

# ePlantLIBRA Plant Food Supplement Report:

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## *Ginkgo biloba*/common ginkgo

### What is *Ginkgo biloba*?

*Ginkgo biloba* or common ginkgo is one of the oldest types of trees in the world. *Ginkgo* is been cultivated all over the world but only can be found in the wild in China. (Royer)

According to Charles Darwin *Ginkgo* is a living fossil. It is the oldest living tree species in the world. After the ice age it was thought that it hadn't survived. In 1691 Englebert Kaempfer, a German Physician and Botanist, discovered in China a *ginkgo biloba* tree. It was not the same tree as its ancient ancestors due to environmental changes. (Nelson)

The tree normally reaches a height of 20–35 m, some specimens in China are known being over 50 m. The tree has an angular shaped crown and long, somewhat erratic branches, and is usually deep rooted and resistant to wind and snow damage. A combination of resistance to disease, insect-resistant wood and the ability to form aerial roots and sprouts makes *ginkgo* long-lived, with some specimens claimed to be more than 2,500 years old. (Royer). *Ginkgo*'s are also popular subjects for growing as bonsai.

It takes 20-35 years for trees to reach maturity and start bearing seeds. Male and female trees are separate; male trees have pollen-producing catkins while female trees, once fertilised, bear rounded and yellowish seeds with a fleshy outer coat. (Simmonds)



Figure 1 *Ginkgo biloba* leaves and seed. (Health)

### *Ginkgo biloba* as plant food supplement

*Ginkgo* seeds have been used in traditional Chinese medicine for thousands of years, and cooked seeds are occasionally eaten. The seeds, known as ginkgo nuts, are eaten roasted or in birds' nest soup. (Simmonds) In food supplements the leaves are more commonly used instead of seeds or other parts



Figure 2 *Ginkgo Biloba* supplement (remedios caseiros)

## Use

*Ginkgo extracts are commonly used pharmaceutically for (Ginkgo, 2009):*

- Enhancement of memory and concentration
- Treatment for dementia (Alzheimer's disease)
- Improving blood flow to most tissues and organs
- Protection against anti-oxidative cell damage from free radicals
- Relief symptoms premenstrual symptoms
- ...

## Intake

*The daily dose suggested varies between 40 - 120 mg of Ginkgo extract depending on the product/supplement and the intention. The amount of Ginkgo per capsule or tables varies between 40 – 120 mg. (NIH, 2014) The amount of intake can be raised to 240mg/day in case of more serious cases of dementia of Alzheimer's. (Ginkgo biloba, 2014) Besides tablets and capsules ginkgo is also available as tea, tincture or as a cold drink.*

## Contaminant information

*Table 1 summarizes contaminant information on Ginkgo biloba plant parts. This information comes from the ePlantLIBRA<sup>1</sup> database which used MoniQA<sup>2</sup> for determination of the contaminants.*

Contaminant	Regulatory plant classification	MRL: max residue level	Unit	Analysis
Aflatoxin B1 (seed)	2.1.4. Tree nuts, other than the tree nuts listed in 2.1.2 and 2.1.3, to be subjected to sorting, or other physical treatment, before human consumption or use as an ingredient in foodstuffs	5	µg/kg	Regulation (EC) 401/2006
Aflatoxin B1+B2+G1+G2 (seed)	2.1.4. Tree nuts, other than the tree nuts listed in 2.1.2 and 2.1.3, to be subjected to sorting, or other physical treatment, before human consumption or use as an ingredient in foodstuffs	10	µg/kg	Regulation (EC) 401/2006
Pesticides (leaves)	063. Herbal infusions from (b) leaves and herbs	MRLs for mate (0632030) apply	mg/kg	Regulation (EC) No 396/2005 and its Annex amendments
Pesticides (seed)	012. Tree nuts	MRLs for tree nuts - other (0120990) apply	mg/kg	Regulation (EC) No 396/2005 and its Annex amendments

**Table 1 Contaminant information on Ginkgo biloba (EuroFIR AISBL PlantLIBRA, 2014)**

<sup>1</sup> The ePlantLIBRA database (<http://ePlantLIBRA.eurofir.eu/>) contains quality evaluated compositional, beneficial and adverse effects data on bioactive composition in Plant Food Supplements.

<sup>2</sup> International Association for Monitoring and Quality Assurance in the Total Food Supply Chain

## Composition (EuroFIR AISBL PlantLIBRA, 2014)

According ePlantLIBRA following compounds occur are unique to *Ginkgo biloba*:

- Bilobalide
- Ginkgolide A
- Ginkgolide B
- Ginkgolide C
- Ginkgolide J
- Ginkgotoxin
- Terpene trilactones

The following tables and charts report the amount of the above described compounds in *Ginkgo biloba* plant parts and in plant food supplements obtained from scientific publications.

