Essential phospholipids – the latest evidence reviewed

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Disclosures

- Consultant to many pharmaceutical companies: Abbott, Novo Nordisk, Lunatus, Merck Sharp & Dohme, Julphar, Sanofi, Takeda, Janssen, Bristol Myers Squibb, AstraZeneca, Sandoz, Tabuk, Hikma, Holistol and Synergy
- Member of several advisory boards
- Lecturer for many pharmaceutical companies locally, regionally and internationally
Learning objectives

1. Understand the importance of treating non-alcoholic fatty liver disease (NAFLD) early and the need for more effective therapies with a consistent clinical evidence base.

2. Explore the potential of EPL as an adjunctive therapy to improve clinical outcomes for patients with NAFLD.

3. Review the current clinical evidence supporting the use of essential phospholipid (EPL) in the supportive treatment of liver diseases.
Why treat patients with NAFLD?

**Long-term outcomes for patients with NAFLD and non-alcoholic steatohepatitis (NASH):**

- Increased overall mortality vs people without NAFLD\(^1,2\)
- May pose a risk of cardiovascular disease above and beyond traditional cardiovascular disease risk factors\(^2-4\)
- Together with type 2 diabetes mellitus (T2DM) pose a greater risk of hypertension\(^5\)
- May be a risk factor for chronic kidney disease, colorectal cancer, endocrinopathies (including thyroid dysfunction, and osteoporosis\(^6,7\))
- Have an increased rate of liver-related mortality\(^1,2\)
- When advanced fibrosis and cirrhosis occur, patients are at increased risk for hepatocellular carcinoma\(^2,8\)

NAFLD, non-alcoholic fatty liver disease
Current medical treatments are experimental

The facts

- There is an **inconsistent evidence base** for the effect of medications used for the treatment of comorbid conditions associated with NAFLD
  - Traditional standard of care (SOC) agents lack supportive research
- **Hepatoprotective agents** remain an important, reliable part of the treatment of NAFLD as adjunctive therapies

The tools

- **Traditional**
  - N-acetyl cysteine
  - R-alpha lipoeic acid (ALA)
  - Choline bitartrate
  - Artichoke extract
  - Dandelion root: taraxacin and inulin
  - Turmeric: curcumin
  - Liv. S2 (Hemalaya plants)
  - Gansu (Ganoderma)

- **Hepatoprotectives**
  - Milk thistle extract (Silymarin)
  - EPL (Essentiale® Forte)
  - Ursodeoxycholic acid
  - Vitamin E (anti-oxidant)
  - Glutathione
  - SAMe

- **Medicines under production**
  - Milk thistle extract (Silymarin)
  - EPL (Essentiale® Forte)
  - Ursodeoxycholic acid
  - Vitamin E (anti-oxidant)
  - Glutathione
  - SAMe

- **Investigational treatment**
  - Obeticholic acid
  - Elafibrinor
  - Selonsertib
  - Emricasan
  - Cenicriviroc
  - Aramcol

- **Lifestyle**

DPP-4, dipeptidyl peptidase-4; EPL, essential phospholipids; GLP-1, glucagon-like peptide-1; NAFLD, non-alcoholic fatty liver disease; PPAR, peroxisome proliferatory-activated receptor; SAMe, S-adenosylmethionine

Figure adapted from Dajani A, AbuHammour A. Saudi J Gastroenterol 2016;22:91–105
Role of phospholipids in mammalian cells: recovery and maintenance

• Activation of phospholipid-dependent enzymes
• Metabolic effects:
  – Accelerate synthesis of lipoproteins and convert neutral fats and cholesterol into easily metabolized forms
  – Activate synthesis of RNA and normalize protein metabolism
  – Increase synthesis of glycogen in the liver
• Improve detoxification function of the liver
• Decrease fatty infiltration of hepatocytes
• Inhibit or correct fibrogenic processes
• Influence apoptosis
• Anti-inflammatory and anti-oxidant properties

*Phospholipids are indicated as adjunctive treatment only. ASH, alcoholic steatohepatitis; EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease
How familiar are you with the clinical evidence supporting the use of EPL in patients with NAFLD?

1. I am fully up to date with the latest data on EPL
2. I am aware of some data on the use of EPL
3. I am aware of data for other hepatoprotective agents, but not for EPL
4. I am not aware of data supporting the use of pharmacotherapies in patients with NAFLD

EPL, essential phospholipid; NAFLD, non-alcoholic fatty liver disease.
Previous literature reviews of EPLs

Key findings:

1. EPLs accelerate the improvement of NAFLD symptoms, supported by imaging procedures such as ultrasonography support.

2. EPL supplementation is associated with numerous health benefits, including preventing lipid accumulation in the liver; however, it was highlighted that more research was needed.

