Cell membranes and essential phospholipids

Phospholipids are crucial components of the protective lipid bilayers of all cellular and sub-cellular membranes. Forty per cent of these selectively permeable membranes consist of the phospholipid phosphatidylcholine (PC), which is essential for cellular differentiation, proliferation and regeneration. PCs control membrane-dependent metabolic processes, including those of membrane-bound proteins (e.g. the enzymes Na⁺-K⁺-ATPase, lipoprotein lipase, lecithincholesterol acyltransferase and cytochrome oxidase) and receptors (e.g. of insulin), and release their bound polyunsaturated fatty acids when needed as precursors of cytoprotective eicosanoids (for review, see Gundermann, 2011). The integrity and composition of the phospholipid structure has a vital role in the membranes’ fluidity and functionality. Any damage to the thin and delicate membranes can cause cells to die. Supplementation with PC is essential to replenish cell membranes. Essential phospholipids (EPLs) contain a highly purified extract of polyenylphosphatidylcholine (PPC) molecules from soybean, with standardised contents of 73–79% to 92–96% (3-sn-phosphatidyl)choline, whose main active ingredient is 1,2-dilinoleoylphosphatidylcholine (DLPC). This is not produced in the body and provides the best clinical benefits differentiating it from other phospholipids, lecithins, or other dietary or sourced extracts which contain as little as 20% PC. Administration of EPLs directly improves the amount of DLPC in tissue membranes, increasing membrane fluidity and stability and enhancing membrane-dependent functions. The latter include regulating the activity of membrane-bound enzyme systems, inhibiting cytochrome P4502E1 (CYP2E1) involved in the oxidation of ethanol, and reducing free radicals and enzymes involved in oxidative stress. EPLs can protect cells by effectively blocking cell degeneration and inflammatory fibrosis. PC is well-tolerated and non-toxic and is generally regarded as safe (GRAS) by the FDA, the highest level of safety.

The role of EPLs in liver disease

The primary site of DLPC incorporation from EPLs is in the liver, which has an especially quick turnover of cells, incorporating over 300,000 square feet of membranes. Indeed, EPLs have been used for more than three decades with more pharmacological and clinical studies undertaken with this supplement than probably any other alternative or complementary medicine. There is evidence of direct protective and regenerative effects of EPLs on the biomembranes of hepatocytes and sinus endothelia following damage to the cell membrane through toxic, inflammatory, allergic, metabolic or immunological reactions. The liver, being the first organ to receive substances from the gut, is the most vulnerable to drug-induced injury (e.g. immunosuppressants, cholesterol lowering drugs); the negative effects of poor lifestyle habits (e.g. fatty diet, excessive alcohol consumption); and infections, in particular, viral and bacterial hepatitis. Regardless of the origin, liver diseases result from phospholipid damage to cell membranes linked to depleted phospholipid levels, altered phospholipid composition and/or reduced membrane fluidity. Once the hepatocyte structural damage exceeds the liver’s
powerful ability to regenerate and exhausts all the reserved protective anti-oxidants and PCs, membrane fluidity is lost, and excess collagen accumulates, promoting fibrosis (scarring) and eventually cirrhosis. Although EPLs do not single-handedly cure chronic liver disease, the membrane-regulating effects slow disease progression, frequently normalising the well-being of patients.

Liver disease in South Africa

Mortality from liver disease in South Africa has been estimated at 11.27 deaths per 100 000 standardised for age. Infectious liver disease is likely very widespread due to the high profile HIV epidemic (6.3 million people in 2013 alone with 330 000 new infections), and the associated high prevalence of hepatitis B (5–20% of the population) and tuberculosis (TB). Furthermore, non-infectious non-alcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease worldwide, is on the rise due to the prolonged use of antiretroviral drugs for HIV, and corticosteroids or other immunosuppressive drugs, as well as due to lifestyle diseases such as obesity and diabetes, which will be discussed further below.

The urgency of containing the HIV and TB epidemics has overshadowed awareness until recently of the increasing poor lifestyle habits of South Africans. At least a quarter of the population (5–20% of the population) and tuberculosis (TB). Furthermore, non-infectious non-alcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease worldwide, is on the rise due to the prolonged use of antiretroviral drugs for HIV, and corticosteroids or other immunosuppressive drugs, as well as due to lifestyle diseases such as obesity and diabetes, which will be discussed further below.

The benefits of EPL in liver disease

Non-alcoholic fatty liver disease

NAFLD is thought to be a hepatic expression of metabolic disorders (such as hypertension, hyperlipidaemia, obesity, glucose intolerance), which likely contribute to its rapidly escalating prevalence.

Growing evidence suggests that NAFLD is an independent risk factor for cardiovascular disease, chronic kidney disease and type 2 diabetes. Insulin resistance causes accumulation of fatty acids in the liver, which in the presence of oxidative stress, ATP depletion and mitochondrial dysfunction, is a leading cause of hepatocellular injury. Nearly 70-80% of diabetics have NAFLD, which leads to non-alcoholic steatohepatitis (NASH), a progressive fibrotic disease which can result in cirrhosis, hepatocellular carcinoma and death.