Figure 3 structure of bilobalide

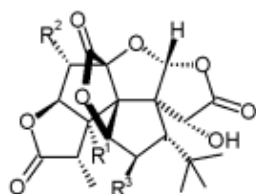


Figure 4 Structure of ginkgolide

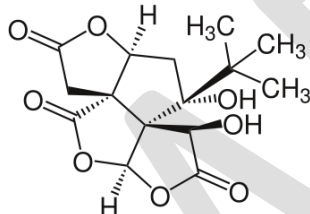


Figure 5 structure of terpene trilactones

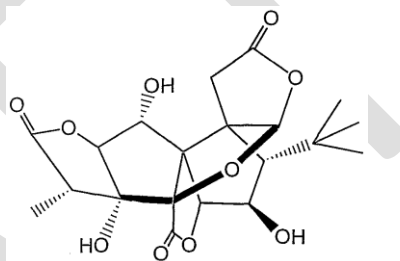


Chart 1 Bilobalide in *Ginkgo biloba* leaves

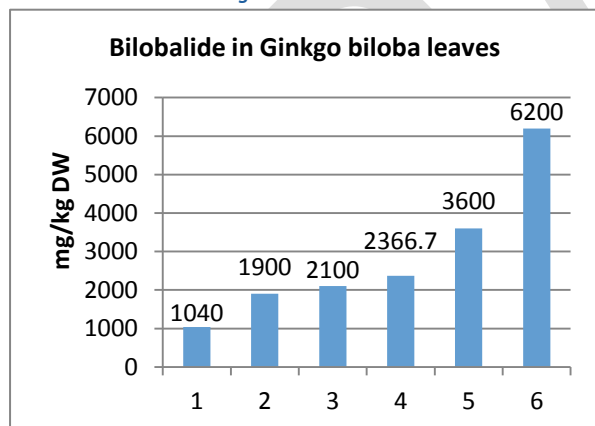


Chart 2 Ginkgo compounds in *Ginkgo biloba* leaves

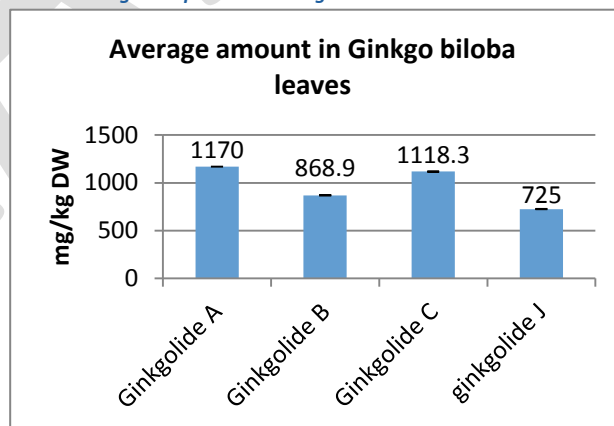


Chart 1 shows that the documented quantity of bilobalide in leaves varies between 1040 and 6200 mg/kg DW. The reason for this can be the sample date or season or the place where the trees grow. The same applies for chart 2; average composition of the most important compounds in *Ginkgo biloba* leaves. Although the average level of ginkgolide A is 1170 mg/kg DW the range covers 200 and 3000 mg/kg DW<sup>3</sup>. The amount of ginkgotoxin in the leaves has not reported in any publications. However table 1 shows levels in other plant parts.

<sup>3</sup> See appendix for detailed chart

Ginkgotoxin in seed or kernel (mg/kg DW)	Ginkgotoxin in skin or bran (mg/kg DW)
171	7.15
177	
179	

**Table 2 Ginkgotoxin in Ginkgo biloba plants**

The amount of ginkgotoxin is the highest in the seeds or kernels (average 175.6 mg/kg DW) of Ginkgo biloba; the amount in the skin (7.15 mg/kg DW) or other parts is around 24 times lower. Ginkgotoxin is also found in smaller amount Plant Food Supplements.

**Chart 3 Amount TTT in Ginkgo biloba leaves**

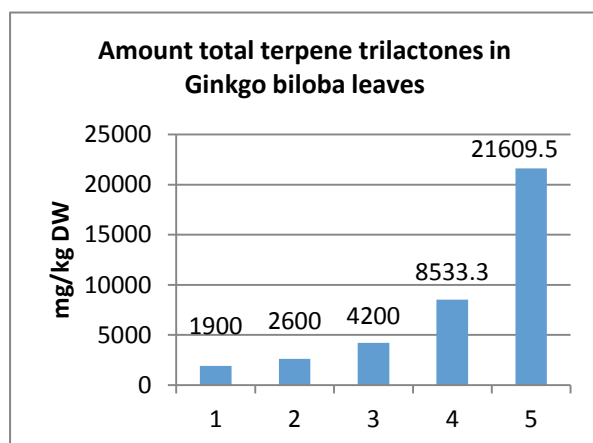


Chart 3 shows the amount of total terpene trilactones in leaves, the large differences in measured values can be explained by the origin, age and the growing altitude of the trees.

**Chart 4 Amount of Bilobalide in Ginkgo tablets**

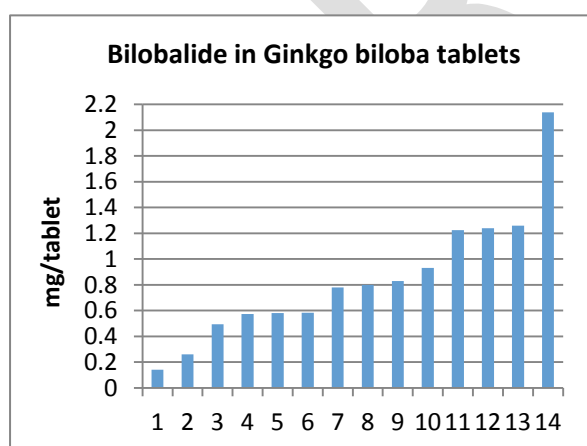


Chart 4 shows the amount of Bilobalide in Ginkgo biloba tablets. A comparison with the amount in dried leaves can't be made because there is insufficient data on the weight of tablets or capsules used or quantity of leaf in the products. The diversity of the amount bilobalide recovered is again large mostly due to different tablets with different concentrations that are used.