3. EPLs accelerate the improvement of NAFLD, with no clinically relevant side effects reported. Additional RCTs should be conducted to understand synergistic effects of EPLs with other drugs.

4. EPL treatment in combination with anti-diabetic therapy or interventions for obesity was associated with significantly greater reductions in ALT, TG and total cholesterol.

ALT, alanine aminotransferase; EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; RCT, randomized controlled trials; TG, triglycerides

Narrative literature review of EPLs

Rationale

Treatment guidelines from China and Latvia suggest the possibility of using hepatoprotective agents in patients with NAFLD, such as the highly purified extract of phosphatidylcholines from soybeans: EPLs.1–4

EPLs are recommended for use in patients with NAFLD in China, Latvia, Russia and Poland.1,3,5,6 In 2017, EPLs accounted for >45% of all hepatoprotective agents sold in Russia.2

The aim of this review was to discuss the use of hepatoprotective agents as supportive treatment in patients with NAFLD or NASH, with specific focus on data regarding EPL use.

EPL, essential phospholipid; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis


Narrative literature review of EPLs

Search methodology

- **Databases**: PubMed and Embase
- **Timeframe**: From inception to August 2018 and updated in December 2020
- **Studies included**: Where EPLs were used to treat patients with NAFLD, NASH or non-specified fatty liver disease
- **Search terms**: Relevant MeSH terms for disease names and EPL, and possible brand names and generic Seanames for EPL
- **Grey search**: Clinical databases from China and Russia, where EPL is widely used

Search results were manually reviewed to identify suitable studies for inclusion.

An additional search of PubMed was conducted to identify research relevant to other hepatoprotective agents.

EPL, essential phospholipid; MeSH, medical subject headings; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Narrative literature review of EPLs

49 studies investigating oral EPL in patients with NAFLD, NASH or non-specified fatty liver disease with no other liver pathologies were identified.

29 studies were excluded due to the use of non-standard hepatoprotective agents (e.g. Chinese herbal products) or insufficient focus on NAFLD.

20 studies were included in this review.

Search results:

- Of the 20 studies included:
  - 12 were conducted in China
  - Four were conducted in Russia
  - One was conducted in UAE, India, Poland and Italy
  - 16 were randomised (two were double-blind one was single-blind)
  - Four were open label
  - Trial durations ranged from 2 weeks to 24 months
  - EPL doses were most commonly 456 mg t.i.d, 1800 mg/day or 1800 mg t.i.d

EPL, essential phospholipid; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; t.i.d, three times a day.
In one study, EPL treatment over 6 months resulted in **transaminase reductions in 80%** of patients with NAFLD alone (mean reduction, ALT=54.6 IU, AST=48.7 IU)¹

After 6 months of EPL treatment, **liver ultrasonography** results showed an improvement from baseline in **29.2%** of patients with NAFLD alone¹

**Elastography** results also showed an improvement from baseline in **14.2%** of patients with NAFLD alone after 6 months of EPL treatment (mean reduction, 3.1 K pascal)¹

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EPL, essential phospholipid; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; t.i.d, three times a day


Narrative literature review of EPLs

Results: Efficacy of EPL in patients with NAFLD and comorbidities

<table>
<thead>
<tr>
<th>NAFLD and T2DM</th>
<th>NAFLD and hyperlipidaemia or obesity</th>
</tr>
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<tbody>
<tr>
<td><strong>Six studies included patients with NAFLD and T2DM</strong></td>
<td><strong>Four studies included patients with NAFLD and hyperlipidaemia or obesity</strong></td>
</tr>
<tr>
<td>EPLs given as <strong>adjunctive therapy</strong> to metformin or SOC in patients with NAFLD and T2DM are associated with <strong>improved clinical outcomes</strong> compared with T2DM-specific treatment alone†-3</td>
<td>EPL therapy resulted in <strong>improvements in clinical outcomes</strong> for patients with NAFLD and hyperlipidaemia or obesity4-6</td>
</tr>
<tr>
<td>**In one study of patients with NAFLD and T2DM:**2</td>
<td>**In one study of patients with NAFLD and obesity:**7</td>
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<tr>
<td></td>
<td><strong>PPC + sibutramine</strong></td>
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<tr>
<td></td>
<td><strong>Sibutramine</strong></td>
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<tr>
<td></td>
<td><strong>PPC + sibutramine resulted in slower fibrosis progression than sibutramine alone, p&lt;0.05</strong></td>
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<tr>
<td></td>
<td><strong>Significant reduction in steatosis from baseline†</strong></td>
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<td></td>
<td><strong>Significant improvement in ultrasound results in 92.0% of patients from baseline†</strong></td>
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<tr>
<td></td>
<td><strong>Significant increase in steatosis from baseline†</strong></td>
</tr>
<tr>
<td></td>
<td><strong>No change in ultrasound results in 23.3% of patients from baseline</strong></td>
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<tr>
<td></td>
<td><strong>P&lt;0.05</strong></td>
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Overall response rate* (%)

