Ginkgo biloba

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Nome botanico

Ginkgo biloba L. *(Ginkgoaceae)*

Parti usate

Foglie.

Componenti principali

Terpenlattoni: Ginkgolidi, bilobalide. Flavonoidi: flavonoli glicosidi, biflavoni, flavan-3-oli, proantocianidine.

Attività farmacologica

Attività antiaggregante piastrinica. Attività protettrice dell'endotelio vascolare e regolatoria del flusso ematico. Attività anti-ischemica. Attività neuroprotettiva. Azione antiossidante. Azione antiallergica.

Impiego clinico

Disturbi vascolari. Insufficienza cerebrovascolare del settore carotideo (deficit dell'attenzione e della memoria) e vertebrale (disturbi neurosensoriali quali capogiri/vertigini, ronzii auricolari, disturbi vestibolari). Trattamento sintomatico delle arteriopatie croniche ostruttive periferiche (claudicatio intermittens). Condizioni di fragilità capillare. Trattamento sintomatico di sindromi di demenza da lievi a moderate.

Controindicazioni

Si sconsiglia l'uso di preparati contenenti Ginkgo nelle donne in stato di gravidanza e durante l'allattamento.

Avvertenze e speciali precauzioni d'uso

Se si stanno assumendo farmaci anticoagulanti o antiaggreganti piastrinici, consultare il medico prima di assumere il prodotto. Si raccomanda prudenza nello stato pre-operatorio.

Interazioni

Il *Ginkgo biloba* può potenziare l'azione dei farmaci antiaggreganti piastrinici e anticoagulanti.

Effetti indesiderati

In alcuni casi sono stati riportati disturbi gastrointestinali, emicrania e reazioni allergiche a carico della pelle.

Note Bibliografiche

Composizione

I componenti caratteristici del fitocomplesso di *Ginkgo biloba* sono rappresentanti da terpeni e flavonoidi[1]. I terpeni[2] principali sono dei diterpeni trilattonici chiamati ginkgolidi (A, B, C e J), che differiscono nel numero e nella posizione dei loro gruppi idrossilici, e il sesquiterpene trilattone bilobalide. La droga ad uso farmaceutico dovrebbero contenere non meno dello 0,1% di terpenlattoni, calcolati come somma di bilobalide e ginkgolidi A, B e C[3]. I flavonoidi del Ginkgo sono principalmente rappresentati da flavonoli glicosidi[4,5] del tipo della quercetina, del kaempferolo, dell'isoramnetina e della miricetina; sono inoltre presenti diglicosidi esterificati con acido p-cumarico[6]. Altri flavonoidi comprendono biflavoni del tipo dell'amentoflavone: bilobetina, ginkgetina, isoginkgetina, sciadopitisina; in minori quantità abbiamo poi flavoni (apigenina, luteolina, e loro glicosidi); flavan-3-oli e proantocianidine: (+)-catechina, (-)-epicatechina, (-)-epigallocatechina e (+)-gallocatechina; flavanoli (diidromiricetina)[7].

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1 *Ding S, Dudley E, Plummer S, Tang J, Newton RP, Brenton AG. B Fingerprint profile of Ginkgo biloba nutritional supplements by LC/ESI-MS/MS. Phytochemistry. 2008 May;69(7):1555-64.*

2 *Ding S, Dudley E, Song Q, Plummer S, Tang J, Newton RP, Brenton AG. Mass spectrometry analysis of terpene lactones in Ginkgo biloba. Rapid Commun Mass Spectrom. 2008;22(6):766-72.*

3 *Ginkgo Leaf - Ginkgo folium. European Pharmacopeia. Council of Europe. 6th Edition 2009..*

4 *Li J, Yu L, Zeng Y. First Medical College of PLA, Guangzhou. Determination of flavonol glycosides in the leaf of Ginkgo biloba L. by TLC scanning. Chung Kuo Chung Yao Tsa Chih 1996; 21: 106-8, 128.*

5 *Lin LZ, Chen P, Ozcan M, Harnly JM. Chromatographic profiles and identification of new phenolic components of Ginkgo biloba leaves and selected products. J Agric Food Chem. 2008 Aug 13;56(15):6671-9.*

6 "Flavonoids in plants used for the treatment of various cardiovascular, cancer diseases have been reported to possess potential protective effects against oxidative injury. Ginkgo biloba leaves, known for their antioxidant activity, were chosen for this study. In this paper, 12 **flavonoids in G. biloba leaves were identified by HPLC-diode array detection (DAD)-electrospray ionization MS. HPLC-DAD coupled with chemiluminescence detection was used to determine free radical scavenging activity of flavonoids. It was found that the flavonol glycosides could markedly inhibit the luminescent signal, which indicated that they are mainly responsible for the antioxidant activities of G. biloba leaves**. Total antioxidant activity of these flavonoids was used to evaluate the differences of G. biloba leaves collected in 13 habitats. **The combination of chemical and activity analysis can provide a valid method to quantify the bioactive components in G. biloba leaves**, and this may be a more rational approach to the quality assessment of G. biloba leaves." *(Ding XP, Qi J, Chang YX, Mu LL, Zhu DN, Yu BY. Quality control of flavonoids in Ginkgo biloba leaves by high-performance liquid chromatography with diode array detection and on-line radical scavenging activity detection. J Chromatogr A. 2009 Mar 13;1216(11):2204-10).*

7 "The chemical analysis and quality control of Ginkgo leaves, extracts, phytopharmaceuticals and some herbal supplements is comprehensively reviewed. The review is an update of a similar, earlier review in this journal [T.A. van Beek, J. Chromatogr. A 967 (2002) 21-55]. Since 2001 over 3000 papers on Ginkgo biloba have appeared, and about 400 of them pertain to chemical analysis in a broad sense and are cited herein. The more important ones are discussed and, where relevant, compared with the best methods published prior to 2002. In the same period over 2500 patents were filed on Ginkgo and the very few related to analysis are mentioned as well. **Important constituents include terpene trilactones, i.e. Ginkgolide A, B, C, J and bilobalide, flavonol glycosides, biflavones, proanthocyanidins, alkylphenols, simple phenolic acids, 6-hydroxykynurenic acid, 4-O-methylpyridoxine and polyprenols**. In the most common so-called "standardised" Ginkgo

Nelle foglie di *Ginkgo biloba* sono poi presenti polisaccaridi[8], fitosteroli, carotenoidi e minime quantità di acidi alchilfenolici a catena lunga (acidi ginkgolici)[9,10].

Farmacocinetica

Mediante tecniche di radiomarcatura si è visto che circa il 60% dell'estratto di Ginkgo somministrato per os viene assorbito dal primo tratto dell'intestino tenue, raggiungendo il picco ematico dopo circa 90 minuti, e restando su livelli terapeuticamente significativi per circa 5 ore. La droga si concentra particolarmente bene nel tessuto nervoso[11]. La farmacocinetica dei singoli principi attivi del *Ginkgo biloba* è stata studiata nel volontario sano, con riferimento a tre dei principali componenti dell'estratto: i ginkgolidi A e B e il bilobalide. Il Ginkgo è stato somministrato sotto forma di soluzione orale; la biodisponibilità è stata calcolata in confronto con una somministrazione endovenosa del fitocomplesso, a dosi di principi attivi variabili fra 0.90 e 3.36 mg. La biodisponibilità sistemica dopo somministrazione

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extracts and phytopharmaceuticals several of these classes are no longer present. **About 130 new papers deal with the analysis of the terpene trilactones. They are mostly extracted with methanol or water or mixtures thereof. Supercritical fluid extraction and pressurised water extraction are also possible.** Sample clean-up is mostly by liquid-liquid extraction with ethyl acetate although no sample clean-up at all in combination with LC/MS/MS is gaining in importance. Separation and detection can be routinely carried out by RP-HPLC with ELSD, RI or MS, or by GC/FID or GC/MS after silylation. **Hydrolysis followed by LC/MS allows the simultaneous analysis of terpene trilactones and flavonol aglycones. No quantitative procedure for all major flavonol glycosides has yet been published because they are not commercially available. The quantitation of a few available glycosides has been carried out but does not serve a real purpose. After acidic hydrolysis to the aglycones quercetin, kaempferol and isorhamnetin and separation by HPLC, quantitation is straightforward and yields by recalculation an estimation of the original total flavonol glycoside content.** A profile of the genuine flavonol glycosides can detect poor storage or adulteration. Although the toxicity of Ginkgo alkylphenols upon oral administration has never been undoubtedly proven, most suppliers limit their content in extracts to 5 ppm and dozens of papers on their analysis were published. One procedure in which a methanolic extract is directly injected on a C8 HPLC column appears superior in terms of sensitivity (<5 ppm), separation, simplicity and validation and will be incorporated in the European Pharmacopoeia. Alternatively GC/MS and ELISA methods can be used. **A sharp contrast to the plethora of papers on terpene trilactones, flavonol glycosides, and Ginkgolic acids forms the low number of papers on biflavones, proanthocyanidins, simple phenolics, simple acids, and other constituents that make up the remaining 70% of Ginkgo standardised extracts. More research in this direction is clearly needed. For the analysis of Ginkgo proanthocyanidins (7%) for instance, no reliable assays are yet existing.** Finally the growing literature on pharmacokinetic and fingerprinting studies of Ginkgo is briefly summarised." *(Van Beek TA, Montoro P. Chemical analysis and quality control of Ginkgo biloba leaves, extracts, and phytopharmaceuticals. J Chromatogr A. 2009 Mar 13;1216(11):2002-32).*

[8] *Kraus J. Water-soluble polysaccharides from Ginkgo biloba leaves. Phytochemistry 1991; 30: 3017-20.*

[9] *He X, Bernart MW, Nolan GS, Lin L, Lindenmaier MP. High-performance liquid chromatography-electrospray ionization-mass spectrometry study of Ginkgolic acid in the leaves and fruits of the Ginkgo tree (Ginkgo biloba). J Chromatogr Sci. 2000 Apr;38(4):169-73.*

[10] "In May 1997, the German Institute for Drugs and Medicinal Products (BfArM) sent a comunication to manufacturers of Ginkgo biloba leaf extracts and other Ginkgo preparations regarding the levels of Ginkgolic acid in finished Ginkgo preparations (maximum 5 ppm).… This is done because Ginkgolic acids are chemicals classified as alkylphenols of the urushiol type, and are associated with contact allergic responses, especially dermatitis. Ginkgolic acids are found in relatively high concentrations in the seed cover of Ginkgo biloba but are also found in lower concentrations in Ginkgo leaf." *(Thiele A., 1997. Averting of drug-induced risks, grade II: pharmaceuticals containing Ginkgo biloba leaves. Comunication to Dr. W. Schwabe, GmbH & Co., May 27.*

[11] *Ude C, Paulke A, Schubert-Zsilavecz M, Wurglics M. Chemistry, pharmacokinetics and metabolism of Ginkgo extract. Pharm Unserer Zeit. 2009;38(5):418-23.*

orale è compresa fra il 76% e l'88% della dose somministrata. La somministrazione del fitocomplesso con il cibo non altera la biodisponibilità totale, anche se il T_{max} è leggemente aumentato. L'emivita plasmatica dei ginkgolidi A e B e del bilobalide è risultata, rispettivamente, di 4.50, 10.57 e 3.21 ore[12]. L'assorbimento orale dei flavonoli glicosidi del *Ginkgo biloba* in differenti forme farmaceutiche è stato studiato confrontando capsule, gocce e compresse, e misurando le concentrazioni plasmatiche di quercetina, kempferolo ed isoramnetina. Le tre formulazioni risultano sostanzialmente sovrapponibili, anche se le gocce mostrano una AUC ("area under curve") leggermente, ma non significativamente, maggiore, e le capsule un T_{max} più prolungato delle altre forme[13,14]. Infine, alcuni AA. Italiani hanno

[12] "The pharmacokinetics of Ginkgolide A, Ginkgolide B and Bilobalide, which are compounds extracted from the dried leaves of the Ginkgo biloba tree, were investigated in 12 young healthy volunteers (six men and six women; mean ± SD age = 25 ± 5 years) after single-dose administration of Ginkgo biloba extract. Subjects were given, on three occasions, Ginkgo biloba extract as a solution either orally (in fasting conditions and after a standard meal) or intravenously; corresponding to single doses of Ginkgolide A, Ginkgolide B and Bilobalide ranging from 0.90 mg to 3.36 mg. After each dosing, blood and urine samples were collected for up to 36 h and 48 h, for measurements of Ginkgolide A, Ginkgolide B and Bilobalide. Plasma and urine concentrations of these compounds were quantitatively measured by gas chromatography/mass spectrometry using negativechemical ionization, by applying a very sensitive method which allowed plasma concentrations as low as 0.2 ng/ml of each compound to be measured. When given orally, while fasting, the extents of bioavailability are high, as shown by bioavailability coefficients (FAUC) mean (± SD) values equal to 0.80 (± 0.09), 0.88 (± 0.21)and 0.79 (± 0.30) for Ginkgolide A, Ginkgolide B and Bilobalide respectively. Food intake does not change AUC quantitatively but increases Tmax. For the three compounds of interest, after oral dosing while fasting, differences can be noted for the elimination half-lives (T1/2Z), which exhibit mean values equal to 4.50, 10.57 and 3.21 h, as well as mean residence times (MRT), equal to 5.86, 11.25 and 4.89 h, for Ginkgolide A, Ginkgolide B and Bilobalide respectively." *(Fourtillan JB, Brisson AM, Girault J, Ingrand I, Decourt JP, Drieu K, Jouenne P, Biber A. Pharmacokinetic properties of Bilobalide and Ginkgolides A and B in healthy subjects after intravenous and oral administration of Ginkgo biloba extract (EGb 761). Therapie 1995;50: 137-44).*

[13] "A sensitive LC-ESI-MS method with a solid-phase extraction was established for the determination of bilobalide, Ginkgolide A and Ginkgolide B in human plasma; **bioavailability and pharmacokinetics of three different Ginkgo biloba L. preparations have been investigated**. The preparations used in the present single-dose pharmacokinetic study were different formulations of Ginkgo biloba L. extracts (Geriaforce tincture, new Ginkgo fresh plant extract tablets and EGb 761) with various excipients. The analysis of Ginkgo terpene lactones was performed by LC-MS on a Zorbax((R)) SB-C18 column. The mobile phase consisted of water + 0.1% acetic acid and methanol 68/32 (v/v) to 49/51 (v/v) at a flow rate of 200 muL/min. Bilobalide, Ginkgolide A and Ginkgolide B were monitored using the selected-ion monitoring (SIM) mode at m/z of 325, 453 and 423, respectively. The amounts of the active compounds (terpene lactones) in the administered products were in the low-mg range per dose. **The assay method was successfully applied to the study of the pharmacokinetics and bioavailability of bilobalide, Ginkgolide A and Ginkgolide B in humans**. The resulting maximum concentrations (median) of bilobalide, Ginkgolide A and Ginkgolide B in plasma after administration of the maximum daily dose of the different Ginkgo products were 3.53, 3.62, and 1.38 ng/mL respectively after administration of Geriaforce tincture; 11.68, 7.36, and 4.18 ng/mL, respectively after taking Ginkgo fresh plant extract tablets; and 26.85, 16.44, 9.99 ng/mL, respectively after administration of EGb 761 tablets. **These data are relevant to demonstrate relative bioavailabilities of different Ginkgo biloba L. preparations.**" *(Woelkart K, Feizlmayr E, Dittrich P, Beubler E, Pinl F, Suter A, Bauer R.I. Pharmacokinetics of bilobalide, Ginkgolide A and B after administration of three different Ginkgo biloba L. preparations in humans. Phytother Res. 2010;24 (3):445-450.*

[14] "Eighteen healthy volunteers received three different formulations of Ginkgo biloba: capsules (A) and drops (B) (delivered by Agon Pharma), and tablets (C) in equal an quantity, orally as a single dose, at an interval of at least five days. The pharmacokinetic parameters of the most important flavonoid glycosides: quercetin, kaempferol and isorhamnetin were established. The bioavailability was estimated using capsules as a standard formulation. Only the time to reach the peak concentration (tmax) of quercetin, kaempforol and isorhamnetin administered in the form of capsules, was significantly prolonged as compared with drops and tablets. Area under the curve (AUC) was the largest for formulation B for all the evaluated flavonoid glycosides, however the differences were not statistically significant. **It is concluded that the three formulations of Ginkgo biloba extract are bioequivalent.**" *(Wojcicki J, Gawronska-Szklarz B, Bieganowski W, Patalan M, Smulski HK, Samochowiec L, Zakrzewski J. Comparative pharmacokinetics and bioavailability of flavonoid glycosides of Ginkgo biloba after a single oral administration of*

studiato nel ratto il metabolismo dei flavonoidi contenuti nelle foglie di *Ginkgo biloba*: l'assenza di glicosidi e agliconi nelle urine depone per una completa metabolizzazione dei flavonoidi entro 24 ore dalla somministrazione[15,16].

Farmacologia e meccanismo di azione

Le azioni integrate dei componenti del *Ginkgo biloba* conferiscono ai preparati della droga un ampio spettro d'azione che interessa le turbe vascolari – a livello della microcircolazione periferica, nella microangiopatia diabetica, in proctologia, nelle arteriopatie obliteranti degli arti inferiori, nella malattia di Raynaud e in particolar modo nell'insufficienza circolatoria cerebrale, nelle conseguenze dell'ictus, negli acufeni e nelle sindromi vertiginose – e un'ampia varietà di disturbi cognitivi legati all'età, come le sindromi di demenza da lievi a moderate, comprese la demenza di Alzheimer di grado lieve-moderato, la demenza vascolare (p.e. demenza multiinfartuale) e le forme miste[17].

Effetti emoreologici. L'estratto secco standardizzato delle foglie di *Ginkgo biloba*[18] viene impiegato per il trattamento dell'insufficienza cerebrovascolare, da lieve a moderata, ed anche per disturbi periferici della circolazione. I lattoni terpenici del *Ginkgo biloba*, in particolare il ginkgolide B e poi nell'ordine i ginkgolidi A, C e J, risultano dei potenti e selettivi inibitori del PAF (Platelet Activating Factor), un mediatore fosfolipidico intercellulare prodotto dalle piastrine, dai leucociti, dai macrofagi e dalle cellule endoteliali vascolari. Questo mediatore è implicato in molte condizioni patologiche, quali aggregazione piastrinica, tromboformazione, reazioni infiammatorie e allergiche (asma, anafilassi), ischemia cardiaca e cerebrale, rigetto di trapianti, alcune malattie renali e del SNC, ecc. Per questo i ginkgolidi – ed alcuni loro derivati sintetici – sono stati sviluppati come presidi terapeutici per alcune di queste patologie[19].

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three formulations to healthy volunteers. Mater Med Pol 1995; 27: 141-6).

15 *Pietta PG, Gardana C, Mauri PL, Maffei-Facino R, Carini M. Identification of flavonoid metabolites after oral administration to rats of a Ginkgo biloba extract. J Chromatogr B Biomed Appl 1995; 673: 75-80.*

16 *Pietta PG, Gardana C, Mauri PL. Identification of Ginkgo biloba flavonol metabolites after oral administration to humans. J Chromatogr B Biomed Appl 1997; 693: 249-55.*

17 *Smith JV, Luo Y. Studies on molecular mechanisms of Ginkgo biloba extract. Appl Microbiol Biotechnol. 2004 May;64(4):465-72.*

18 "Estratto secco standardizzato di Ginkgo EGB 761: si tratta di un estratto secco idroacetonico prodotto dalle foglie del *Ginkgo biloba* L. che contiene dal 22,0 al 27,0 per cento di flavonoidi, espressi come flavonglicosidi (Mr 756,7) e dal 5,0 al 7,0 per cento di terpenlattoni, che comprendono dal 2,8 al 3,4 per cento di ginkgolidi A, B e C, e dal 2,6 al 3,2 per cento di bilobalide. Tale estratto è tra i meglio caratterizzati ed è quello per il quale sono disponibili il maggior numero di dati scientifici di efficacia. Pertanto, i risultati ottenuti sono applicabili a tutti gli altri estratti di G. biloba." *(ESCOP Monographs. The Scientific Foundation for Herbal Medicinal Products. Second edition, Thieme, 2003.)*

19 "Ginkgolides are unique twenty-carbon terpenes, occurring naturally only in the roots and leaves of Ginkgo biloba. The molecules incorporate a tert-butyl group and six 5-membered rings, and are specific and potent antagonists of platelet-activating factor (PAF), a potent inflammatory autacoid. Studies in animal models with the most potent Ginkgolide, BN 52021, and other specific PAF antagonists have demonstrated that PAF plays an important role in pathologies such as asthma, shock, ischemia, anaphylaxis, graft rejection, renal disease, CNS disorders and numerous inflammatory conditions. **Ginkgolides are now being**

La specificità dei ginkgolidi per i recettori del PAF appare così elevata che alcuni AA. hanno suggerito l'aggregazione piastrinica da PAF come metodo per la standardizzazione biologica degli estratti di *Ginkgo biloba*[20, 21]. Inoltre essi inibiscono il legame del PAF ai leucociti e alle piastrine, riducono la chemiotassi leucocitaria e la degranulazione dei polimorfonucleati e ostacolano la loro produzione di radicali liberi e di leucotriene B4. I ginkgolidi accelerano il catabolismo del PAF nel comparto endocellulare e riducono i livelli di calcio all'interno delle piastrine. I ginkgolidi antagonizzano la vasocostrizione coronarica indotta dal PAF, la tromboformazione carotidea indotta da stimolazione elettrica e la trombosi mesenterica provocata dal PAF. Sono altresì in grado di ridurre le lesioni d'organo causate dalla legatura della carotide e gli spasmi arteriosi a livello del microcircolo, grazie anche a liberazione di EDRF (Endothelium Derived Relaxing Factor) e prostaciclina e ad inibizione della fosfodiesterasi. Poiché l'EDRF è inattivato dagli anioni superossido e la prostaciclina dai radicali idrossilici e dai perossidi lipidici, è possibile che il Ginkgo protegga queste sostanze grazie alla sua spiccata attività antiradicalica[22]. Anche i flavonoidi del Ginkgo (soprattutto glicosidi flavonici e biflavoni) svolgono azione capillaroprotettrice (vitamina P-simile), stabilizzano le membrane cellulari ed impediscono la perossidazione lipidica e la formazione di radicali liberi[23].