A recent plethora of randomised controlled blinded studies on patients with NAFLD alone or with diabetes type 2 or mixed hyperlipidaemia have been carried out using EPL (Essentielle®) treatment versus standard diet and exercise and/or diaminonitroguanidine (a traditional Chinese medicine with liver protective properties). Across the board, all studies (ranging in size from 74 to 220 subjects; in dosage 465 to 1 800 mg/day of EPL; in duration of 4 to 72 weeks) have reported significant improvements in clinical parameters. These included improved clinical symptoms (e.g. ~80% of patients showed a satisfactory clinical response after 72 weeks); reduced serum transaminases, triglycerides and cholesterol levels; normalised abdominal ultrasonography; and improved liver stiffness and size. Reducing the dose may result in temporary short relapses before serum transaminase levels return to normal, while significant reductions in serum cholesterol and triglyceride levels were reported only after 90 days in one study. Thus, although clear clinical benefits have been seen after just four weeks, long-term treatment is needed in preventing NAFLD, especially since there is no curative agent. Indeed, liver biopsy results of NAFLD patients treated with 1 368 mg of daily PPL in a long-term prospective study over seven years showed that the progress of hepatic fibrosis was significantly slower than in a control group on a dietary and physical regimen and 1 000 mg/day metformin. Furthermore, there was a significant increase in steatosis in this control group over the long term, while there was a reduction in the EPL-treated group.

NAFLD due to anti-tuberculosis treatment

EPLs have been shown to be effective in normalising serum ALT and AST levels in those taking anti-TB drugs. The results of a study conducted in 240 patients with pulmonary tuberculosis treated with EPL 900 mg/day in conjunction with a standard anti-TB regimen of isoniazid, streptomycin and rifampicin showed a 50% reduction in the incidence of elevated transaminase values compared to a control group taking the hepatotoxic tuberculostatics without EPL (incidence of 11.7 and 20.7%, respectively). Furthermore, patients taking EPL reported only mild digestive disturbances, whereas some control patients presented with pronounced jaundice and elevated bilirubin, alkaline phosphatase, and serum transaminase (> 50 U/l) levels. Thus, this study and others show a prophylactic efficacy of EPLs in the presence of hepatotoxic tuberculostatics; early complications are prevented and liver disorders are delayed, resulting in fewer withdrawals from anti-TB treatment.

Infectious liver disease due to hepatitis B

In sub-Saharan Africa, 44% of cirrhotic liver disease and 47% of hepatocellular carcinoma cases are attributed to hepatitis B. In TB patients who have concomitant hepatitis B, the hepatic damage caused by anti-TB treatment increases by 50% in those with positive hepatitis B antigen markers and by 95% in those with hepatitis B DNA. Treating these patients with EPL significantly reduces the hepatic damage and shortens its duration, allowing...
the chemotherapy to continue for the full course and increasing the likelihood of effectively treating the TB.\textsuperscript{35}

EPLs also show significant effectiveness in chronic hepatitis B patients with no co-morbidities. Specifically, improvement is seen in serum markers of liver fibrosis, indicating a reversal of fibrosis before progression to cirrhosis. EPLs are also effective in acute viral hepatitis at reducing serum aminotransferases and speeding up bilirubin metabolism to aid recovery from jaundice.\textsuperscript{36}

**Alcoholic fatty liver disease (AFLD)**

Excessive alcohol consumption, resulting in AFLD, is a leading cause of disability and death worldwide,\textsuperscript{6,37} and cannot be ignored. The liver is the site of 80% of alcohol metabolism\textsuperscript{6} and chronic alcohol consumption results in various biochemical alterations with major metabolic consequences on the liver.\textsuperscript{6} Alcohol is very calorific and replaces fatty acids as the normal substrate of mitochondria, resulting in a reduction in lipid oxidation. The oxidation of ethanol increases alcohol dehydrogenase activity and the hepatic synthesis of fatty acids and triglycerides (causing steatosis); increases the toxic mediator, acetaldehyde; and reduces lipoprotein synthesis.\textsuperscript{6,37} EPLs reduce oxidative stress and stabilise these metabolic processes, thus restoring liver membrane structure and function.\textsuperscript{38} The highly unsaturated fatty acid side-chains in EPLs protect cells by helping to emulsify fats in food and stimulating the sensitivity of fat to lipase, accelerating steatolysis and reducing fat accumulation in the body.\textsuperscript{39}

Several recent randomised, blinded, controlled, clinical trials from China (N=52–72) have shown significant positive effects of EPLs in AFLD patients with cirrhosis.\textsuperscript{20,39,40} In all of these studies, taking intravenous glucose infusions with EPL (Essentiale®) four times a day for four to five weeks significantly improved clinical and laboratory parameters irrespective of the cause of the fatty liver disease (AFLD or NAFLD).\textsuperscript{38}

**Conclusion**

The epidemic map of South Africa highlights the rising need to treat and prevent liver damage secondary to metabolic syndrome and infectious diseases. The evidence reviewed here strongly indicates that EPLs, which have a high percentage of purified DLPC, are a highly effective and tolerable option to protect and stimulate regeneration of liver cells.

**Conflict of interest**

Dr Mothilal is the Medical Director and Dr Lai is the Medical Advisor of Sanofi-Aventis South Africa (Pty) Ltd, a member of the SANOFI Group.

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