	Ginkgolide A	Ginkgolide B	Ginkgolide C	Ginkgolide J	Ginkgotoxin <sup>4</sup>	Terpene trilactones total
mg/kg DW	11882.57	7474.52	7989.69	3231.89	17.6	44174.09
mg/l	57.79	18.32	37.53	37.22	3.33	216.28
mg/tablet	94.18	57.53	31.34	30.29	/	3.08

*Table 3 Average amount of ginkgolides, ginkgotoxin and total terpene trilactones in dried, liquid and tablet samples*

Table 2 shows the average amount of the most important *Ginkgo biloba* compounds analysed in different types of plant food supplements. There are no results of the amount of ginkgotoxin expressed in mg/tablet. The higher amount of ginkgotoxin expressed in mg/kg DW is caused by the amount found in capsules and tablets (3 references in EPlantLIBRA) which lies between 32 and 86 mg/kg DW. The other values are lower and are from analysis of boiled or canned *Ginkgo* seeds; they vary between 0.8 and 25 mg/kg DW. All the used samples except for determination of ginkgotoxin (expressed in mg/kg DW) are made from leaves or leaves extracts.

### **Beneficial effects (EuroFIR AISBL PlantLIBRA, 2014)**

3 Papers have been reported in EPlantLIBRA with clinical trials on beneficial effects of *Ginkgo biloba* supplements.

#### **1. Does *Ginkgo biloba* reduce the risk of cardiovascular events? (Kuller, 2009)**

This randomised, double-blind, placebo controlled study investigated the effects of *Ginkgo biloba* extract (EGb 761) on incidence of fatal and non-fatal cardiovascular events in men and women aged >75 years.

##### **Amount:**

- 120mg *Ginkgo biloba* extract (containing 28.8mg flavone glycosides and 7.2mg terpene lactones) twice daily. *Ginkgo biloba* extract was supplied by Schwabe Pharmaceuticals, Germany.

##### **Result:**

- There was no significant difference in CHD/CVD mortality between *Ginkgo biloba* and placebo groups.
- There was no significant difference in hospitalisations for cardiovascular events between groups (among those with no self-reported history of CVD at baseline).
- There was a significant reduction in peripheral vascular disease (PVD) events in subjects taking *Ginkgo biloba* supplement compared with placebo.

##### **Conclusion:**

- The data do not support the use of *Ginkgo biloba* to reduce the risk of cardiovascular events.
- However, further study may be indicated on the effects of *Ginkgo biloba* on risk of PVD.

<sup>4</sup> See appendix for detailed table and charts

## **2. *The use of Ginkgo biloba in Raynaud's disease: a double-blind placebo-controlled trial (Muir A, 2002)***

*This double-blind, randomized, placebo controlled study investigated the clinical efficacy of Ginkgo biloba extract for the treatment of RP (Raynaud's phenomenon).*

### **Amount:**

- 360 mg Seredrin (Ginkgo biloba extract) per day.

### **Result:**

- There was a significant decrease in attacks per day compared to placebo group.
- There was a reduction of 56% in number of attacks per week in treatment group, compared to a 27% reduction in placebo.
- There were no significant differences in haemorrheology (blood rheology) between the two groups.

### **Conclusion:**

- A significant reduction in the number of Raynaud's attacks per day has been observed, however a small sample size was included in this study and it should be seen as a pilot study.

## **3. *Short-term oral ingestion of Ginkgo biloba extract (EGb 761) reduces malondialdehyde levels in washed platelets of type 2 diabetic subjects (Kudolo G, 2005)***

*This study was designed to examine the efficacy of EGb 761 as a free radical scavenger in platelets harvested from Type 2 Diabetes Mellitus subjects with and without hypercholesterolemia.*

### **Amount:**

- 120 mg daily for 3 months (containing 24% Ginkgo flavone glycosides and 6% terpenes).

### **Result:**

- There was a significantly reduced platelet thiobarbituric acid reacting substances (TBARS) in both the normal and hypercholesterolemic subjects.

### **Conclusion:**

- The ingestion of EGb 76 for 3 months by Type 2 Diabetes Mellitus subjects significantly inhibits platelet MDA (malondialdehyde) accumulation. No dose response effect studied.

### **Adverse effects (EuroFIR AISBL PlantLIBRA, 2014)**

3 papers have been reported in EPlantLIBRA with Adverse effects of *Ginkgo biloba* seeds, 31 have been reported from Plant Food Supplements.

#### **1. *Ginkgo biloba* Seeds (Hasegawa, 2006) (Miwa, 2001) (Kajiyama, 2002)**

**Type patient:**

- 2 children (2 years old) and 1 37 year old women

**Amount:**

- 50-80 *Ginkgo biloba* nuts/seeds (result of 3 reports)

**Adverse effect:**

- Generalized tonic convulsion, with eyes deviation and symmetric extremities extention
- Vomiting and diarrhea
- epileptic seizure

**Diagnose:**

- A high concentration of 4'-O-methylpyridoxine (ginkgotoxin) was present in the patient's serum and urine.
- *Ginkgo* nut poisoning

#### **2. *Ginkgo biloba* supplement**

**Type patient:**

- Men and women age between 33 and 83 years old.
- Different types of prehistory or no significant prehistory.

