \rightarrow \text{H}_2\text{O}_2$ is strongly promoted, and a conversion under NO inward transfer from $^*\text{O}_2^- \rightarrow ^*\text{ONOO}^-$ (peroxynitrite radical) largely ceases. Since catalase and glutathione peroxidase produce H_2O and O_2 from hydrogen peroxide, the $^*\text{OH}$ hydroxyl radical production is minimized. This effect is reflected by a decrease in the oxLDL/LDL ratio; the share of oxLDL generated through lipid peroxidation, in total LDL is diminished. This presumption is substantiated by the proof of a direct linear correlation between SOD and oxLDL/LDL ($r = 0.89$; $p < 0.0077$).

There are several theories how oxLDL is created in vivo. In the blood plasma, there are many antioxidants, so that an extended oxidation of LDL particles could hardly take place. Moreover, endothelial cells of liver sinusoids and Kupffer's cells which are copiously occupied by scavenger receptors [46], would immediately remove modified LDL from the circulation. Most probably, the oxidation occurs in the vascular wall itself. There, microdomains could develop, small spaces largely devoid of antioxidants [49]. In the vascular wall,

Numerous clinical studies proved that ginkgo extract has a marked vasodilating effect by improving the endothelium and smooth muscle function [4,10,12]. In pharmacologic investigations, a significant increase in smooth

adhesion to vascular endothelial cells) to improve blood flow and tissue perfusion [4]. Furthermore, the protection of NO against free radical attack (inhibition of peroxynitrite formation) can be added to the list of vasomotor actions of ginkgo. Thus, the increase in cAMP and cGMP causes vasorelaxation, a beneficial effect in the bypass patients in whom the bypass should remain open. The [cAMP] increase which was actually observed for the first time, was quite surprising for us. We assume that cAMP is augmented because in blood vessels, the NO release is generally combined with a co-release of PGI₂ [cf. 10]. The latter would then increase the cAMP concentration. Alternatively, an inhibition of α -adrenoceptors might be discussed.

Summary

According to these results and explanations, it is evident to compare the effects of the ginkgo extract with those of statins (Figure 13). Although, for example, the nano-platelet reduction can amount to 45–50 percent after a single dose application of

fluvastatin without any lipid lowering [39] and is thus considerably stronger than after ginkgo intake, a significantly higher risk for and wider spectrum of side effects remains for statins.

In conclusion, even though this is a pilot study, we could measure remarkable effects in these cardiovascular high-risk patients after a 2-month Ginkgo biloba (EGb 761) medication (Figure 14): arteriosclerotic nano-platelet formation and size were diminished; the special extract did not change blood lipid composition; the anti-arteriosclerotic effect is possibly due to an upregulation in the body's own radical scavenging enzymes and an attenuation of the risk factors oxLDL/LDL and Lp(a); ginkgo increased the concentration of the vasodilating nucleotides cAMP and cGMP. Of course, further clinical studies are needed to corroborate these findings. ■

muscle cGMP concentration was measured, which can be explained by a stimulation of NO release from vascular endothelial cells [19,32]. After a 2-month EGb 761-intake we found the concentration of cAMP elevated by 37.5 percent and of cGMP by 27.7 percent, respectively. To our knowledge, in this study it was observed for the first time that the cAMP and cGMP concentration distinctly increased in the blood of the patients under ginkgo therapy. This emphasizes the membrane diffusibility for cyclic nucleotides [5,8,28], which are even transported in the kidney [2,31]. This means that the strong rise in cyclic nucleotide concentrations in the blood of the patients reflects a similar enhancement within the cells. Such ginkgo-induced increases in cAMP and cGMP concentration could function both abuminally (providing vasodilatation) and lumenally (reducing platelet aggregation, and platelet and leukocyte

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The effect of Ginkgo in comparison to frequently applied synthetic cholesterol lowering substances (statins)

- Different mechanism of action
- Clinically similar order of magnitude in reduction of nano-platelet formation and size
- Lower spectrum in side effects

Figure 13:

Conclusion

- The special Ginkgo extract EGb 761 effectively diminished atherosclerotic nano-platelet formation in cardiovascular high-risk patients and reduced plaque size
- The special extract did not change blood lipid composition
- The atherosclerosis inhibiting effect is possibly due to an upregulation in the body's own radical scavenging enzymes and an attenuation of the risk factors oxLDL/LDL and Lp(a)
- Ginkgo increased the concentration of the vasodilating substances cAMP and cGMP
- The ROS scavenger qualities, the positive influence on oxidative stress and the vasoprotective effects of Ginkgo predestine this phytochemical dietary supplement for prevention against endothelial dysfunction and atherosclerosis. Thus, Ginkgo should be assigned a fixed rank among the anti-aging medical therapeutics.

Figure 14:

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Anmerkung der Redaktion:

Das im Artikel erwähnte Studienpräparat, Rökan® novo, Spitzner Arzneimittel, D-Ettingen (Wirkstoff EGb 761, 120 mg) existiert in der Schweiz nicht.

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