PLAQUEX® ORAL

Contents

Serving size: 1 softgel
Active ingredient per serving: 900 mg Polyenylphosphatidylcholine
[Unsaturated phosphatidylcholine from highly purified soy bean (*Glycine max*) extract]

Other ingredients: gelatin, glycerin, safflower oil, ethanol, purified water, sunflower glycerides. Contains soybeans.

Indications *

- Hypercholesterolemia
- Hyperlipoproteinaemia
- Promotes healthy liver function
- Increased platelet aggregation
- Decreased blood rheology

Dosage

2-3 softgels per day, before meals

Side effects

Slight gastrointestinal disturbance (stomach), diarrhea

Pharmacokinetics

The relative absorption rates of radioactive PPC in man are higher than 90 %. About 40 to 80 % of the PPC absorbed are incorporated into the vasoprotective HDL. EPL accumulated chiefly in the liver, spleen and lungs and phospholipid fractions of the serum lipoproteins were exchanged for EPL from the serum. The mean elimination rates from the plasma after 15 minutes, 75 minutes and 10 h are approx. 80 %, 92 % and 99 % of the administered active principle.

Chemistry

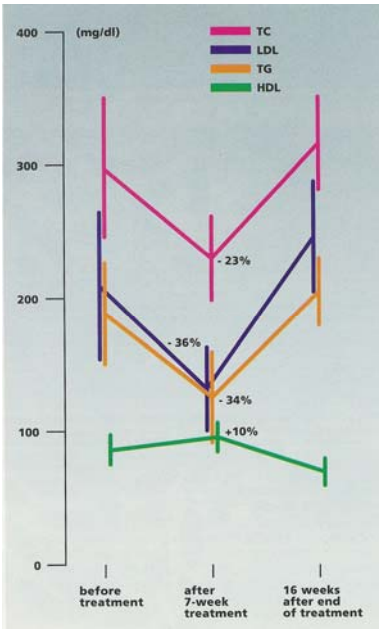
Essential phospholipids (EPL) are a highly purified phosphatidylcholine fraction isolated from soy beans. The substance is particularly rich in polyunsaturated fatty acids, with linoleic acid accounting for approx. 70 % and is therefore also termed polyenylphosphatidylcholine (PPC).

Study summaries

1. Reduction of serum lipids

By diet an increase of serum lipids was triggered for 2 to 8 weeks. Then EPL was introduced and serum lipids monitored:

- HDL increased
- LDL, TG, VLDL decreased



Investigation on Rhesus monkeys after a 10-year period of high cholesterol diet and a 7 week period of EPL application. Assessment of serum total cholesterol, LDL, HDL and TG at baseline, 7 weeks after start of EPL and 16 weeks after completion of EPL.

Effects on Lipoproteins

The action of EPL was reflected in an increase of HDL cholesterol and a decrease in LDL cholesterol, VLDL triglycerides as well as reduced ratio of LDL/HDL cholesterol.

