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. Review the **current clinical** evidence supporting the use of **essential phospholipid (EPL)** in the supportive treatment of liver diseases

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

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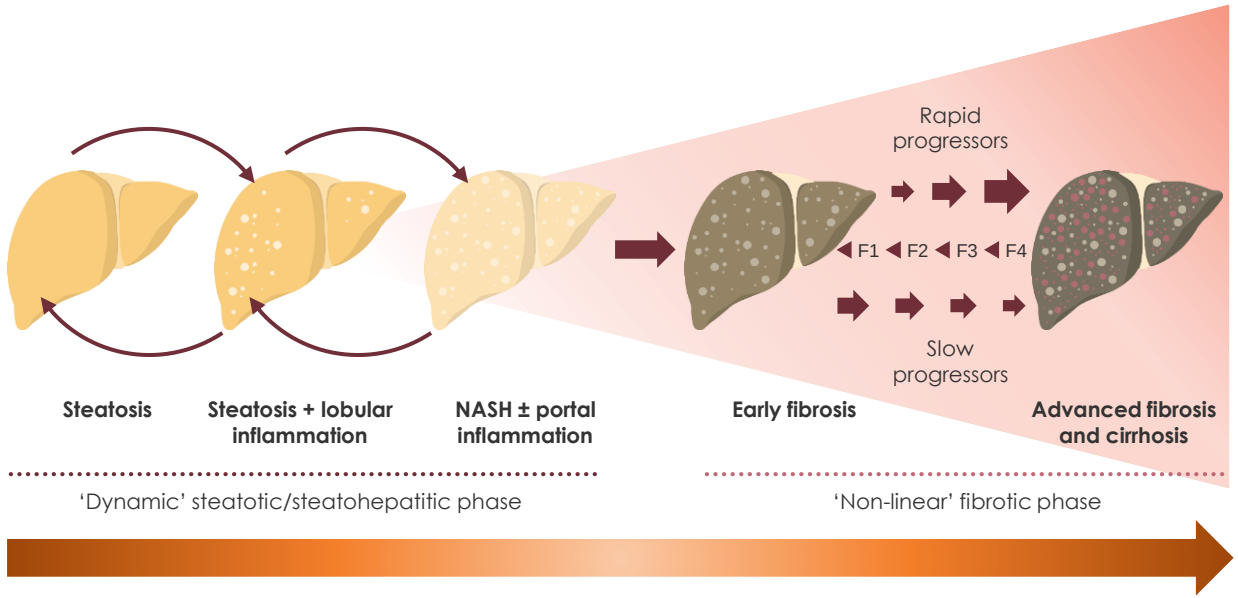
Why treat patients with NAFLD?

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

1. Adams LA, et al. Gastroenterology 2005;129:113–21; 2. Söderberg C, et al. Hepatology 2010;51:595–602; 3. Wójcik-Cichy K, et al. Clin Exp Hepatol 2018;4:1–6; 4. Schwimmer JB, et al. PLoS ONE 2014;9:e112569; 5. Ding X, et al. Int J Endocrinol 2017;2017:5262560; 6. Velarde-Ruiz Velasco JA, et al. Rev Gastroenterol Mex 2019;84:472–81; 7. Armstrong MJ, et al. Hepatology 2014;59:1174–97; 8. Yatsuji S, et al. J Gastroenterol Hepatol 2009;24:248–54

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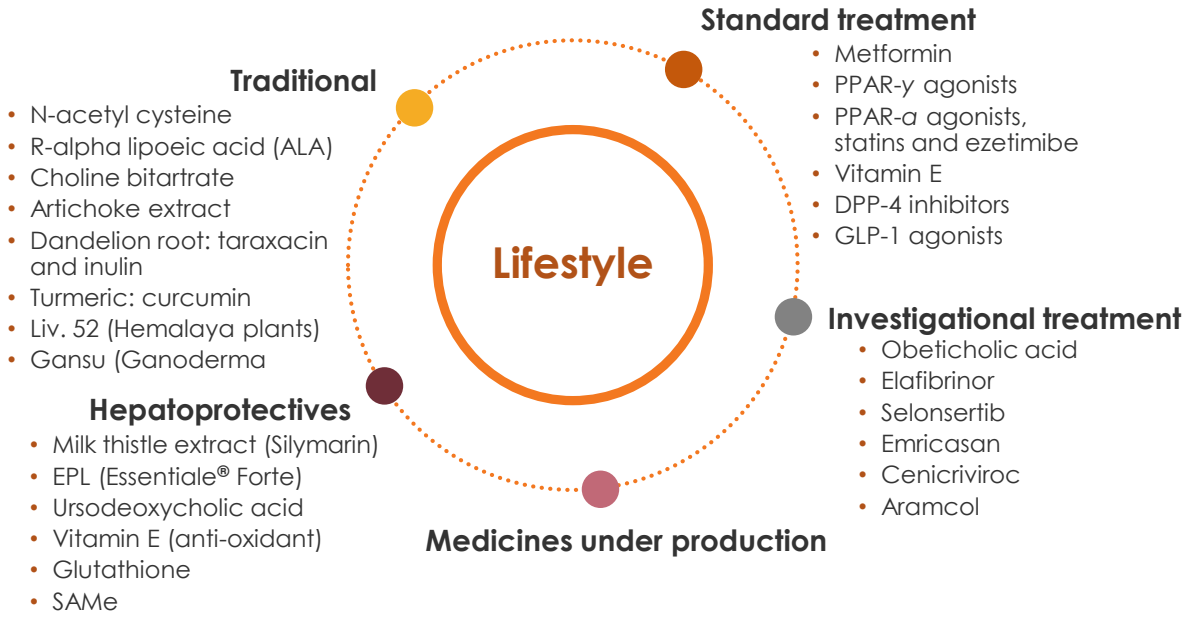
Current medical treatments are experimental

