2nd GLOBAL LIVER HEALTH FORUM

# ESSENTIAL PHOSPHOLIPIDS – PERSPECTIVES ON THE MOA


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# ESSENTIAL PHOSPHOLIPIDS – PERSPECTIVES ON THE MOA

## Introduction to NAFLD/MAFLD and current management strategies

The liver is responsible for approximately 500 functions carried out by hepatocytes, including digestion, storage, protein synthesis, detoxification, and metabolism.[1] Globally, an estimated 844 million people have chronic liver disease.[2] NAFLD/MAFLD is one of the most common chronic liver diseases worldwide,[3] however, there are currently no FDA-approved drugs for treating NAFLD/MAFLD and its management consists of treating the liver disease as well as the associated metabolic comorbidities such as obesity, hyperlipidemia, insulin resistance and T2DM.[4]

## The importance of phospholipids (PL) in cell membranes and the potential role of EPL in treating NAFLD/MAFLD

PL are key components of cellular and sub-cellular membranes. The most abundant PL in mammalian tissues are phosphatidylcholine (PC) and phosphatidylethanolamine (PE).[5] Changes in the hepatic PC/PE molar ratio have been linked to the development of NAFLD/MAFLD in humans.[5] PL provide cell integrity and support membrane fluidity and permeability,[6] and the PC/PE ratio is a key regulator of membrane integrity.[6] Damage to liver cell membranes and the organelles originate from reduced PL levels or altered PL composition, and lead to decreased membrane fluidity.[6]

EPL is a highly purified extract of PPC molecules from soybeans. 1,2-di-linoleoyl phosphatidylcholine (DLPC) is the lead compound in the active ingredient, whose phosphatidylcholine molecules have specified amounts of 72–96% of PL in EPL.[6] EPL have been shown to exert membrane-stabilizing, membrane-repairing and antioxidant actions that can be used to treat NAFLD/MAFLD.[7] In a comparative study of five EPL preparations for the treatment of NAFLD, Essentiale Forte had a significantly higher PC:PE (12.9 ± 2.2) ratio compared with each of the other generic PPCs investigated. The higher PC:PE ratio observed in Essentiale Forte suggests that it may have a substantial clinical benefit in the early treatment of hepatic disorders.[8]

## Preclinical evidence for the MoA of EPL – the effect on membrane fluidity

Pre-clinical trials have provided insights into multiple MoAs of EPL that are potentially involved in their hepatoprotective effects.

The impact of EPL, PPC and PI on hepatocyte function has been investigated *in vitro*.[9] The effects of EPL (0.1 and 0.25 mg/mL), and its constituents, PPC and phosphatidylinositol (PI) (both at 0.1 and 1 mg/mL), in human hepatocyte cell lines (HepG2, HepaRG, steatotic HepaRG) versus untreated cells were assessed in terms of membrane fluidity, cell apoptosis, and hepatocyte transport function.[9]



The addition of EPL (0.1 and 0.25 mg/mL) resulted in a significant increase in membrane fluidity of HepG2 cells compared with untreated cells. PPC and PI (0.1 and 1 mg/mL) significantly increased membrane fluidity of HepG2 cells compared with untreated cells.[9]

In HepaRG cells, only the addition of PI 1 mg/mL conferred a significant increase in membrane fluidity compared with untreated cells. In steatotic HepaRG cells, PI 1 mg/mL significantly increased membrane fluidity compared with untreated cells. EPL and PPC did not have a significant impact on the membrane fluidity of HepaRG and steatotic HepaRG cells at the concentrations tested.[9]

## Preclinical evidence for the MoA of EPL – the effect on apoptosis and hepatocellular transport

In HepG2 cells, EPL (0.1 and 0.25 mg/mL), PPC 1 mg/mL, and PI (0.1 and 1 mg/mL) all significantly reduced tamoxifen-induced apoptosis. Intamoxifen-treated HepaRG cells, addition of EPL, PPC or PI did not impact apoptosis, although a trend for reduced rates of apoptosis was observed. Similarly, a trend for reduced rates of tamoxifen-induced apoptosis was observed following the addition of EPL, PPC or PI to steatotic HepaRG cells, although this was not significant.[9]

In HepG2 cells, EPL (0.1 and 0.25 mg/mL) and PI (0.1 and 1 mg/mL) significantly increased BCRP activity. However, EPL, PPC and PI had no significant effect on the BRCP activity *in vitro* in either HepaRG or steatotic HepaRG cells. MRP-2 activity was not affected by any PL in HepG2 cells, but MRP-2 activity was significantly increased by EPL, PI (1 mg/mL) and PPC 1 mg/mL in HepaRG cells and by PI (1 mg/mL) in steatotic HepaRG cells. P-GP activity was significantly increased by all compounds in HepG2 cells; PI 1 mg/mL significantly increased P-GP activity in HepaRG and steatotic HepaRG cells.[9]

## References


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BCRP, breast cancer resistance protein; EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic-associated fatty liver disease; MoA, mechanisms of action; MRP2, multidrug resistance-associated protein 2; PC, phosphatidylcholine; P-GP, permeability glycoprotein; PE, Phosphatidylethanolamine; PL, phospholipids; PPC, polyenylphosphatidylcholine; T2DM, type 2 diabetes mellitus.

## Learning objectives:

- Gain awareness of the burden of NAFLD/MAFLD and the need for new treatments
- Understand the importance of PL in cell membranes and the potential role of EPL in treating NAFLD/MAFLD
- Become familiar with the preclinical evidence for the MoA of EPL with respect to the effect on membrane fluidity, cell apoptosis, and hepatocellular transport

## Main takeaways:

- EPL are used to treat liver diseases, including NAFLD/MAFLD, because of their hepatoprotective properties
- Several potential MoA of EPL have been elucidated from pre-clinical studies
- EPL, PPC, and PI have been shown to increase hepatocyte membrane fluidity, decrease apoptosis and increase hepatocellular transport *in vitro*
- As a result of these MoA, EPL may improve liver function and confer hepatoprotective effects

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic-associated fatty liver disease; MoA, mechanisms of action; PI, phosphatidylinositol; PPC, polyenylphosphatidylcholine;

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