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developed as therapeutic agents and very promising results have been obtained in clinical trials on shock, organ preservation and thermal injury." *(Braquet P, Hosford D. Ethnopharmacology and the development of natural PAF antagonists as therapeutic agents. J Ethnopharmacol 1991; 32: 135-9).*

20 *Ekman L, Fransson D, Claeson P, Johansson M. Development of an alternative method for determination of terpene lactones in Ginkgo dry extract. Pharmeur Bio Sci Notes. 2009 Oct;2009(1):67-72.*

21 "The determination of the inhibition of PAF (platelet-activating factor)-induced platelet aggregation has been proposed as a biological standardization method for commercially available Ginkgo biloba extracts by measuring the characteristic pharmacological effect of Ginkgolides in vitro. The determination is specific for Ginkgolides A, B, C, and J and is not influenced by other constituents present in Ginkgo biloba extracts. IC_{50} values of Ginkgolide B can be used to standardize various Ginkgo extracts produced by special extraction methods with respect to equi-effective Ginkgolide B contents." *(Steinke B, Muller B, Wagner H. Biological standardization of Ginkgo extracts. Planta Med 1993; 59: 155-60).*

22 "Atherosclerosis is a chronic inflammatory process with increased oxidative stress in vascular endothelium. Ginkgo biloba extract (GbE), extracted from Ginkgo biloba leaves, has commonly been used as a therapeutic agent for cardiovascular and neurological disorders. T**he aim of this study was to investigate how GbE protects vascular endothelial cells against the proatherosclerotic stressor oxidized low-density lipoprotein (oxLDL) in vitro.** Human umbilical vein endothelial cells (HUVECs) were incubated with GbE (12.5-100 microg/ml) for 2 h and then incubated with oxLDL (150 microg/ml) for an additional 24 h. Subsequently, reactive oxygen species (ROS) generation, antioxidant enzyme activities, adhesion to monocytes, cell morphology, viability, and several apoptotic indexes were assessed. Our data show that ROS generation is an upstream signal in oxLDL-treated HUVECs. Cu,Zn-SOD, but not Mn-SOD, was inactivated by oxLDL. In addition, oxLDL diminished expression of endothelial NO synthase and enhanced expression of adhesion molecules (ICAM, VCAM, and E-selectin) and the adherence of monocytic THP-1 cells to HUVECs. Furthermore, oxLDL increased intracellular calcium, disturbed the balance of Bcl-2 family proteins, destabilized mitochondrial membrane potential, and triggered subsequent cytochrome c release into the cytosol and activation of caspase-3. These detrimental effects were ameliorated dose dependently by GbE ($P < 0.05$). **Results from this study may provide insight into a possible molecular mechanism underlying GbE suppression of the oxLDL-mediated vascular endothelial dysfunction.**" *(Ou HC, Lee WJ, Lee IT, Chiu TH, Tsai KL, Lin CY, Sheu WH. Ginkgo biloba extract attenuates oxLDL-induced oxidative functional damages in endothelial cells. J Appl Physiol. 2009 May;106(5):1674-85).*

23 *Ren DC, Du GH, Zhang JT. Protective effect of Ginkgo biloba extract on endothelial cell against damage induced by oxidative stress. J Cardiovasc Pharmacol. 2002 Dec;40(6):809-14.*

L'attività antiossidante (e antinfiammatoria) determina, accanto alla riduzione della permeabilità capillare, un'efficace protezione dell'endotelio dei vasi sanguigni[24], prevenendo il danno chimico da agenti ossidanti e da altre sostanze ad azione lesiva e/o irritativa sulla parete vasale, caratteristica della patogenesi dei processi aterosclerotici/trombotici [25]. Gli effetti del *Ginkgo biloba* sulla circolazione includono quindi il mantenimento della microcircolazione, la riduzione della viscosità ematica, la protezione contro l'emolisi (cattura di radicali liberi), l'inibizione dell'aggregazione trombocitica e l'aumento della velocità di flusso. Gli effetti sulle pareti dei vasi includono il miglioramento del tono delle arteriole e delle venule, la regolazione dell'equilibrio trombossano/prostaciclina, il miglioramento della funzionalità delle pareti dei capillari e la stabilizzazione della permeabilità capillare. L'effetto sui tessuti si manifesta con l'inibizione dell'edema citotossico da ischemia, l'aumento del consumo di ossigeno e dell'utilizzazione del glucosio, e la prevenzione della perossidazione lipidica mediante la neutralizzazione dei radicali liberi. Inoltre, il Ginkgo è utile anche nel trattamento per neuropatie diabetiche, degenerazione maculare, e altri problemi circolatori. Tutti questi effetti sono stati dimostrati da una serie di esperimenti sia *in vitro* che *in vivo* e da prove cliniche[26].

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[24] "**Dietary antioxidants are frequently proposed as protective agents for the vascular endothelium during the onset of atherosclerosis**. This protection may occur at two distinct levels. **First, they prevent oxidative modification of atherogenic lipoproteins (LDL). Second, they can provide a cellular protection against oxidized LDL-mediated endothelium dysfunction, although this mechanism remains poorly considered in many instances.** To gain insight into the mechanism underlying such cellular protection against oxidized LDL, **we examined the impact of a popular traditional medicine, an extract from Ginkgo biloba with well-known antioxidant properties, on two endothelial cells properties: cell adhesion and ionic homeostasis**. Cellular lipoperoxides levels were also measured as a marker of cellular oxidative stress. Human umbilical-vein endothelial cells were exposed to native (nat-) or oxidized (ox-) LDL, the latter prepared to be compatible with clinically observed levels of oxidation. Although nat-LDL had little effect, ox-LDL increased endothelial adhesive properties (35%, $p<0.01$) and lipoperoxidation (45%, $p<0.01$). Na,K-ATPase activity, a key regulator of ionic homeostasis, was significantly decreased after exposure to nat-LDL (30%, $p<0.01$) and dramatically depressed after exposure to ox-LDL (65%, $p<0.001$). **The standardized preparation of Ginkgo biloba EGb-761 totally protected adhesive properties and endothelial lipoperoxide levels. Moreover, it limited the decrease in Na,K-ATPase activity induced by ox-LDL to levels similar to nat-LDL. This suggests that EGb-761 protects endothelial adhesive properties and helps prevent the disruption of ionic homeostasis**. The EGb-761-mediated inhibition of ox-LDL-induced lipoperoxide levels in endothelial cells appears to be an important mechanism by which Ginkgo biloba extract protects endothelial properties." *(Pierre SV, Lesnik P, Moreau M, Bonello L, Droy-Lefaix MT, Sennoune S, Duran MJ, Pressley TA, Sampol J, Chapman J, Maixent JM. The standardized Ginkgo biloba extract Egb-761 protects vascular endothelium exposed to oxidized low density lipoproteins. Cell Mol Biol (Noisy-le-grand). 2008 Oct 26;54 Suppl:OL1032-42).*

[25] "To compare the antioxidant activity amongst the extract of Ginkgo biloba (EGb) and its main components, flavonoids and terpenoids. The induction of EGb, flavonoids and terpenoids on a typical antioxidant enzyme, glutamate cysteine ligase catalytic subunit (GCLC), in cell lines was detected by Western-blot. The effects of EGb, flavonoids and terpenoids on superoxide anion radical (O2*(-)), hydroxyl radical (OH*), rat erythrocyte hemolysis and lipid peroxidation of rat liver homogenate were determined by respective activity methods. **EGb and flavonoids but not terpenoids were demonstrated significantly to induce the antioxidant enzyme (GCLC), directly scavenge O2*(-), OH* and inhibit rat erythrocyte hemolysis and lipid peroxidation of rat liver homogenate.** Compared these antioxidant activities between EGb and flavonoids, the activities of flavonoids were weaker than those of EGb, which contains similar dose of flavonoids. **EGb has stronger antioxidant activities than flavonoids, but terpenoids did not show antioxidant activity in this research**." *(Liu XP, Luan JJ, Goldring CE. Comparison of the antioxidant activity amongst Ginkgo biloba extract and its main components. Zhong Yao Cai. 2009 May;32(5):736-40).*

[26] "…We examined the history of extract from Ginkgo biloba leaves (GBE) usage and reviewed the literature on its effects on the cardiovascular system. In the extensive studies involving cell cultures and animal models, GBE has been shown to exert its action through diverse mechanisms. **GBE has been reported to have antioxidant properties, to modify vasomotor function, to reduce adhesion of blood cells to endothelium, to inhibit activation of platelets and smooth muscle cells,**

Effetti neurologici. Il fitocomplesso del *Ginkgo biloba* possiede attività neuroprotettiva, sia in conseguenza della migliorata perfusione ematica cerebrale sia per un'azione diretta sui neurotrasmettitori e sulle cellule neuronali, delle quali regolarizza il metabolismo e la funzionalità[27]. È stata tra l'altro dimostrata per la droga un'attività nootropa, probabilmente dovuta alla stimolazione di alcuni centri colinergici dell'encefalo e di alcuni recettori di tipo muscarinico e risultante in un miglioramento della memoria a breve termine e del quoziente di apprendimento[28]. Lo stress ossidativo può accelerare la cascata dei processi patologici che conducono alla demenza ed alla malattia cerebrovascolare, ed infatti uno dei principali meccanismi con cui il *Ginkgo biloba* esplicherebbe il suo effetto protettivo sono proprio i suoi effetti antiossidanti. Oltre ai flavonoidi, anche i ginkgolidi sono dotati di un'azione antiradicalica; inibiscono inoltre la liberazione di cortisolo in risposta allo stress, inducendo una diminuzione dell'espressione del recettore periferico per le benzodiazepine (PBR)[29] a livello della corteccia

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to affect ion channels, and to alter signal transduction. In addition, relevant clinical trials with GBE are being carried out, particularly in the treatment of arterial and venous insufficiency and in the prevention of thrombosis." *(Zhou W, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C. Clinical use and molecular mechanisms of action of extract of Ginkgo biloba leaves in cardiovascular diseases. Cardiovasc Drug Rev. 2004 Winter;22(4):309-19).*

27 "The Ginkgo biloba extract has been therapeutically used for several decades to increase peripheral and cerebral blood flow as well as for the treatment of dementia. The extract contains multiple compounds such as flavonoids and terpenoids that are thought to contribute to its neuroprotective and vasotropic effects. **In this review, we summarize the experimental results on the mechanism of neuroprotection induced by standardized extract of Ginkgo biloba leaves (EGb 761) and its constituents. The effects described mostly in animals include those on cerebral blood flow, neurotransmitter systems, cellular redox state and nitric oxide level.** Furthermore, we discuss the current status of clinical trials as well as undesired side effects of EGb 761." *(Ahlemeyer B, Krieglstein J. INeuroprotective effects of Ginkgo biloba extract. Cell Mol Life Sci. 2003 Sep;60(9):1779-92).*

28 "In order to clarify the mechanism of Ginkgo biloba extract (GBE) on learning and memory, **we studied the effect of GBE on spatial memory deficits induced by diphenhydramine, pyrilamine and scopolamine using the eight-arm radial maze performance of rats, in comparison with donepezil**. Total error (TE), reference memory error (RME) and working memory error (WME) were used as indices of spatial memory deficits. Both GBE and donepezil caused a potent antagonistic effect on the increase in TE, RME and WME induced by diphenhydramine. GBE and donepezil also antagonized scopolamine-induced spatial memory deficits. Although the antagonistic effect of GBE on pyrilamine-induced spatial memory deficits was weak, a significant difference was observed with TE and WME. However, donepezil caused no antagonistic effect on pyrilamine-induced memory deficits. **From these findings, we concluded that the effects of GBE are mainly contributable to cholinergic activity and perhaps partly due to a histaminergic mechanism**." *(Yamamoto Y, Adachi Y, Fujii Y, Kamei C. Ginkgo biloba extract improves spatial memory in rats mainly but not exclusively via a histaminergic mechanism. Brain Res. 2007 Jan 19;1129(1):161-5).*

29 "**In vitro studies using biochemical, pharmacological and molecular approaches demonstrated that the peripheral-type benzodiazepine receptor (PBR) is a mitochondrial protein, involved in the regulation of cholesterol transport from the outer to the inner mitochondrial membrane, the rate-determining step in steroid biosynthesis**. **In vivo animal models and ontogeny studies validated the role of PBR in steroidogenesis**. (...). Indeed, cholesterol uptake and transport by bacteria cells was induced upon PBR expression. Amino acid deletion and site-directed mutagenesis studies identified a cholesterol recognition/interaction amino acid consensus sequence in the cytoplasmic carboxy-terminus of the receptor. In vitro reconstitution experiments demonstrated that the 18 kDa PBR protein binds with high affinity both drug ligands and cholesterol, suggesting that this protein might serve numerous functions considering the critical role of cholesterol in membrane biogenesis and human pathology. In this context, **PBR expression correlated with the quality of kidney preservation, indicating that it might serve as an index of kidney and mitochondrial viability during ischemia-reperfusion injury**. PBR overexpression was also found to be a prognostic indicator of the aggressive phenotype in breast, colorectal and prostate cancers. Moreover, **in Alzheimer's disease brain specimens, PBR levels were increased and paralleled the elevated neurosteroid synthesis observed in specific brain areas. The role for PBR in these pathological conditions remains to be elucidated. paralleled the elevated neurosteroid synthesis observed in specific brain areas**." *(Papadopoulos V. Peripheral benzodiazepine receptor: structure and function in health and disease. Ann Pharm Fr. 2003 Jan;61(1):30-50).*

surrenalica[30]. Gli stadi precoci del morbo di Alzheimer sono caratterizzati dalla produzione del peptide amiloide beta 42, dalla perdita progressiva delle sinapsi neuronali e da un ingravescente declino delle funzioni cognitive. Uno studio in vitro ha indicato che l'estratto del *Ginkgo biloba* ha un effetto inibitorio sull'aggregazione della beta-amiloide – uno dei principali fattori patogenetici dell'invecchiamento cerebrale – e protegge i neuroni dalla sua tossicità[31], suggerendo un altro meccanismo mediante il quale la droga potrebbe essere efficace nella prevenzione della demenza[32]. Uno studio nel ratto ha valutato l'effetto dell'EGB 761 nella prevenzione e nel trattamento dei disturbi cognitivi incluso il morbo di Alzheimer e in particolare sul metabolismo della Amyloid precursor protein (APP) in ratti transgenici per la APP umana. Questi animali ricevevano per os l'EGB 761 alla dose di 300 mg/kg/die per 1 e per 16 mesi. Si è visto che dopo 16 mesi vi era un significativo calo della APP di circa il 50% nella corteccia cerebrale ma non nell'ippocampo. Questo risultato non era osservabile dopo 1 mese di trattamento. Lo studio indica che la somministrazione cronica dell'EGB 761 nel ratto può favorire il catabolismo della APP[33]. L'aggiunta di amiloide beta 42 a neuroni corticali o ippocampali coltivati in

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30 *Pretner E, Amri H, Li W, Brown R, Lin CS, Makariou E, Defeudis FV, Drieu K, Papadopoulos V. Cancer-related overexpression of the peripheral-type benzodiazepine receptor and cytostatic anticancer effects of Ginkgo biloba extract (EGb 761). Anticancer Res. 2006 Jan-Feb;26(1A):9-22).*

31 "Beta-amyloid (Abeta) deposition likely plays a causal role in the lesions that occur in Alzheimer's disease (AD). The Ginkgo biloba extract EGb 761 is widely prescribed in the treatment of cognitive deficits that are associated with normal and pathological brain aging such as AD. **We have investigated here the potential effectiveness of EGb 761 against cell death produced by Abeta fragments on primary cultures of hippocampal cells, these cells being severely damaged in AD**. **A co-treatment with EGb 761 protected cells against toxicity induced by Abeta fragments in a concentration dependent manner. The effect of EGb 761 was even significant if added up to 8 hr to cells and was shared by its flavonoid fraction CP 205, whereas the terpenes bilobalide and ginkgolide B were ineffective. EGb 761 also displayed protective effects against toxicity produced by either H2O2 or nitric oxide, two neurotoxic agents that possibly mediate Abeta toxicity. Moreover, EGb 761, and to a lesser extent CP 205, completely blocked Abeta-induced events, such as reactive oxygen species accumulation and apoptosis.** Taken together, these results and those obtained by other groups highlight the neuroprotective abilities of EGb 761 against dysfunction and death of neurons caused by Abeta deposits." *(Bastianetto S, Quirion R. EGB 761 is a neuroprotective agent against beta-amyloid toxicity. Cell Mol Biol (Noisy-le-grand). 2002 Sep;48(6):693-7).*

32 "…The **addition of Abeta1-42 to cortical or hippocampal neurons reduced the amounts of cell associated synaptophysin, a pre-synaptic membrane protein that is essential for neurotransmission, indicating synapse damage**. The effects of Abeta1-42 on synapses were apparent at concentrations approximately 100 fold less than that required to kill neurons; the synaptophysin content of neuronal cultures was reduced by 50% by 50 nM Abeta1-42. **Pre-treatment of cortical or hippocampal neuronal cultures with Ginkgolides A or B, but not with myrecitin or quercetin, protected against Abeta1-42-induced loss of synaptophysin. This protective effect was achieved with nanomolar concentrations of Ginkgolides**. Previous studies indicated that the Ginkgolides are platelet-activating factor (PAF) receptor antagonists and here we show that Abeta1-42-induced loss of synaptophysin from neuronal cultures was also reduced by pre-treatment with other PAF antagonists (Hexa-PAF and CV6209). PAF, but not lyso-PAF, mimicked the effects Abeta1-42 and caused a dose-dependent reduction in the synaptophysin content of neurons. This effect of PAF was greatly reduced by pre-treatment with Ginkgolide B. In contrast, Ginkgolide B did not affect the loss of synaptophysin in neurons incubated with prostaglandin E2. Conclusion: **Pre-treatment with Ginkgolides A or B protects neurons against Abeta1-42-induced synapse damage. These Ginkgolides also reduced the effects of PAF, but not those of prostaglandin E2, on the synaptophysin content of neuronal cultures, results consistent with prior reports that Ginkgolides act as PAF receptor antagonists. Such observations suggest that the Ginkgolides are active components of Ginkgo biloba preparations and may protect against the synapse damage and the cognitive loss seen during the early stages of AD.**" *(Bate C, Tayebi M, Williams A. Ginkgolides protect against amyloid-beta1-42-mediated synapse damage in vitro. Mol Neurodegener. 2008 Jan 7;3:1).*

33 "…**The aim of the present feeding trial was to investigate the effects of EGb761 and its major constituents on the**

vitro provocava una netta riduzione del loro contenuto di sinaptofisina, una proteina presinaptica di membrana essenziale per la neurotrasmissione, indicando quindi un danno di membrana. I danni alla membrana causati dalla amiloide beta 42 si verificavano a dosi 100 volte inferiori a quelle necessarie per uccidere i neuroni, con riduzioni medie di sinaptofisina di circa il 50%. Il pretrattamento dei neuroni corticali con l'EGB 761, ma non con la quercetina o la miricetina da sole, proteggeva le cellule dai danni membranari provocati dalla amiloide beta 42. È stato anche osservato che il calo della sinaptofisina era ridotto anche da antagonisti specifici del PAF, e siccome il *Ginkgo biloba* è un potente antagonista del PAF questo meccanismo concorre a spiegare l'azione protettiva di questa droga. Peraltro l'EGB 761 non modificava la perdita di sinaptofisina causata nei neuroni dall'incubazione con la PGE_2. Lo studio indica che l'EGB 761 ha azione protettiva contro il danno neuronale indotto dalla amiloide beta 42 grazie a un effetto protettivo sulle sinapsi e ad un'azione anti PAF[34]. Il bilobalide sembra regolare il consumo cerebrale di glucosio, determinando un aumento dei livelli neuronali di ATP. Esercita inoltre una azione trofica e protettiva sulle cellule di Schwann e sui neuroni corticali cerebrali[35], dal momento

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expression of genes encoding for proteins involved in the pathogenesis of AD in mouse brain. Six month old C57B6 mice were fed semi synthetic diets enriched with either EGb761 or one of its main fractions, flavonols and terpenelactones, respectively, over a period of 4 weeks. Thereafter, mRNA of α-secretase, neprilysin, amyloid precursor protein (App), App binding protein-1 and acetylcholine esterase was quantified in hippocampus and cortex. **EGb761 and its flavonol fraction had no effects on relative mRNA levels of the respective genes in mouse brain. However, the terpenelactone fraction significantly decreased the mRNA levels of App in the hippocampus**. Taken together, a 4 week dietary treatment with EGb761 or its main fractions had only moderate effects on mRNA levels of AD related genes in cortex and hippocampus of mice." *(Augustin S, Rimbach G, Augustin K, Cermak R, Wolffram S. Gene Regulatory Effects of Ginkgo biloba Extract and Its Flavonol and Terpenelactone Fractions in Mouse Brain. J Clin Biochem Nutr. 2009 November; 45(3): 315–321).*

[34] "The early stages of Alzheimer's disease (AD) are closely associated with the production of the Aβ1–42 peptide, loss of synapses and gradual cognitive decline. Since some epidemiological studies showed that EGb 761, an extract from the leaves of the Ginkgo biloba tree, had a beneficial effect on mild forms of AD, t**he effects of some of the major components of the EGb 761 extract (ginkgolides A and B, myricetin and quercetin) on synapse damage in response to Aβ1–42 were examined**. Results: The addition of Aβ1–42 to cortical or hippocampal neurons reduced the amounts of cell associated synaptophysin, a pre-synaptic membrane protein that is essential for neurotransmission, indicating synapse damage. The effects of Aβ1–42 on synapses were apparent at concentrations approximately 100 fold less than that required to kill neurons; the synaptophysin content of neuronal cultures was reduced by 50% by 50 nM Aβ1–42. **Pre-treatment of cortical or hippocampal neuronal cultures with ginkgolides A or B, but not with myrecitin or quercetin, protected against Aβ1–42-induced loss of synaptophysin. This protective effect was achieved with nanomolar concentrations of ginkgolides**. Previous studies indicated that the ginkgolides are platelet-activating factor (PAF) receptor antagonists and here we show that Aβ1–42-induced loss of synaptophysin from neuronal cultures was also reduced by pre-treatment with other PAF antagonists (Hexa-PAF and CV6209). PAF, but not lyso-PAF, mimicked the effects Aβ1–42 and caused a dose-dependent reduction in the synaptophysin content of neurons. This effect of PAF was greatly reduced by pre-treatment with ginkgolide B. In contrast, ginkgolide B did not affect the loss of synaptophysin in neurons incubated with prostaglandin E2. Conclusion: **Pre-treatment with ginkgolides A or B protects neurons against Aβ1–42-induced synapse damage. These ginkgolides also reduced the effects of PAF, but not those of prostaglandin E2, on the synaptophysin content of neuronal cultures, results consistent with prior reports that ginkgolides act as PAF receptor antagonists. Such observations suggest that the ginkgolides are active components of Ginkgo biloba preparations and may protect against the synapse damage and the cognitive loss seen during the early stages of AD**." *(Bate C, Tayebi M, Williams A. Ginkgolides protect against amyloid-β1–42-mediated synapse damage in vitro. Molecular Neurodegeneration 2008;7:*

[35] "**To investigate the effects of bilobalide on the activation of NF-kappaB, and apoptosis of dopaminergic neurons induced by 6-hydroxydopamine (6-OHDA).** A **rat model of Parkinson's disease** was produced with a unilateral infusion of 6-OHDA (8 mug) into the substantia nigra par compact. Bilobalide was administered 5, 10, and 20 mg/kg (ip) once a day for

che la rigenerazione nervosa dopo denervazione chirurgica in animali da esperimento è nettamente superiore negli animali trattati con questa droga rispetto a quelli che ricevevano il placebo[36]. Non modifica l'attività motoria spontanea dell'animale. È noto che nell'animale anziano si ha un calo dei recettori cerebrali per la serotonina di circa il 20% rispetto all'animale giovane, senza alterazione del legame sostanza-recettore. Il Ginkgo aumenta del 33% il numero di questi recettori, dovuto probabilmente al positivo effetto della droga sulle membrane neuronali, legato anche all'effetto antiradicalico. La droga inibisce anche la progressiva perdita di recettori alfa-1-adrenergici 5-HT_{1A} e muscarinici connessa con l'avanzare dell'età[37].