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



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

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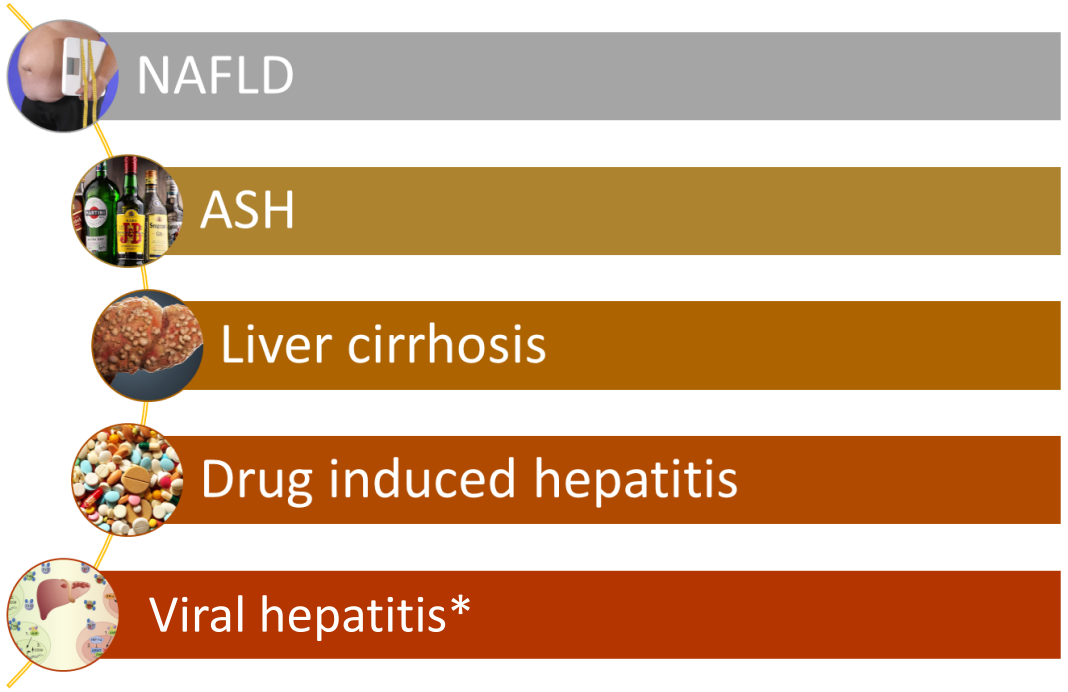
Role of phospholipids in mammalian cells: recovery and maintenance

- 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

Indication



*Phospholipids are indicated as adjunctive treatment only. ASH, alcoholic steatohepatitis; EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease
Gundermann KJ, et al. Pharmacol Rep 2011;63:643–59

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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.

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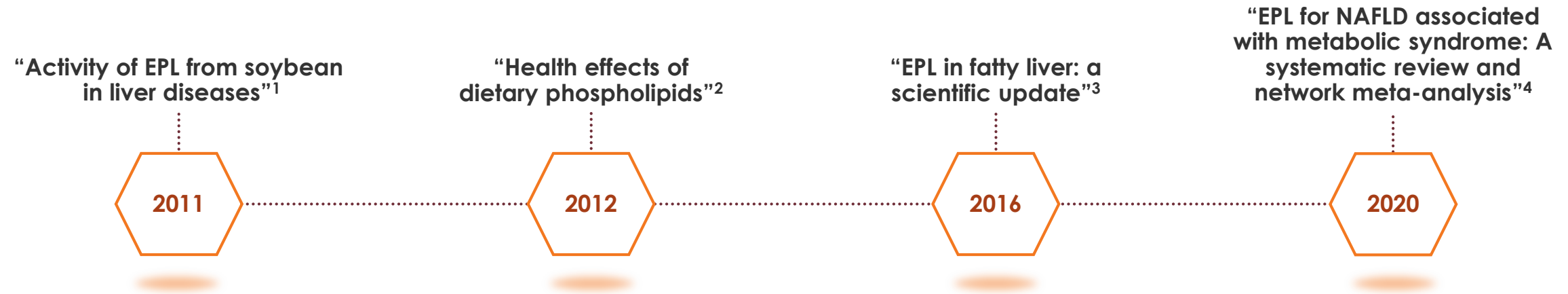
Previous literature reviews of EPLs



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

1. Gundermann KJ, et al. Pharmacol Rep 2011;63:643–59; 2. Küllenberg D, et al. Lipids Health Dis 2012;11:3; 3. Gunderman KJ, et al. Clin Exp Gastroenterol 2016;9:105–17; 4. Dajani A, et al. World J Clin Cases 2020;8:5235–49

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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

1. Fan JG, et al. J Dig Dis 2019;20:163–73; 2. Varganova DL, et al. Conchrane Database Syst Rev 2019;4:CD013301; 3. Society of Digestive Diseases (Latvia) 2020. Available from: https://www.globalliverforum.com (Accessed May 2020); 4. Gundermann KJ, et al. Clin Exp Gastroenterol 2016;9:105–17; 5. Russian Scientific Liver Study 2015. Available from: http://www.rsls.ru/files/Guidelines-RSLS-NASH-2016-01-03.pdf (Accessed May 2020); 6. Hartleb M, et al. Med Prakt 2019;10:47–74
Dajani A, et al. Drugs Ther Perspect 2020;37:249–64

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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.
Dajani A, et al. Drugs Ther Perspect 2020;37:249–64

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Narrative literature review of EPLs

Search results

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

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.
Dajani A, et al. Drugs Ther Perspect 2020;37:249–64

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Narrative literature review of EPLs

Results: Efficacy of EPL in patients with NAFLD alone

11 studies of patients with NAFLD only were included in this review

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 alone[1]

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]

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

1. Dajani A, et al. Arab J Gastroenterol 2015;16:99–104
Dajani A, et al. Drugs Ther Perspect 2020;37:249–64

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Narrative literature review of EPLs

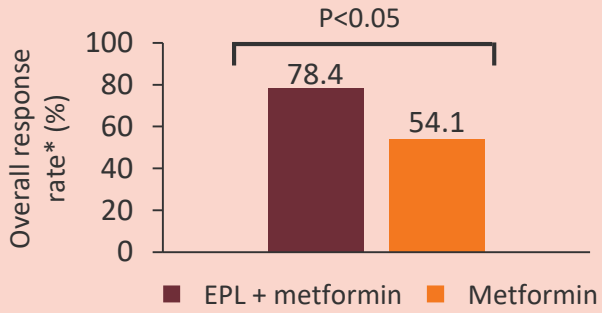
Results: Efficacy of EPL in patients with NAFLD and comorbidities

NAFLD and T2DM

Six studies included patients with NAFLD and T2DM

EPLs given as **adjunctive therapy** to **metformin** or **SOC** in patients with NAFLD and T2DM are associated with **improved clinical outcomes** compared with T2DM-specific treatment alone[1–3]

In one study of patients with NAFLD and T2DM:[2]



NAFLD and hyperlipidaemia or obesity

Four studies included patients with NAFLD and hyperlipidaemia or obesity

EPL therapy resulted in i**mprovements in clinical outcomes** for patients with NAFLD and hyperlipidaemia or obesity[4–6]

In one study of patients with NAFLD and obesity:[7]

PPC + sibutramine
- Significant reduction in steatosis from baseline†
- Significant improvement in ultrasound results in 92.0% of patients from baseline†

Sibutramine
- Significant increase in steatosis from baseline†
- No change in ultrasound results in 23.3% of patients from baseline

PPC + sibutramine resulted in slower fibrosis progression than sibutramine alone, p<0.05