**Amount:**

- 40mg – 240mg from 1 -4 times a day.
- 29% of the papers didn't report any intake amount.

#### **Adverse effect:**

- (Spontaneous intracerebral) haemorrhage mostly in combination with anticoagulants. In some cases death has been reported
- Nose bleeds, ecchymosis on hands and arms after minor trauma
- Bilateral subdural hematomas
- Severe apraxia, change from mild to moderate cognitive deficits
- Hematoma
- Erythematous eruption
- Possible severe hepatitis and multiacinar dropout, no proof if it's due Ginkgo or other product in supplement
- Frequent ventricular arrhythmia
- Paroxysmal atrial fibrillation

#### **Diagnose:**

- Inhibiting erythrocyte and platelet aggregation which cause bleeding.
- Sinus rhythm with frequent ventricular premature beats.

### **Causality assessment**

Chart 5 Causality assessment adverse effect data

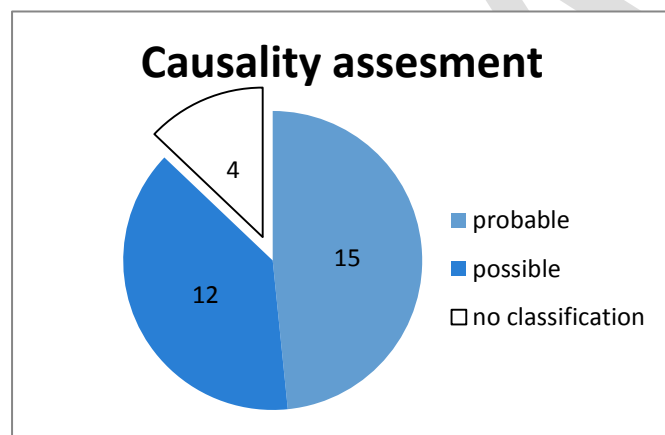


Chart 5 shows the amount of possible and probable interactions of Ginkgo biloba in the observed adverse effects. In 4 papers no classification was given due to lack of information or that no good judgement could be made.

### **Conclusions**

There is scientific evidence that Ginkgo biloba extract/supplement can be used to reduce the number of Raynaud's attacks per day, it can reduce platelet thiobarbituric acid reacting substances (TBARS) and it inhibits platelet MDA accumulation in normal and hypercholesterolemic Type 2 Diabetes Mellitus subjects.

There is also scientific evidence that Ginkgo biloba seeds and supplements can cause adverse effects in children and adults. In case of nut ingestion there is proof that the adverse effects are been caused by ginkgotoxin. In the other cases it has not been linked to a specific compound.



## Bibliography

- EuroFIR AISBL PlantLIBRA. (2014). ePlantLIBRA. Retrieved march 27, 2014, from ePlantLIBRA:  
<http://eplantlibra.eurofir.eu/>
- Ginkgo. (2009). Retrieved march 26, 2014, from WebMD: <http://www.webmd.com/vitamins-supplements/ingredientmono-333-GINKGO.aspx?activeIngredientId=333&activeIngredientName=GINKGO>
- Ginkgo biloba. (2014). Retrieved march 31, 2014, from acupuncture today:  
[http://www.acupuncturetoday.com/herbcentral/ginkgo\\_biloba.php](http://www.acupuncturetoday.com/herbcentral/ginkgo_biloba.php)
- Hasegawa, S. O. (2006). Ginkgo nut intoxication in a 2-year-old male. *Pediatr Neurol*, 275-276.
- Health. (n.d.). Retrieved march 25, 2014, from Top News: <http://topnews.in/health/files/Ginkgo-biloba.jpg>
- Kajiyama, Y. F. (2002). Ginkgo seed poisoning. *Pediatrics*, 325-327.
- Kudolo G, D. D. (2005). Short-term oral ingestion of Ginkgo biloba extract (EGb 761) reduces malondialdehyde levels in washed platelets of type 2 diabetic subjects. *Diabetes Research and Clinical Practice*, 29-38.
- Kuller, L. (2009). Does Ginkgo biloba reduce the risk of cardiovascular events. *Cardiovascular Quality and Outcomes* 3, 1-7.
- Miwa, H. I. (2001). Generalized convulsion after consuming a large amount of Ginkgo nuts. *Epilepsia*, 280-282.
- Muir A, R. R. (2002). The use of Ginkgo biloba in Raynaud's disease: a doubleblind placebo-controlled trial. *Vascular Medicine* 7, 265-267.
- Nelson, B. (n.d.). Nelson ginkgo history. Retrieved march 28, 2014, from herballegacy:  
[http://www.herballegacy.com/Nelson\\_Ginkgo\\_History.html](http://www.herballegacy.com/Nelson_Ginkgo_History.html)
- NIH. (2014, march). Dietary Supplement Label Database. Retrieved march 31, 2014, from National Institute of Health:  
<http://www.dsld.nlm.nih.gov/dsld/lstProducts.jsp?db=adsl&pagenum=1&pagesize=15&view=table&list=g&item=ginkgo>
- remedios caseiros. (n.d.). Retrieved march 26, 2014, from <http://www.remedios-caseiros.com/remedios/ginkgo-biloba-combate-sintomas-ma-circulacao-do-sangue.html>
- Royer, e. a. (n.d.). ginkgo biloba. Retrieved march 25, 2014, from wikipedia:  
[http://en.wikipedia.org/wiki/Ginkgo\\_biloba](http://en.wikipedia.org/wiki/Ginkgo_biloba)
- Simmonds, M. (n.d.). Ginkgo biloba (maidenhair tree). Retrieved march 31, 2014, from KEW:  
<http://www.kew.org/science-conservation/plants-fungi/ginkgo-biloba>

