1st GLOBAL LIVER HEALTH FORUM

Essential phospholipids. Mechanism of action in liver disease explained

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Flash for webinar (~20 mins)

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Phospholipids in the liver

The liver is responsible for around 500 bodily functions, including digestion, nutrient storage, protein synthesis, detoxification and metabolism.[1] Liver cells (hepatocytes) have membranes comprising primarily of a bilayer of phospholipids (PL), which influence their fluidity, integrity, and function.[2] In particular, phosphatidylcholine (PPC) is the most abundant form of PL in the cell membranes of hepatocytes.[2,3]

Essential phospholipids (EPL)

EPL supplements are indicated for liver diseases of various origins. They contain PPC derived from highly purified soybean extract. The main active ingredient is 1,2-dilinoleoylphosphatidylcholine (DLPC), which differentiates EPL from phospholipids derived from the diet.[3] "Essential" in EPL refers to essential fatty acids comprising the acyl moieties of the polyunsaturated phospholipids.[3]

Of five commercially available EPL preparations, Essentiale® Forte® has been found by comparative analysis to have the highest phosphatidylcholine (PtdCho) levels (61.9 mol%) and lowest phosphatidylethanolamine (PtdEtn) levels (4.9 mol%). It might therefore be considered that Essentiale® Forte® is the most beneficial of the available hepatoprotective NAFLD treatments.[4]

Essentiale® Forte: Mechanism of Action

EPL increase hepatocyte membrane fluidity and counter the effects of increased cellular cholesterol in liver disease by modifing membrane lipid composition in a way that protects against the development of insulin resistance,[5–7] and demonstrate an anticholestatic effect.[8,9] They also exert detoxification effects including inhibition of lipid peroxidation,[10,11] reduce liver steatosis, fibrosis and cirrhosis,[12–15] and stimulate liver regeneration.[16–18]

Study of the effects of PPC on the biochemical processes in hepatocytes suggests that EPL have multiple modes of action in liver diseases. Upregulation of beta-oxidation of fatty acids,[19] and contribution to the formation of very low-density lipoproteins (VLDL)[20] aids elimination of lipids from the hepatocyte.[19,21] Inhibition of triglyceride synthesis proteins helps reduce the quantity of lipids in liver cells.[22]

EPL: essential phospholipids; **NAFLD:** non-alcoholic fatty liver disease; **NASH:** non-alcoholic steatohepatitis; **HCC:** hepatocellular carcinoma; **ALD:** alcoholic liver disease; **CHC:** chronic hepatitis; **HRQoL:** health related quality of life.

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EPL have multiple modes of action in liver diseases	
Restore cell membrane structure	Stimulate liver regeneration
Increase cell membrane fluidity	Correct or inhibit fibrogenic processes
Enhance membrane-associated metabolic functions	Influence apoptosis
Reduce or normalise peroxidative reactions	Stabilise bile composition
Decrease cytolysis	Modulate lipid metabolism
Improve excretory, detoxifying/clearing, and synthesizing capacity of the liver	Diminish or abolish fatty infiltration and hepatocyte necrosis
Improve immune properties	Decrease experimental hepatocarcinogenesis

Clinical Efficacy of EPL

Evidence from clinical studies has demonstrated the efficacy of EPL in the management of NAFLD/NASH with or without T2DM. They have been shown to improve liver structure by decreasing the progression of fatty infiltration of the liver and slowing down hepatic fibrogenesis and steatosis,[3,13] reduce liver size and improve liver function through a reduction in transaminase levels,[23] reduce triglycerides and cholesterol levels,[24] and improve clinical status.[23]

Essentiale® Forte® has displayed statistically significantly greater benefit, variously relative to placebo, inosine+vitamin C, vitamin E, or vitamin therapy, with respect to the following endpoints: ALT, AST, response rate, histology, ultra-sonography, and reported symptoms.[25–29]