*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

1. Li Z. Inner Mongol Journal of Traditional Chinese Medicine 2013;31:10–1; 2. Sun C et al. Clinical Focus 2008;23:1272–3; 3. Wu CY. Pract Clin Med 2015;16:3–5; 4. Maev IV, et al. BMJ Open Gastroenterol 2019;6:e000307; 5. Maev IV, et al. BMJ Open Gastroenterol 2020;7:e000368; 6. Maev IV, et al. BMJ Open Gastroenterol 2020;7:e000341; 7. Sas E et al. Gut 2012;61:A216–A7
Dajani A, et al. Drugs Ther Perspect 2020;37:249–64

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Narrative literature review of EPLs

Results: Efficacy of EPL in patients with NASH

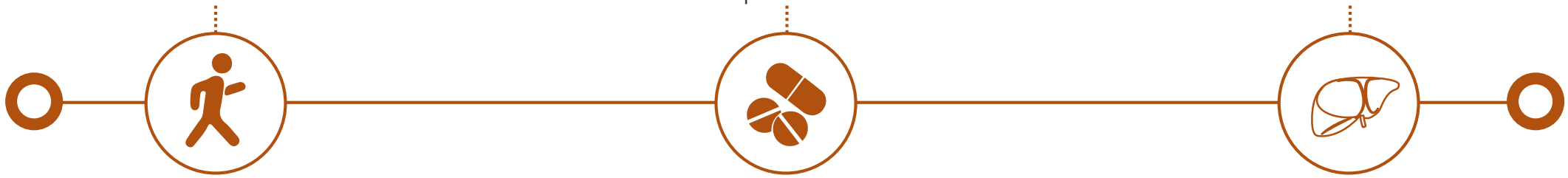
Three studies reported on EPL use in patients with NASH, with or without T2DM

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 paramteters[2]

EPL + metformin resulted in significant reductions in:[2]

- 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 alone[1]

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

1. Zhan G, et al. Clin Hepatol 2013;16:505–8; 2. Sas E, et al. Journal of Hepatology 2013;58:S549
Dajani A, et al. Drugs Ther Perspect 2020;37:249–64

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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.

1. Du Q. Chin J Gastro Hepa 2004;13; 2. Jiang J-Z. Drugs & Clinic. 2015;30:176–8
Dajani A, et al. Drugs Ther Perspect 2020;37:249–64

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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 NALFD, 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

Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

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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

Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

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Clinical assessment

	Lone NAFLD		Diabetic NAFLD		Hyperlipidaemic NAFLD	
	Patients	After treatment	Patients	After treatment	Patients	After treatment
Asymptomatic, n (%)	70 (61.9)	92 (81.4)	64 (59.8)	85 (79.4)	55 (52.9)	80 (76.9)
Symptomatic, n (%)	43 (38.1)	21 (18.6)	43 (40.2)	22 (20.6)	49 (47.1)	24 (23.1)
General symptoms, n (%)						
Asthenia	13 (30.2)	3 (14.3)	19 (44.2)	4 (18.2)	19 (44.2)	13 (30.2)
Sleeping disorder	13 (30.2)	2 (9.5)	13 (30.2)	3 (13.6)	13 (30.2)	8 (18.6)
Irritability	14 (32.6)	3 (14.3)	21 (48.8)	6 (27.3)	21 (48.8)	6 (13.9)
GI symptoms, n (%)						
Postprandial distress	12 (27.9)	4 (19.0)	21 (48.8)	6 (27.3)	21 (42.9)	9 (20.9)
Flatulence	13 (30.2)	6 (28.6)	21 (48.8)	8 (36.4)	21 (42.9)	18 (41.9)
RUQ pain	9 (20.9)	2 (9.5)	9 (20.9)	4 (18.2)	9 (18.3)	4 (9.3)
Nausea	8 (18.6)	2 (9.5)	8 (18.6)	3 (13.6)	8 (16.3)	7 (16.3)
Heartburn	5 (11.6)	3 (14.3)	5 (11.6)	2 (9.1)	5 (10.2)	2 (4.7)
Clinical finding, n (%)						
Jaundice	4 (9.3)	2 (9.5)	5 (11.6)	2 (9.1)	5 (10.2)	3 (7.0)
Hepatomegaly	9 (20.9)	4 (19.0)	13 (30.2)	2 (9.1)	13 (26.5)	11 (25.6)
		P<0.01		P<0.01		P<0.01

GI, gastrointestinal; NAFLD, non-alcoholic fatty liver disease; RUQ, right upper quadrant
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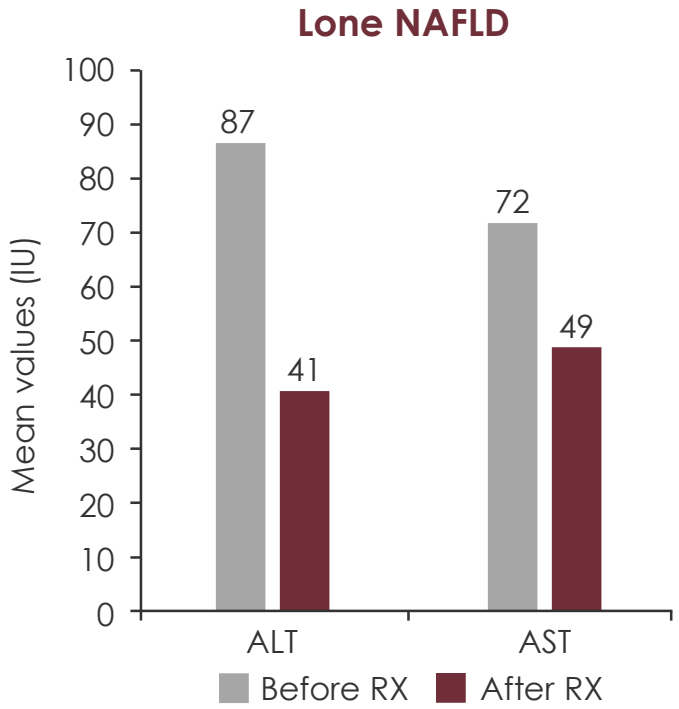
Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

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
Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