<table>
<thead>
<tr>
<th>EPL + metformin</th>
<th>Metformin</th>
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<tbody>
<tr>
<td>78.4</td>
<td>54.1</td>
</tr>
</tbody>
</table>

*Overall response rate was defined as symptoms and physical signs show improvement; liver ultrasonic appearance shows that fatty liver improves or decreases, p<0.05

EPL, essential phospholipid; NAFLD, non-alcoholic fatty liver disease; SOC, standard of care; T2DM, type 2 diabetes mellitus


Narrative literature review of EPLs

Results: Efficacy of EPL in patients with NASH

Three studies reported on EPL use in patients with NASH, with or without T2DM

EPL therapy + lifestyle interventions resulted in reduction the proportion of patients with severe fatty liver disease, from 40.5% to 4.8% (P<0.01 vs baseline and EPL alone)¹

EPL therapy in combination with metformin improved ALT, AST and GGT from baseline (P<0.05) in patients with NASH and T2DM. Patients receiving metformin alone did not have improvements in these parameters²

EPL + metformin resulted in significant reductions in:

- Ultrasonographic signs of fatty liver in 81.6% of patients
- Steatosis – patients in the metformin only group experienced a significant increase in steatosis

EPL therapy as supportive pharmacotherapy to lifestyle intervention for NASH resulted in improved clinical outcomes compared with EPL alone³

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipid; GGT, gamma glutamyl transferase; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus

Narrative literature review of EPLs

Results: Efficacy of EPL in patients with other fatty liver disease

Six studies reported on EPL use other fatty liver disease, all of which were comparative, and two of which contained >100 patients.

EPL therapy was superior to vitamins + inosine and to herbal medicines on some outcomes, including improvement in clinical symptoms, reductions in ALT (96.8 ± 70.1 vs 43.5 ± 19.4) and TBIL (19.5± 8.2 vs 13.2± 8.0), respectively (P<0.05)\(^1,2\)

EPL therapy + silybin meglumine resulted in a reduction in number of patients with severe fatty liver from \(n=17\) to \(n=4\) after 2 months\(^2\)

EPL + reduced glutathione resulted in a reduction in number of patients with severe fatty liver from \(n=16\) to \(n=0\) after 2 months\(^2\)

EPL therapy was generally associated with improved clinical symptoms and outcome measures in patients with fatty liver disease.

TBIL, total bilirubin; TC, total cholesterol.
Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

Open label, randomized observational study

Method – three arms:

1. **Patients with lone NAFLD** (N=113)
2. **Patients with T2DM and NAFLD**: patients with T2DM on metformin and/or pioglitazone (N=107)
3. **Patients with hyperlipidaemia and NAFLD**: patients with mixed-type hyperlipidaemia on atorvastatin and/or ezetimibe (N=104)

- **Inclusion criteria**:
  - Patients aged 14–80 years
  - Diagnosis of lone NAFLD, NAFLD with T2DM on pioglitazone and/or metformin or NAFLD with hyperlipidaemia on a statin and/or ezetimibe
- **Study duration**: 72 weeks
- **Compliance**: considered satisfactory if the patient achieved ≥80% of medications prescribed, follow-up appointments and consultations, doing laboratory work, ultrasound, elastography scanning

Endpoints: Clinical, laboratory echographic and elastrographic responses to EPL

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus

Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

Treatment procedure

• Counselling provided to advise on a standard diet and exercise

• Study drug: EPL
  – 1800 mg (six capsules) a day in three divided doses for 24 weeks then;
  – 900 mg (three capsules) a day in three divided doses for 48 weeks