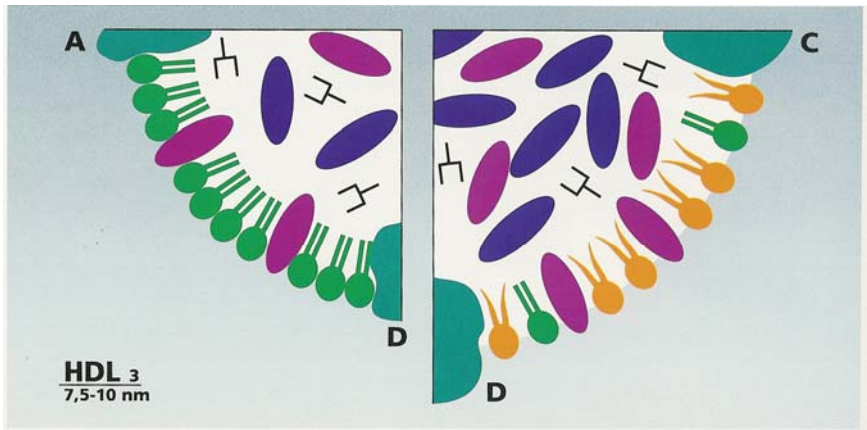


Fig. 13a: Normal surface capacity for

Fig. 13b: Increased surface capacity after EPL

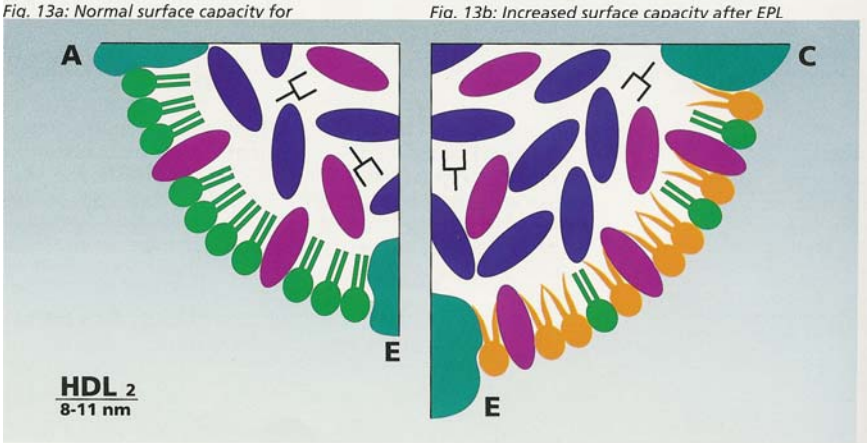


Fig. 14a: Normal cholesterol ester content

Fig. 14b: Enhanced cholesterol ester content after EPL incorporation

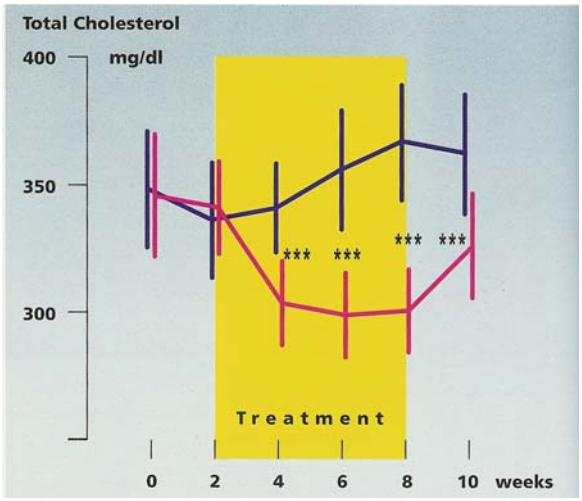
Body-own phospholipids
"Essential" phospholipids
Triglycerides (TG)
Free Cholesterol (Ch)
Cholesterol-esters (Ch-Esters)
Apolipoproteins (A, C, D, E)

Effects on serum cholesterol:

In the majority of trials an average reduction of total serum cholesterol by 12 to 19 % was observed under treatment with EPL; in some of the trial groups mean values were reduced by more than 20 % as against initial values, yet others were lowered by 7 to 10 % only.

In a documentation of 15 clinical trials with a duration of EPL treatment ranging between 1 and 12 months, total serum cholesterol was lowered by 8.8 to 28.2% (107). The level of initial values, the route of administration, EPL dosage and duration of treatment seem to be the main determinants for the slope of the reduction. Nine to 20 days of intravenous EPL treatment for instance, already caused a reduction of total serum cholesterol of approx. 13 % (91,92,95,144 and 146).

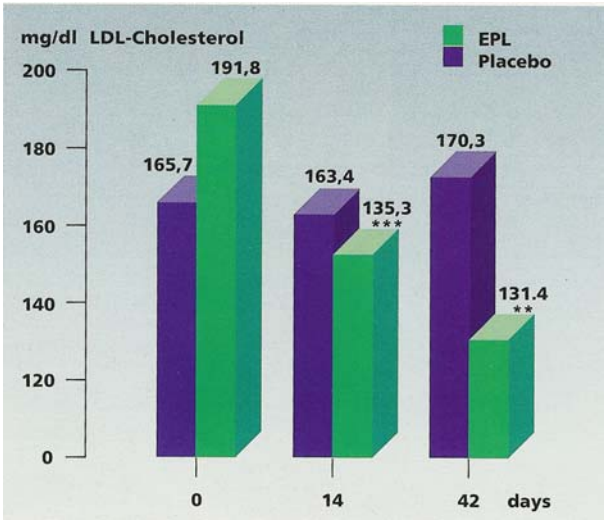
An initially simultaneous administration of EPL ampoules and capsules led to a pronounced decrease in cholesterol (82); the author had introduced treatment on a dosage scheme of 250 mg i.v. + 875 mg orally and observed a further, though markedly slower decrease in cholesterol concentration when continuing treatment on oral EPL alone (chart below).