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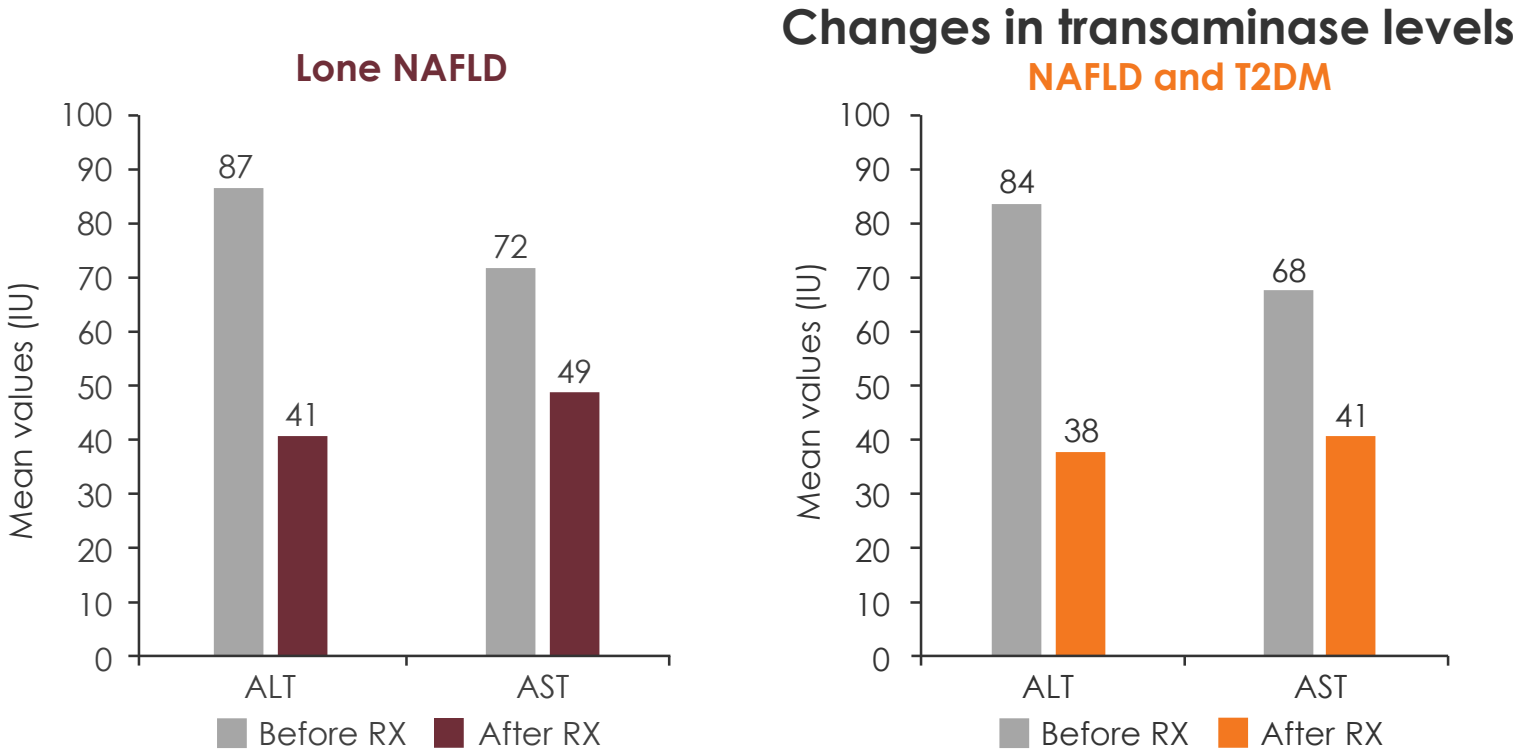

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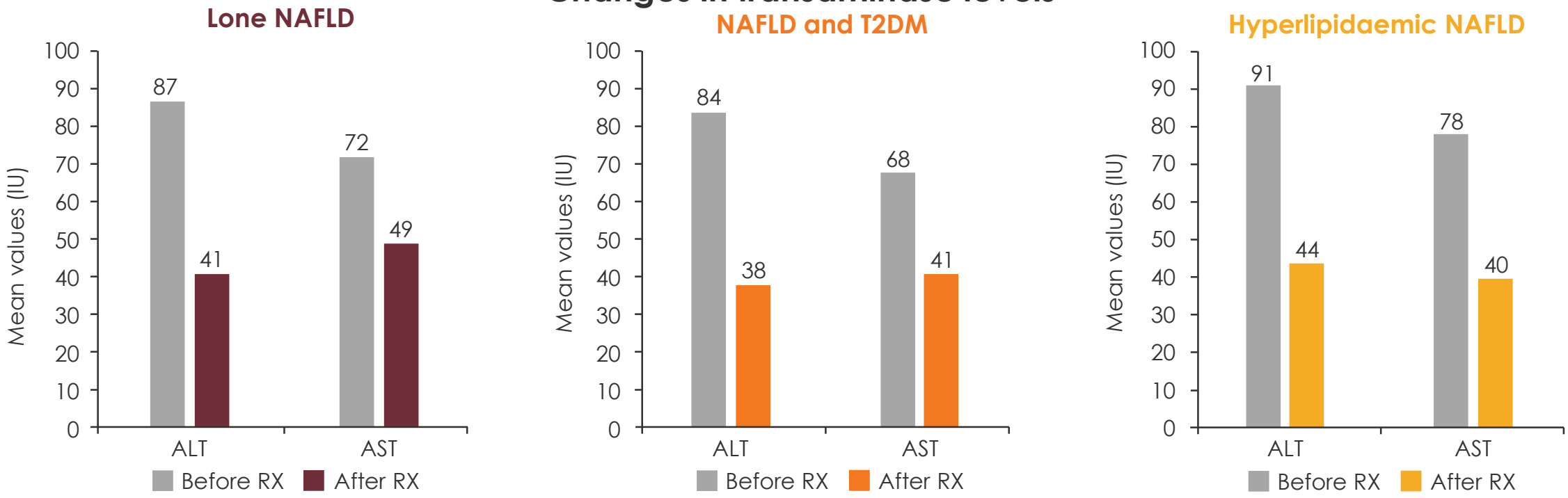

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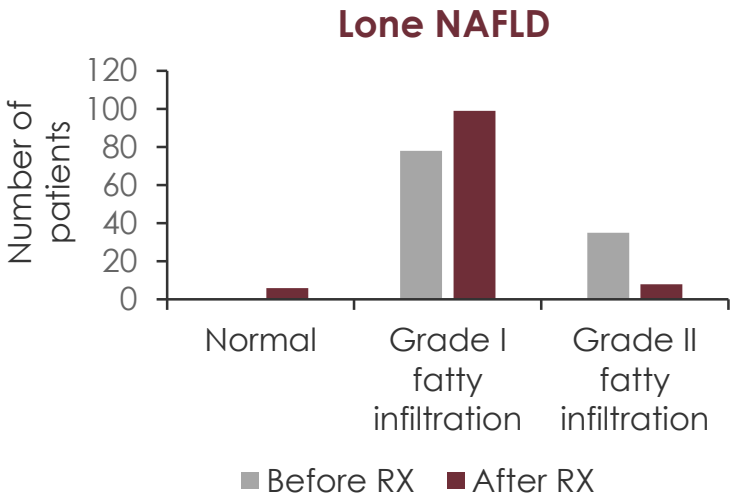
Ultrasonography findings



Overall improvement in echography 29.2%

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; RX, prescription
Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