• Medications for comorbid conditions:
  – Metformin
  – Pioglitazone
  – Atorvastatin
  – Ezetimibe

Patients on insulin, DPP-4 inhibitors and GLP-1 RA were excluded

Patients on other statins were included; however, those on fenofibrate were excluded

DPP-4, dipeptidyl peptidase-4; EPL, essential phospholipids; GLP-1 RA, glucagon-like peptide-1 receptor agonist
### Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

**Clinical assessment**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Lone NAFLD</th>
<th>After treatment</th>
<th>Diabetic NAFLD</th>
<th>After treatment</th>
<th>Hyperlipidaemic NAFLD</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asymptomatic, n (%)</strong></td>
<td>70 (61.9)</td>
<td>92 (81.4)</td>
<td>64 (59.8)</td>
<td>85 (79.4)</td>
<td>55 (52.9)</td>
<td>80 (76.9)</td>
</tr>
<tr>
<td><strong>Symptomatic, n (%)</strong></td>
<td>43 (38.1)</td>
<td>21 (18.6)</td>
<td>43 (40.2)</td>
<td>22 (20.6)</td>
<td>49 (47.1)</td>
<td>24 (23.1)</td>
</tr>
<tr>
<td><strong>General symptoms, n (%)</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Asthenia</td>
<td>13 (30.2)</td>
<td>3 (14.3)</td>
<td>19 (44.2)</td>
<td>4 (18.2)</td>
<td>19 (44.2)</td>
<td>13 (30.2)</td>
</tr>
<tr>
<td>Sleeping disorder</td>
<td>13 (30.2)</td>
<td>2 (9.5)</td>
<td>13 (30.2)</td>
<td>3 (13.6)</td>
<td>13 (30.2)</td>
<td>8 (18.6)</td>
</tr>
<tr>
<td>Irritability</td>
<td>14 (32.6)</td>
<td>3 (14.3)</td>
<td>21 (48.8)</td>
<td>6 (27.3)</td>
<td>21 (48.8)</td>
<td>6 (13.9)</td>
</tr>
<tr>
<td><strong>GI symptoms, n (%)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Postprandial distress</td>
<td>12 (27.9)</td>
<td>4 (19.0)</td>
<td>21 (48.8)</td>
<td>6 (27.3)</td>
<td>21 (42.9)</td>
<td>9 (20.9)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>13 (30.2)</td>
<td>6 (28.6)</td>
<td>21 (48.8)</td>
<td>8 (36.4)</td>
<td>21 (42.9)</td>
<td>18 (41.9)</td>
</tr>
<tr>
<td>RUQ pain</td>
<td>9 (20.9)</td>
<td>2 (9.5)</td>
<td>9 (20.9)</td>
<td>4 (18.2)</td>
<td>9 (18.3)</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (18.6)</td>
<td>2 (9.5)</td>
<td>8 (18.6)</td>
<td>3 (13.6)</td>
<td>8 (16.3)</td>
<td>7 (16.3)</td>
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<tr>
<td>Heartburn</td>
<td>5 (11.6)</td>
<td>3 (14.3)</td>
<td>5 (11.6)</td>
<td>2 (9.1)</td>
<td>5 (10.2)</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td><strong>Clinical finding, n (%)</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Jaundice</td>
<td>4 (9.3)</td>
<td>2 (9.5)</td>
<td>5 (11.6)</td>
<td>2 (9.1)</td>
<td>5 (10.2)</td>
<td>3 (7.0)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>9 (20.9)</td>
<td>4 (19.0)</td>
<td>13 (30.2)</td>
<td>2 (9.1)</td>
<td>13 (26.5)</td>
<td>11 (25.6)</td>
</tr>
</tbody>
</table>

GL, gastrointestinal; NAFLD, non-alcoholic fatty liver disease; RUQ, right upper quadrant

Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

Changes in transaminase levels

Figures represent mean changes in transaminases before and after treatment for all three treatment groups
ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; RX, prescription

Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

Figures represent mean changes in transaminases before and after treatment for all three treatment groups

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; RX, prescription; T2DM, type 2 diabetes mellitus

Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

Changes in transaminase levels

Lone NAFLD

<table>
<thead>
<tr>
<th></th>
<th>ALT</th>
<th>AST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before RX</td>
<td>87</td>
<td>72</td>
</tr>
<tr>
<td>After RX</td>
<td>41</td>
<td>49</td>
</tr>
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NAFLD and T2DM