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7 d, starting 6 d prior to the 6- OHDA infusion. The rats were subjected to locomotor activity and rotational behavior testing 2 or 3 weeks after the 6-OHDA infusion. The expressions of tyrosine hydroxylase (TH) and NF-kappaB p65 were examined by immunofluorescence. The loss of dopaminergic neurons was detected by Nissl's staining. Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling was used to identify apoptosis. Results: **The behavioral changes due to 6-OHDA were significantly restored by bilobalide pretreatment. Bilobalide inhibited the 6-OHDA-induced loss of TH-positive neurons, decreased the activation of NF-kappaB, and protected dopaminergic neurons from apoptosis remarkably**. **NF-kappaB activation contributes to the 6-OHDA-induced loss of dopaminergic neurons, and the inhibition of the NF-kappaB pathway is likely to be involved in the neuroprotective effect of bilobalide**." *(Li LY, Zhao XL, Fei XF, Gu ZL, Qin ZH, Liang ZQ. Bilobalide inhibits 6-OHDA-induced activation of NF-kappaB and loss of dopaminergic neurons in rat substantia nigra. Acta Pharmacol Sin. 2008 May;29(5):539-47).*

[36] "Dysfunctions in the serotonergic system have been implicated in several neurological disorders such as depression. Elderly individuals who have been diagnosed with clinical depression show elevated cases of neurodegenerative diseases. This has led to suggestions that modulating the serotonin (5-HT) system could provide an alternative method to current therapies for alleviating these pathologies. **The neuroprotective effects of bilobalide in vitro have been documented. We aim to determine whether bilobalide affects the 5-HT system in the nematode C. elegans.** The wild type worms, as well as well-characterized 5-HT mutants, were fed with bilobalide in a range of concentrations, and several 5-HT controlled behaviors were tested. Results: We observed that **bilobalide significantly inhibited 5-HT-controlled egg-laying behavior in a dose-dependent manner**, which was blocked in the 5-HT receptor mutants (ser-4, mod-1), but not in the 5-HT transporter (mod-5) or synthesis (tph-1) mutants. **Bilobalide also potentiated a 5-HT-controlled, experience-dependent locomotory behavior, termed the enhanced slowing response in the wild type animals**. However, this effect was fully blocked in 5-HT receptor mod-1 and dopamine defective cat-2 mutants, but only partially blocked in ser-4 mutants. We also demonstrated that acetylcholine transmission was inhibited in a transgenic C. elegans strain that constitutively expresses Abeta, and bilobalide did not significantly affect this inhibition. CONCLUSION: **These results suggest that bilobalide may modulate specific 5-HT receptor subtypes, which involves interplay with dopamine transmission**. Additional studies for the function of bilobalide in neurotransmitter systems could aid in our understanding of its neuroprotective properties." *(Brown MK, Luo Y. Bilobalide modulates serotonin-controlled behaviors in the nematode Caenorhabditis elegans. BMC Neurosci. 2009 Jun 22;10:62).*

[37] "…EGb 761 is currently used as symptomatic treatment for cerebral insufficiency that occurs during normal ageing or which may be due to degenerative dementia, vascular dementia or mixed forms of both, and for neurosensory disturbances. Depressive **symptoms of patients with Alzheimer's disease (AD) and aged non-Alzheimer patients may also respond to treatment with EGb 761 since this extract has an "anti-stress" effect. Basic and clinical studies, conducted both in vitro and in vivo, support these beneficial neuroprotective effects of EGb 761. EGb 761 has several major actions; it enhances cognition, improves blood rheology and tissue metabolism, and opposes the detrimental effects of ischaemia**. Several mechanisms of action are useful in explaining how EGb 761 benefits patients with AD and other age-related, neurodegenerative disorders. In animals, **EGb 761 possesses antioxidant and free radical-scavenging activities**, **it reverses age-related losses in brain alpha 1-adrenergic, 5-HT1A and muscarinic receptors, protects against ischaemic neuronal death, preserves the function of the hippocampal mossy fiber system, increases hippocampal high-affinity choline uptake, inhibits the down-regulation of hippocampal glucocorticoid receptors, enhances neuronal plasticity, and counteracts the cognitive deficits that follow stress or traumatic brain injury**. Identified chemical constituents of EGb 761 have been associated with certain actions. **Both flavonoid and ginkgolide constituents are involved in the free radical-scavenging and antioxidant effects of EGb 761** which decrease tissue levels of reactive oxygen species (ROS) and inhibit membrane lipid peroxidation. **Regarding EGb 761-induced regulation of cerebral glucose utilization, bilobalide increases the respiratory control ratio**

Il Ginkgo svolge inoltre un'azione neuroprotettiva specifica nei confronti dell'ippocampo: l'estratto aumenta, nell'ippocampo del ratto, il numero dei recettori muscarinici postsinaptici, ostacolando in tal modo il declino della funzione colinergica cerebrale tipico degli animali anziani. La somministrazione del Ginkgo aumenta del 28% il legame della noradrenalina ai propri recettori nel ratto anziano, e ciò conferma l'attività pronoradrenergica di questa droga[38]. Uno studio nel ratto ha indagato l'effetto dell'EGB 761 sui livelli cerebrali di catecolamine, di dopamina e di serotonina e su quelli plasmatici di corticosterone, in animali sottoposti a stress da prigionia. Si è visto che l'EGB 761 alla dose di 14 mg/kg/die favoriva l'aumento delle catecolamine cerebrali, della dopamina e della serotonina indotto dallo stress e incrementava anche i livelli plasmatici di corticosterone. Nel corpo striato aumenta anche i livelli di dopamina e del suo metabolita acido diidrossifenilacetico[39]. Le azioni su queste amine cerebrali possono concorrere a spiegare le attività di stimolo delle funzioni

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of mitochondria by protecting against uncoupling of oxidative phosphorylation, thereby increasing ATP levels, a result that is supported by the finding that bilobalide increases the expression of the mitochondrial DNA-encoded COX III subunit of cytochrome oxidase. **With regard to its "anti-stress" effect, EGb 761 acts via its ginkgolide constituents to decrease the expression of the peripheral benzodiazepine receptor (PBR) of the adrenal cortex**." *(DeFeudis FV, Drieu K. Ginkgo biloba extract (EGb 761) and CNS functions: basic studies and clinical applications. Curr Drug Targets. 2000 Jul;1(1):25-58).*

38 "**Effect of administration of the standardized extract of Ginkgo biloba leaves (EGb 761) on learning, memory and exploratory behavior was estimated in water maze and hole-board tests**. Rats (18-month old) received for three months EGb 761 at doses: 50, 100 and 150 mg/kg b.w. per day. After completion of the behavioral experiment, concentrations of neurotransmitters were estimated in selected brain regions. **ANOVA demonstrated significant differences in the content of monoamines and metabolites between the treatment groups compared to the control.** The increased level of 5-hydroxytryptamine (5-HT) in the hippocampus and 5-HIAA (5-HT metabolite) in the prefrontal cortex correlated positively with the retention of spatial memory. Positive correlation between platform crossings in SE during the probe trial and neurotransmitter turnover suggest improvement of spatial memory. L**ong-term administration of Ginkgo biloba extract can improve spatial memory and motivation with significant changes in the content and metabolism of monoamines in several brain regions.**" *(Blecharz-Klin K, Piechal A, Joniec I, Pyrzanowska J, Widy-Tyszkiewicz E. Pharmacological and biochemical effects of Ginkgo biloba extract on learning, memory consolidation and motor activity in old rats. Acta Neurobiol Exp (Wars). 2009; 69(2):217-31).*

39 "(...). The search for effective and safe alternatives from natural sources especially plant products should, therefore, continue. Forced immobilization is one of the best explored models of stress in rats and the role of corticosterone, serotonin and catecholamines, i.e. norepinephrine (NE), dopamine (DA) is well documented. **Numerous studies have shown that Ginkgo biloba has antioxidant and neuroprotective properties and utility in cerebrovascular insufficiency and impaired cerebral performance. We investigated the effect of G. biloba on whole brain catecholamine, serotonin and plasma corticosterone levels following 1, 2 and 4 h restraint stress using HPLC and also plasma corticosterone using luminescence spectrophotometry**. **G. biloba extract (14 mg/kg p.o.) restored restraint stress-induced elevation in whole brain levels of catecholamines (NE, DA), 5-HT and plasma corticosterone to near normal levels.** Further studies are warranted to explore the clinical potential of this encouraging lead in the management of stress and to elucidate the mechanisms involved." *(Shah ZA, Sharma P, Vohora SB.Ginkgo biloba normalises stress-elevated alterations in brain catecholamines, serotonin and plasma corticosterone levels. Eur Neuropsychopharmacol. 2003 Oct;13(5):321-5).*

mnenmoniche[40], antidepressiva e ansiolitica tipiche di questa droga[41].

Attività biologiche ed impieghi clinici descritti in letteratura

Medicina popolare. Definito anche "fossile vivente", il *Ginkgo biloba* è l'unico superstite della famiglia delle *Ginkgoaceae*, un gruppo di Gimnosperme di origini molto antiche estintosi oltre 200 milioni di anni fa[42]. Il primo utilizzo medicinale del Ginkgo risale al 2800 a.C., al tempo dell'imperatore Shen-Nung, considerato il padre della medicina cinese secondo la quale la pianta era in grado di tenere lontano la vecchiaia e la morte (probabilmente per i suoi effetti emoreologici). Per queste sue proprietà, l'infuso delle foglie di Ginkgo è chiamato "tè dell'eterna giovinezza". I preparati di Ginkgo venivano inoltre diffusamente impiegati per le loro proprietà toniche e contro le allergie. In Cina, il seme essiccato e lavorato è utilizzato nelle prescrizioni per l'asma, tosse con flemma, enuresi,

40 "**Effect of administration of the standardized extract of Ginkgo biloba leaves (EGb 761) on learning, memory and exploratory behavior was estimated in water maze and hole-board tests**. Rats (18-month old) received for three months EGb 761 at doses: 50, 100 and 150 mg/kg b.w. per day. After completion of the behavioral experiment, concentrations of neurotransmitters were estimated in selected brain regions. ANOVA demonstrated **significant differences in the content of monoamines and metabolites between the treatment groups compared to the control**. **The increased level of 5-hydroxytryptamine (5-HT) in the hippocampus and 5-HIAA (5-HT metabolite) in the prefrontal cortex correlated positively with the retention of spatial memory**. Positive correlation between platform crossings in SE during the probe trial and neurotransmitter turnover suggest improvement of spatial memory. **Long-term administration of Ginkgo biloba extract can improve spatial memory and motivation with significant changes in the content and metabolism of monoamines in several brain regions**." *(Blecharz-Klin K, Piechal A, Joniec I, Pyrzanowska J, Widy-Tyszkiewicz E. Pharmacological and biochemical effects of Ginkgo biloba extract on learning, memory consolidation and motor activity in old rats. Acta Neurobiol Exp (Wars). 2009;69(2):217-31).*

41 "**Experimental and clinical data suggest that extracts of Ginkgo biloba improve cognitive function**. However, the neurochemical correlates of these effects are not yet fully clarified. T**he purpose of this study was to examine the effects of acute and repeated oral administration of the standardized extract EGb 761((R)) on extracellular levels of dopamine, noradrenaline and serotonin (5-HT), and the dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the prefrontal cortex (PFC) and striatum of conscious rats.** Experimental approach: Monoamines and their metabolites were monitored by the use of microdialysis sampling and HPLC with electrochemical or fluorescence detection. Key results: **A single oral dose of EGb 761 (100 mg.kg(-1)) had no effect on monoamine levels. However, following chronic (100 mg.kg(-1)/14 days/once daily) treatment, the same dose significantly increased extracellular dopamine and noradrenaline levels, while 5-HT levels were unaffected. Chronic treatment with EGb 761 showed dose-dependent increases in frontocortical dopamine levels and, to a lesser extent, in the striatum. The extracellular levels of HVA and DOPAC were not affected by either acute or repeated doses.** (...). Conclusions and implications: Th**e present results demonstrate that chronic but not acute treatment with EGb 761 increased dopaminergic transmission in the PFC. This finding may be one of the mechanisms underlying the reported effects of G. biloba in improving cognitive function.**" *(Yoshitake T, Yoshitake S, Kehr J. The Ginkgo biloba extract EGb 761((R)) and its main constituent flavonoids and Ginkgolides increase extracellular dopamine levels in the rat prefrontal cortex. Br J Pharmacol. 2010 ;159 (3):659-668.*

42 "Ginkgo biloba is one of the oldest, still existing plants. Extracts from its leaves were already used in ancient China whereas in the Western World, they have been utilized only since the Sixties when it became technically possible and feasible to isolate the essential substances of Ginkgo biloba. **Pharmacologically, there are two groups of substances which are of some significance: the flavonoids, effective as oxygen-free radical scavengers, and the terpenes (i.e. the Ginkgolides) with their highly specific action as platelet activating factor (PAF) inhibitors**. Clinically important indications for Ginkgo biloba extracts are cerebral insufficiency and atherosclerotic disease of peripheral arteries of intermediate severity. In several placebo-controlled clinical studies, symptoms of cerebral insufficiency have been effectively and significantly influenced." *(Z'Brun A. Ginkgo: myth and reality. Schweiz Rundsch Med Prax 1995; 84: 1-6).*

disturbi della mucosa vaginale, bronchiti con asma, diuresi frequente.

Azione sul microcircolo: effetti anti-ischemici. Sono numerosi i lavori sperimentali e clinici che hanno messo in evidenza gli effetti del *Ginkgo biloba* sull'apparato cardiovascolare, sul tono della muscolatura liscia arteriolare, sul microcircolo capillare e venoso e sulle piastrine circolanti[43]. L'attività anti-PAF dei ginkgolidi, infatti, si traduce principalmente in una azione fluidificante ematica che rende più agevole perfusione di tessuti ed organi, contrastando l'ipossia che danneggia l'endotelio in presenza di un rallentato deflusso ematico[44]. Ne derivano una serie di applicazioni terapeutiche in molte patologie cardiovascolari, in quanto tale azione è particolarmente utile in presenza di sclerosi vascolare[45]. L'effetto è stato messo chiaramente in evidenza nell'uomo, misurando la velocità di transito di globuli rossi all'interno di microcapillari osservati in microscopia ottica e l'indice di

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43 "**Ginkgo biloba special extract exerts positive effects on hemorheology and platelet aggregation, is a free radical scavenger and possesses PAD antagonistic properties, protects against hypoxia and ischemia, hampers an experimentally induced cerebral edema, has favourable properties on neurotransmitters and enhances cerebral blood flow.** Clinically [it] has proven favourable effects on intellectual deficiency, equilibrium disturbances and peripheral artery occlusions thus being a drug with a clear cut indication for these diseases." *(Hitzenberger G. The effect of Ginkgo biloba special extract (EGb 761, Tebofortan). Wien Med Wochenschr 1992; 142: 371-9).*

44 "To evaluate the effect of Ginkgo biloba extract (EGb) on hepatic microcirculation and portal hypertension in CCl4 treated rats. Methods: **Twenty-five male Wister rats were divided into a blank, a CCl4 treated and a CCl4 plus EGb treated group, and all were treated for 10 weeks**. The free portal vein pressures were measured through catheterizations. Hepatic sinusoidal endothelial cells and other parameters of hepatic microcirculation were studied with transmission electron microscopy. The amounts of malondialdehyde (MDA), endothelin (ET-1), platelet-activating factor (PAF), nitric oxide (NO), cNOS and iNOS in the liver tissues were determined. Results: The portal vein pressure of the CCl4 plus EGb treated group was (7.4 +/- 0.6) mm Hg while the pressure of the CCl4 treated group was (8.7 +/- 0.8) mm Hg. **Aggregation of blood cells or microthrombosis in hepatic sinusoids, deposition of collagen in hepatic sinusoids and spaces of Disse, injury of endothelial cells and capillarization of hepatic sinusoid were significantly milder in the EGb group.** The amounts of MDA, ET-1, PAF, NO and iNOS were markedly lower in the CCl4 plus EGb treated group than in the CCl4 treated group. **The results demonstrated that EGb can decrease the portal vein pressure and improve hepatic microcirculation in CCl4 treated rats. The mechanisms of this effect may involve its inhibition on ET-1, PAF, lipid peroxidation, and down regulation of the hepatic iNOS and NO expressions.**" *(Zhang CQ, Zhu YH, Wang J, Liang B, Xu HW, Qin CY. The effect of Ginkgo biloba extract on portal hypertension and hepatic microcirculation in rats. Zhonghua Gan Zang Bing Za Zhi. 2007 Apr;15(4):245-8).*

45 "**In patients with coronary artery disease (CAD), coronary blood flow is usually impaired due to imbalanced vasoactive substances such as nitric oxide (NO) and endothelin-1 (ET-1). The study was designed to test the effects of Ginkgo biloba extract (GBE) on the distal left anterior descending coronary artery (LAD) blood flow and plasma NO and ET-1 levels**. Eighty CAD patients were randomly assigned to GBE (n = 42) and control (n = 38) groups. The LAD blood flow was assessed non-invasively using Doppler echocardiography at baseline and after 2 weeks. GBE treatment demonstrated a significant improvement in maximal diastolic peak velocity (MDPV), maximal systolic peak velocity (MSPV) and diastolic time velocity integral (DTVI) compared with controls (14.61 +/- 4.51% vs 0.67 +/- 2.66%, 9.03 +/- 4.81% vs 0.34 +/- 2.67% and 14.69 +/- 5.08% vs 0.68 +/- 3.00%, respectively, $p < 0.01$). NO was increased by 12.42% ($p < 0.01$), whereas ET-1 was decreased by 5.82% ($p < 0.01$). The NO/ET-1 ratio was increased by 19.47% ($p < 0.01$). A linear correlation was confirmed between the percentage change in LAD blood flow and in NO, ET-1 or NO/ET-1 ratio following GBE treatment. **The results suggest that GBE treatment in CAD patients led to an increase of LAD blood flow, which might at least be related partly to the restoration of the delicate equilibrium between NO and ET-1.**" *(Wu YZ, Li SQ, Zu XG, Du J, Wang FF. Ginkgo biloba extract improves coronary artery circulation in patients with coronary artery disease: contribution of plasma nitric oxide and endothelin-1. Phytother Res. 2008 Jun;22(6):734-9).*

aggregabiltà eritrocitaria, sempre su microcapillari di volontari sani[46,47]. Il *Ginkgo biloba* mostra una buona biodisponibilità dopo somministrazione orale nell'uomo, e gli effetti benefici della droga sui parametri emoreologici appaiono particolarmente evidenti in pazienti con retinopatia diabetica, nei quali i parametri relativi alla funzionalità del microcircolo, come la deformabilità eritrocitaria e la viscosità ematica, risultano significativamente alterati[48]. In soggetti con lesioni aterosclerotiche dell'arco aortico e delle arterie coronarie la somministrazione di *Ginkgo biloba* determina un significativo aumento del microcircolo e del flusso coronarico[49]. Anche in 42 pazienti con alterazioni

46 **"In a randomized placebo controlled single-blind cross-over study of n = 10 apparently healthy subjects the influence of Ginkgo biloba (Kaveri) on blood fluidity and cutaneous microcirculation was studied**. Microcirculation was measured before and every 30 min for 4 h after administration of Ginkgo biloba; fluidity of blood was determined before and after 1, 2 and 4 h. Significant changes in blood pressure or heart rate were found neither during Ginkgo phase nor placebo phase. **Haematocrit, plasma viscosity, erythrocyte rigidity, thrombocyte and leukocyte count as well as thrombocyte aggregation and the number of circulating thrombocyte aggregates were also not influenced by the Ginkgo nor the placebo solution. In contrast a remarkable influence on the erythrocyte aggregation was observed: comparing two samples a significant decrease by 15.6% (p less than 0.001) with regard to the initial value was observed after 2 h.** The blood flow in the nail fold capillaries also increased significantly by about 57% (p less than 0.004) 1 h after administration." *(Jung F, Mrowietz C, Kiesewetter H, Wenzel E. Effect of Ginkgo biloba on fluidity of blood and peripheral microcirculation in volunteers. Arzneimittelforschung. 1990 May;40(5):589-93).*

47 *He J, Lin J, Li J, Zhang JH, Sun XM, Zeng CM. Dual effects of Ginkgo biloba leaf extract on human red blood cells. Basic Clin Pharmacol Toxicol. 2009 Feb;104(2):138-44.*

48 "Abnormal haemorrheological property changes in erythrocyte deformability, plasma and blood viscosity, and blood viscoelasticity may play very important roles in the development of microangiopathies in diabetes mellitus (DM). **In this study, we demonstrate the improvement in abnormal haemorrheological parameters in DM with ingestion of Ginkgo biloba extract 761 (Egb 761).** Methods: Haemorrheological parameters before and 3 months after Egb 761 oral ingestion were determined in **25 type 2 DM patients with retinopathy**. These parameters included lipid peroxidation stress of erythrocytes, erythrocyte deformability, plasma and blood viscosity, blood viscoelasticity, and retinal capillary blood flow velocity. Results: **After taking Egb 761 orally for 3 months, the blood viscosity was significantly reduced at different shear rates, by 0.44 +/- 0.10 (gamma = 400), 0.52 +/- 0.09 (gamma = 150) and 2.88 +/- 0.57 (gamma = 5). Viscoelasticity was significantly reduced in diabetic patients by 3.08 +/- 0.78 (0.1 Hz)**. The level of erythrocyte malondialdehyde (MDA) was reduced by 30%; however, the deformability of erythrocyte was increased by 20%. And lastly, retinal capillary blood flow rate was increased from 3.23 +/- 0.12 to 3.67 +/- 0.24 cm min(-1). Conclusion: **In this preliminary clinical study, 3 months of oral administration of Egb 761 significantly reduced MDA levels of erythrocytes membranes, decreased fibrinogen levels, promoted erythrocytes deformability, and improved blood viscosity and viscoelasticity, which may facilitate blood perfusion**. Furthermore, it effectively improved retinal capillary blood flow rate in type 2 diabetic patients with retinopathy." *(Huang SY, Jeng C, Kao SC, Yu JJ, Liu DZ. Improved haemorrheological properties by Ginkgo biloba extract (Egb 761) in type 2 diabetes mellitus complicated with retinopathy. Clin Nutr. 2004 Aug;23(4):615-21).*

49 "Ginkgo biloba extract (GBE) has well-documented cardioprotective effects on coronary flow and positive effects on vasodilation through endothelium-derived nitric oxide in experimental animals, but these impacts in patients with coronary artery disease (CAD) have not yet been investigated. We designed this study to test the effects of GBE on distal left anterior descending coronary artery (LAD) blood flow and endothelium-dependent brachial artery flow-mediated dilation (FMD) in patients with CAD. Eighty CAD patients were randomly assigned to either GBE or saline (control) groups. LAD blood flow and brachial artery FMD were measured non-invasively using high-resolution ultrasound before and after intravenous administration of GBE or saline. **GBE significantly increased LAD blood flow in maximal diastolic peak velocity (MDPV), maximal systolic peak velocity (MSPV) and diastolic time velocity integral (DTVI) compared with the control group (16.14 +/- 10.93 % vs. 0.28 +/- 2.14 %, 9.14 +/- 8.23 % vs. 0.79 +/- 2.56 %, and 15.23 +/- 7.28 % vs. 0.42 +/- 2.43 %, respectively, p < 0.01). Brachial artery FMD was also increased by 69.75 % (from 3.95 +/- 1.49 % to 6.55 +/- 2.51 %, p < 0.01).** A linear correlation was found between the percentage changes in MDPV, MSPV, or DTVI of LAD blood flow and the percentage change in brachial artery FMD following treatment with GBE (r = 0.612, 0.486, or 0.521, respectively, p < 0.01). In summary, **our data demonstrate that GBE treatment in CAD patients leads to an increase of LAD blood flow in MDPV, MSPV and DTVI, and the increase**

visco-elastiche del microcircolo il Ginkgo determina un aumento dose-dipendente del microcircolo cutaneo, dimostrato con l'esame ecografico Doppler[50]. Studi più recenti confermano che, anche quando somministrato ad individui sani, l'estratto secco standardizzato di *Ginkgo biloba* influisce positivamente sulle caratteristiche emoreologiche dei soggetti trattati, migliorando il microcircolo cutaneo[51].