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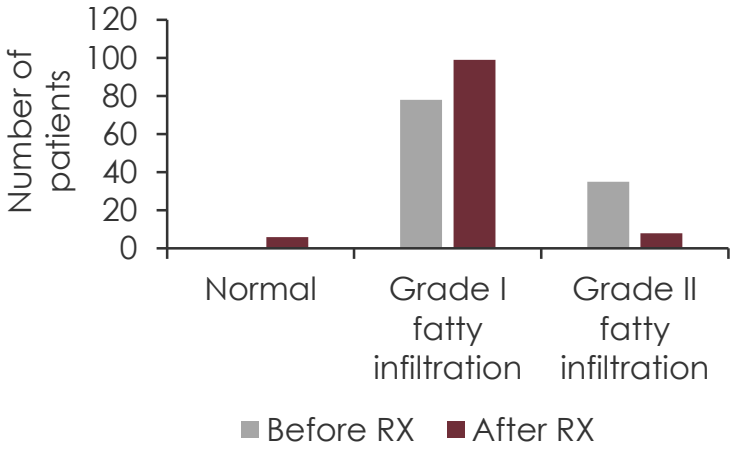
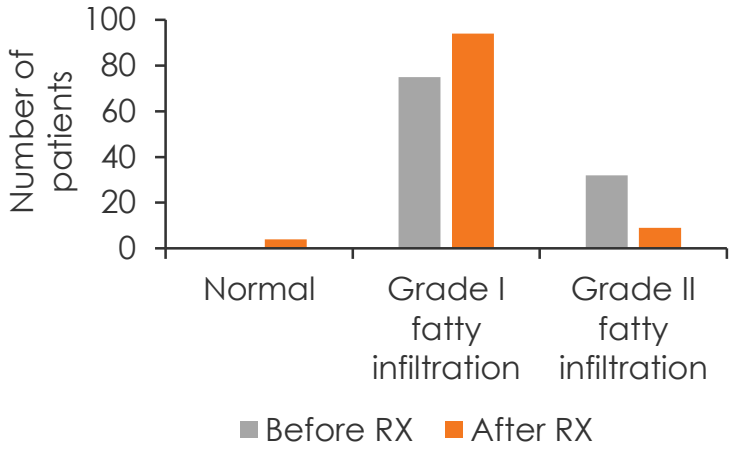
Ultrasonography findings

Lone NAFLD



Overall improvement in echography 29.2%

NAFLD and T2DM



Overall improvement in echography 23.4%

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; RX, prescription; type 2 diabetes mellitus
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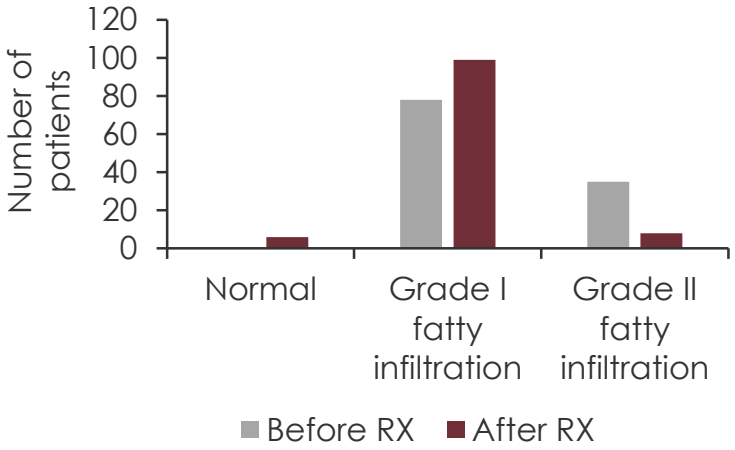
Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

Ultrasonography findings

Lone NAFLD



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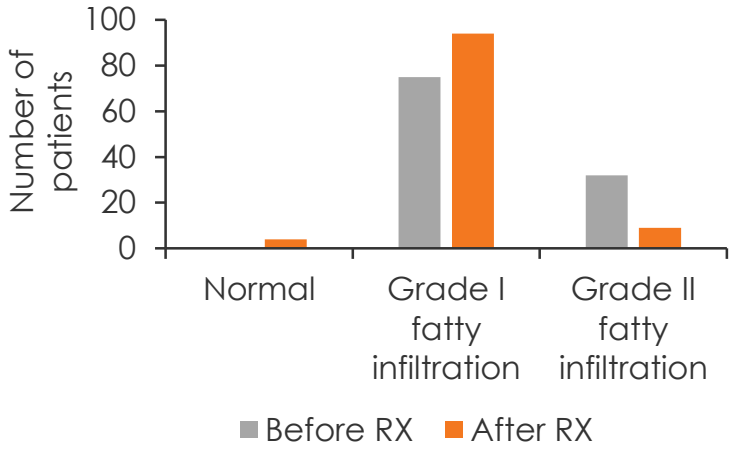
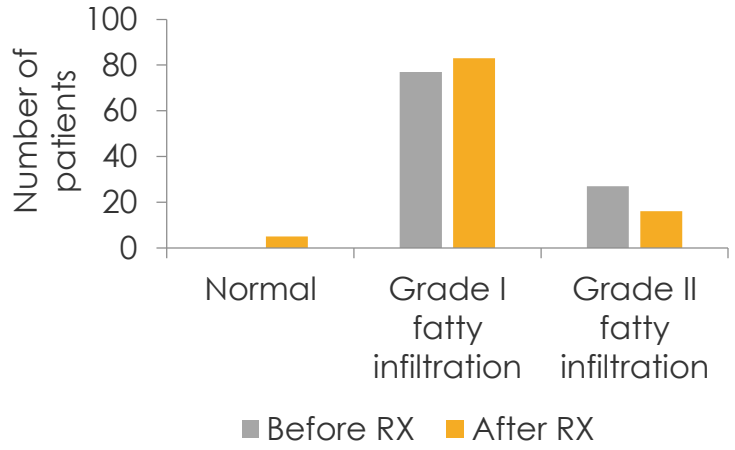
NAFLD and T2DM



Overall improvement in echography 23.4%

Hyperlipidaemic NAFLD



Overall improvement in echography 20.2%

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; RX, prescription; T2DM, type 2 diabetes mellitus
Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

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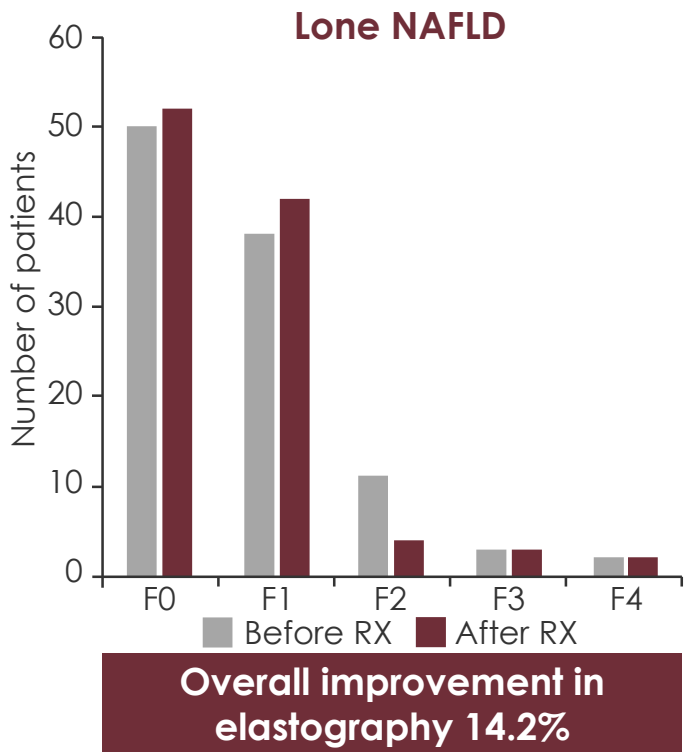
Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