<table>
<thead>
<tr>
<th></th>
<th>ALT</th>
<th>AST</th>
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</thead>
<tbody>
<tr>
<td>Before RX</td>
<td>84</td>
<td>68</td>
</tr>
<tr>
<td>After RX</td>
<td>38</td>
<td>41</td>
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Hyperlipidaemic NAFLD

<table>
<thead>
<tr>
<th></th>
<th>ALT</th>
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<tr>
<td>Before RX</td>
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<td>78</td>
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Figures represent mean changes in transaminases before and after treatment for all three treatment groups

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; RX, prescription; T2DM, type 2 diabetes mellitus

Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

Ultrasonography findings

Overall improvement in echography 29.2%

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; RX, prescription
Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

**Ultrasonography findings**

**Lone NAFLD**

- Normal: Before RX, After RX
- Grade I fatty infiltration: Before RX, After RX
- Grade II fatty infiltration: Before RX, After RX

**NAFLD and T2DM**

- Normal: Before RX, After RX
- Grade I fatty infiltration: Before RX, After RX
- Grade II fatty infiltration: Before RX, After RX

**Overall improvement in echography**

- Lone NAFLD: 29.2%
- NAFLD and T2DM: 23.4%

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; RX, prescription; type 2 diabetes mellitus

Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

**Ultrasonography findings**

**Lone NAFLD**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I fatty infiltration</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Grade II fatty infiltration</td>
<td>0</td>
<td>20</td>
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Overall improvement in echography 29.2%

**NAFLD and T2DM**

<table>
<thead>
<tr>
<th>Grade</th>
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<th>After RX</th>
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<tbody>
<tr>
<td>Normal</td>
<td></td>
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<tr>
<td>Grade I fatty infiltration</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Grade II fatty infiltration</td>
<td>20</td>
<td>40</td>
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Overall improvement in echography 23.4%

**Hyperlipidaemic NAFLD**

<table>
<thead>
<tr>
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<tbody>
<tr>
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<tr>
<td>Grade II fatty infiltration</td>
<td>40</td>
<td>60</td>
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Overall improvement in echography 20.2%

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; RX, prescription; T2DM, type 2 diabetes mellitus

Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

Elastography findings

Overall improvement in elastography 14.2%

EPL, essential phospholipids; F, fibrosis stage; NAFLD, non-alcoholic fatty liver disease; RX, prescription

Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

EPL, essential phospholipids; F, fibrosis stage; NAFLD, non-alcoholic fatty liver disease; RX, prescription; T2DM, type 2 diabetes mellitus


Overall improvement in elastography 26.1%
Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

EPL, essential phospholipids; F, fibrosis stage; NAFLD, non-alcoholic fatty liver disease; RX, prescription; T2DM, type 2 diabetes mellitus

EPL in patients with NAFLD and cardiometabolic comorbidities: results from the MANPOWER study

A 24-week, observational, multicentre, prospective study conducted across 6 federal districts of Russia

N=2843 patients with NAFLD were recruited

n=2263 (80.8%) patients had ≥2 cardiometabolic comorbidities; obesity/overweight were most commonly reported

n=2837 (99.8%) were prescribed 1.8 g of EPL therapy t.i.d.

At baseline, the most frequently identified abnormalities on ultrasound were liver hyperechogenicity (84.0%) and heterogeneous liver structure (62.9%)

At Week 24:

• Significant improvements from baseline in liver echogenicity was observed in 1932 patients (68.3%), p<0.05

• Significant improvements from baseline in liver structure were observed in 1207 patients (42.7%), p<0.05

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; t.i.d., three times a day

Clinical evidence for EPL in patients with NAFLD
EPL reduced histologic changes in patients with NAFLD

- Double-blind, placebo-controlled clinical study of 30 patients with histology-proven NAFLD, T2DM and HBsAg negative receiving EPL (Essentiale® Forte) 1800 mg/day or placebo for 6 months
- Patients were recommended to maintain a dietary regimen and baseline biopsies were provided

Treatment with EPL improved steatosis in comparison with placebo according to biopsy results (with no difference in weight loss among groups)

*International Nonproprietary Names or Trade Names are used in this presentation only for scientific purposes and not to promote, raise awareness of or focus on advantages of a pharmacy or a pharmaceutical company. EPL, essential phospholipids; HBsAg, hepatitis B surface antigen; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

Patients with NASH and diabetes: treatment with EPL and anti-diabetics versus treatment with anti-diabetics only