Total cholesterol in serum during a 6-week double-blind treatment with PPC (2.7 g/day orally) and a 2-week follow-up period without medication in patients (n=10; red line) undergoing dialysis for at least 1 year in comparison with controls (n=10; blue line).

Effects on LDL cholesterol in serum:

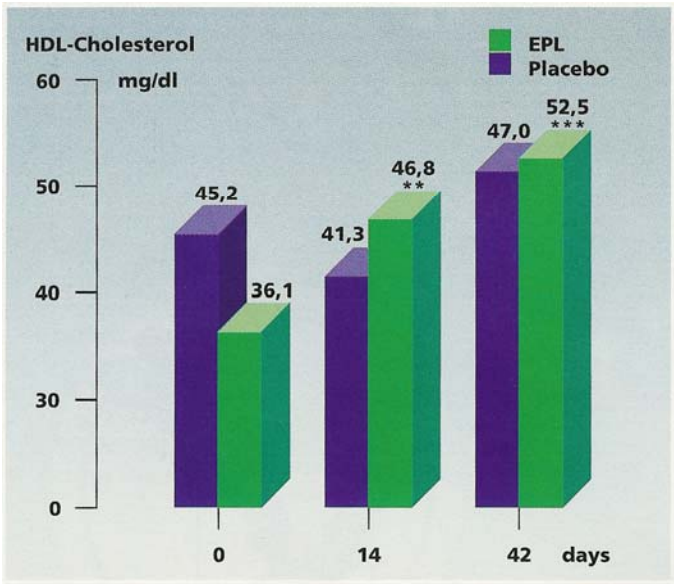
P. Dewailly et al. (100) and A.K. Horsch et al. (117) carried out double-blind trials against placebo with oral doses of 2.7 g EPL/d or of 1.8 g EPL/d resp.; already on the 14th day of treatment they registered a drop in LDL cholesterol of 12 % and 20 % respectively.
In a controlled cross-over study (83) mean reductions of 25.8 % in the initial LDL cholesterol levels were obtained within a 2-month therapy period.
After a treatment period of up to 218 days M. Murakami et al. (138) achieved average reductions of 25.5 %; P. Saba et al. (151) observed a mean reduction of pathological initial values of 27.9 % within 129 days of treatment.



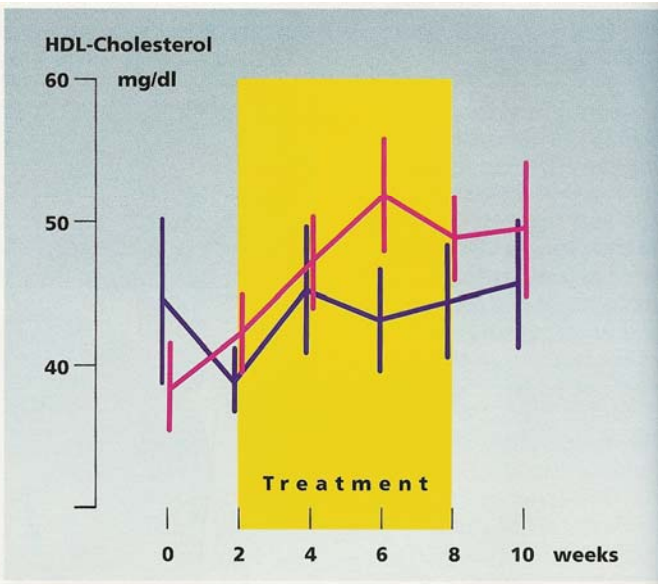
Lowering of serum LDL-cholesterol in patients (n=13) with hypercholesterolaemia type IIb and IV after a 14-day and a 42-day double-blind treatment with 1,8 g EPL/d in comparison with controls (n=15).
=2p<0.01, *=2p<0.001

Effects on HDL cholesterol in serum

- H. Iszumi observed an increase in HDL cholesterol from 13.4 – 20 % in diabetic patients with 12 months treatment with
  1.5 g EPL daily (oral).
- Other authors found an increase between 10 and 45 % with various initial values. Very low initial values were raised while high initial values were hardly influenced.