Risulta di particolare interesse anche l'osservazione sperimentale che l'estratto ottenuto dalle foglie di Ginkgo, valutato in vitro nel plasma umano con metodo fluorimetrico, mostra un'attività fibrinolitica comparabile a quella di farmaci come la streptochinasi e l'urochinasi; tale effetto inibitorio su tutta la coagulazione del sangue, rendono la droga un complemento utile in presenza di tromboflebiti, varici, angina e malattie cardiovascolari in genere[52].

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response might relate to the improved endothelium-dependent vasodilatory capacity. CAD: coronary artery disease DTVI: diastolic time velocity integral FMD: flow-mediated dilation GBE: GINKGO BILOBA extract LAD: distal left anterior descending coronary artery MDPV: maximal diastolic peak velocity MSPV: maximal systolic peak velocity NO: nitric oxide TTDE: transthoracic Doppler echocardiography." *(Wu Y, Li S, Cui W, Zu X, Wang F, Du J. Ginkgo biloba extract improves coronary blood flow in patients with coronary artery disease: role of endothelium-dependent vasodilation. Planta Med. 2007 Jun;73(7):624-8).*

50 "In a randomized open clinical trial involving 42 patients with pathological visco-elasticity values, the effect of a single intravenous injection of 50, 100, 150 or 200 mg of the Ginkgo biloba…. on the microcirculation of the skin (Doppler flowmetry) and the visco-elasticity of whole blood was investigated… **The present study thus confirms the positive effect of EGb 761 on the microcirculation and whole-blood visco-elasticity in patients with pathological visco-elasticity values,** already found in earlier studies, and shows it to be dependent on the dose employed." *(Koltringer P, Langsteger W, Klima G, Reisecker F, Eber O. Hemorheologic effects of Ginkgo biloba extract EGb 761. Dose-dependent effect of EGb 761 on microcirculation and viscoelasticity of blood. Fortschr Med 1993; 111: 170-2).*

51 "20 Ginkgo biloba extract has been advocated for the improvement of blood circulation in circulatory disorders. **This study investigated the effect of the Gingko biloba extract EGb 761 on skin blood flow in healthy volunteers and accompanying changes in urinary metabolites. Twenty-seven healthy middle-aged subjects participated in a randomized, double-blind, placebo-controlled, crossover study. Subjects received 240 mg/d EGb 761 or placebo for periods of 3 weeks. Skin blood flow was measured on the forefoot using laser Doppler flowmetry and changes in urinary metabolites were identified by a combination of nuclear magnetic resonance (NMR) spectroscopy and multivariate data analysis (MVDA). These measurements were performed on 24-h urine samples collected at the end of the intervention periods.** Following EGb 761 treatment, overall mean skin blood flow was significantly reduced as compared with placebo. Remarkably, the change of skin blood flow after EGb 761 intervention was proportionally related to blood flow after placebo treatment: subjects showed either an increased, decreased or unaltered skin blood flow. NMR/MDVA analyses showed that urinary metabolic patterns differed depending on the change in baseline blood flow after treatment with EGb 761. **The present findings substantiate that EGb 761 has a multi-directional modulating action on blood flow in healthy subjects and support findings of a vasoregulatory role of this extract.** Moreover, the results indicate that metabolic fingerprinting provides a powerful means to identify biochemical markers that are associated with functional changes." *(Boelsma E, Lamers RJ, Hendriks HF, van Nesselrooij JH, Roza L. . Evidence of the regulatory effect of Ginkgo biloba extract on skin blood flow and study of its effects on urinary metabolites in healthy humans. Planta Med. 2004 Nov;70(11):1052-7).*

52 "A multitude of factors are involved in regulating the blood coagulation homeostatic processes in the body, which may ultimately lead to thromboemboli and thrombosis. The resolution of blood clots after healing is as important as clot formation at the site of a vascular lesion. This is accomplished by fibrinolytic drugs such as streptokinase (SK) and urokinase. (…) **In the present study, the fibrinolytic effect of Ginkgo biloba was investigated**. A polyphenolic method was used to obtain Ginkgo extract from its leaves. **The fibrinolytic effects of SK (positive control) were compared with those of Ginkgo extract using a fluorometry method.** In producing a labelled clot, fibrinogen was labelled with the fluorescent agent fluorescein isothiocyanate and precipitated in the presence of Ca2+. SK (100 U/mL to 1000 U/mL) and Ginkgo extract were added to labelled fibrin in a plasma environment at dilutions of 1, 1:10, 1:100 and 1:1000 (volume/volume). The fluorescence of the solution was measured between 15 min and 60 min later. A linear relationship was observed between the fluorescence measured and SK

Inoltre, dal momento che "gli estratti di *Ginkgo biloba* esplicano la loro attività endotelioprotettiva non solo sulle arteriole, ma anche sui capillari e sulle venule, il Ginkgo agisce bene anche sul complesso dei disturbi varicosi, sulla sindrome post-trombotica e sull'ulcera varicosa…."Weiss, 1996). Ancora, dopo un trattamento per 6-8 settimane, il *Ginkgo biloba* determina una vasodilatazione del distretto cocleare ed antagonizza la riduzione del flusso cocleare indotta dall'acido salicilico, risultando potenzialmente utile nei soggetti con ipoperfusione cocleare (aterosclerosi del distretto vertebrale)[53]. Le principali attività farmacologiche del *Ginkgo biloba* sono imputate ai ginkgolidi, che risultano dei potenti e selettivi inibitori del PAF. Ulteriori ipotesi sul meccanismo d'azione del *Ginkgo biloba* derivano dall'osservazione che, in vivo, il fitocomplesso riduce la contrazione della muscolatura liscia arteriolare indotta dall'aggregazione piastrinica, analogamente a quanto avviene con un inibitore selettivo dei recettori del trombossano (U63557). Questa analogia suggerisce che il *Ginkgo biloba* possa agire bloccando, oltre ai recettori del PAF, anche quelli per il trombossano[54]. È possibile anche

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concentrations ranging from 300 U/mL to 700 U/mL. Ginkgo extract displayed a remarkable effect in resolving the clot. As Ginkgo extract remained in the environment, fluorescence increased notably, showing a time-dependent relationship. Overall, **the results indicate that the effects of Ginkgo extract on the fibrinolytic system are similar to those of SK; hence, this herbal extract can be used as a complement to or a substitute for SK**. Additionally, it is proposed that the effects of the active ingredients of Ginkgo extract should be studied in animals. Further studies are warranted for evaluating the possible side effects and toxicity of Ginkgo extract in human subjects." *(Naderi GA, Asgary S, Jafarian A, Askari N, Behagh A, Aghdam RH. Fibrinolytic effects of Ginkgo biloba extract. Exp Clin Cardiol 2005;10(2):85-87).*

53 "Ginkgo biloba extract (EGb 761) was administered orally for 4 or 6 weeks to healthy adult guinea pigs… **Post-mortem morphometric measurements of cochlear vessels in the spiral lamina revealed a vasodilating effect of the extract in four of ten animals following 6 weeks of treatmen**t… These findings indicate that EGb 761 may help to improve oxygenation in cochleas with compromised blood flow." *(Didier A, Droy-Lefaix MT, Aurousseau C, Cazals Y. Effects of Ginkgo biloba extract (EGb 761) on cochlear vasculature in the guinea pig: morphometric measurements and laser Doppler flowmetry. Eur Arch Otorhinolaryngol 1996; 253: 25-30).*

54 "**Twelve non-diabetic volunteers (age=39+/-13 years, BMI=23.5+/-3.5) undertook a randomized double-blind placebo-controlled crossover study in which they ingested either 120 mg of EGb 761 or a placebo daily for 3 months and then switched to the other test capsules for the next 3 months**. Platelet aggregation in platelet-rich plasma (PRP) was performed at the end of each 3-month arm, with or without 1-min incubation with graded doses of EGb 761. In the placebo cycles, AA-stimulated TXB2 production was 2581 +/-1337 pg/10(6) platelets (range 897-5485) compared to 1668 +/- 992 pg/10(6) platelets (range 6-1668) in the EGb 761 cycles ($p < 0.005$). Incubation of PRP with EGb 761 (150 microg/ml) completely inhibited platelet aggregation accompanied by inhibition of TXB2 synthesis in all subjects both in the placebo (<200 pg TXB2/10(6) platelets) and EGb 761 cycles (< 120 TXB2/10(6) platelets) ($p < 0.0001$). **These results support EGb 761-mediated inhibition of platelet TXB2 synthesis in vivo.**" *(Kudolo GB, Wang W, Barrientos J, Elrod R, Blodgett J. The ingestion of Ginkgo biloba extract (EGb 761) inhibits arachidonic acid-mediated platelet aggregation and thromboxane B2 production in healthy volunteers. J Herb Pharmacother. 2004;4(4):13-26).*

che i componenti del Ginkgo abbiano un effetto diretto sulla muscolatura liscia vascolare[55],[56]. L'azione vasodilatante del Ginkgo sui grossi vasi come l'aorta, studiata in modelli animali, risulta essere particolarmente evidente con l'avanzare dell'età[57]. Un'altra componente importante degli effetti benefici della droga sul microcircolo è poi certamente rappresentata dall'azione antiradicalica del fitocomplesso[58]. Il *Ginkgo biloba* è stato anche associato al Ginseng per il trattamento dei

[55] "**This study was aimed at investigating the effects of extract of Ginkgo biloba (EGb) on cerebral vasospasm and microcirculatory perfusion after subarachnoid hemorrhage (SAH).** An endovascular piercing method was used to induce Wistar rat SAH models, and animals were divided into sham-operated, vehicle controls, and EGb-treated groups. EGb was injected intraperitoneally 30 minutes before operation and was repeated every 6 hours, with a single dose of 15 mg/kg bw. Diameters of basilar arteries before and after operation were measured. Microcirculatory blood perfusion of parietal lobe cortex was detected using a laser Doppler flow-meter probe within 24 hours. Endothelin-1 levels in both plasma and brain tissue were detected at different time points. The results showed that SAH caused an immediate drop in microcirculatory blood flow in vehicle controls, which persisted for 24 hours. Endothelin-1 levels in both plasma and brain tissue increased after SAH. **EGb partly reversed spasms of the basilar artery and antagonized a drop in microcirculatory blood flow. EGb also prevented an increase in endothelin-1 both in plasma and in brain tissue. In conclusion, EGb, by antagonizing the overproduction of endo- thelin-1, partly reverses cerebral vasospasm and improves microcirculation**, and thus relieves secondary ischemic brain injury after experimental SAH." *(Sun BL, Zhang J, Wang XC, Xia ZL, Yang MF, Zhang SM, Ye WJ, Yuan H. Effects of extract of Ginkgo biloba on spasms of the basilar artery and cerebral microcirculatory perfusion in rats with subarachnoid hemorrhage. Clin Hemorheol Microcirc. 2003;29(3-4):231-8).*

[56] "The effect of intravenously administered Ginkbo biloba extract (EGb 761) on the vasospastic response to platelet activation has been assessed using a cutaneous flap preparation in anaesthetized mice… **Collectively, these findings indicate that platelet factors can play a significant role in cutaneous vasospasm, and that EGb 761, via an action on the thromboxane pathway, could be useful in treating Raynaud's phenomenon and other vascular disorders which involve increased thromboxane production.**" *(Stucker O, Pons C, Duverger JP, Drieu K, D'Arbigny P. Effect of Ginkgo biloba extract (EGb 761) on the vasospastic response of mouse cutaneous arterioles to platelet activation. Int J Microcirc Clin Exp 1997; 17:61-6).*

[57] "**Age-related modulation in vasodilating actions induced by Ginkgo biloba extract (GBE) and bilobalide, a main constituent of GBE, were examined using rat aorta ring strips**. Wistar rats from 5 to 25 weeks old were used, and the isolated aorta ring strips were fixed in Krebs–Henseleit solution. Results: **GBE and bilobalide concentration-dependently dilated norepinephrine (NE)-induced vasoconstriction in all aged rats. The vasodilating actions generally decreased in accordance with aging**. GBE at 1 mg/ml decreased from 28.4±3.8% (n=5) in 5-week-old rats to 23.7±7.1 (n=7) in 25-week-old rats, but not significantly. GBE (3 mg/ml)-induced vasodilation was maximum by 73.7±2.1% (n=4, P<0.001) in 10-week-old rats. **GBE had the marked vasodilation at younger ages and further decreased it with developing ages. In the rats older than 20 weeks, however, GBE tended to rather increase the strength of vasodilating action.** On the other hand, the vasorelaxation induced by 30 μmol/l bilobalide significantly decreased from 11.8±1.4% (n=4) in 5-week-old rats to 2.3±1.5% (n=5, P<0.01) in 25-week-old rats, and by 100 μmol/l from 20.2±3.4% (n=4) to 5.6±2.5% (n=5, P<0.01), respectively. **Bilobalide had the similar age-related actions**. The age-dependent attenuation was produced milder by bilobalide than by GBE. At lower concentrations, however, bilobalide caused the weak vasocontriction in 20- and 25-week-old rats. Conclusion: **GBE and bilobalide possess a similar characteristic for age-related modification, clinically suggesting the more effective actions of GBE for elder persons.**" *(Seiichiro Nishida, Hiroyasu Satoh. Age-related changes in the vasodilating actions of Ginkgo biloba extract and its main constituent, bilobalide, in rat aorta. Clinica Chimica Acta. 2005 April; Vol. 354, Issues 1-2, p.141-146).*

[58] "Besides alterations in cardiomyocytes themselves, **diabetic cardiopathy is characterized by interstitial and microvascular disorders**. On the assumption that a specific heart muscle disease develops due to permanently increased oxidative stress on liberation of oxygen-free radicals, adjuvant application of antioxidative therapeutics appears promising in preventing or delaying long-term diabetic complications and protecting the myocardium against acute ischemia. **We have investigated the effects of Ginkgo biloba extract (EGb 761), a radical scavenger, against diabetes-induced myocardial interstitium and microvasculature damage, and against additional ischemia/reperfusion injury in spontaneously diabetic BioBreeding/ Ottawa Karlsburg (BB/OK) rats modelling diabetic cardiac infarction**. Morphological and morphometric parameters in the heart muscle were evaluated by light and electron microscope. We used immunohistochemistry to investigate collagen protein expression as a marker for tissue remodelling together with endothelial nitric oxide synthase (eNOS) protein expression as a marker for endothelial-dependent vasodilation. We also evaluated inflammation response caused by neuropeptide Substance

disturbi del microcircolo. Le proprietà emoreologiche di questa associazione sono state studiate in 10 volontari sani: il prodotto determina una riduzione della pressione sistolica anche a dosi moderate, ed una riduzione di quella diastolica e della frequenza cardiaca a dosi più elevate. Anche l'aggregazione piastrinica e la velocità eritrocitaria all'interno dei capillari hanno mostrato un significativo miglioramento[59]. Da tutti questi dati farmacologici, sperimentali e clinici, deriva l'impiego terapeutico del *Ginkgo biloba* nelle arteriopatie periferiche di I e II grado *(claudicatio intermittens)*, nella cardiopatia ischemica e nelle cerebrovasculopatie su base aterosclerotica; nel morbo di Raynaud ed in altre patologie spastiche dei vasi.

Insufficienza cerebrovascolare. Il *Ginkgo biloba* trova indicazione nella malattia cerebrovascolare su base aterosclerotica e, particolarmente, nelle condizioni di cattiva perfusione delle arterie carotidee e vertebrali (ICV)[60] che si manifestano generalmente negli anziani con deficit delle funzioni cognitive (concentrazione e memoria), labilità emozionale, ridotta percezione sensoriale e minore resistenza alla fatica, vertigini e ronzii auricolari, disturbi visivi, ecc.

Demenza senile, demenza vascolare e morbo di Alzheimer. L'osservazione che il *Ginkgo biloba* migliora le amnesie tipiche di alcune forme di insufficienza cerebrovascolare (demenza aterosclerotica), ha aperto il campo allo studio del Ginkgo anche per altre forme di insufficienza

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P and interacting mast cells in the diabetic heart. Our results revealed that A) Diabetic myocardium appears more vulnerable to ischemia/reperfusion injury than normal myocardium with regard to myocardial interstitium and microvessel ultrastructure, as well as eNOS protein expression; B) Inflammation response increases in diabetic animals exposed to ischemia/reperfusion injury compared to controls; C) **Pre-treatment of diabetic myocardium with EGb results in an improvement of impaired endothelial-dependent vasodilation in diabetes and additional ischemia/ reperfusion**, diminished mast cell and substance P accumulation, and better preserved myocardial ultrastructure compared to unprotected myocardium. In conclusion, E**Gb may act as a potent therapeutic adjuvant in diabetics with respect to ischemic myocardial injury**, and may contribute to preventing late complications in diabetic cardiopathy." *(Schneider R, Welt K, Aust W, Löster H, Fitzl G. Cardiac ischemia and reperfusion in spontaneously diabetic rats with and without application of EGb 761: II. Interstitium and microvasculature. Histol Histopathol. 2009 May;24(5):587-98).*

[59] "Gincosan is a combined preparation containing 60 mg Ginkgo biloba and 100 mg ginseng, standardized of 24% Ginkgo flavone glycosides and 4% ginsenosides. Hemorrheological and circulatory effect as well as blood pressure behavior after the administration of gincosan were studied in an acute trial on 10 voluntary subjects with a mean age of 26 years. Systolic blood pressure decreased significantly both for the large-dose (120 mg Ginkgo biloba +200 mg ginseng) and low-dose administration (60 mg Ginkgo biloba +100 mg ginseng). Diastolic blood pressure and heart rate decreased only in the high dosage group. The pathologically increasedspontaneous platelet aggregation is reduced by both dosages. Erythrocyte velocity in nail fold capillaries increased significantly only in the high dosage group. The parallel group comparison of the high dosage and placebo group showed that they differ only significantly concerning the erythrocyte rigidity, erythrocyte velocity in nail fold capillaries and spontaneous platelet aggregation. A trend towards a decrease in the systolic blood pressure is revealed ($p<0.1$)." *(Kiesewetter H, Jung F, Mrowietz C, Wenzel E. Hemorrheological and circulatory effects of Gincosan. Int J Clin Pharmacol Ther Toxicol 1992; 30: 97-102).*

[60] "By means of a critical review we tried to establish whether there is evidence from controlled trials in humans on the efficacy of Ginkgo biloba extracts in cerebral insufficiency. The methodological quality of 40 trials on Ginkgo and cerebral insufficiency was assessed using a list of predefined criteria of good methodology, and the outcome of the trials was interpreted in relation to their quality… **Positive results have been reported for Ginkgo biloba extracts in the treatment of cerebral insufficiency**. The clinical evidence is similar to that of a registered product which is prescribed for the same indication. However, further studies should be conducted for a more detailed assessment of the efficacy." *(Kleijnen J, Knipschild P. Ginkgo biloba for cerebral insufficiency. Br J Clin Pharmacol 1992; 34: 352-8).*

delle funzioni cognitive. Il Ginkgo è risultato efficace nei soggetti con demenza o altri tipi di deficit della memoria, ed è raccomandato da molti AA. come nootropo di prima scelta, specialmente in considerazione della sua elevata tollerabilità[61]. L'attenuazione dei fenomeni amnesici – specialmente a carico della memoria recente – può contribuire moltissimo al miglioramento anche degli aspetti psicologici legati all'invecchiamento cerebrale e alla demenza[62,63].