**Study design:** Randomized, prospective, blinded clinical trial

**Objective:** To evaluate the efficacy of EPL

**Patients:** Patients with NASH and T2DM controlled by diet and metformin (N=215)
- Investigational group: 178 patients received EPL + SOC for 6 months
- Control group: 37 patients received SOC for 6 months

**Standard care:** Diet, metformin and physical activity regimen
- 114 patients in the EPL group and 37 patients in the control group were followed-up for up to 7 years

**Outcomes:** Liver function markers and ultrasound results

EPL, essential phospholipids; NASH, non-alcoholic steatohepatitis; SOC, standard of care; T2D, type 2 diabetes
Sas E, et al. J Hepatol 2013;58:S409–S566
Patients with NASH and diabetes: treatment with EPL and anti-diabetics vs treatment with anti-diabetics only

Results

All liver enzymes were significantly reduced with Essentiale® Forte vs SOC

<table>
<thead>
<tr>
<th>Study endpoints</th>
<th>Essentiale® Forte (N=178)</th>
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<tbody>
<tr>
<td><strong>ALT, IU/L</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>56.5 ± 28.6</td>
</tr>
<tr>
<td>6 months</td>
<td>35.2 ± 18.4</td>
</tr>
<tr>
<td>P value</td>
<td>P=0.02</td>
</tr>
<tr>
<td><strong>AST, IU/L</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>39.0 ± 9.0</td>
</tr>
<tr>
<td>6 months</td>
<td>26.5 ± 7.2</td>
</tr>
<tr>
<td>P value</td>
<td>P=0.04</td>
</tr>
<tr>
<td><strong>γ-GT, IU/L</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>38.2 ± 11.4</td>
</tr>
<tr>
<td>6 months</td>
<td>27.5 ± 8.6</td>
</tr>
<tr>
<td>P value</td>
<td>P=0.03</td>
</tr>
</tbody>
</table>

Significant reductions in HbA1c, leading to improved glycemic control, were observed in 98/114 patients (86%) on Essentiale® Forte

Data are mean ± SD
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c, glycated haemoglobin; γ-GT, gamma glutamyl transferase; SOC, standard of care
Sas E, et al. J Hepatol 2013;58:S409–S566
Patients with NASH and diabetes: treatment with EPL and anti-diabetics vs treatment with anti-diabetics only

Results (continued)

- Hepatic echotexture was significantly improved with EPL vs SOC
- Sonographic signs of fatty liver significantly decreased with EPL vs SOC

Change in hepatic echotexture and signs of fatty liver with EPL

<table>
<thead>
<tr>
<th>Study</th>
<th>EPL (N=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound studies (hepatic echotexture)</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>101/152 (66.4%)*</td>
</tr>
<tr>
<td>No change</td>
<td>7/152 (4.6%)</td>
</tr>
<tr>
<td>Sonographic signs of fatty liver</td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td>93/114 (81.6%)**</td>
</tr>
</tbody>
</table>

The development of hepatic fibrosis was significantly slower with EPL compared with control (P=0.03)

*P=0.02; **P<0.05. Data shown as n(%)

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; SOC, standard of care
Sas E, et al. J Hepatol 2013;58:S409–S566
EPL versus other comparators used in treating patients with NAFLD: EPL and ursodeoxycholic acid (UDCA)

In a comparative, double-blind study to compare the efficacy of UDCA and Essentiale® Forte in patients with early-stage NAFLD (N=40):

- A trend towards improved symptoms and ultrasound findings was observed in the EPL group vs the UDCA group.
- More consistent improvements in liver function tests were found in the EPL group vs the UDCA group.

### Mean liver function tests after 12 weeks of treatment

<table>
<thead>
<tr>
<th></th>
<th>Essentiale® Forte group (N=20)</th>
<th>UDCA group (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AST (U/L)</td>
<td>ALT (U/L)</td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>85.7 ± 68.1</td>
<td>79.9 ± 68.0</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>67.5 ± 61.5</td>
<td>67.5 ± 61.5†</td>
</tr>
</tbody>
</table>

*Patients received Essentiale® Forte, two capsules, three times per day for 3 months. †Patients received UDCA, 7–10 mg/kg once daily for 3 months. Data are mean ± SD. ‡P ≤0.05. ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate transaminase; NAFLD, non-alcoholic fatty liver disease.