## References EPlantLIBRA database

- ARENZ, A., KLEIN, M., FIEHE, K., GROB, J., DREWKE, C., HEMSCHIEDT, T., LEISTNER, E. 1996. Occurrence of Neurotoxic 4'-O-Methylpyridoxine in *Ginkgo biloba* Leaves, *Ginkgo* Medications and Japanese *Ginkgo* Food. *Planta Medica*, 62(6), 548,551.
- BEBBINGTON, A., KULKARNI, R. AND ROBERTS, P. 2005. Persistent bleeding after total hip arthroplasty caused by herbal self-medication. *The Journal of arthroplasty*, 20(1), 125,126.
- BENJAMIN, J., MUIR, T., BRIGGS, K. AND PENTLAND, B. 2001. A case of cerebral haemorrhage - Can *Ginkgo biloba* be implicated? *Postgrad Med J*, 77, 112,113.
- BENT, S., GOLDBERG, H., PADULA, A. AND AVINS, A. 2005. Spontaneous bleeding associated with *Ginkgo biloba*: a case report and systematic review of the literature. *J Gen Intern Med*, 20, 657,661.
- CASTELLOTE VARONA, F. J. A. A. M., M.P. 2005. *Ginkgo biloba* and cerebral hemorrhage. *An Med Interna*, 22(4), 199.
- CHEN, D., KLESMER, J., GIOVANNIELLO, A. AND KATZ, J. 2002. Mental status changes in an alcohol abuser taking Valerian and *Ginkgo biloba*. *The American Journal of Addictions*, 11, 75,77.
- CHIU, A. E., LANE, A. T. AND KIMBALL, A. B. 2002. Diffuse morbilliform eruption after consumption of *Ginkgo biloba* supplement. *J Am Acad Dermatol*, 46, 145,146.
- CHOI, Y. H., CHOI, H.-K., HAZEKAMP, A., BERMEJO, P., SCHILDER, Y., ERKELENS, C. AND VERPOORTE, R. 2003. Quantitative analysis of bilobalide and ginkgolides from *ginkgo biloba* leaves and *ginkgo* products using <sup>1</sup>H-NMR. *Chemical and pharmaceutical bulletin*, 51, 158-161.
- CIANFROCCA, C., PELLICCIA, F., AURUTI, A. AND SANTINI, M. 2002. *Ginkgo biloba*-induced frequent ventricular arrhythmia. *Ital heart J*, 3, 689,691.
- CROOM, E., PACE, R., PALETTI, A., SARDONE, N., GRAY, D. 2007. Single-Laboratory Validation for the Determination of Terpene Lactones in *Ginkgo biloba* Dietary Supplement Crude Materials and Finished Products by High-Performance Liquid Chromatography with Evaporative Light-Scattering Detection. *Journal of AOAC International*, 90(3), 647,658.
- DE JAGER, L. S., PERFETTI, G. A., DIACHENKO, G. W. 2005. Analysis of ginkgolides and bilobalide in food products using LC-APCI-MS. *Journal of Pharmaceutical and Biomedical Analysis*, 41 (5), 1552,1559.
- DENG, F., ZITO, S. W. 2002. Development and validation of a gas chromatographic-mass spectrometric method for simultaneous identification and quantification of marker compounds including bilobalide, ginkgolides and flavonoids in *Ginkgo biloba* L. extract and pharmaceutical preparations. *Journal of Chromatography A*, 986(1), 121,127.
- DENG, F. AND ZITO, S. W. 2003. Development and validation of a gas chromatographic-mass spectrometric method for simultaneous identification and quantification of marker compounds including bilobalide, ginkgolides and flavonoids in *Ginkgo biloba* L. extract and pharmaceutical preparations. *Journal of Chromatography A*, 986, 121,127.
- DESTRO, M. W., SPERANZINI, M. B., CAVALHEIRO FILHO, C., DESTRO, T. AND DESTRO, C. 2005. Bilateral haematoma after rhytidoplasty and blepharoplasty following chronic use of *Ginkgo biloba*. *The British Association of Plastic Surgeons*, 58, 100,101.
- DING, C., CHEN, E. AND LINDSAY, R. C. 2007. Natural accumulation of terpene trilactones in *Ginkgo biloba* leaves: variation by gender, age and season. *European Food Research Technology*, 224, 615,621.
- DING, S., DUDLEY, E., PLUMMER, S., TANG, J., NEWTON, R. P., BRENTON, A. G. 2006. Quantitative determination of major active components in *Ginkgo biloba* dietary supplements by liquid chromatography/mass spectrometry. *Rapid Communications in Mass Spectrometry*, 20, 2735,2760.
- DUBBER, M.-J., KANFER, I. 2006. Determination of terpene trilactones in *Ginkgo biloba* solid oral dosage forms using HPLC with evaporative light scattering detection. *Journal of Pharmaceutical and Biomedical Analysis*, 41(1), 135,140.
- FESSENDEN, J. M., WITTENBORN, W. AND CLARKE, L. 2001. *Ginkgo biloba*: a case report of herbal medicine and bleeding postoperatively from a laparoscopic cholecystectomy. *THE AMERICAN SURGEON*, 67, 33,35.
- FONG, K. C. A. K., P. E. 2003. Retrobulbar haemorrhage associated with chronic *Ginkgo biloba* ingestion. *Postgrad Med J*, 79, 531,532.
- GANZERA, M., ZHAO, J., KHAN, I. A. 2001. Analysis of Terpenelactones in *Ginkgo biloba* by High Performance Liquid Chromatography and Evaporative Light Scattering Detection. *Chemical and Pharmaceutical Bulletin*, 49(9), 1170,1173.
- GILBERT, G. J. 1997. *Ginkgo biloba*. *Neurology*, 48, 1137.