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References

1. Franciscus A. An overview of the liver. HCSP. Version 1. April 2015.
2. Hussein JS. Cell membrane fatty acids and health. International Journal of Pharmacy and Pharmaceutical Sciences. 2013;5:38–46.
3. Gundermann KJ, *et al.* Activity of essential phospholipids (EPL) from soybean in liver diseases. Pharmacol Rep. 2011;63:643-659.
4. Lüchtenborg C, *et al.* Lipid Profiles of Five Essential Phospholipid Preparations for the Treatment of Nonalcoholic Fatty Liver Disease: A Comparative Study. Lipids. 2020;55(3):271–8.
5. Perona JS. Membrane lipid alterations in the metabolic syndrome and the role of dietary oils. Biochimica et Biophysica Acta. 2017;1859:1690–703.
6. Dargel R, *et al.* Microsomal phospholipid pattern and liver ultrastructure of aging rats following treatment with essential phospholipids. Gastroenterol J. 1991;51:73–7.
7. Zierenberg O, *et al.* Effect of polyenephosphatidylcholine on cholesterol uptake by human high density lipoprotein. Atherosclerosis. 1981;39:527–42.
8. Lamireau T, *et al.* Dietary lecithin protects against cholestatic liver disease in cholic acid-fed Abcb4- deficient mice. Pediatr Res. 2007,61(2):185–90.
9. Golochevskaia VS, *et al.* Essential phospholipids in combined therapy of chronic circulatory insufficiency. Klin Med (Mosk). 1997;75(5):30–3.
10. Martelli A, *et al.* Protective effect of phophatidylcholine on hepatic lipid peroxidation in rats. Med Sci Res. 1989;17:995–6.
11. Klinger W, *et al.* Z Gastroenterol. 1991;29(Suppl 2):14–17.
12. Qinglan J, *et al.* Gene expressions in adipose tissue of NAFLD rats intervened on with polyene phosphatidylcholine. J Med Research. 2008;37.
13. Lee HS, *et al.* Beneficial effects of phosphatidylcholine on high-fat diet-induced obesity, hyperlipidemia and fatty liver in mice.Life Sci. 2014;118:7–14.
14. Lieber CS, *et al.* Phosphatidylcholine protects against fibrosis and cirrhosis in the baboon. Gastroenterology. 1994;106:152–9.
15. Aleynik SI, *et al.* Polyenylphosphatidylcholine prevents carbon tetrachloride-induced lipid peroxidation while it attenuates liver fibrosis. J Hepatol. 1997;27:554–61.
16. Holeček M, *et al.* Effect of polyunsaturated phosphatidylcholine on liver regeneration onset after hepatectomy in the rat. Arzneimittelforschung. 1992;42:337–9.
17. Kropáčová K & Misúrová E. The influence of essential phospholipids (ESSENTIALE) on liver regeneration in gamma irradiated rats. Physiol Res. 1995;44:241–7.
18. Kožurková M, *et al.* The effect of essentiale on histones and nucleic acids in liver and blood-forming tissues of rats irradiated with gamma-rays. Radiats Biol Radioecol. 1999;39:388–93.
19. Tzeng J, *et al.* An Ideal PPAR Response Element Bound to and Activated by PPARα. PLoS ONE. 2015;10:e0134996.
20. Choi SH & Ginsberg HN. Increased very low density lipoprotein (VLDL) secretion, hepatic steatosis, and insulin resistance. Trends Endocrinol Metab. 2011;22:353–63.
21. Mehedint MG & Zeisel SH. Choline's role in maintaining liver function: new evidence for epigenetic mechanisms. Curr Opin Clin Nutr Metab Care. 2013;16:339–45.
22. Matías Caviglia J, *et al.* Phosphatidylcholine deficiency upregulates enzymes of triacylglycerol metabolism in CHO cells. J Lipid Res. 2004;45:1500–9.
23. Gundermann KJ, *et al.* Essential phospholipids in fatty liver: a scientific update. Clin Exp Gastroenterol 2016;9:105–117.
24. Holecek M, *et al.* Effect of polyunsaturated phosphatidylcholine on liver regeneration onset after hepatectomy in the rat. Arzneimittelforschung. 1992;42:337–9.
25. Knüchel F. Double-blind study in patients with alcoholic toxic fatty liver. Effect of essential phospholipids on enzyme behavior and lipid composition of the serum. Med Welt. 1979;30:411.
26. Xu B, *et al.* Clinical Observation of 24 Cases of Essentiale Treating Alcoholic Fatty Liver. Sichuan Medical Journal. 2007;28:10.
27. Sas E, *et al.* Polyunsaturated phosphatidylcholine reduces insulin resistance and hepatic fibrosis in patients with alcoholic liver disease. Results of randomized blinded prospective clinical study. J Hepatol 2013;58(Suppl 1):S549.
28. Schüller-Pérez A & González-San Martín F. Controlled study with polyunsaturated phosphatidylcholine versus placebo in alcoholic fatty steatosis. Med Welt 1985;36:517.
29. Hazuka V & Roubal R. Polyunsaturated phosphatidylcholine (EPL) + vitamin B complex in the treatment of alcoholic liver disease. Clin Ter. 1987;123:369–75.

What does a NAFLD patient journey look like? Importance of HR-QoL

Learning objectives:

Understand the roles of phospholipids in hepatocytes and the key characteristics and composition of EPL.

Review the pre-clinical evidence for EPL in liver disease and understand their pleiotropic mechanisms of action.

Describe clinical evidence that supports the use of EPL in the management of patients with fatty liver disease with and without type 2 diabetes.

Main take aways:

Essential phospholipids display a favorable safety profile, with low risks of adverse events and drug interactions.

Essential phospholipids have demonstrated efficacy in NAFLD/ NASH in clinical studies.

Essential phospholipids are a valuable adjuvant therapy in fatty liver disease (ALD, NAFLD).

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