### EPL for NAFLD associated with metabolic syndrome: a systematic review and network meta-analysis (1/2)

#### Disease severity

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>EPL + ADs</th>
<th>ADs</th>
<th>Weight (%)</th>
<th>Risk ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun (2008)</td>
<td>37</td>
<td>37</td>
<td>65.1</td>
<td>0.40 (0.08, 0.19)</td>
<td></td>
</tr>
<tr>
<td>Li (2013)</td>
<td>37</td>
<td>43</td>
<td>34.9</td>
<td>0.29 (0.03, 0.21)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>74</td>
<td>80</td>
<td>100.0</td>
<td>0.34 (0.10, 1.21)</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun (2008)</td>
<td>15</td>
<td>13</td>
<td>54.6</td>
<td>0.43 (0.18, 0.99)</td>
<td></td>
</tr>
<tr>
<td>Li (2013)</td>
<td>80</td>
<td>29</td>
<td>45.4</td>
<td>0.52 (0.30, 0.90)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>95</td>
<td>109</td>
<td>100.0</td>
<td>0.56 (0.23, 1.39)</td>
<td></td>
</tr>
<tr>
<td><strong>Mild</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun (2008)</td>
<td>21</td>
<td>13</td>
<td>55.4</td>
<td>1.62 (0.96, 2.72)</td>
<td></td>
</tr>
<tr>
<td>Li (2013)</td>
<td>10</td>
<td>13</td>
<td>44.6</td>
<td>0.77 (0.38, 1.56)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>31</td>
<td>26</td>
<td>100.0</td>
<td>1.16 (0.56, 2.39)</td>
<td></td>
</tr>
<tr>
<td><strong>None</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun (2008)</td>
<td>8</td>
<td>5</td>
<td>24.5</td>
<td>1.60 (0.58, 4.44)</td>
<td></td>
</tr>
<tr>
<td>Li (2013)</td>
<td>23</td>
<td>11</td>
<td>75.5</td>
<td>0.29 (0.17, 0.37)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>31</td>
<td>16</td>
<td>100.0</td>
<td>1.96 (1.18, 3.24)</td>
<td></td>
</tr>
</tbody>
</table>

#### Disease response

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>EPL + ADs</th>
<th>ADs</th>
<th>Weight (%)</th>
<th>Risk ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unchanged</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun (2008)</td>
<td>8</td>
<td>17</td>
<td>33.5</td>
<td>0.47 (0.23, 0.95)</td>
<td></td>
</tr>
<tr>
<td>Yin (2000)</td>
<td>12</td>
<td>25</td>
<td>60</td>
<td>0.20 (0.11, 0.36)</td>
<td></td>
</tr>
<tr>
<td>Li (2013)</td>
<td>6</td>
<td>15</td>
<td>63</td>
<td>0.40 (0.17, 0.93)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>205</td>
<td>140</td>
<td>100.0</td>
<td>0.32 (0.18, 0.56)</td>
<td></td>
</tr>
<tr>
<td><strong>Partial improvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun (2008)</td>
<td>8</td>
<td>5</td>
<td>37</td>
<td>2.33 (1.60, 4.44)</td>
<td></td>
</tr>
<tr>
<td>Yin (2000)</td>
<td>35</td>
<td>125</td>
<td>60</td>
<td>5.03 (2.60, 9.63)</td>
<td></td>
</tr>
<tr>
<td>Li (2013)</td>
<td>8</td>
<td>43</td>
<td>43</td>
<td>26.4 (11.4, 58.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>205</td>
<td>140</td>
<td>100.0</td>
<td>0.89 (0.48, 1.70)</td>
<td></td>
</tr>
<tr>
<td><strong>Significant improvement</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sun (2008)</td>
<td>12</td>
<td>9</td>
<td>37</td>
<td>3.33 (1.64, 2.78)</td>
<td></td>
</tr>
<tr>
<td>Yin (2000)</td>
<td>78</td>
<td>125</td>
<td>60</td>
<td>12.48 (4.11, 37.92)</td>
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</tr>
<tr>
<td>Li (2013)</td>
<td>29</td>
<td>21</td>
<td>43</td>
<td>38.3 (11.4, 127.92)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>119</td>
<td>33</td>
<td>100.0</td>
<td>2.53 (0.87, 7.35)</td>
<td></td>
</tr>
<tr>
<td><strong>Any Improvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun (2008)</td>
<td>29</td>
<td>20</td>
<td>37</td>
<td>2.44 (1.45, 4.03)</td>
<td></td>
</tr>
<tr>
<td>Yin (2000)</td>
<td>113</td>
<td>125</td>
<td>60</td>
<td>1.75 (1.36, 2.25)</td>
<td></td>
</tr>
<tr>
<td>Li (2013)</td>
<td>37</td>
<td>28</td>
<td>43</td>
<td>3.95 (1.30, 11.78)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>205</td>
<td>140</td>
<td>100.0</td>
<td>1.30 (0.12, 1.79)</td>
<td></td>
</tr>
</tbody>
</table>