L'incidenza e prevalenza della demenza nelle fasce più anziane della popolazione sono in aumento (Neurology 2008;70:1730-1). Si calcola che il numero di casi nei soggetti ultraottantenni sia destinato a quintuplicarsi entro il 2050 ed uno degli obiettivi principali delle ricerche in corso è quello di ritardare l'insorgenza e/o la progressione dei sintomi cognitivi. La demenza è una sindrome caratterizzata da un declino cognitivo che interferisce con la funzionalità quotidiana e con l'autonomia. Nella grande maggioranza dei casi la sindrome è riferibile alla malattia di Alzheimer (AD), un disturbo neurodegenerativo che riguarda selettivamente alcune aree cerebrali tra cui le vie colinergiche a proiezione corticale che hanno origine nel nucleo basale di Meynert. La malattia di Alzheimer è associata alla presenza di placche extracellulari di beta-amiloide e grovigli intracellulari neurofibrillari nella corteccia cerebrale e nella sostanza grigia sottocorticale che causano danni cerebrali e alterano le funzioni cognitive in circa il 16% delle persone con più di 85 anni[64]. Un anziano su dieci presenta lievi segni di decadimento cognitivo e risulta a rischio per la malattia di Alzheimer. Quattro processi contribuiscono alla formazione delle lesioni presenti nel cervello delle persone con malattia di Alzheimer: la produzione di amiloide, la formazione dei grovigli neurofibrillari, l'infiammazione e la

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61 "According to the latest research the therapy of dementia includes following strategies: above all there is a necessity for thoroughly diagnostic tests to exclude diseases which secondary induce reduced brain function. **The early onset of non pharmacological treatments e.g. "brain-jogging" is essential. Pharmacological therapy with nootropics (e.g. Codergocrin, Nicergolin, Ginkgo biloba, Piracetam, Pyritinol, Naftidrofuryl) is recommended as early as possible,** because they have no relevant side effects." *(Reisecker F. Therapy approaches in cerebral cognitive deficits: neuropsychiatric aspects. Wien Med Wochenschr 1996; 146: 546-8).*

62 "In contrast to other kinds of psychotropic drugs, nootropics or cognition enhancing drugs may be indicated, not for the direct treatment of the pathology itself, but for improving or restoring the remaining brain functions… L. Israel examined in two placebo-controlled studies the effects of either 160 mg/d of Ginkgo biloba extractum (GBE) or piracetam 2.4 or 4.8 g/d, combined with a memory training program, in nondemented patients complaining of memory problems. **The results of both studies suggest that nootropic drug treatment and memory training have each an effect on different cognitive functions and, hence, are complementary.**" *(Deberdt W. Interaction between psychological and pharmacological treatment in cognitive impairment. Life Sci. 1994. 55(25-26). P 2057-66).*

63 "The efficacy of the Ginkgo biloba special extract EGb 761 in outpatients with presenile and senile primary degenerative dementia of the Alzheimer type (DAT) and multi-infarct dementia (MID) according to DSM-III-R was investigated in a prospective, randomized, double-blind, placebo-controlled, multi-center study. After a 4-week run-in period, 216 patients were included in the randomized 24-week treatment period. These received either a daily oral dose of 240 mg EGb 761 or placebo… The frequency of therapy responders in the two treatment groups differed significantly in favor of EGb 761, with $p < 0.005$ in Fisher's Exact Test. **The intent-to-treat analysis of 205 patients led to similar efficacy results. Thus, the clinical efficacy of the Ginkgo biloba special extract EGb 761 in dementia of the Alzheimer type and multi-infarct dementia was confirmed. The investigational drug was found to be well tolerated.**" *(Kanowski S, Herrmann WM, Stephan K, Wierich W, Horr R. Proof of efficacy of the Ginkgo biloba special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. Pharmacopsychiatry 1996; 29: 47-56).*

64 *Cummings JL et al. Guidelines for managing Alzheimer's disease part I: Assessment. American Family Physician 2002;65(11):2263-2272.*

neurodegenerazione o morte cellulare[65]. Ciascun processo contribuisce sia autonomamente sia in relazione agli altri nel provocare il danno cerebrale. La neurodegenerazione e la perdita di dendriti causata dalla presenza di placche di beta-amiloide produce una diminuzione nella produzione di acetilcolina. Una perdita compresa tra 60-90% dell'attività colinergica è responsabile del deficit cognitivo e della perdita delle funzioni mnesiche. Nella malattia di Alzheimer si osserva anche una diminuzione tra 50-70% dell'attività serotoninergica, somatostatina 40-60% e norepinefrina 30-70%. L'utilizzo degli inibitori dell'acetilcolinesterasi, seppure con qualche riserva[66], ritarda temporaneamente il decorso della demenza, e sull'efficacia di nuove classi di farmaci nel modificare il ritmo di progressione della malattia di Alzheimer si accentrano oggi la maggior parte degli studi. Fra le strategie proposte, ha ricevuto notevole impulso, specie negli Stati Uniti, il possibile impiego di composti naturali, quali il *Ginkgo biloba*: ai principi attivi contenuti negli estratti idroacetonici secchi delle foglie di questa pianta vengono riconosciute, fra le altre, proprietà antiossidanti e possibili effetti sul metabolismo dell'amiloide. Da almeno una decina d'anni vengono pubblicati trials clinici su questo utilizzo del *Gingko biloba* effettuati con modelli sperimentali differenti e soprattutto su fasce d'età assai diverse. E nonostante la metanalisi dei primi studi (fino al 1998) avesse segnalato un minimo beneficio, un risultato abbastanza assodato è che la sua somministrazione della droga in persone sane al di sotto dei 60 anni di età sembra fornire vantaggi estremamente limitati se non trascurabili. L'impiego controllato degli estratti di *Ginkgo biloba* nel trattamento dei sintomi cognitivi della demenza di tipo Alzheimer ha dato peraltro risultati contradditori[67,68], mentre non è

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65 *Kumar-Singh S. Cerebral amyloid angiopathy: pathogenetic mechanisms and link to dense amyloid plaques. Genes Brain Behav. 2008 Feb;7 Suppl 1:67-82.*

66 *AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2000;363:2105-15.*

67 "Objective: To assess the efficacy and safety of EGb in Alzheimer disease and multi-infarct dementia. Design: A 52-week, randomized double-blind, placebo-controlled, parallel-group, multicenter study. Patients: Mildly to severely demented outpatients with Alzheimer disease or multi-infarct dementia (309), without other significant medical conditions. Primary outcome measures: Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Geriatric Evaluation by Relative's Rating Instrument (GERRI), and Clinical Global Impression of Change (CGIC). …Conclusions: **EGb 761 (120 mg/d) was safe and appears capable of stabilizing and, in a substantial number of cases, improving the cognitive performance and the social functioning of demented patients for 6 months to 1 year.** Although modest, the changes induced by EGb were objectively measured by the ADAS-Cog and were of sufficient magnitude to be recognized by the caregivers in the GERRI." *(Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. JAMA. 1997 Oct 22-29;278(16):1327-32).*

68 "Previous studies of Ginkgo biloba extract (GbE) in patients with various forms of cognitive impairment or dementia have shown promising results. Objective: **To determine the clinical efficacy of GbE in mild to moderate dementia of the Alzheimer type**. DESIGN: **Randomized, placebo-controlled, double-blind, parallel-group, multicenter trial.** Setting: Outpatient clinics of universities and private research centers specialized in dementia. Patients: 513 outpatients with uncomplicated dementia of the Alzheimer's type scoring 10 to 24 on the Mini-Mental State Examination and less than 4 on the modified Hachinski Ischemic Score, free of other serious illnesses and not requiring continuous treatment with any psychoactive drug. Intervention: 26-week treatment with GbE at daily doses of 120 mg or 240 mg or placebo. Main outcomes: Cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC). Results: **There were no significant between-group differences for the whole sample.** There was little cognitive and functional decline of the placebo-treated patients, however. **For a subgroup of patients with neuropsychiatric**

ancora stato definitivamente accertato se l'uso di questi composti in soggetti anziani senza deficit cognitivi possa avere un effetto preventivo sulla comparsa dei sintomi. Questo ultimo aspetto è stato indagato in uno studio pubblicato sulla rivista Neurology[69]: 118 anziani di età ≥ 85 anni, senza deficit cognitivi, sono stati randomizzati a ricevere in doppio cieco un estratto secco standardizzato di Ginkgo biloba (GBE, 240 mg/die), (n=60) o placebo (n=58) per un periodo di 42 mesi. L'analisi primaria dei dati non ha mostrato un effetto "protettivo" del trattamento con Ginkgo sul declino delle capacità cognitive nei soggetti studiati. È emerso invece il dato statisticamente significativo (p< 0,01) di un maggior numero di eventi avversi cerebrovascolari nel gruppo di soggetti trattati con GBE. Da un'analisi secondaria, che ha tenuto conto della compliance dei partecipanti allo studio nell'assunzione del trattamento, sembrerebbe invece emergere un possibile effetto del GBE nella prevenzione del declino cognitivo. Come correttamente sottolineano gli Autori (Dodge et al.), le dimensioni di questo studio hanno permesso solo di mostrare un possibile effetto preventivo della droga; e per una solidità statistica ottimale servirebbe una popolazione di qualche migliaio di individui e una maggiore durata del follow-up. Anche una Cochrane review pubblicata nel 2007 aveva constatato che le prove a beneficio dell'attività preventiva del Ginkgo nei confronti del declino cognitivo negli individui affetti da demenza non erano affatto convincenti, in quanto l'effetto dell'estratto risultava essere appena superiore al placebo[70]. A conclusioni analoghe sembra tuttavia

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symptoms there was a greater decline of placebo-treated patients and significantly better cognitive performance and global assessment scores for the patients on GbE. Conclusion: **The trial did not show efficacy of GbE, however, the lack of decline of the placebo patients may have compromised the sensitivity of the trial to detect a treatment effect**. Thus, the study remains inconclusive with respect to the efficacy of Gb." *(Schneider LS, DeKosky ST, Farlow MR, Tariot PN, Hoerr R, Kieser M. A randomized, double-blind, placebo-controlled trial of two doses of Ginkgo biloba extract in dementia of the Alzheimer's type. Curr Alzheimer Res. 2005 Dec;2(5):541-51).*

69 "**To assess the feasibility, safety, and efficacy of Ginkgo biloba extract (GBE) on delaying the progression to cognitive impairment in normal elderly aged 85 and older**. Methods: **Randomized, placebo-controlled, double-blind, 42-month pilot study with 118 cognitively intact subjects randomized to standardized GBE or placebo.** Kaplan-Meier estimation, Cox proportional hazard, and random-effects models were used to compare the risk of progression from Clinical Dementia Rating (CDR) = 0 to CDR = 0.5 and decline in episodic memory function between GBE and placebo groups. In the intention-to-treat analysis, there was no reduced risk of progression to CDR = 0.5 (log-rank test, p = 0.06) among the GBE group. There was no less of a decline in memory function among the GBE group (p = 0.05). In the secondary analysis, where we controlled the medication adherence level, the GBE group had a lower risk of progression from CDR = 0 to CDR = 0.5 (HR = 0.33, p = 0.02), and a smaller decline in memory scores (p = 0.04). There were more ischemic strokes and TIAs in the GBE group (p = 0.01). In unadjusted analyses, **Ginkgo biloba extract (GBE) neither altered the risk of progression from normal to Clinical Dementia Rating (CDR) = 0.5, nor protected against a decline in memory function. Secondary analysis taking into account medication adherence showed a protective effect of GBE on the progression to CDR = 0.5 and memory decline. Results of larger prevention trials taking into account medication adherence may clarify the effectiveness of GBE**. More stroke and TIA cases observed among the GBE group requires further study to confirm." *(Dodge HH, Zitzelberger T, Oken BS, Howieson D, Kaye J. A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. Neurology. 2008 May 6;70(19 Pt 2):1809-17).*

70 "…To assess the efficacy and safety of Ginkgo biloba for dementia or cognitive decline. Search strategy: Trials were identified on 10 October 2006 through a search of the Cochrane Dementia and Cognitive Improvement Group's Specialized Register which contains records from all main medical databases (MEDLINE, EMBASE, CINAHL, PsycINFO, SIGLE, LILACS), from ongoing trials databases such as Clinicaltrials.gov and Current Controlled Trials and many other sources… Randomized, double-blind studies, in which extracts of Ginkgo biloba at any strength and over any period were compared with placebo for their effects on people with acquired cognitive impairment, including dementia, of any degree of severity... Results: Clinical global improvement as

giungere anche la sperimentazione multicentrica statunitense GEM Study (Ginkgo Evaluation of Memory Study)[71], il più ampio e lungo studio clinico controllato, non sponsorizzato dall'industria farmaceutica, progettato proprio per valutare l'efficacia dell'estratto standardizzato di *Ginkgo biloba* nella prevenzione primaria della demenza e i cui risultati sono stati pubblicati nella primavera del 2009. Lo studio, randomizzato, multicentrico, in doppio cieco, promosso dal National Center for Complementary and Alternative Medicine (NCCAM) e dal National Institute on Aging of the National Institutes of Health (NIH), è stato realizzato dal 2000 al 2008 in diversi Centri accademici degli Stati Uniti e ha coinvolto 3.069 soggetti di età uguale o superiore ai 75 anni con normale livello cognitivo o decadimento cognitivo lieve. L'età media dei partecipanti all'ingresso nello studio era di 79,1 anni ed il 46% erano donne. Il follow up medio è stato di 6,1 anni. L'obiettivo primario dello studio GEM era quello di verificare se 240 mg/die di estratto secco standardizzato di *G. biloba* erano efficaci nel diminuire "l'incidenza di demenza da ogni causa" e in particolare del morbo di Alzheimer (MA), in

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assessed by the physician, was dichotomized between participants who showed improvement or were unchanged and those who were worse. **There are benefits associated with Ginkgo (dose greater than 200 mg/day) at 24 weeks (207/276 compared with 178/273, OR 1.66, 95% CI 1.12 to 2.46, P=.001) (2 studies), but not for the lower dose. Cognition shows benefit for Ginkgo (any dose) at 12 weeks (SMD -0.65, 95% CI -1.22 to -0.09 P=0.02, 5 studies) but not at 24 weeks.** Five studies assessed activities of daily living (ADLs), using different scales. Some scales are more comprehensive than just ADLs. **The results show benefit for Ginkgo (dose less than 200 mg/day) compared with placebo at 12 weeks (MD -5.0, 95% CI -7.88, -2.12, p=0.0007, one study), and at 24 weeks (SMD -0.16, 95% CI -0.31 to -0.01, p=0.03, 3 studies) but there are no differences at the higher dose.** No study assessed mood and function separately, but one study used the ADAS-Noncog, which assesses function over several domains, but not cognitive function. There was no difference between Ginkgo and placebo. There are no significant differences between Ginkgo and placebo in the proportion of participants experiencing adverse events. There are no data available on Quality of Life, measures of depression or dependency. Authors' conclusions: **Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods**, **were small, and we cannot exclude publication bias.** The evidence that Ginkgo has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unconvincing**."** *(Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD003120. Update of: Cochrane Database Syst Rev. 2007 Apr 18;(2):CD003120).*

[71] "**Objective:** To determine whether G. biloba slows the rates of global or domain-specific cognitive decline in older adults**. Design, setting, and participants:** The Ginkgo Evaluation of Memory (GEM) study, a randomized, double-blind, placebo-controlled clinical trial of 3069 community-dwelling participants aged 72 to 96 years, conducted in 6 academic medical centers in the United States between 2000 and 2008, with a median follow-up of 6.1 years. **Intervention:** Twice-daily dose of 120-mg extract of G. biloba (n = 1545) or identical-appearing placebo (n = 1524). **Main outcome measures: Rates of change over time in the Modified Mini-Mental State Examination (3MSE), in the cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-Cog), and in neuropsychological domains of memory, attention, visual-spatial construction, language, and executive functions, based on sums of z scores of individual tests. Results: Annual rates of decline in z scores did not differ between G. biloba and placebo groups in any domains, including memory (0.043; 95% confidence interval [CI], 0.034-0.051 vs 0.041; 95% CI, 0.032-0.050), attention (0.043; 95% CI, 0.037-0.050 vs 0.048; 95% CI, 0.041-0.054), visuospatial abilities (0.107; 95% CI, 0.097-0.117 vs 0.118; 95% CI, 0.108-0.128), language (0.045; 95% CI, 0.037-0.054 vs 0.041; 95% CI, 0.033-0.048), and executive functions (0.092; 95% CI, 0.086-0.099 vs 0.089; 95% CI, 0.082-0.096). For the 3MSE and ADAS-Cog, rates of change varied by baseline cognitive status (mild cognitive impairment), but there were no differences in rates of change between treatment groups (for 3MSE, P = .71; for ADAS-Cog, P = .97). There was no significant effect modification of treatment on rate of decline by age, sex, race, education, APOE*E4 allele, or baseline mild cognitive impairment (P > .05). Conclusion:** Compared with placebo, the use of G. biloba, 120 mg twice daily, did not result in less cognitive decline in older adults with normal cognition or with mild cognitive impairment." *(Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, Saxton J, Lopez OL, Dunn LO, Sink KM, DeKosky ST; Ginkgo Evaluation of Memory (GEM) Study Investigators. Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial. JAMA. 2009 Dec 23;302(24):2663-70).*

pazienti anziani con funzioni cognitive normali oppure in pazienti con danno cognitivo lieve (MCI, Mild Cognitive Impairment); mentre gli obiettivi secondari dello studio erano di valutare l'effetto del Ginkgo sui seguenti endpoint: declino cognitivo generale, inabilità funzionale, mortalità totale ed incidenza di malattie cardiovascolari[72]. La diagnosi di demenza era effettuata mediante i criteri DSM-IV da una commissione di esperti clinici. I soggetti sono stati assegnati in modo casuale a ricevere un estratto di *Ginkgo biloba*, 120 mg per 2 volte al giorno, oppure un placebo. Nel corso della durata dello studio, in media 6 anni, a 523 partecipanti è stata diagnosticata la demenza, di cui 246 (16,1%) nel gruppo del placebo e 277 (17,9%) nel gruppo trattato con Ginkgo. La percentuale non differiva tra i due gruppi, e la droga non ha prodotto alcun effetto sulla progressione della malattia. Non sono state riscontrate differenze statisticamente significative nel tasso di eventi avversi gravi e anche il tasso di mortalità era simile nei 2 gruppi di trattamento. Non furono osservate differenze significative neppure nel'incidenza di malattia coronariche (infarto del miocardico, angina, angioplastiche, bypass delle coronarie) o di ictus nei due gruppi di trattamento. In particolare, i tassi di emorragia non erano differenti nei due gruppi di trattamento e negli gli individui che assumevano aspirina ed assegnati al Ginkgo o al placebo. Anche se furono osservati il doppio di ictus emorragici nel gruppo di Ginkgo rispetto al gruppo del placebo (16 contro 8), il numero dei casi era minimo e le differenze non significative al'analisi statistica. Gli AA. concludono pertanto che la capacità degli estratti di Ginkgo di arginare la riduzione di facoltà mentali come memoria e concentrazione non erano superiori rispetto ai soggetti che avevano ricevuto soltanto un placebo. Tra le obiezioni metodologiche allo studio, tuttavia, il fatto che i dati potrebbero essere stati falsati da una diffusa mancata adesione alle dosi programmate nel trial. E nonostante lo studio GEM rappresenti ad oggi il trial condotto in prevenzione di durata maggiore, un altro potenziale limite potrebbe essere la

72 "The epidemic of late life dementia, prominence of use of alternative medications and supplements, and initiation of efforts to determine how to prevent dementia have led to efforts to conduct studies aimed at prevention of dementia. **The GEM (Ginkgo Evaluation of Memory) study was initially designed as a 5-year, randomized double-blind, placebo-controlled trial of Ginkgo biloba, administered in a dose of 120 mg twice per day as EGb761, in the prevention of dementia (and especially Alzheimer's disease) in normal elderly or those with mild cognitive impairment. The study anticipates 8.5 years of participant follow-up. Initial power calculations based on estimates of incidence rates of dementia in the target population (age 75+) led to a 3000-person study, which was successfully recruited at four clinical sites around the United States from September 2000 to June 2002. Primary outcome is incidence of all-cause dementia; secondary outcomes include rate of cognitive and functional decline, the incidence of cardiovascular and cerebrovascular events, and mortality.** Following screening to exclude participants with incident dementia at baseline, an extensive neuropsychological assessment was performed and participants were randomly assigned to treatment groups. All participants are required to have a proxy who agreed to provide an independent assessment of the functional and cognitive abilities of the participant. Assessments are repeated every 6 months. Significant decline at any visit, defined by specific changes in cognitive screening scores, leads to a repeat detailed neuropsychological battery, neurological and medical evaluation and MRI scan of the brain. The final diagnosis of dementia is achieved by a consensus panel of experts. Side effects and adverse events are tracked by computer at the central data coordinating center and unblinded data are reviewed by an independent safety monitoring board. **Studies such as these are necessary for this and a variety of other potential protective agents to evaluate their effectiveness in preventing or slowing the emergence of dementia in the elderly population**." *(DeKosky ST, Fitzpatrick A, Ives DG, Saxton J, Williamson J, Lopez OL, Burke G, Fried L, Kuller LH, Robbins J, Tracy R, Woolard N, Dunn L, Kronmal R, Nahin R, Furberg C; GEMS Investigators. The Ginkgo Evaluation of Memory (GEM) study: design and baseline data of a randomized trial of Ginkgo biloba extract in prevention of dementia. Contemp Clin Trials. 2006 Jun;27(3):238-53).*

durata del follow up in quanto, poiché il periodo che intercorre tra gli iniziali cambiamenti cerebrali e il riscontro clinico di demenza è abbastanza lungo, è possibile che qualche effetto dell'estratto di Ginkgo, positivo o negativo, possa necessitare di un periodo di tempo maggiore per manifestarsi. Lo studio GEM dimostra comunque la fattibilità di trial sulla prevenzione primaria dell'Alzheimer e può servire come modello per altri studi.

Un'altra sperimentazione particolarmente ampia sulla reale efficacia del Ginkgo nelle demenze è il GuidAge Study europeo[73], sempre con oltre 3000 pazienti trattati ma con alcune differenze nei dosaggi e negli *outcomes* da valutare, che includono anche il trattamento e non solo la prevenzione di demenza senile ed Alzheimer[74,75]. In ogni caso, alla luce del rapporto beneficio/rischio poco favorevole degli anticolinesterasici, l'estratto standardizzato di *Ginkgo biloba*, con le opportune precauzioni d'uso soprattutto riguardo alle potenziali interazioni farmacologiche, potrebbe essere un'alternativa per alcuni soggetti insieme a misure di sostegno sociali e psicologiche.