Increase of serum HDL cholesterol in patients with hypercholesterolaemia type IIb and IV after 14 and 42 day treatment with 1.8g EPL / day



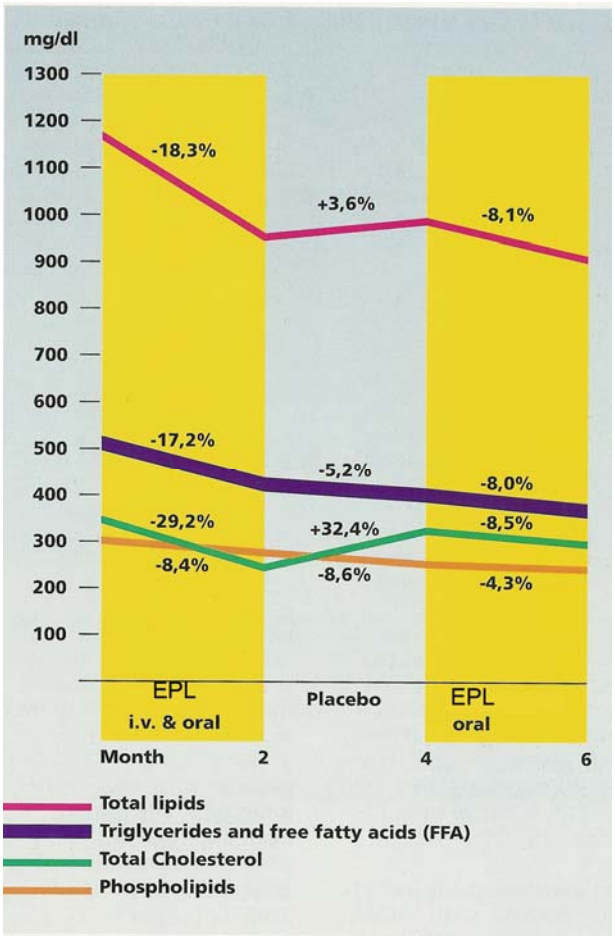
HDL cholesterol in serum during 6 weeks double blind treatment with 2.7g EPL/day and 2 week follow up without medication undergoing dialysis for at least 1 year in comparison with controls

Effects on LDL/ HDL Ratio

- An open study for 4 weeks with ivy. EPL of 0.5-1 g/d showed decrease from 4.3 to 2.8 in the LDL/HDL ratio.
- A controlled study by S. Uchida showed that the decrease is dose related: most noticeable at doses of 1.5-2.25 g/d showed a 24 % reduction.
- The rise of HDL was more pronounced in non-smokers compared to smokers.

Effects on serum triglycerides

- TG was treated with EPL in a total of 2734 patients.
- The extent of the reduction depends on the length of treatment and the inital TG level. Close to normal levels were lowered only slightly while high levels were lowered significantly. The mean values are a 25 % drop.



Percentage changes in the individual lipid fractions in the course of two-month treatment periods separated by a placebo period. (n= 17)

2. Influence on enzyme activity in serum and aorta

L-CAT

- Lecithin-acyl-transferase is synthesized in the liver. It promotes the esterification of free cholesterol in plasma so the free cholesterol on the surface of lipoproteins, erythrocyte membranes or in cells can be taken up by HDL, esterified and be eventually eliminated from plasma.
  The supply of EPL rich in unsaturated fatty acids activates LCAT activity while saturated fatty acids diminish its activity.
- A controlled study by G. Salvioli with EPL infusions for 5 days at a dose of 2 g/d in patients with liver disease found the LCAT activity increased from 31.2 to 65.5 micromole/l/h.
- Another trial involving patients with chronic liver disease showed after 2 weeks EPL treatment 1.8 g/d an incrase in LCAT activity and improved liver function.

Lipases

Lipoprotein Lipase (LPL) as well as hepatic triglyceride lipases (HTGL) lyse the TG in chylomicrons and VLDL. They thus initiate the transition of the VLDL into lipoproteins of higher density that are crucial for the uptake and transport of cholesterol.
Their enzymatic activity is governed by apoproteins and phospholipids the unsaturated fatty acid content of which is of decisive importance in this context.