AD anti-diabetic treatment; CI, confidence interval; EPL, essential phospholipids

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SANOFI data on file

Manuscript accepted – SANOFI data on file
EPL for NAFLD associated with metabolic syndrome: a systematic review and network meta-analysis (2/2)

Results of a direct meta-analysis of RCTs comparing the effect of treatment with EPLs + AD vs AD therapy

A: Significant clinical improvement of steatosis stage as assessed by ultrasonography, four studies\(^1-^4\) (total n=357), mean treatment 3.97 months

B: Change in AST, two studies\(^2,^5\) (total n=202), mean treatment 4.76 months

---

**A**

Significant clinical improvement (ultrasonography) and AST levels\(^6\)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Improved significant (proportion of patients) PR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun C. (2008)</td>
<td>0.32 [0.17, 0.48]</td>
</tr>
<tr>
<td>Sas E. (2013)</td>
<td>0.66 [0.59, 0.74]</td>
</tr>
<tr>
<td>Yin D. (2000)</td>
<td>0.62 [0.54, 0.71]</td>
</tr>
<tr>
<td>Li Z. (2013)</td>
<td>0.67 [0.53, 0.81]</td>
</tr>
</tbody>
</table>

RE Model (Q=16.67, df=3, p=0.00, I\(^2\)=82.0%)

**B**

AST change from baseline (U/l)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>MN [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu Y. (2009)</td>
<td>-17.00 [-19.63, -14.37]</td>
</tr>
<tr>
<td>Sas E. (2013)</td>
<td>-12.50 [-13.53, -11.47]</td>
</tr>
</tbody>
</table>

RE Model (Q=9.76, df=1, p=0.00, I\(^2\)=89.8%)

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AD anti-diabetic treatment; AST, aspartate aminotransferase; CI, confidence interval; EPL, essential phospholipids; MN, raw mean; PR, proportion of responders; RCTs, randomized controlled trials; RE, random effects

Narrative literature review of EPLs

Safety

Of the 25 studies included in this review, only three reported safety data

EPL therapy was generally well tolerated. The most commonly reported AEs were mild gastrointestinal events.

In an 8-week, randomised, parallel-group study in patients with fatty liver disease, abdominal discomfort was:

- Reported in 2/76 patients receiving EPL therapy + silybin meglumine
- Reported in 3/74 patients receiving EPL therapy + glutathione
- Resolved with symptomatic treatment

The most common AEs among elderly patients with NAFLD or patients with NAFLD and comorbid T2DM included mild gastrointestinal dysfunction, diarrhoea or dizziness/headaches.

AE, adverse event; EPL, essential phospholipid; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus


Narrative literature review of EPLs

Results: evidence supporting the use of hepatoprotective of EPLs

Level of existing evidence supporting the efficacy of various treatments for NAFLD/NASH

UDCA
Vitamin D
Resveratrol
EPLs
Vitamin E* (+ Vitamin C)

Phyllanthus
Glycyrrhizic acid
Garcia
Coenzyme Q10
Ademetionine
Silymarin
Artichoke
Lack of improvement or deterioration
Low probability of improvement
Medium probability of improvement
High probability of improvement
Very high probability of improvement

Likelihood of improvement of clinically meaningful parameters

*Vitamin E has been used in either combination or very high dose. EPL, essential phospholipid; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; UDCA, ursodeoxycholic acid
**Conclusions**

1. Many existing treatments for NAFLD are **experimental, costly, or lack a consistent evidence base**

2. Results of comparative studies confirm that EPL given as adjunctive therapy to metformin or SOC in patients with T2DM, and as an adjunctive therapy to sibutramine in patients with obesity, is associated with better NAFLD clinical outcomes

3. **Adjunctive therapy with hepatoprotective treatments** may offer a reliable therapeutic strategy for NAFLD

4. Further studies are required to fully delineate the **role of EPL across the NAFLD continuum** and support their use in the management of liver disease

---

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SOC, standard of care; T2DM, type 2 diabetes mellitus