Inoltre, una metanalisi pubblicata nel 2009, che ha valutato l'effetto dell'EGB 761 nel trattamento della demenza sia di tipo vascolare sia di tipo Alzheimer, indica che l'EGB 761 può essere utile nel trattamento della demenza su base vascolare o nell'Alzheimer. Sono stati inseriti 10 studi controllati di buona qualità, dei quali 4 erano studi di grandi dimensioni mentre 6 erano studi di piccole dimensione. Per quanto riguardava gli studi di grandi dimensioni, in 3 su 4 di questi l'EGB 761 era significativamente superiore al placebo nel miglioramento della performance cognitiva e del comportamento; anche negli studi di piccole dimensioni si notava che in 5 su 6 di questi l'EGB 761 era significativamente superiore al placebo nel miglioramento della performance cognitiva e del

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73 "**Primary and secondary prevention strategies for Alzheimer's disease (AD) are urgently needed.** We have initiated a five-year prospective prevention study involving patients spontaneously reporting memory complaints. The primary objective is to determine the effect of treatment with EGb 76 on the rate of conversion from memory complaints to AD using survival analysis. Ambulatory patients aged at least 70 years who spontaneously reported a memory complaint during a GP or memory centre consultation were eligible for inclusion. Patients with major objective memory impairment or clinically relevant symptoms of anxiety and depression were excluded**. Subjects were randomised to receive either EGb 761 120mg bid or matching placebo. Participants undergo an annual visit at a memory centre, where a series of neuropsychological tests are administered to assess cognitive function (Grober and Buschke, Trail-Making and controlled oral word association tests) and cognitive status (MMS and CDR). Functional status is evaluated with the Instrumental Activities of Daily Living questionnaire.** The primary outcome is the transition to a diagnosis of AD (DSM-IV and NINCDS-ADRDA criteria), determined at the annual memory centre visit. A total of 4066 patients were screened for participation, of whom 2854 fulfilled the eligibility criteria and were entered into the study. Their mean age was 76.8+/-4.4 years and 66.7% were female**. The mean MMSE score was 27.8+/-1.7 and 55.5% presented a CDR score of 0.5. This study will enable us to evaluate the efficacy of EGb761 in the prevention of AD, and to assess the usefulness of various baseline characteristics as predictors of conversion to AD in this population." (***Andrieu S, Ousset PJ, Coley N, Ouzid M, Mathiex-Fortunet H, Vellas B; GuidAge study: a 5-year double blind, randomised trial of EGb 761 for the prevention of Alzheimer's disease in elderly subjects with memory complaints. i. rationale, design and baseline data. Curr Alzheimer Res. 2008 Aug;5(4):406-15).*

74 *Vellas B, Andrieu S, Ousset PJ, Ouzid M, Mathiex-Fortunet H. The GuidAge study: methodological issues: a 5-year double-blind randomized trial of the efficacy of EGb 761 for prevention of Alzheimer disease in patients over 70 with a memory complaint. Neurology. 2006;67(9)(suppl 3):S6-S11.*

75 *Williamson JD, Vellas B, Furberg C, Nahin R, Dekosky ST. Comparison of the design differences between the Ginkgo Evaluation of Memory study and the GuidAge study. J Nutr Health Aging. 2008 Jan;12(1):73S-9S.*

comportamento. La valutazione dei risultati indica anche che l'EGB 761 può avere un effetto ottimale soprattutto in pazienti con sintomi neuropsichiatrici, che peraltro sono la maggioranza dei pazienti con demenza. La risposta clinica positiva all'EGB 761 era abbastanza simile a quella ottenibile coi farmaci inibitori delle colinesterasi. In uno studio clinico è stato anche paragonato l'effetto dell'EGB 761 a quello del donepezil e si è riscontrato che l'efficacia dei due prodotti era similare, senza una superiorità significativa di uno rispetto all'altro. La tollerabilità dell'EGB 761 in questi studi è stata indicata come buona o molto buona[76]. In assenza di sindromi di demenza, i deficit della memoria dell'anziano si manifestano in maniera più o meno evidente proporzionalmente allo stato di compromissione delle strutture circolatorie. La condizione estrema è rappresentata dalla cosiddetta insufficienza cerebrale associata all'invecchiamento. Age-Associated Memory Impairment, AAMI), nella quale una grave insufficienza delle vie colinergiche si determina in conseguenza di più fattori interagenti fra loro, primo fra tutti un rallentamento del microcircolo cerebrale che, se particolarmente gravi, può mettere in discussione l'autosufficienza del soggetto. Seppure i risultati appaiano controversi, alcuni studi suggeriscono i potenziali benefici del'estratto di *Ginkgo biloba* in queste condizioni, soprattutto in seguito a somministrazione cronica[77,78].

Deficit mnemonici. È ormai assodato che l'esposizione allo stress cronico provoca, sia nell'animale sia nell'uomo, un'alterazione in senso peggiorativo delle funzioni cognitive, del comportamento e della memoria. In questo studio è stato esaminato l'effetto dell'estratto secco standardizzato di *Ginkgo biloba* EGB 761 nella prevenzione e nel trattamento dei disturbi cognitivi conseguenti allo stress cronico. Gli animali (ratti) erano esposti quotidianamente per 2 ore a eventi stressogeni oppure ricevevano un'iniezione di corticosterone da 5 mg/kg per 3 settimane, il che provocava deficit cognitivi e del comportamento piuttosto evidenti. Il pretrattamento degli animali con EGB 761 alla dose di 100 mg/kg dato 30 minuti prima dell'evento stressogeno o dell'iniezione di corticosterone

[76] "The Ginkgo biloba extract EGb 761 interferes with pathomechanisms relevant to dementia, such as Abeta aggregation, mitochondrial dysfunction, insulin resistance, and hypoperfusion. **The efficacy of EGb 761 in the treatment of dementia (Alzheimer's disease and vascular dementia) has been studied in 10 randomised, controlled, double-blind clinical trials. I**n three of the four large trials conducted in accordance with recent recommendations EGb 761 was significantly superior to placebo with respect to cognitive performance and one or more further (global, functional or behavioural) outcomes demonstrating the clinical relevance of the findings. The findings from the six smaller trials are in line with those of the large trials. One trial was inconclusive, but of questionable external validity due to uncommonly rigorous patient selection. **Subgroup analyses of this study together with the findings from the most recent clinical trial suggest that EGb 761 may be most beneficial to patients with neuropsychiatric symptoms, who actually constitute the majority of dementia patients. Delay in symptom progression, rates of clinically significant treatment response and numbers needed to treat (NNT) found for EGb 761 are in the same range as those reported for cholinesterase inhibitors. In an exploratory trial comparing EGb 761 and donepezil, no statistically significant or clinically relevant differences were seen. Hence, EGb 761 has its place in the treatment of dementia.**" *(Kasper S, Schubert H. Ginkgo biloba extract EGb 761 in the treatment of dementia: evidence of efficacy and tolerability. Fortschr Neurol Psychiatr. 2009 Sep;77(9):494-506).*

[77] *Bäurle P, Suter A, Wormstall H. Safety and effectiveness of a traditional ginkgo fresh plant extract - results from a clinical trial. Forsch Komplementmed. 2009 Jun;16(3):156-61.*

[78] *Mix JA, Crews WD Jr. A double-blind, placebo-controlled, randomized trial of Ginkgo biloba extract EGb 761 in a sample of cognitively intact older adults: neuropsychological findings. Hum Psychopharmacol. 2002 Aug;17(6):267-77.*

riduceva in modo consistente il deficit cognitivo e comportamentale. Lo studio indica che l'EGB 761 può essere utile per combattere le conseguenze dell'esposizione allo stress cronico a livello del sistema nervoso centrale nel ratto[79].

L'ippocampo riveste un ruolo di primaria importanza nell'apprendimento e nella memoria associativa e, in particolare, risultano essenziali due vie nervose colinergiche: la via nucleo basale-corticale, che origina dalla base dell'encefalo (nucleo di Meynert) e proietta alla corteccia frontale, e la via setto-ippocampale, che origina nella parte centrale dell'encefalo (setto mediale) e proietta all'ippocampo. Evidenze sperimentali e cliniche dimostrano che quando l'efficienza di queste vie nervose si riduce compaiono i primi deficit della memoria a breve termine, generalmente in misura proporzionale alla perdita dell'efficienza neuronale. Queste stesse vie nervose sono inoltre importanti nel mantenere un efficiente stato di attivazione della corteccia frontoparietale, a sua volta correlato con la capacità di ideazione ed elaborazione concettuale. Uno studio su frazioni di neuroni colinergici dell'ippocampo ha dimostrato che il *Ginkgo biloba*, alla concentrazione di 100µg/ml, stimola la captazione di colina – il precursore dell'acetilcolina – da parte dei neuroni, aumentando la sintesi del neurotrasmettitore, e studi recenti confermano che gli effetti della droga sulla memoria sono principalmente da attribuire all'attività colinergica della droga e, in parte, anche ad una attività istaminergica[80]. Sempre nell'ippocampo, il Ginkgo ha dimostrato di agire sui neuroni modificando la risposta intracellulare (secondi messaggeri) a stimoli nervosi. Quando sottoposti ad un ECS, i neuroni dell'ippocampo mostrano un aumento delle concentrazione intracellulari di acidi grassi liberi (FFA) e diacilglicerolo (DAC), provenienti dall'attivazione della fosfolipasi C. Negli animali pretrattati con *Ginkgo biloba* l'accumulo di FFA all'interno della cellula è minore, l'aumento del DAC è ritardato nel tempo, ed il DAC che si forma è eliminato molto più rapidamente. Gli effetti

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79 "**In this study, we tested preventive effects of a natural medicine the extract of Ginkgo biloba (EGB 761) on post-stress cognitive dysfunction**. Exposure to chronic restraint stress in rats and psychosocial stress in humans has been shown to alter cognitive functions such as learning and memory and have been linked to the pathophysiology of mood and anxiety disorders. Our findings indicate that chronic restraint stress impaired egocentric spatial memory as observed in the eight-arm radial maze but it did not alter the allocentric spatial memory in the Morris water maze. In control rats EGB 761 (100mg/kg, orally) improved spatial memory in these two tests. Also, **EGB 761 normalized cognitive deficits seen in rats chronically stressed or treated with an 'equivalent' dose of exogenous corticosterone (5mg/kg, subcutaneously). We conclude that, in rats, repeated administration of EGB 761 prevents stress- and corticosterone-induced impairments of spatial memory.**" *(Walesiuk A, Braszko JJ. Preventive action of Ginkgo biloba in stress- and corticosterone-induced impairment of spatial memory in rats. Phytomedicine. 2009 Jan;16(1):40-6).*

80 "**In order to clarify the mechanism of Ginkgo biloba extract (GBE) on learning and memory, we studied the effect of GBE on spatial memory deficits induced by diphenhydramine, pyrilamine and scopolamine using the eight-arm radial maze performance of rats, in comparison with donepezil.** Total error (TE), reference memory error (RME) and working memory error (WME) were used as indices of spatial memory deficits. Both GBE and donepezil caused a potent antagonistic effect on the increase in TE, RME and WME induced by diphenhydramine. GBE and donepezil also antagonized scopolamine-induced spatial memory deficits. Although the antagonistic effect of GBE on pyrilamine-induced spatial memory deficits was weak, a significant difference was observed with TE and WME. However, donepezil caused no antagonistic effect on pyrilamine-induced memory deficits. From these findings, **we concluded that the effects of GBE are mainly contributable to cholinergic activity and perhaps partly due to a histaminergic mechanism.**" *(Yamamoto Y, Adachi Y, Fujii Y, Kamei C. Ginkgo biloba extract improves spatial memory in rats mainly but not exclusively via a histaminergic mechanism. Brain Res. 2007 Jan 19;1129(1):161-5).*

del Ginkgo sono meno marcati nella corteccia cerebrale, e dimostrano un intervento sulla formazione dei secondi messaggeri[81]. Sperimentalmente, l'estratto etanolico di *Ginkgo biloba* antagonizza l'amnesia indotta nel topo dalla scopolamina – un antagonista dell'acetilcolina che disturba la funzionalità dei neuronicolinergici - o dalla difenidramina, un antistaminico anti-H_1[82], e sempre nel topo l'estratto della droga, somministrato giornalmente per 4 settimane, facilita l'apprendimento di informazioni e l'elaborazione di un comportamento attivo[83]. In un modello di apprendimento passivo, il Ginkgo previene l'effetto amnesico della scopolamina con una potenza che risulta sovrapponibile a quella di altri agenti anti-demenza, ma con una migliore tollerabilità[84]. C'è infine un ultimo aspetto dell'invecchiamento cerebrale da considerare. Nel ratto anziano è dimostrata una diminuzione del numero e del binding dei recettori $5HT_{1A}$. Il trattamento prolungato con *Ginkgo biloba* del ratto anziano ripristina la funzionalità di questi recettori, mentre non ha alcun effetto nel ratto giovane. Inoltre, *in vivo* il Ginkgo stimola l'uptake della 5-idrossitriptamina in sinaptosomi di corteccia cerebrale di ratto[85]. Un effetto simile è descritto sui recettori α_2 adrenergici cerebrali,

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81 "The effect of Ginkgo biloba extract (EGb 761) treatment (100 mg/kg/day, per os, for 14 days) on electroconvulsive shock (ECS)-induced accumulation of free fatty acids (FFA) and diacylglycerols (DAG) was analyzed in rat cerebral cortex and hippocampus… **This study shows that EGb 761 treatment affects, with high selectivity, lipid metabolism and lipid-derived second messenger release and removal in the hippocampus, while affecting to a lesser extent the cerebral cortex.**" *(Rodriguez de Turco EB, Droy-Lefaix MT, Bazan NG. Decreased electroconvulsive shock-induced diacylglycerols and free fatty acid accumulation in the rat brain by Ginkgo biloba extract (EGb 761): selective effect in hippocampus as compared with cerebral cortex. J Neurochem1993; 61: 1438-44).*

82 **"**Ginkgo biloba extract is widely used as a herbal medicine or dietary supplement in Europe, since Ginkgo biloba extract is effective in facilitation of learning and recollection of memories. However, little is known about the mechanism of the action of Ginkgo biloba extract on learning and memory enhancements. On the other hand, it **is well known that cholinergic, histaminergic and glutamatergic systems play a crucial role in learning and memory in animals**. Therefore, in order to elucidate the mechanism of Ginkgo biloba extract on memory, we studied and clarified the effect of Ginkgo biloba extract on spatial memory deficits induced by scopolamine, diphenhydramine or MK-801 using eight-arm radial maze performance. **It was found that Ginkgo biloba extract improved the spatial memory deficits induced by scopolamine. Ginkgo biloba extract also caused repair to spatial memory deficits induced by diphenhydramine.** On the other hand, no significant effect was observed with MK-801-induced spatial memory deficits. **These findings suggest that the effect of Ginkgo biloba extract is mediated not only by the cholinergic system but also by the histaminergic system to induce learning and memory enhancements.**" *(Yamamoto Y, Adachi Y, Fujii Y, Kamei C. Effect of Ginkgo biloba extract on memory deficits in radial maze performance induced by some drugs in rats. Nihon Shinkei Seishin Yakurigaku Zasshi. 2005 Apr;25(2):85-90).*

83 "The effects of an extract of Ginkgo biloba (EGb 761) on acquisition, performance, and retention of mice in an appetitive operant conditioning were investigated… **The results indicated that Ginkgo biloba facilitated memory processes.** EGb 761 quickened the acquisition and improved the performance of the two-response sequence: The number of correct responses was increased and correct responses were performed more frequently in the most effective manner." *(Winter E. Effects of an extract of Ginkgo biloba on learning and memory in mice. Pharmacol Biochem Behav 1991; 38: 109-14).*

84 "Amnesia can be induced in rats in the passive avoidance paradigm by administration of scopolamine, a central muscarinic receptor antagonist. Tacrine or galanthamine, inhibitors of acetylcholinesterase, given in conjunction with scopolamine partially reversed the scopolamine-induced deficit in passive avoidance performance… **Piracetam, an extract of Ginkgo biloba, dihydroergocristine and a combination of raubasine with dihydroergocristine, all attenuated the amnesia induced by scopolamine.**" *(Chopin P, Briley M. Effects of four non-cholinergic cognitive enhancers in comparison with tacrine and galanthamine on scopolamine-induced amnesia in rats. Psychopharmacology 1992; 106: 26-30).*

85 "The Ginkgo biloba extract (EGb 761) added to a synaptosomal fraction prepared from mice cerebral cortex modified [3H]5-hydroxytryptamine ([3H]5-HT) uptake in a biphasic manner. **Between 4 and 16 µg mL-1 EGb 761 increased significantly the**

che risultano diminuiti nel ratto anziano. Un trattamento cronico con *Ginkgo biloba* non modifica la densità di questi recettori nel ratto giovane, mentre ne determina un aumento del 28% circa nel ratto anziano[86]. È probabile che gli effetti della droga non siano specifici per un recettore, ma siano la conseguenza di un effetto sulla fluidità e sulla funzionalità della membrana cellulare. È probabile anche che la risposta terapeutica al trattamento con *Ginkgo biloba* del paziente con demenza senile o aterosclerotica sia il risultato integrato degli effetti sui recettori[87] soprattutto dei recettori del PAF e dell'attività antiossidante del fitocomplesso[88]. Uno studio nel ratto ha valutato l'effetto dell'EGB 761 sulla trasmissione sinaptica e sulla plasticità dei neuroni ippocampali in ratti giovani e in ratti anziani. Questo perché l'ippocampo è molto importante per la memoria[89]. Si è visto che la somministrazione in acuto dell'EGB 761 aumentava l'eccitabilità neuronale nei ratti anziani aumentando le scariche elettriche e l'eccitabilità dei neuroni ippocampali, mentre negli animali giovani non vi erano effetti apprezzabili. Nell'uso cronico l'EGB 761 mostrava effetti simili. Questi

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[3H]5-HT uptake (maximum + 23%)… Since at the usual therapeutic doses of EGb 761, the effective concentrations of the components responsible for this increase are likely to be reached in the brain, one may suggest that this effect could contribute to the therapeutic effect of EGb 761." *(Ramassamy C, Christen Y, Clostre F, Costentin J. The Ginkgo biloba extract, EGb761, increases synaptosomal uptake of 5-hydroxytryptamine: in-vitro and ex-vivo studies. J Pharm Pharmacol 1992; 44: 943-5).*

86 "[3H]Rauwolscine binding to α2-adrenoceptors in cerebral cortex and hippocampus membranes of young (4 months) and aged (24 months) Wistar rats has been investigated… **Chronic treatment with Ginkgo biloba extract did not alter [3H] rauwolscine binding in the hippocampus of young rats, but significantly increased (28%) the [3H]rauwolscine binding density in aged rats.** These data confirm the previously described age-related noradrenergic alteration and suggest that noradrenergic activity in aged rats is more susceptible to Ginkgo biloba extract treatment." *(Huguet F, Tarrade T. 2-adrenoceptor changes during cerebral ageing. The effect of Ginkgo biloba extract. J Pharm Pharmacol 1992; 44: 24-7).*

87 "Investigation of [3H]8-hydroxy-2(di-n-propylamino)tetralin binding to 5-HT1A receptors in cerebral cortex membranes of Wistar rats showed that the maximal number of binding sites (Bmax) was reduced significantly (22%) in aged (24-month-old) as compared with young (4-month-old) animals… T**ogether with data in the literature, they also suggest a restorative effect in aged rats, associated with decreased receptor density resulting from the protective action of Ginkgo biloba extract treatment on neuronal membrane.**" *(Huguet F, Drieu K, Piriou A. Decreased cerebral 5-HT1A receptors during ageing: reversal by Ginkgo biloba extract (EGb 761). J Pharm Pharmacol 1994; 46: 316-8).*

88 "Ginkgo biloba (Ginkgoaceae) is an ancient Chinese tree which has been cultivated and held sacred for its health-promoting properties. **There is substantial experimental evidence to support the view that Ginkgo biloba extracts have neuroprotective properties under conditions such as hypoxia/ischemia, seizure activity and peripheral nerve damage**… Taken together, the evidence suggests that Ginkgo biloba extracts are worthy of further investigation as potential neuroprotectant agents." *(Smith PF, Maclennan K, Darlington CL. The neuroprotective properties of the Ginkgo biloba leaf: a review of the possible relationship to platelet-activating factor (PAF). J Ethnopharmacol 1996; 50: 131-9).*

89 "Extracts from the leaves of Ginkgo biloba have been suggested to be useful in the treatment of various symptoms of impaired brain functions in advanced age. To elucidate specific mechanisms of the possible clinical benefit, the effects of Ginkgo biloba extract Ginkobene on cognitive information-processing were investigated by means of long-latency auditory event-related potentials. In a double-blind placebo-controlled study, 48 patients (29 women and 19 men) aged between 51 and 79 years with the diagnosis of age-associated memory impairment had 57 days' treatment with a daily dosage of 3 x 40 mg Ginkobene or placebo. (…) When compared to the placebo group, in the Ginkobene group no consistent and unequivocal changes on N1, P2, N2,and P300 amplitudes or on N1, P2, and N2 latencies were observed. P300 latency was shortened by 31 ms, 38 ms, and 32 ms in the Ginkgo biloba group after acute, chronic, and superimposed drug administration. It may therefore be hypothesized that the decrease of P300 latency in the Ginkgo biloba group may reflect shorter stimulus-evaluation time." *(Semlitsch HV, Anderer P, Saletu B, Binder GA, Decker KA. Cognitive psychophysiology in nootropic drug research: effects of Ginkgo biloba on event-related potentials (P300) in age-associated memory impairment. Pharmacopsychiatry 1995; 28: 134-42).*

risultati indicano un'interazione dell'EGB 761 con il sistema glutaminergico e potrebbero essere importanti per spiegare l'azione di questo estratto sui processi mnesici anche nell'uomo[90]. Questi dati farebbero pensare ad una azione del *Ginkgo biloba* sulla funzionalità dei neuroni colinergici, ma anche altre attività del fitocomplesso potrebbero contribuire agli effetti sulla memoria. È dimostrato, infatti, che nel ratto anziano la fluidità delle membrane neuronali è ridotta e che esiste un parallelismo fra fluidità di membrana e grado di compromissione delle funzioni cognitive. Inoltre, l'attività ossidante dei radicali liberi contribuisce moltissimo alla perdita della normale fluidità di membrana. Alcuni AA. hanno mostrato una correlazione fra attività antiamnesica del *Ginkgo biloba* nel ratto anziano, attività antiossidante del fitocomplesso e fluidità di membrana[91]. È stata poi dimostrata in seguito a somministrazione acuta (singola dose) e subacuta (7 giorni di trattamento) dell'estratto EGB 761 nel ratto, un'attività di modulazione dell'espressione genica di proteine associate alla plasticità sinaptica (GAP-43, CREB-1, GFAP) - note per il loro coinvolgimento nello sviluppo del sistema nervoso e nell'organizzazione del network neuronale - in specifiche regioni cerebrali quali la corteccia prefrontale, l'amigdala e l'ippocampo. Tali proteine possono risultare utili marcatori per la valutazione degli interventi farmaco-terapeutici per il mantenimento dell'efficienza delle funzioni cognitive, e uno studio più approfondito sui meccanismi plastici che consentono il rimodellamento assonale ed il recupero dell'efficacia sinaptica potrebbe fornire una preziosa chiave di lettura per la miglior comprensione dei meccanismi di recupero del sistema nervoso[92]. Sulla base di questi dati