- GRAY, D. E., MESSER, D., PORTER, A., HEFNER, B., LOGAN, D., HARRIS, R. K., CLARK, A. P., ALGAIER, J. A., OVERSTREET, J. D., SMITH, C. S. 2007. Analysis of Flavonol Aglycones and Terpenelactones in *Ginkgo biloba* Extract: A comparison of High-Performance Thin-Layer Chromatography and Column High-Performance Liquid Chromatography. *Journal of AOAC International*, 90(5), 1203,1209.
- HASEGAWA, S., ODA, Y., ICHIIYAMA, T., HORI, Y. AND FURUKAWA, S. 2006. *Ginkgo* nut intoxication in a 2-year-old male. *Pediatr Neurol*, 35, 275,276.
- HAUSER, D., GAYOWSKI, T. AND SINGH, N. 2002. Bleeding complication precipitated by unrecognized *Ginkgo biloba* use after liver transplantation. *Transpl Int*, 15, 377,379.
- JAYASEKERA, N., MOGHAL, A. AND KASHIF, F. 2005. Herbal medicines and postoperative haemorrhage. *Anaesthesia*, 60, 725,726.
- JENSEN, A. G., NDJOKI, K., WOLFENDER, J.-L., HOSTETTMANN, K., CAMPONOVO, F. AND SOLDATI, F. 2002. Liquid chromatography-atmospheric pressure chemical ionisation/mass spectrometry: a rapid and selective method for the quantitative determination of ginkgolides and bilobalide in *ginkgo* leaf extracts and phytopharmaceuticals. *Phytochemical Analysis*, 13, 31,38.
- JENSEN, A. G., NDJOKO, K., WOLFENDER, J.-L., HOSTETTMANN, K., CAMPONOVO, F., SOLDATI, F. 2002. Liquid Chromatography-Atmospheric pressure Chemical Ionisation/Mass Spectrometry: A Rapid and Selective Method for the Quantitative Determination of Ginkgolides and Bilobalide in *Ginkgo* Leaf Extracts and Phytopharmaceuticals. *Phytochemical analysis*, 13 (1), 31,38.
- KAJIYAMA, Y., FUJII, K., TAKEUCHI, H. AND MANABE, Y. 2002. *Ginkgo* seed poisoning. *Pediatrics*, 109, 325,327.
- KAUR, P., CHAUDHARY, A., SINGH, B., GOPICHAND 2009. Optimization of extraction technique and validation of developed RP-HPLC-ELSD method for determination of terpene trilactones in *Ginkgo biloba* leaves. *Journal of Pharmaceutical and Biomedical Analysis*, 50(5), 1060,1064.
- KOBAYASHI, D., YOSHIMURA, T., JOHNO, A., SASAKI, K., WADA, K. 2011. Toxicity of 4'-O-methylpyridoxine-5'-glucoside in *Ginkgo biloba* seeds. *Food Chemistry*, 126(3), 1198,1202.
- KUDOLO G, D. D. B. J. 2005. Short-term oral ingestion of *Ginkgo biloba* extract (EGb 761) reduces malondialdehyde levels in washed platelets of type 2 diabetic subjects. *Diabetes Research and Clinical Practice*, 68, 29, 38.
- KULLER L.H., I. D. G., FITZPATRICK A.L., CARLSON M.C., MERCADO C., LOPEZ O.L., BURKE G.L., FURBERG C.D. AND DEKOSKY S.T. 2009. Does *Ginkgo biloba* reduce the risk of cardiovascular events? *Circulation: Cardiovascular Quality and Outcomes*, 3, 1,7.
- KUPIEC, T. A. R., V. 2005. Fatal seizures due to potential herb-drug interactions with *Ginkgo biloba*. *Journal of Analytical Toxicology*, 29, 755,758.
- LAWRENCE, G. A., SCOTT, P.M. 2005. Improved Extraction of Ginkgotoxin (4'-O-methylpyridoxine) from *Ginkgo biloba* Products. *Journal of AOAC International*, 88(1), 26,29.
- LEE, A. N. A. W., V.P. 2004. Activation of autoimmunity following use of immunostimulatory herbal supplements. *Arch Dermatol*, 140, 723,727.
- MACVIE, O. P. A. H., B.A. 2005. Vitreous haemorrhage associated with *Ginkgo biloba* use in a patient with age related macular disease. *Br J Ophthalmol*, 89, 1378.
- MARQUES, V. A. F., A. 2009. Chlorogenic acids and related compounds in medicinal plants and infusions. *Food Chemistry*, 113, 1370,1376.
- MATTHEWS, M. K. 1998. Association of *Ginkgo biloba* with intracerebral hemorrhage. *Neurology*, 50, 1933.
- MEISEL, C., JOHNE, A. AND ROOTS, I. 2003. Fatal intracerebral mass bleeding associated with *Ginkgo biloba* and ibuprofen. *Atherosclerosis*, 167(2), 367.
- MILLER, L. G. A. F., B. 2002. Possible subdural hematoma associated with *Ginkgo biloba*. *J Herbal Pharmacother*, 2, 57,63.
- NAPOLITANO, J. G., GODECKE, T., RODRIGUEZ-BRASCO, M.F, JAKI, B.U., CHEN, S-N, LANKIN, D.C., PAULI, G.F. 2012. The Tandem of Full Spin Analysis and qHNMR for the Quality Control of Botanicals Exemplified with *Ginkgo biloba*. *Journal of Natural Products*, 75(2), 238,248.
- OLSZEWSKQ, M. A. 2012. New validated high-performance liquid chromatographic method for simultaneous analysis of ten flavanoid aglycones in plant extracts using a C18 fused-core column and acetonitrile-tetrahydrofuran gradient. *Journal of Separation Science*, 35(17), 2174,2183.
- PEDROSO, J. L., HENRIQUES AQUINO, C.C., ESCORCIO BEZERRA, M.L., BAIENSE, R.F., SUAREZ, M.M., DUTRA, L.A., BRAGA-NETO, P. AND POVOAS BARSOTTINI, O.G. 2011. *Ginkgo biloba* and cerebral bleeding: a case report and critical review. *Neurologist*, 17, 89,90.
- PENNISI, R. S. 2006. Acute generalized exanthematous pustulosis induced by the herbal remedy *Ginkgo biloba*. *Med J Aust*, 184(11), 583,584.