- Desreumaux et al isolated lipases from healthy individuals and incubated them in vitro with substrates of different phospholipids. Activation of LPL and HTGL was highest when incubated in EPL.

- Zulic et at. treated 80 patients with hyperlipoproteinaemia for6 weeks with 1.05 g EPL/d. The activity of LPL increased 25 %. Another study with 45 patients treated with 1.8 g EPL /d for 3 weeks showed a 40 % increase in LPL activity.

EPL increases the activity of lipoprotein lipase and hepatic triglyceride lipase. Cholesterol esterification with linoleic acid is increased as well as the uptake of cholesterol esters into serum lipoproteins due to the activation of LCAT.

3. Influence on lipid peroxidation

Lipid peroxides contribute to the progression of atherogenic lesions in vascular walls.

W. Klinger reported at the Asian Pacific Association for the Study of the Liver in Djakarta in 1990; a 10-week application of 100 and 300 mg of EPL/kg b.w. to ageing rats not only resulted in a decrease in aortic lipid peroxidation products, but also in an increase in glutathione levels in the liver, plasma and aortic tissue of rats in particular. The glutathione-dependent antioxidative capacity in the aortic walls was found to increase markedly. As a whole, the values of the investigated parameters approached those of the young rats. Hence EPL produced, under the given test conditions, distinct anti oxidative effects.

A study by V.L. Kalmykova and E.B. Zakharova in patients with a.p. Showed improved resistance of erythrocyte membranes as a consequence of inhibited lipid peroxidation.

4. Influence on red blood cell fluidity and platelet aggregation

S. Yoritsune et al. (179), among others, have described a close relationship between high lipid levels in serum and an increased tendency to adhesion and aggregation of platelets. Platelet aggregates are considered to be one of the factors contributing to atheroma formation in the vascular wall.

Deposits enhance the sensitivity of the vascular wall towards substances that are released from the platelets after their aggregation and which lead to an increase in vessel wall permeability. This in turn encourages and accelerates the accumulation of further plasma constituents- such as lipids- in the injured wall.
A leading role in stimulating the proliferation and migration of smooth muscle cells from the media to the intimae is attributed to a growth factor that is synthesized and released by the platelets (platelet derived growth factor= PDGF).

Apart from a reduction of serum lipids under EPL treatment, the authors of the trials summarized below also observed a favourable effect on platelet membranes. Such investigations mostly involved patients suffering form coronary heart disease or diabetes, since the question of a possible effect on increased platelet aggregation is of particular interest in these diseases.

S.S. Belousova et al. (88) attributed the decrease in platelet aggregation observed under EPL to the shifting of cholesterol from the platelet membrane into the EPL-enriched HDL. Platelet aggregation was shown to slow down.
The optical density of the aggregates decreased. The changes did not vary during the 3-month follow-up phase after EPL treatment. Reduced platelet sensitivity towards substances provoking aggregation (e.g. collagen) became evident.

A similar phenomenon was described y O. Fakrhi et al. (106). They used the relative dispersion of light transmission fluctuations as a parameter and measured platelet aggreagation by means of an electron optical analyser.
10 days treatment with 1 g i.v. EPL/d and 30 days of daily oral administration of 1.8 g EPL clearly reduced the sensitivity of thrombocytes to ADP (also ref. to 93). This was related to an inhibitory effect on the ADP-induced rise in Ca++ in the platelets. Moreover, the authors observed an inhibition of PAF-induced platelet aggregation both in vitro and in vivo.
A.S. Blagosklonov et al. confirmed an improved passage of red blood cells through micro filters and the normalisation of RBC aggregation in their patient group. Parallel to haemabsorption their patients had received i.v. injections of 500 mg of EPL and after that had taken 1.8 g of EPL/d for 3 months.

Summary

Essential phospholipids given orally concurrent with and in-between Plaquex infusions benefit the overall treatment results by reducing LDL, increasing HDL, reducing triglycerides, reducing lipid peroxidation, improving red blood cell fluidity and reducing platelet aggregation.

July 2012

* These statements have not been evaluated by the FDA