Elastography findings



Overall improvement in elastography 14.2%

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

Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

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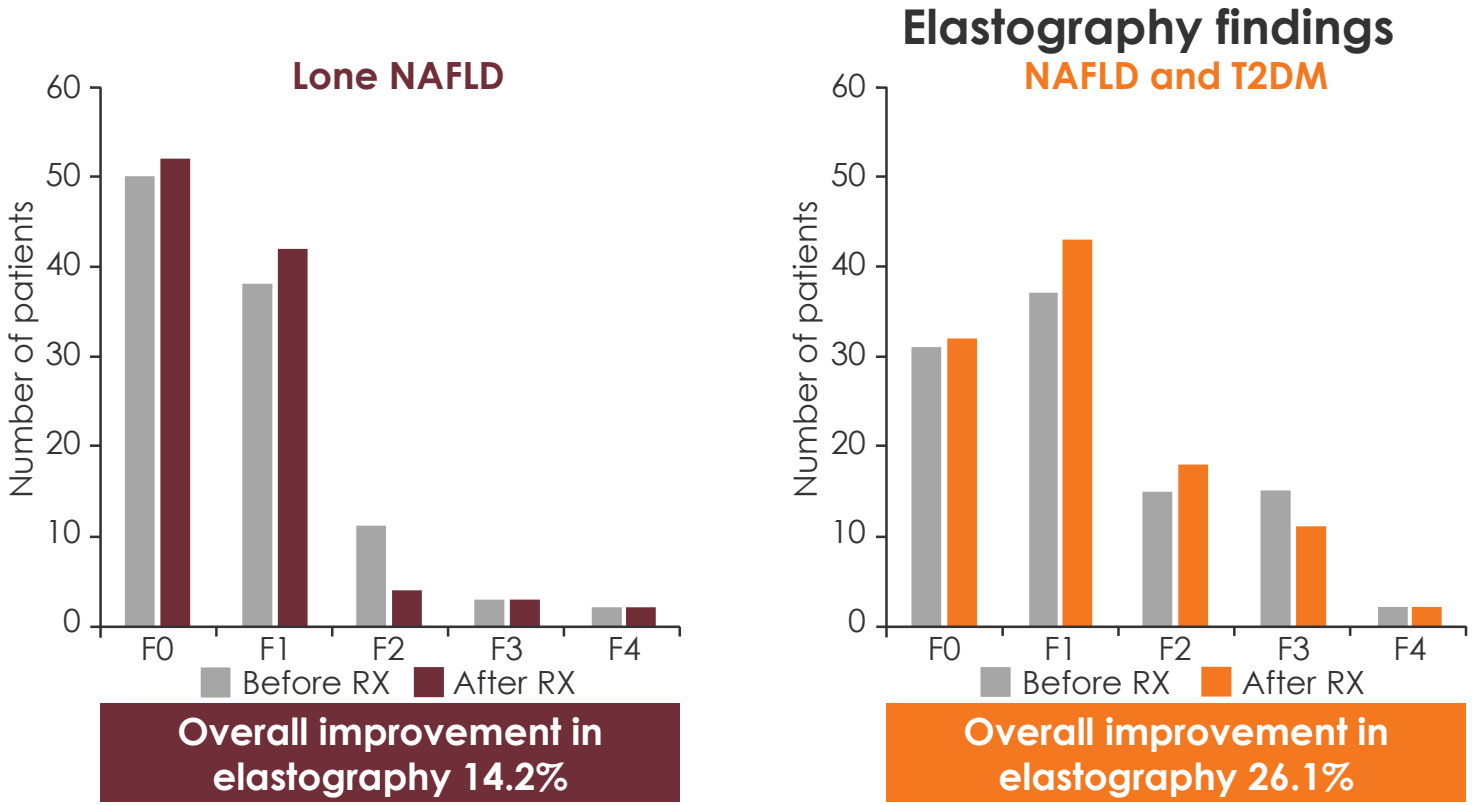
Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience



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

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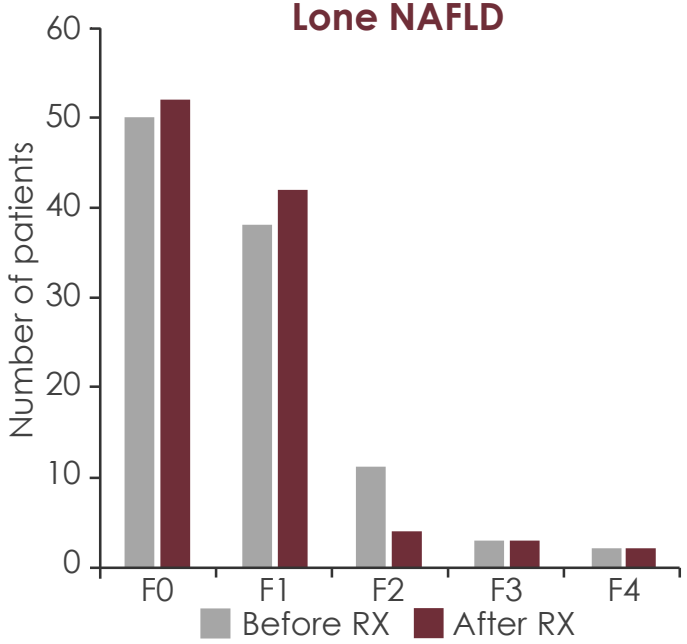
Evaluation of EPL in patients with NAFLD without or with relevant comorbidities: UAE experience