- PRUTHI, R. K., SCHMIDT, K.A., SLABY, J.A. AND RODRIGUEZ, V. 2007. Platelet dysfunction induced by herbal supplements in a patient with mild hemophilia A. *J Thromb Haemost*, 5, 2556,2558.
- PURROY GARCIA, F., MOLINA, C. AND ALVAREZ SABIN, J. 2002. Spontaneous cerebellar haemorrhage associated with *Ginkgo biloba* ingestion. *Medicina Clinica (Barc)*, 19(15), 596,597.
- ROSENBLATT, M. A. M., J. 1997. Spontaneous hyphema associated with ingestion of *Ginkgo biloba* extract. *The New England Journal of Medicine*, 336(15), 1108.
- ROWIN, J. A. L., S.L. 1996. Spontaneous bilateral subdural hematomas associated with chronic *Ginkgo biloba* ingestion. *Neurology*, 46, 1775,1776.
- RUSSO, V., RAGO, A., RUSSO, G.M., CALABRÒ, R. AND NIGRO, G. 2011. *Ginkgo biloba*: An ancient tree with new arrhythmic side effects. *Journal of Postgraduate Medicine*, 57(3), 221.
- SCOTT, P. M., LAU, B.P.-Y., LAWRENCE, G.A., LEWIS, D.A. 2000. Analysis of *Ginkgo biloba* for the presence of ginkgotoxin and ginkgotoxin 5'-glucoside. *Journal of AOAC International*, 83(6), 1313,1320.
- TANG, D., YANG, D., TANG, A., GAO, Y., JIANG, X., MOU, J., YIN, X. 2010. Simultaneous chemical fingerprint and quantitative analysis of *Ginkgo biloba* extract by HPLC-DAD. *Analytical and Bioanalytical Chemistry*, 396(8), 3087,3095.
- VALE, S. 1998. Subarachnoid haemorrhage associated with *Ginkgo biloba*. *Lancet*, 352, 36.
- WANG, S.-F., LUO, X.-L., SHAO, Q., CHENG, Y.-Y., QU, H.-B. 2009. Simple method for simultaneous quantitation and fingerprint analysis of *ginkgo biloba* tablets by high performance liquid chromatography-UV-Evaporative light scattering detector. *Chemical research in Chinese Universities*, 25(1), 25,30.
- WHITING, P. W., CLOUSTON, A. AND KERLIN, P. 2002. Black cohosh and other herbal remedies associated with acute hepatitis. *The Medical Journal of Australia*, 177(8), 440,443.
- WOELKART, K., FEIZLMAYR, E., DITTRICH, P., BEUBLER, E., PINL, F., SUTER, A., BAUER, R. 2010. Pharmacokinetics of bilobalide, ginkgolide A and B after administration of three different *Ginkgo biloba* L. preparations in humans. *Phytotherapy research*, 24(3), 445,450.
- YAO, X., SHANG, E., ZHOU, G., TANG, Y., GUO, S., SU, S., JIN, C., QIAN, D., QIN, Y., DUAN, J.-A. 2012. Comparative Characterization of Total Flavonol Glycosides and Terpene Lactones at different Ages, from Different Cultivation Sources and Genders of *Ginkgo biloba* Leaves. *International journal of Molecular Sciences*, 13(8), 10305,10315.