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[90] "It has not been uniform to date that the Ginkgo biloba extracts enhance cognitive function in aged animals, and the mechanisms of action remain difficult to elucidate. **In this study, the Morris water maze task and electrophysiological methods were used to study the effects of repeated daily administration of EGb 761, a standardized extract from G. biloba leaves, on hippocampal-dependent spatial learning and memory and synaptic plasticity of aged rats.** The adult subjects perform the Morris water maze task better than aged rats, as a cellular mechanism, the hippocampal long-term potentiation (LTP) elicited from adult animals is robust (139.29±2.7%). In addition, the spatial learning and memory of aged rats that had been fed on an EGb 761-supplemented diet (60 mg kg–1) for 30 days were significantly better than those of control aged rats. The magnitude of LTP (116.63±3.6%) recorded in vivo from the hippocampus CA1 area of aged rats was significantly enhanced by EGb 761 (60 mg kg–1). In conclusion, **the spatial learning and memory of aged rats is worse than that of young subjects, and EGb 761, acting as a 'cognitive enhancer', has benefit on synaptic plasticity and cognition in aged rats. The present data further confirmed that enhancement of synaptic plasticity of the hippocampus might ameliorate the deficit in spatial learning and memory in aged rats.**" *(Yongfu Wang, Lei Wang, Jing Wu, Jingxia Cai. The in vivo synaptic plasticity mechanism of EGb 761-induced enhancement of spatial learning and memory in aged rats. Br J Pharmacol. 2006 May; 148(2): 147–153).*

[91] "Decreases in cell membrane fluidity may be a major mechanism of age-related functional decline. A prime cause for the decline of membrane fluidity may be the presence of free radicals. **Ginkgo biloba extract EGb761 protects neuronal cell membranes from free radical damage in vitro**… Taken together, **these results indicate that EGb 761 independently improves changes in passive avoidance learning and brain membrane fluidity.**" *(Stoll S, Scheuer K, Pohl O, Muller WE. Ginkgo biloba extract (EGb 761) independently improves changes in passive avoidance learning and brain membrane fluidity in the aging mouse. Pharmacopsychiatry 1996; 29:144-9).*

[92] "Although it has been suggested that the standardized Ginkgo biloba leaf extract (Egb 761) may have a beneficial effect on memory, the cellular and molecular changes that underlie this process are not yet well defined. **The present study evaluated the effects of acute (one dose) or subacute treatments (one daily dose/seven days) with EGb 761 (0.5 g kg(-1) and 1.0 g kg(-1)) on rats submitted to a conditioned emotional response (CER) in comparison with positive (4 mg kg(-1) Diazepam) and negative (12%Tween 80) control groups.** To this end, eighty (n=10/group) adult, male, Wistar rats (+/-250-300 g) were used in an off-baseline CER procedure. We here observed that the rats submitted to an acute and subacute EGb 761 treatments had acquisition of fear conditioning. Additionally, we investigate if the expression of genes previously associated with classical

sperimentali, il *Ginkgo biloba* viene pertanto utilizzato nel trattamento dei deficit della memoria recente, dell'attenzione ed di altre funzioni cognitive.

Disturbi visivi associati ad insufficienza cerebrovascolare. Retinopatia diabetica ed ipertensiva. Studi sperimentali e clinici hanno dimostrato una potenziale efficacia dell'estratto standardizzato di *Ginkgo biloba* nel trattamento di alcuni disturbi della vista e di danni del campo visivo associati con l'insufficienza cerebrovascolare cronica, il glaucoma, la degenerazione maculare senile[93] e il diabete mellito[94]. La produzione locale di radicali liberi contribuisce infatti ad alcune malattie

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conditioning (CREB-1 and GAP-43) and new candidate genes (GFAP) are modulated following EGb 761 acute treatment. CREB-1, GAP-43 and GFAP mRNA and protein expressions were evaluated using both quantitative PCR (qPCR) and immunohistochemical analysis, respectively. **We here show, for the first time, that EGb 761 modulated GAP-43, CREB-1 and GFAP expression in the prefrontal cortex, amygdala and hippocampus. We observed an underexpression of GAP-43 in all structures evaluated and over-expression of GFAP in the amygdala and hippocampus following acute G. biloba treatment when compared to control group (Tween; p<0.01). GAP-43 expression was decreased in prefrontal cortex and hippocampus in the subacute treatment with EGb 761. Subacute treatment with EGb 761 lead to a decreased CREB-1 in mPFC (p<0.001) and increased in the hippocampus to 1.0 g kg(-1)G. biloba group (p<0.001)**. The results obtained from immunohistochemical analysis support our aforementioned findings and revealed that the changes in expression occurred within specific regions in the areas evaluated. All together, our findings not only provide new evidence for a role of EGb 761 on memory but also identify molecular changes that underlie the fear memory consolidation." *(Oliveira DR, Sanada PF, Saragossa Filho AC, Innocenti LR, Oler G, Cerutti JM, Cerutti SM. Neuromodulatory property of standardized extract Ginkgo biloba L. (EGb 761) on memory: behavioral and molecular evidence. Brain Res. 2009 May 7;1269:68-89).*

93 "**The therapeutic efficacy of Ginkgo special extract Egb 761 was investigated in a controlled, double-blind trial involving 99 patients with impaired vision due to senile, dry macular degeneration**. **The primary objective target variable was the change in the corrected visual acuity of the more severely impaired eye at baseline, during a six months treatment period with either 240 mg/die (group I = 50 patients) or 60 mg/die (group II = 49 patients) Egb 761.** Marked improvement of the study participants' vision was observed in both treatment groups already after four weeks, with more pronounced improvements in group I (acuity increases by 0.13 in group I vs. 0.10 in group II after 24 weeks). The fraction of patients with improvement of visual acuity > or = 0.2 was nearly twice as large in the group treated with 240 mg/die Egb 761 as in patients receiving the lower dosage (p = 0.08). Subjective health impairments, if present, could be improved during treatment as well. **The investigator rated a favorable tolerability for both dosages of Egb 761. In conclusion, the results demonstrate the therapeutic efficacy of Egb 761 in patients with senile, dry macular degeneration, with obvious benefits in every-day life**." *(Fies P, Dienel A. Ginkgo extract in impaired vision--treatment with special extract EGb 761 of impaired vision due to dry senile macular degeneration. Wien Med Wochenschr. 2002;152(15-16):423-6.).*

94 "We have recently reported that ingestion of **Ginkgo biloba extract (EGb 761) (a) significantly reduced collagen-induced platelet aggregation and thromboxane B2 (TXB2) production in both non-diabetic individuals as well as those with type 2 diabetes mellitus (T2DM), (b) significantly reduced platelet malondialdehyde (MDA), an index of lipid peroxidation, in non-diabetic subjects**. In the present study we report that ingestion of EGb 761 (120 mg daily for 3 months), significantly decreased platelet MDA-thiobarbituric acid reacting substances (TBARS) (41 +/- 9 pmol/10(7) platelets versus 30 +/- 11 pmol/10(7) platelets) (p < 0.005) in T2DM subjects with normal cholesterol levels (total cholesterol, 164 +/- 22 mg/dl; age, 54 +/- 9 years; BMI, 35.0 +/- 8.8 kg/m2, n = 12). In T2DM subjects with high cholesterol (total cholesterol, 218 +/- 15 mg/dl; age, 52 +/- 5 years; BMI, 36.2 +/- 6.6 kg/m2, n = 7), EGb 761 ingestion reduced the platelet TBARS from 29 +/- 9 to 22 +/- 9 pmol/10(7) platelets (p < 0.04). Because ingestion of EGb 761 did not alter platelet counts it is concluded that **EGb 761, probably due to the flavonoid fraction, reduced the TBARS by inhibiting cyclooxygenase (COX)-1-mediated arachidonic acid oxygenation or by reducing the arachidonic acid pool. This is likely to lead to a reduction of platelet hyperactivity, a significant contributor to the development of cardiovascular disease in T2DM patients. Because of other reported beneficial properties of EGb 761, such as stimulation of pancreatic beta-cell function in T2DM subjects with pancreatic exhaustion, it appears that T2DM subjects might benefit from ingesting EGb 761** as a dietary supplement." *(Kudolo GB, Delaney D, Blodgett J. Short-term oral ingestion of Ginkgo biloba extract (EGb 761) reduces malondialdehyde levels in washed platelets of type 2 diabetic subjects. Diabetes Res Clin Pract. 2005 Apr;68(1):29-38).*

degenerative della retina; ad esempio, la reazione proliferativa che segue ad un distacco della retina è probabilmente stimolata dall'attività ossidativa locale. Il danno retinico è essenzialmente dovuto all'ischemia conseguente alla vasocostrizione dell'arteria retinica, ed è mediato dalla produzione locale di radicali liberi. Inoltre, nella retinopatia diabetica è presente un ispessimento della membrana basale dei capillari che comporta un difficoltoso scambio di gas e principi nutritivi fra retina e sangue[95]. L'estratto secco standardizzato di Ginkgo ha mostrato, in queste condizioni, di essere di beneficio, suggerendo l'uso clinico del *Ginkgo biloba* in pazienti con retinopatia diabetica[96,97]. Gli effetti benefici della droga sul flusso ematico oculare, accanto alle spiccate proprietà antiossidanti del fitocomplesso, sembrano confermare l'impiego clinico del *Ginkgo biloba* anche nel glaucoma[98,99]

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95 "**Diabetic retinopathy (DR) is a leading cause of vision loss in the working-age population worldwide. Many observational and preclinical studies have implicated vascular endothelial growth factor (VEGF) in the pathogenesis of DR, and recent successes with anti-VEGF therapy for age-related macular degeneration (AMD) have prompted research into the application of anti-VEGF drugs to DR**. Here we review the numerous early studies that suggest an important potential role for anti-VEGF agents in the management of diabetic retinopathy. Conclusions: For diabetic macular edema, phase II trials of intravitreal pegaptanib and intravitreal ranibizumab have shown short-term benefit in visual acuity. Intravitreal bevacizumab also has been shown to have beneficial short-term effects on both visual acuity and retinal thickness. For proliferative diabetic retinopathy (PDR), early studies suggest that intravitreal bevacizumab temporarily decreases leakage from diabetic neovascular lesions, but this treatment may be associated with tractional retinal detachment (TRD). Furthermore, several studies indicate that bevacizumab is likely to prove a helpful adjunct to diabetic pars plana vitrectomy (PPV) for TRD. Finally, three small series suggest a potential beneficial effect of a single dose of bevacizumab to prevent worsening of DME after cataract surgery. Use of anti-VEGF medications for any of these indications is off-label. Despite promising early reports on the safety of these medications, we eagerly await the results of large, controlled trials to substantiate the safety and efficacy of anti-VEGF drugs for diabetic retinopathy." *(Nicholson BP, Schachat AP. A review of clinical trials of anti-VEGF agents for diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2010 ;248 (7):915-930.*

96 "Early detection of patological function of the retina, before anatomical changes, plays very important role in monitoring of visual complications in patients with diabetes mellitus. **The aim of the study was the evaluation of anatomical and functional changes in visual organ in children and adolescents with long lasting diabetes mellitus type 1 and taking Egb 761 (Tanakan Beaufour Ipsen) as an adjuvant.** Materials and methods: Group consists of 15 patients, age between 11 and 19 years, with diabetes mellitus lasting 6-12 years. All patients had full ophthalmologic examination and color vision tests (Panel D 15 saturated and desaturated). The examination was done 3 times, every 3 months. Egb 761 was given: 1 tablet - 3 times a day, during 3 months. Results: No diabetic retinopathy was found. The results of color vision test were better after therapy (25% of pathological results) and 3 months later (only 4 % of patients). Conclusions: 1. **Egb 761 seems to be good adjuvant in patient with long lasting diabetes mellitus. 2. Color vision tests are sensitive tests of the retinal function and are easy to perform**." *(Bernardczyk-Meller J, Siwiec-Prościńska J, Stankiewicz W, Fichna P, Pecold K, Korman E. Influence of Eqb 761 on the function of the retina in children and adolescent with long lasting diabetes mellitus--preliminary report. Klin Oczna. 2004;106(4-5):569-71).*

97 "…**In this preliminary clinical study, 3 months of oral administration of Egb 761 significantly reduced MDA levels of erythrocytes membranes, decreased fibrinogen levels, promoted erythrocytes deformability, and improved blood viscosity and viscoelasticity, which may facilitate blood perfusion.** Furthermore, it effectively improved retinal capillary blood flow rate in type 2 diabetic patients with retinopathy." *(Huang SY, Jeng C, Kao SC, Yu JJ, Liu DZ. Improved haemorrheological properties by Ginkgo biloba extract (Egb 761) in type 2 diabetes mellitus complicated with retinopathy. Clin Nutr. 2004 Aug;23(4):615-21).*

98 "At the present time, GBE is the best documented of all the complementary medicinal agents and seems to have the greatest potential value. **Ginkgo biloba extract has numerous properties that theoretically should be beneficial in treating non-IOP-dependent mechanisms in glaucoma. Its multi-ple beneficial actions, including increased ocular blood flow, antioxidant activity, platelet activating factor inhibitory activity, nitric oxide inhibition, and neuroprotective activity, combine to suggest that GBE could prove to be of major therapeutic value in the treatment of glaucoma**." *(Ritch R. Complementary therapy for the treatment of glaucoma: a perspective. Ophthalmol Clin North Am. 2005 Dec;18(4):597-609).*

99 "Conclusions: **Pretreatment and early posttreatment with EGb 761 is an effective neuroprotectant in a rat model of**

ed in alcune affezioni ischemiche dell'occhio.

Disturbi audiovestibolari. Una sperimentazione ha valutato l'effetto del *Ginkgo biloba* alla dose di 50 mg/kg/die sui disturbi dell'equilibrio indotti nel gatto da neurectomia vestibolare unilaterale. È emerso che il recupero funzionale è significativamente più rapido nell'animale trattato col ginkgo rispetto a quello che riceveva il placebo, e ciò potrebbe essere dovuto al miglioramento dei meccanismi di plasticità coinvolti nella compensazione vestibolare. Infatti si è vista una più rapida rioccupazione sinaptica nel nucleo vestibolare mediano deafferentato, il che potrebbe significare che la droga possiede proprietà neurotrofiche e/o neuritogeniche che accelerano il recupero funzionale dopo danno alle strutture del sistema nervoso centrale. Si è notato che ratti trattati con alte dosi di gentamicina mostravano spiccati danni auricolari ad un esame col microscopio elettronico a scansione, con accumulo di antibiotico nell'intera struttura cocleare e in particolare nell'organo del Corti, nella stria vascularis e nei fibrociti di tipo 3. Il pretrattamento degli animali con EGB 761 riduceva notevolmente questi danni, dimostrandosi così in grado di proteggere le strutture auricolari del ratto dai danni indotti dalla gentamicina. Una metanalisi pubblicata nel 2004 ha indagato l'effetto del ginkgo sul tinnito. Sono state controllate tutte le principali banche dati medicali fino al Dicembre 2003 e sono stati selezionati solo gli studi clinici controllati. Sono stati identificati 12 studi che soddisfacevano i requisiti richiesti. Altri dieci studi sono stati esclusi perché metodologicamente non corretti. Nessuno dei trials riguardanti il tinnito in pazienti con insufficienza cerebrale aveva i requisiti qualitativi per rientrare nella metanalisi in oggetto. Si è notato che il miglioramento del tinnito indotto dal *Ginkgo biloba* era molto lieve e ai limiti della significatività statistica, con una bassa incidenza di effetti avversi[100].

Arteriopatia cronica ostruttiva periferica *(claudicatio intermittens)*. Il fitocomplesso del *Ginkgo biloba* è stato utilizzato nell'arteriopatia cronica ostruttiva periferica (COPD). L'efficacia terapeutica della droga nella *claudicatio intermittens* è significativa anche se modesta, come documentato da diversi lavori clinici in doppio cieco, controllati con placebo nonché da metanalisi e review sistematiche. Essendo la COPD una patologia di tipo ischemico che coinvolge i vasi arteriosi degli arti inferiori, l'efficacia dei trattamenti farmacologici viene generalmente valutata sulla base del "Treadmill test" la distanza di camminamento in assenza di dolore) e della pressione transcutanea di ossigeno (TcPO2), indice diretto di perfusione ematica periferica. Diversi studi, in parte contrastanti, hanno evidenziato la superiorità del Ginkgo rispetto al placebo nel migliorare la circolazione degli

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chronic glaucoma." *(Hirooka K, Tokuda M, Miyamoto O, Itano T, Baba T, Shiraga F. The Ginkgo biloba extract (EGb 761) provides a neuroprotective effect on retinal ganglion cells in a rat model of chronic glaucoma. Curr Eye Res. 2004 Mar;28(3):153-7).*

100 *Hilton M, Stuart E. Royal Devon & Exeter Hospital, Barrack Rd, Exeter, Devon, UK, EX2 5DW. Ginkgo biloba for tinnitus. Cochrane Database Syst Rev. 2004;(2):CD003852.*

arti inferiori ed incrementare la distanza di camminamento in assenza di dolore nella COPD[101,102]. Gli effetti del Ginkgo nella patologia occlusiva periferica sarebbero riconducibili all'inibizione del PAF da parte dei ginkgolidi e all'azione antiradicalica del fitocomplesso della droga. Una metanalisi ha cercato di fare il punto sulla letteratura esistente fino all'anno 2000 per quanto riguarda Ginkgo e claudicatio. Sono stati selezionati 8 lavori clinici controllati di soddisfacente qualità. Si è visto che la distanza di marcia nei pazienti trattati con il Ginkgo era mediamente di 34 m. maggiore rispetto a quella dei soggetti trattati col placebo in cinque studi. In altri 3 studi, nei quali i pazienti dovevano camminare alla velocità di 3 km/h con una pendenza del 12%, vi era sempre una certa superiorità del Ginkgo, con 33 m. in più percorsi dai pazienti del gruppo verum rispetto a quelli del gruppo placebo. Gli effetti collaterali registrati in tutti questi studi sono stati lievi e transitori. La metanalisi conclude che l'EGB 761 può essere utile in pazienti con arteriopatia obliterante degli arti inferiori, ma che il suo effetto in questa patologia è moderato[103]. Uno studio clinico controllato ha valutato l'effetto di 300 mg/die di EGB 761 sulla distanza di marcia e sui parametri cardiovascolari di 62 pazienti affetti da claudicatio intermittens di età compresa tra 70 e 80 anni. Si misuravano la distanza di marcia e l'intensità del dolore ai polpacci, la vasodilatazione mediata dal flusso e la qualità della vita pre e post terapia. Al termine dello studio i pazienti del gruppo verum avevano un prolungamento del tempo di marcia di 91 secondi rispetto a quelli del gruppo placebo, un valore che non era statisticamente significativo. Nessuno degli altri parametri esaminati si discostava significativamente nel gruppo verum rispetto al gruppo placebo. In entrambi i gruppi gli effetti collaterali registrati sono stati pressochè insignificanti. Lo studio indica che 300 mg/die di EGB 761 inducono solo un lieve incremento del tempo di marcia senza dolore in pazienti affetti da claudicatio intermittens[104].

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101 "…**This study confirmed significantly the rapid antiischemic action of EGb 761 and its value in the management of peripheral arterial occlusive disease at the stage of intermittent claudication.**" *(Mouren X, Caillard P, Schwartz F. Study of the antiischemic action of EGb 761 in the treatment of peripheral arterial occlusive disease by TcPo2 determination. Angiology 1994; 45: 413-7).*

102 *Ernst E. Postgraduate Medical School, University of Exeter/UK. Ginkgo biloba in treatment of intermittent claudication. A systematic research based on controlled studies in the literature. Fortschr Med 1996; 114: 85-87.*

103 "…Eight randomized, placebo-controlled, double-blind trials were included. **Meta-analysis found a significant difference in the increase in pain-free walking distance in favor of Ginkgo biloba** (weighted mean difference: 34 meters, 95% confidence interval [CI]: 26 to 43 meters). In studies using similar methodological features (ergometer speed: 3 km/h, inclination: 12%) this difference was 33 meters in favor of Ginkgo biloba (95% CI: 22 to 43 meters). Adverse effects were rare, mild, and transient. **These results suggest that Ginkgo biloba extract is superior to placebo in the symptomatic treatment of intermittent claudication.**" *(Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. Am J Med. 2000 Mar;108(4):276-81).*

104 "…The objective of this study was **to compare the effects of 300 mg/d of Ginkgo biloba (EGb 761) versus placebo on treadmill walking time and related cardiovascular measures among patients with peripheral artery disease (PAD)**. **A double-blind, placebo-controlled, parallel design trial with a 4-month duration was used. Participants were 62 adults, aged 70 +/- 8 years (mean +/- SD), with claudication symptoms of PAD**. The primary study outcomes were maximal and pain-free walking time on a treadmill. Secondary outcomes included flow-mediated vasodilation, a measure of antioxidant status as assessed by determining antibody levels to epitopes of oxidized low-density lipoprotein, and questionnaires addressing walking impairment and quality of life. Results: **Maximal treadmill walking time increased by 20 +/- 80 and 91 +/- 242 seconds in the placebo and the EGb 761 groups, respectively (P = .12). Pain-free walking time increased by 15 +/- 31 and 21 +/- 43 seconds, respectively (P = .28)**. No significant differences were detected between groups for any of the secondary outcomes.

L'indice di Windsor (rapporto fra pressione sistolica brachiale e crurale) non ha mostrato significative modificazioni, indicando come l'effetto benefico del Ginkgo sia dovuto ad un miglioramento del microcircolo e della perfusione tissutale, in assenza di modificazioni emoreologiche del macrocircolo[105]. Ad analoghi risultati giunge una recente metanalisi (Aprile 2009) che ha valutato l'effetto del Ginkgo in pazienti affetti da claudicatio intermittens. Sono stati inseriti solo gli studi clinici controllati versus placebo, reperendone 14 dotati dei criteri qualitativi richiesti, per un totale di 739 pazienti. Si è notato che il *Ginkgo biloba* riduceva aumentava al limite della significatività statistica (p<0,06) la distanza di marcia percorsa prima dell'insorgenza del dolore versus placebo, con un aumento medio di questa di 64,5 metri su un tappeto rotante alla velocità media di 3,2 km/h. La tollerabilità del Ginkgo è stata definita buona o molto buona in tutti gli studi effettuati. La metanalisi indica che il *Ginkgo biloba* ha un effetto modesto in pazienti affetti da claudicatio intermittens[106].