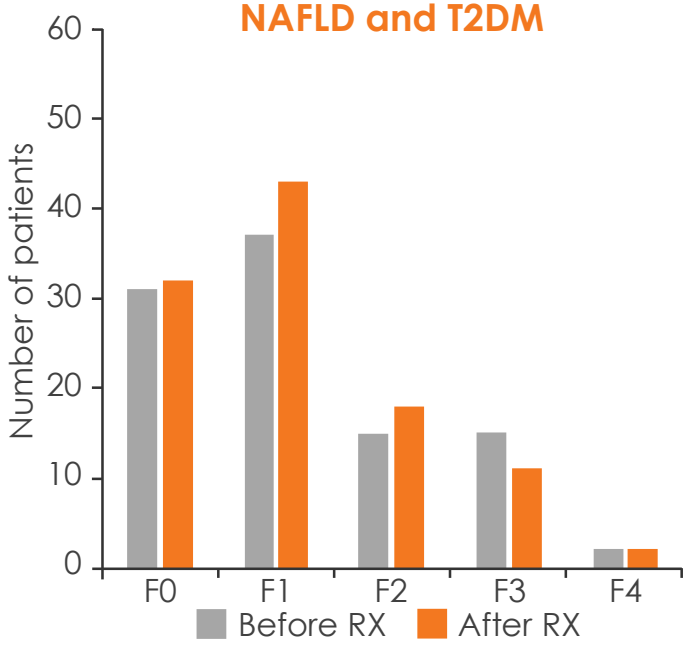
Elastography findings

Lone NAFLD



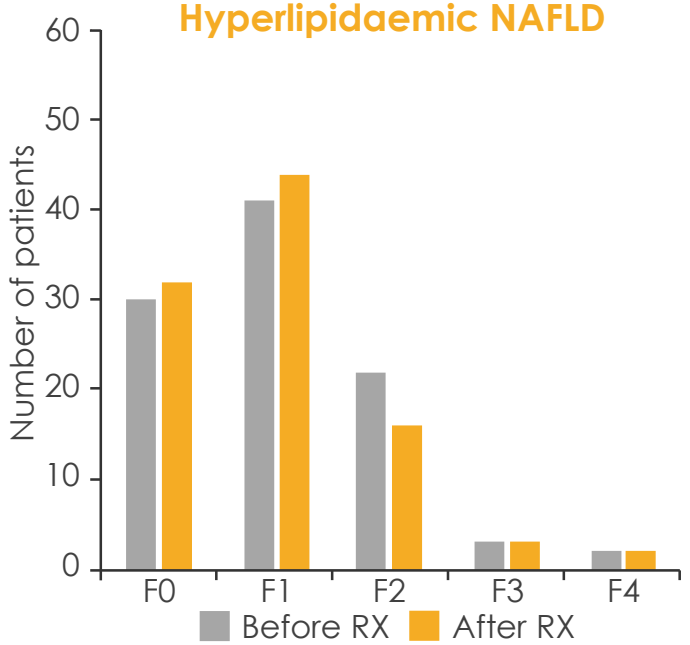
Overall improvement in elastography 14.2%

NAFLD and T2DM



Overall improvement in elastography 26.1%

Hyperlipidaemic NAFLD



Overall improvement in elastography 20.2%

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

Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

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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

Maev I et al. BMJ Open Gastroenterol. 2020;7:e000341.

SANOFI

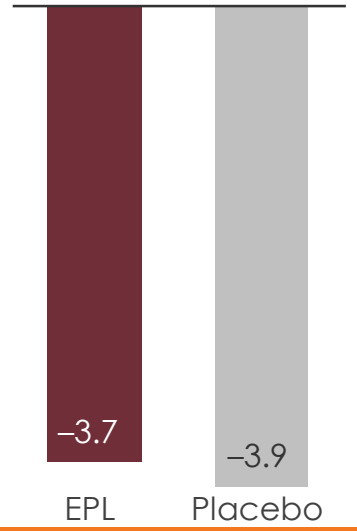
Clinical evidence for EPL in patients with NAFLD

SANOFI

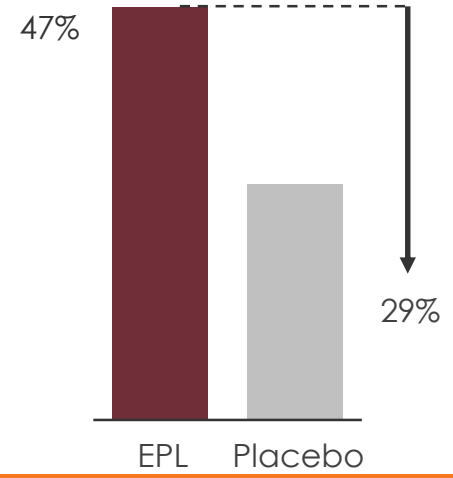
EPL reduced histologic changes in patients with NAFLD

- 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

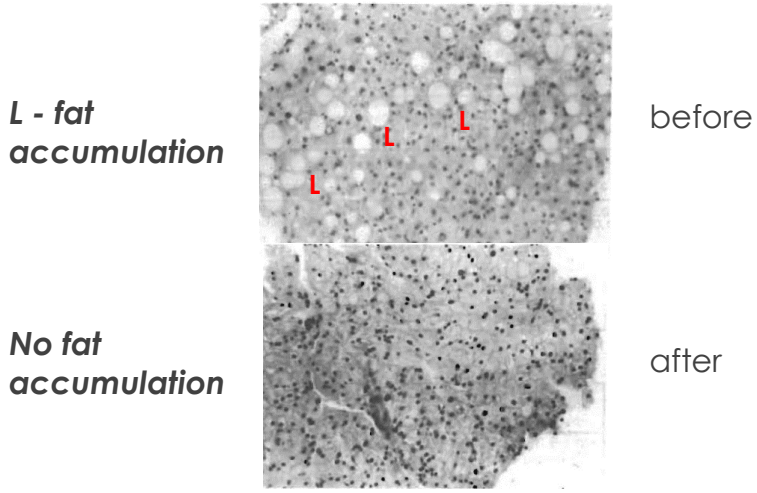
Weight loss in 6 months, kg



Steatosis improvement in 6 months according to biopsies



Example of steatosis improvement before and after therapy (biopsy)



Reversal of steatosis

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
Gonciarz Z, et al. Med Chir Digest 1988;17:61–5

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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 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

Change in liver function tests from baseline to end of study with both treatments

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

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

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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

Study	EPL (N=178)
Ultrasound studies (hepatic echotexture)	
Improvement	101/152 (66.4%)*
No change	7/152 (4.6%)
Sonographic signs of fatty liver	
Decrease	93/114 (81.6%)**

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

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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

	Essentiale® Forte group (N=20)*			UDCA group (N=20)†		
	AST (U/L)	ALT (U/L)	AP (U/L)	AST (U/L)	ALT (U/L)	AP (U/L)
Pre-treatment	85.7 ± 68.1	79.9 ± 68.0	182.6 ± 40.4	63.3 ± 43.1	67.9 ± 49.6	172.1 ± 37.6
Post-treatment	67.5 ± 61.5	67.5 ± 61.5‡	166.6 ± 32.4‡	54.1 ± 43.4	54.1 ± 43.4‡	162.6 ± 21.6