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## Appendix

Chart 6 Amount of ginkgolides in Ginkgo leaves

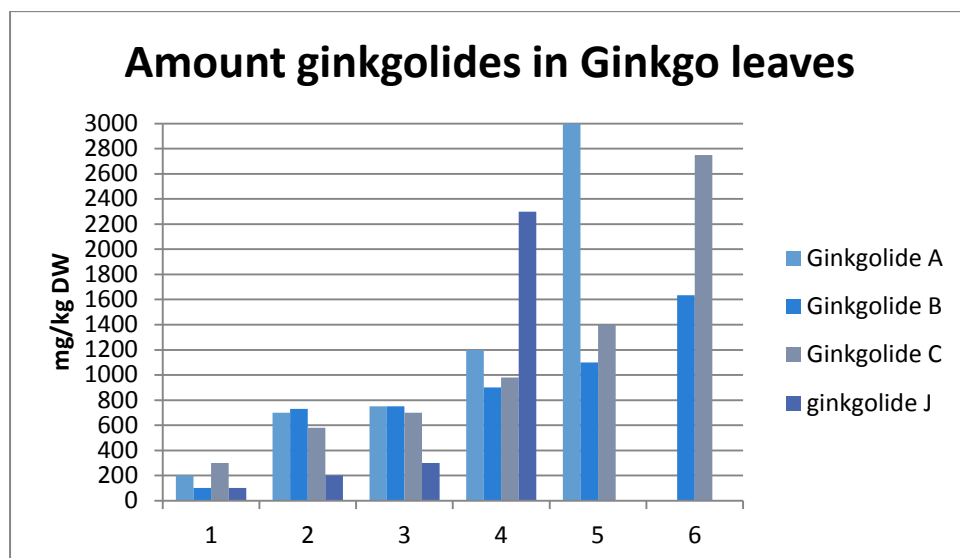
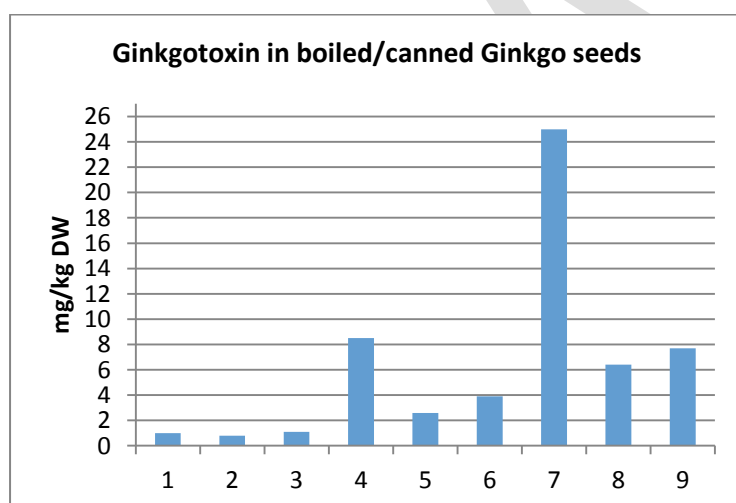
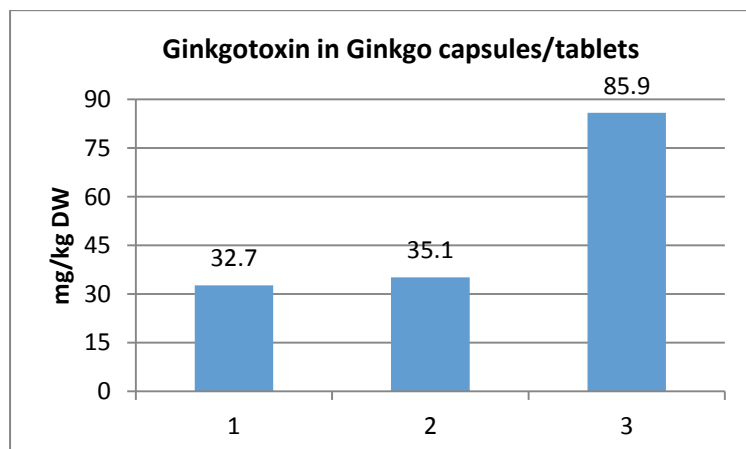


Chart 7 Amount of ginkgotoxin in processed Ginkgo seeds



**Chart 8 Amount of ginkgotoxin in Ginkgo capsules or tablets**



**Table 4 Amount of ginkgotoxin in selected liquid Ginkgo supplements**

	Ginkgo toxin (mg/l)	Ginkgo toxin (mg/l)	Ginkgo toxin (mg/l)	Ginkgo toxin (mg/l)	Ginkgo toxin (mg/l)	Ginkgo toxin (mg/l)
Ginkgo biloba allopathic medication	3.8	7.18	8.13	9.77	/	/
Ginkgo biloba homeopathic medication	0.008	0.015	0.301	0.589	1.5	1.995

Table 3 shows the amount of ginkgotoxin (4'-O-Methylpyridoxine) expressed in mg/l. 2 different types of supplements have been analysed; an allopathic type which contain higher amounts of ginkgotoxin then in comparison with the homeopathic type.