In older adults with PAD, Ginkgo biloba produced a modest but insignificant increase in maximal treadmill walking time and flow-mediated vasodilation. These data do not support the use of Ginkgo biloba as an effective therapy for PAD, although a longer duration of use should be considered in any future trials." *(Gardner CD, Taylor-Piliae RE, Kiazand A, Nicholus J, Rigby AJ, Farquhar JW. . Effect of Ginkgo biloba (EGb 761) on treadmill walking time among adults with peripheral artery disease: a randomized clinical trial. J Cardiopulm Rehabil Prev. 2008 Jul-Aug;28(4):258-65).*

105 "This monocenter, randomized, placebo-controlled double-blind study with parallel-group comparison was carried out in order to demonstrate the efficacy of Ginkgo biloba special extract EGb 761 on objective and subjective parameters of the walking performance in trained patients suffering from peripheral arterial occlusive disease in Fontaine stage IIb. In total 60 patients were recruited (42 men; aged 47-82 years) with angiographically proven peripheral arterial occlusive disease of the lower extremities and an intermittent claudication existing for at least 6 months. No improvement had been shown despite consistent walking training and a maximum pain-free walking distance on the treadmill of less than 150 m was recorded at the beginning of the study. The therapeutic groups were treated with either Ginkgo biloba special extract EGb 761 at a dose of 3 times 1 film-coated tablet of 40 mg per day by oral route or placebo over a duration of 24 weeks following atwo-week placebo run-in phase… The absolute changes in the pain-free walking distance in treatment weeks 8,16 and 24 as against the treatment beginning (median values with 95% confidence interval) led to the following values for the patients treated with Ginkgo biloba special extract EGb 761:19 m (14, 33), 34 m (18, 50) and 41 m (26, 64). The corresponding values in the placebo group were as follows: 7 m (-4, 12), 12 m (5, 22) and 8 m (-1, 21). The advantage of the EGb 761-treated group as compared to the placebo group could be verified statistically at the 3 time points with $p < 0.0001$, $p = 0.0003$ and $p < 0.0001$. The test for the presence of aclinically relevant difference of 20% between EGb 761 and placebo also produced a statistically significant result ($p = 0.008$). The Doppler index remained unchanged in both therapeutic groups: A corresponding statistically significant advantage for the EGb 761 group was observed on a descriptive level for the other parameters tested. The tolerance of the treatment was very good. **The results of this placebo-controlled study show that treatment with Ginkgo biloba special extract EGb 761 produces a statistically highly significant and clinically relevant improvement of the walking performance in trained patients suffering from intermittent claudication with very good tolerance of the study preparation.**" *(Blume J, Kieser M, Placebo-controlled double-blind study of the effectiveness of Ginkgo biloba special extract EGb 761 in trained patients with intermittent claudication. Vasa 1996; 25: 265-74).*

106 "People with intermittent claudication suffer from pain in the muscles of the leg occurring during exercise which is relieved by a short period of rest. Symptomatic relief can be achieved by (supervised) exercise therapy and pharmacological treatments. **Ginkgo biloba is a vasoactive agent and is used to treat intermittent claudication. Objectives: To assess the effect of Ginkgo biloba on walking distance in people with intermittent claudication**. The Cochrane Peripheral Vascular Diseases (PVD) Group searched their Trials Register (last searched 3 February 2009) and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (last searched 2009, Issue 1). We searched MEDLINE/PUBMED (January 1966 to May 2008) and EMBASE (January 1985 to May 2008) and contacted manufacturers. Selection criteria: Randomised controlled trials of Ginkgo biloba extract, irrespective of dosage, versus placebo in people with intermittent claudication. Data collection and analysis: Two authors independently assessed trials for selection, assessed study quality and extracted data. We extracted number of patients, mean walking distances or times and standard deviations. To standardise walking distance or time, caloric

Azione antiallergica. Il *Ginkgo biloba* possiede un'azione antiallergica ed antiasmatica, imputabili sia all'inibizione del PAF che antagonizza la costrizione bronchiale tipica dell'asma[107] sia ad un'azione desensibilizzante diretta su mastociti e basofili, attribuibile alla frazione flavonoidica[108]. La fitoterapia tradizionale cinese utilizza infatti diffusamente il Ginkgo nel trattamento dell'asma e di altre affezioni dell'apparato respiratorio, nonché di manifestazioni allergiche di tipo cutaneo. L'azione dermoprotettiva della droga è anche dovuta al fatto che il fitocomplesso del Ginkgo ha una penetrazione nel torrente ematico piuttosto buona anche in seguito ad applicazione topica.
Uno studio ha valutato gli effetti di un estratto di *Ginkgo biloba* (EGB 761), un antagonista del PAF, in un modello animale di asma bronchiale. Gli animali venivano sensibilizzati tramite la ovalbumina e ricevevano per os 100 o 150 mg/kg di EGB 761 o desametasone o un placebo per 7 giorni. Al termine di questo periodo i ratti venivano sacrificati e le loro vie aeree esaminate. Si è visto che l'EGB 761 a entrambi i dosaggi utilizzati riduceva il numero delle cellule infiammatorie, dei mastociti, lo spessore dell'epitelio e della membrana basale rispetto al placebo, con un effetto abbastanza simile a quello del desametasone. Quest'ultimo era significativamente più efficace per quanto riguardava lo spessore della membrana basale e della muscolatura liscia sub-epiteliale. Lo studio indica che l'EGB 761 può essere utile per combattere l'asma bronchiale indotta dall'ovalbumina nel ratto[109].

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expenditures were used to express the difference between the different treadmill protocols, which were calculated from the speed and incline of the treadmill. Main Results: **Fourteen trials with a total of 739 participants were included. Eleven trials involving 477 participants compared Ginkgo biloba with placebo and assessed the absolute claudication distance.** Following treatment with Ginkgo biloba at the end of the study the absolute claudication distance increased with an overall effect size of 3.57 kilocalories (confidence interval -0.10 to 7.23, P = 0.06), compared with placebo. This translates to an increase of just 64.5 (confidence interval -1.8 to 130.7) metres on a flat treadmill with an average speed of 3.2 km/h. Publication bias leading to missing data or "negative" trials is likely to have inflated the effect size. **Overall, there is no evidence that Ginkgo biloba has a clinically significant benefit for patients with peripheral arterial disease.**" *(Nicolaï SP, Kruidenier LM, Bendermacher BL, Prins MH, Teijink JA. Ginkgo biloba for intermittent claudication. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006888).*

107 *Wilkens J H, Wilkens H, Uffmann J, Bövers J, Fabel H, Frölich J C. Effects of a PAF-antagonist (BN 52063) on bronchoconstriction and platelet activation during exercise induced asthma. Br J Clin Pharmacol. 1990 January; 29(1): 85–91.*

108 *Li GH, Lei XX, Yi YM, Xu BL, Wang HP, Du J. Studies on the effect of Ginkgo biloba extracts on NF-kappaB pathway. Zhong Yao Cai. 2008 Sep;31(9):1357-60.*

109 "**Platelet-activating factor (PAF) is an inflammatory mediator involved in the pathophysiology of asthma, suggesting a therapy antagonizing its effects may play a role in the disease treatment. The aim of the study was to determine the effects of Ginkgo biloba, a PAF antagonist, on lung histology**. T**hirty-five BALB/c mice were divided into five groups; A, B, C, D, and the control. All mice except controls were sensitized and challenged with ovalbumin. Mice in group A (placebo) received saline; group B received G. biloba, 100 mg/kg; group C received G. biloba, 150 mg/kg; and group D received dexamethasone**, 1 mg/kg via orogastric gavage for 7 consecutive days. Chronic structural changes and airway remodeling were evaluated by using light and electron microscopy in all groups. **Evaluation of lung histology indicated that the number of goblet cells, mast cells, thicknesses of epithelium, and basement membrane were significantly improved in groups B and C when compared with group A.** There was no statistically significant difference in thicknesses of subepithelial smooth muscle between groups A, B, and C. When doses of G. biloba were compared with each other, only the number of goblet cells was significantly lower in group C than in group B. **When G. biloba and dexamethasone groups were compared with each other, thicknesses of basement membrane and subepithelial smooth muscle were found to be lower in group D than in groups B and C. G. biloba alleviates all established chronic histological changes of lung except smooth muscle thickness in a mouse model of asthma.**" *(Babayigit A, Olmez D, Karaman O, Ozogul C, Yilmaz O, Kivcak B, Erbil G, Uzuner N. Effects of Ginkgo biloba on airway histology in a mouse model of chronic asthma. Allergy Asthma Proc. 2009 Mar-Apr;30(2):186-91).*

L'attività antiasmatica del Ginkgo è stata confermata nel corso di uno studio controllato condotto versus corticosteroidi su 75 pazienti affetti da asma atopica, dove la droga, ha mostrato di ridurre significativamente l'infiammazione, sia da sola che associata al trattamento farmacologico con corticosteroidi[110]. Il ginkgolide B - che tra i componenti della droga è quello più attivo nell'inibizione del PAF sembra inoltre sinergizzare gli effetti della ciclosporina A nell'inibizione delle reazioni autoimmunitarie in un modello sperimentale di asma[111]. Uno studio clinico controllato ha infine dimostrato che l'estratto di Ginkgo (EGB 761) è utile nel trattamento della congiuntivite allergica stagionale[112].

Attività antinocicettiva. L'estratto di *Ginkgo biloba* si è dimostrato attivo in modelli sperimentali di dolore neuropatico[113]. Molto diffuso, p.e. negli stati post-traumatici, post-erpetici, diabetici,

[110] "To investigate the effect of the Ginkgo Biloba Extract (GBE) on the asthma and examine its possible mechanisms, 75 asthma patients were divided into 4 groups and the patients were respectively treated with fluticasone propionate for 2 weeks or 4 weeks, or treated with fluticasone propionate plus GBE for 2 weeks or 4 weeks. Fifteen healthy volunteers served as healthy controls. (…) It is concluded that **GBE could significantly decrease the infiltration of inflammatory cells such as eosinophils and lymphocytes in the asthmatic airway and relieve the airway inflammation. GBE may decrease the activation of the PKCalpha in the inflammatory cells and thereby decrease the IL-5 level in induced sputum. GBE may be used as a complement to the glucocorticosteroid therapy for asthma**." *(Tang Y, Xu Y, Xiong S, Ni W, Chen S, Gao B, Ye T, Cao Y, Du C. The effect of Ginkgo Biloba extract on the expression of PKCalpha in the inflammatory cells and the level of IL-5 in induced sputum of asthmatic patients. J Huazhong Univ Sci Technolog Med Sci. 2007 Aug;27(4):375-80).*

[111] "**The effects of Ginkgolide B (BN52021) on in vitro activation responses of human peripheral blood mononuclear cells (PBMC) from asthmatic patients** was measured using 2-channel flow cytometric analysis of activation-associated cell surface antigens or ELISA assays for cytokines known to be expressed by PBMC during T1 or T2 immunological activation. **BN52021 is an anti-inflammatory extract of Ginkgo biloba and has been used therapeutically. It is a known inhibitor of platelet activating factor (PAF), which is important in the pathogenesis of asthma, and may synergise with cyclosporin A (CyA) to inhibit pathogenic immune activation in asthmatics**. We compared the inhibitory effects of BN52021 and CyA (1 microM each) on activation of PBMC of asthmatic patients stimulated by phorbol myristate acetate and calcium ionophore. Inhibition of production of the cytokines IL-4 and IL-5 by BN52021 was insignificant compared to CyA. However, BN52021 significantly reversed the increase in activation-associated CD45RA expression, with a trend towards decreased expression of HLA-DR. Lymphocyte activation markers were not significantly altered by CyA. **Since they appear to have differing effects on activated cells, the anti-inflammatory effects of CyA and BN52021 in atopic asthma is potentially additive.** The present approach may be useful for preliminary evaluation of novel therapeutic modalities for asthma treatment." *(Mahmoud F, Abul H, Onadeko B, Khadadah M, Haines D, Morgan G. In vitro effects of Ginkgolide B on lymphocyte activation in atopic asthma: comparison with cyclosporin A. Jpn J Pharmacol. 2000 Jul;83(3):241-5).*

[112] "To investigate the clinical efficacy of a Ginkgo biloba extract associated with hyaluronic acid ophthalmic solution (GB-HA, Trium, SOOFT, Italy), compared to hyaluronic acid ophthalmic solution (HA) alone, in 60 patients with symptomatic seasonal allergic conjunctivitis. (…) **The results suggest that Ginkgo biloba extract may exert therapeutic activity in the treatment of seasonal allergic conjunctivitis**. Hyaluronic acid did not exert any valuable effect on this pathology." *(Russo V, Stella A, Appezzati L, Barone A, Stagni E, Roszkowska A, Delle Noci N. Clinical efficacy of a Ginkgo biloba extract in the topical treatment of allergic conjunctivitis. Eur J Ophthalmol. 2009 May-Jun;19(3):331-6).*

[113] "Neuropathic pain is chronic pain that is caused by an injury to the peripheral or central nervous system. The symptoms of neuropathic pain are continuing pain, hyperalgesia, and allodynia. Ginkgo biloba extract is an oriental herbal medicine that has various pharmacological actions. **We examined the effect of Ginkgo biloba extract, EGb 761, on the mechanical and cold allodynia in a rat model of neuropathic pain.** Methods: Male Sprague-Dawley rats were prepared by tightly ligating the left L5 and L6 spinal nerves. All the rats developed mechanical and cold allodynia 7 days after surgery. Fifty neuropathic rats were assigned into five groups for the intraperitoneal administration of drugs. The study was double-blind and the order of the treatments was randomized. Normal saline and EGb 761 (50, 100, 150, and 200 mg/kg) were administered, respectively, to the individual groups. We examined mechanical and cold allodynia at preadministration and at 15, 30, 60, 90, 120, 150, and 180 min

carcinomatosi, da artrite reumatoide, si tratta di un dolore molto difficile da curare e da alleviare, ed è provocato dal fatto che a livello del sistema nervoso centrale le fibre nervose trasmettono ai centri del dolore, posti nel cervello, segnali errati. Questa disfunzione dell'attività neurologica provoca, quindi, sensazioni dolorose anche in assenza di un danno reale. L'uso di farmaci anti-infiammatori ed analgesici risulta spesso di scarsa efficacia per cui per molti pazienti si ricorre agli oppiacei, il cui uso comporta però rilevanti effetti collaterali. L'attività antinocicettiva del Ginkgo risulta di particolare interesse clinico anche nel dolore infiammatorio acuto[114], dove la droga esibisce effetti comparabili al diclofenac[115].

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after intraperitoneal drug administration. Mechanical allodynia was quantified by measuring the paw withdrawal threshold to stimuli with von Frey filaments of 1.0, 1.4, 2.0, 4.0, 6.0, 8.0, 10.0, 12.0, 15.0, and 26.0 g. Cold allodynia was quantified by measuring the frequency of foot lift with applying 100% acetone. We measured the locomotor function of the neuropathic rats by using the rotarod test to reveal if EGb 761 has side effects, such as sedation or reduced motor coordination. Results: The control group showed no differences for mechanical and cold allodynia. **For the EGb 761 groups, the paw withdrawal thresholds to mechanical stimuli and withdrawal frequencies to cold stimuli were significantly reduced versus the preadministration values and versus the control group. The duration of antiallodynic effects increased in a dose-dependent fashion, and these were maintained for 120 min at the highest dose (P < 0.05). Only at the highest dose (200 mg/kg) did EGb 761 reduce the rotarod performance time. We conclude that Ginkgo biloba extract, EGb 761, attenuates mechanical and cold allodynia in a rat model of neuropathic pain, and it may be useful for the management of neuropathic pain**." *(Kim YS, Park HJ, Kim TK, Moon DE, Lee HJ. The effects of Ginkgo biloba extract EGb 761 on mechanical and cold allodynia in a rat model of neuropathic pain. Anesth Analg. 2009 Jun;108(6):1958-63).*

[114] "**Studies in vitro suggest that the standardised extract of Ginkgo biloba, EGb-761 has anti-inflammatory properties and modulatory effects on key pain-related molecules. This study investigated the analgesic and anti-inflammatory effects of EGb-761 on carrageenan-induced inflammatory and hindpaw incisional pain**. Experimental approach: Adult male Wistar rats (n=6-10/group; 250-420 g) were injected intradermally with carrageenan into the left hindpaw or anaesthetised with isoflurane (2%) and a longitudinal 1 cm incision was made through the skin, fascia and plantaris muscle of the hindpaw. EGb-761 (3, 10, 30, 100 or 300 mg kg(-1)), diclofenac (5 mg kg(-1)) or drug-vehicle was administered 3 h post-carrageenan/post-surgery. Hindpaw withdrawal latency (in seconds) to thermal stimulation, response threshold (in grams) to mechanical stimulation and paw volume were measured. KEY Results: Carrageenan induced significant mechanical allodynia, thermal hyperalgesia and paw oedema at 6 h post-carrageenan, while paw incision surgery induced significant mechanical allodynia and thermal hyperalgesia at 6 and 24 h post-surgery. **Administration of EGb-761 dose-dependently inhibited thermal hyperalgesia and was equally effective as diclofenac (5 mg kg(-1)) in both the carrageenan and hindpaw incision model.** EGb-761 had no effect on carrageenan- or incision-induced mechanical allodynia or paw oedema. Diclofenac significantly reduced mechanical allodynia in both models and carrageenan-induced paw oedema. Conclusions and implications: **EGb-761 dose-dependently alleviates acute inflammatory and surgically induced thermal hyperalgesia and is comparable to diclofenac, a commonly prescribed non-steroidal anti-inflammatory drug. This indicates that EGb-761 has analgesic potential in acute inflammatory pain.**" *(Biddlestone L, Corbett AD, Dolan S. Oral administration of Ginkgo biloba extract, EGb-761 inhibits thermal hyperalgesia in rodent models of inflammatory and post-surgical pain. Br J Pharmacol. 2007 May;151(2):285-91).*

[115] "**Ginkgo biloba extract (GbE) was assessed in models of acute inflammation induced by carrageenan, formalin or capsaicin in the rat, in models of nociceptive pain**, such as hot-plate (55 degrees C) latency, tail-electric stimulation assay and capsaicin-induced paw licking and in the model of acute gastric damage induced by indomethacin. The agent showed marked anti-inflammatory activity in the carrageenan model of paw oedema. When given subcutaneously (s.c.) (25 and 50 mg kg(-1)) 30 min before challenge, GbE inhibited paw oedema with a maximal effect of 43.7 and 56.9%, respectively, at 2h post-carrageenan. Significant inhibition of oedema was also observed when GbE (50 mg kg(-1), s.c.) was given 30 min after carrageenan challenge. The agent was also active p.o. in acute inflammation caused by carrageenan. The administration of GbE with indomethacin, rofecoxib, celecoxib, dexamethasone or melatonin resulted in an additive effect. GbE (50 mg kg(-1), s.c.) caused significant inhibition of formalin-induced paw oedema, but did not reduce the capsaicin-induced paw oedema. In tests of nociception, GbE (25, 50 or 100 mg kg(-1)) decreased in dose-dependent manner the capsaicin-induced hind paw licking time and was similarly effective in the hot-plate assay of nociception. In contrast, when assessed in the tail-electric stimulation test, GbE was only effective in the highest dose (100 mg kg(-1)). In pylorus-ligated rats, GbE (25 or 50 mg kg(-1)) increased gastric acid secretion, but reduced

Tollerabilità. Il *Ginkgo biloba* è una droga ritenuta generalmente sicura. In rari casi sono stati riportati lievi disturbi gastrointestinali, emicrania o reazioni allergiche cutanee. Non sono state riportate reazioni avverse significative neanche in seguito a sovradosaggio in pazienti che hanno ingerito fino a 600 mg di estratto secco in dose singola[116].

Esiste invece un rischio concreto di interazioni farmacologiche, in quanto proprio azione antiaggregante piastrinica dei ginkgolidi, alla base dell'uso di estratti di Ginkgo nell'insufficienza cerebrovascolare e nelle arteriopatie periferiche, ne sconsiglia in realtà l'uso in concomitanza con sostanze dotate della stessa azione farmacologica, come p.e. aspirina e FANS (ibuprofene), o che possono influenzare la coagulazione, come il warfarin[117]. In letteratura sono in effetti descritti diversi casi di emorragia derivante dall'interazione degli estratti della pianta con farmaci che inibiscono l'aggregazione piastrinica e/o la coagulazione[118,119]. Ciò suggerisce la necessità di una attenta sorveglianza nei confronti dei pazienti anziani e/o con patologie predisponenti ad eventi emorragici[120]. L'interazione della droga con gli anticoagulanti orali sembra poi avere una base sia farmacodinamica che farmacocinetica. Infatti, gli estratti di *Ginkgo biloba* sono in grado di inibire il metabolismo microsomiale del warfarin per azione sugli isoenzimi CPY2C9 e CYP3A4 del citocromo P450[121,122]. L'effetto degli estratti di Ginkgo sugli enzimi del citocromo P450 sembra essere responsabile di ulteriori interazioni farmacocinetiche descritte in letteratura. In uno studio di farmacocinetica condotto su volontari sani è stato osservato che l'assunzione concomitante di nifedipina e Ginkgo incrementa i livelli plasmatici del calcio antagonista attraverso l'inibizione dell'isoenzima CYP3A4[123]; in un ulteriore studio è stata evidenziata la capacità degli estratti di Ginkgo

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gastric mucosal damage caused by IND. **Results suggest that GbE may be of clinical value as an anti-inflammatory and analgesic drug alone or in conjunction with NSAIDs.**" *(Abdel-Salam OM, Baiuomy AR, El-batran S, Arbid MS. Evaluation of the anti-inflammatory, anti-nociceptive and gastric effects of Ginkgo biloba in the rat. Pharmacol Res. 2004 Feb;49(2):133-42).*

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di incrementare i livelli ematici di omeprazolo con un meccanismo coinvolgente il CYP2C19[124].
Il medesimo meccanismo potrebbe render conto della riduzione delle concentrazioni plasmatiche di fenitoina e acido valproico osservate in un paziente con epilessia in corso di trattamento con Ginkgo.

[124] *Yin OQ, Tomlinson B, Waye MM, Chow AH, Chow MS. Pharmacogenetics and herb-drug interactions: experience with Ginkgo biloba and omeprazole. Pharmacogenetics.2004 Dec;14(12):841-50.*