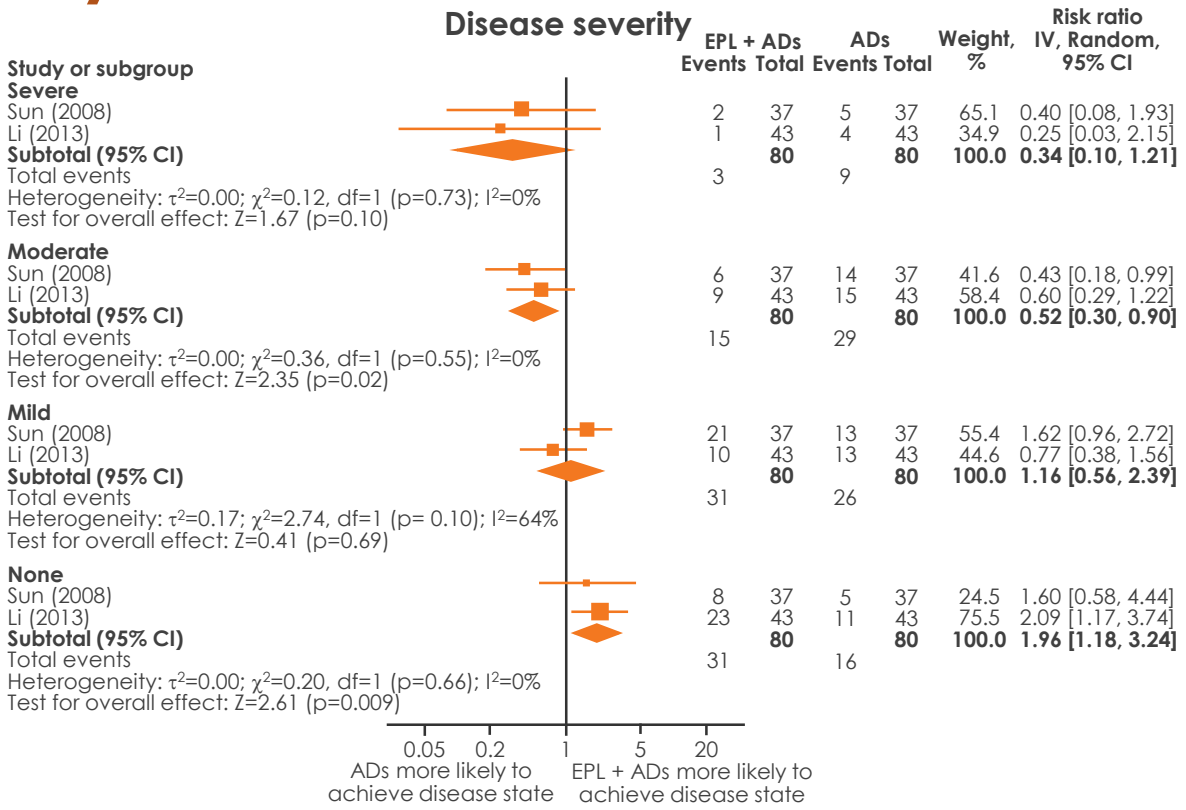
*Patients received Essentiale® Forte, two capsules, three times per day for 3 months. †Patients received UDCA, 7–10 mg/kg once daily for 3 months. Data are mean ± SD. ‡P ≤0.05. ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate transaminase; NAFLD, non-alcoholic fatty liver disease

1. Arvind N, et al. IJCP 2006;16:10:21–4

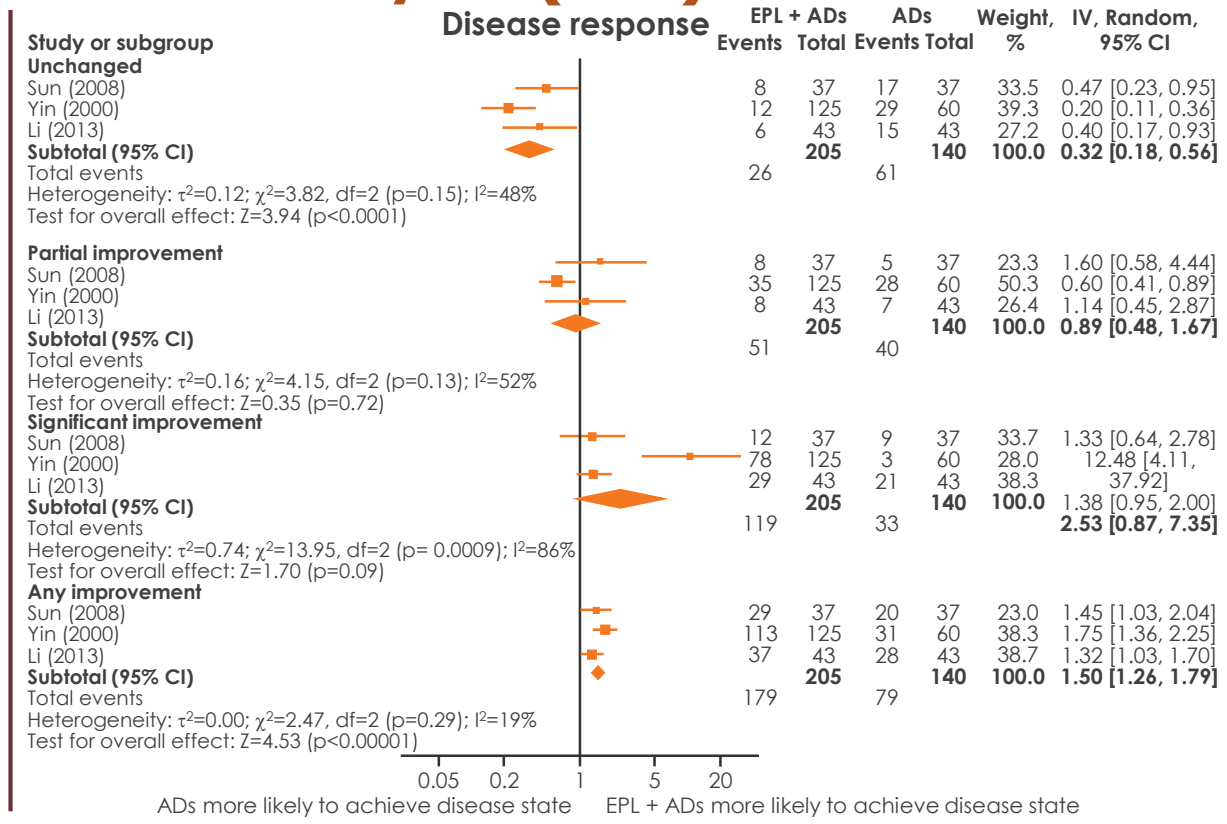
SANOFI

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

Disease severity



Disease response



AD anti-diabetic treatment; CI, confidence interval; EPL, essential phospholipids
Manuscript accepted – Sanofi data on file

SANOFI

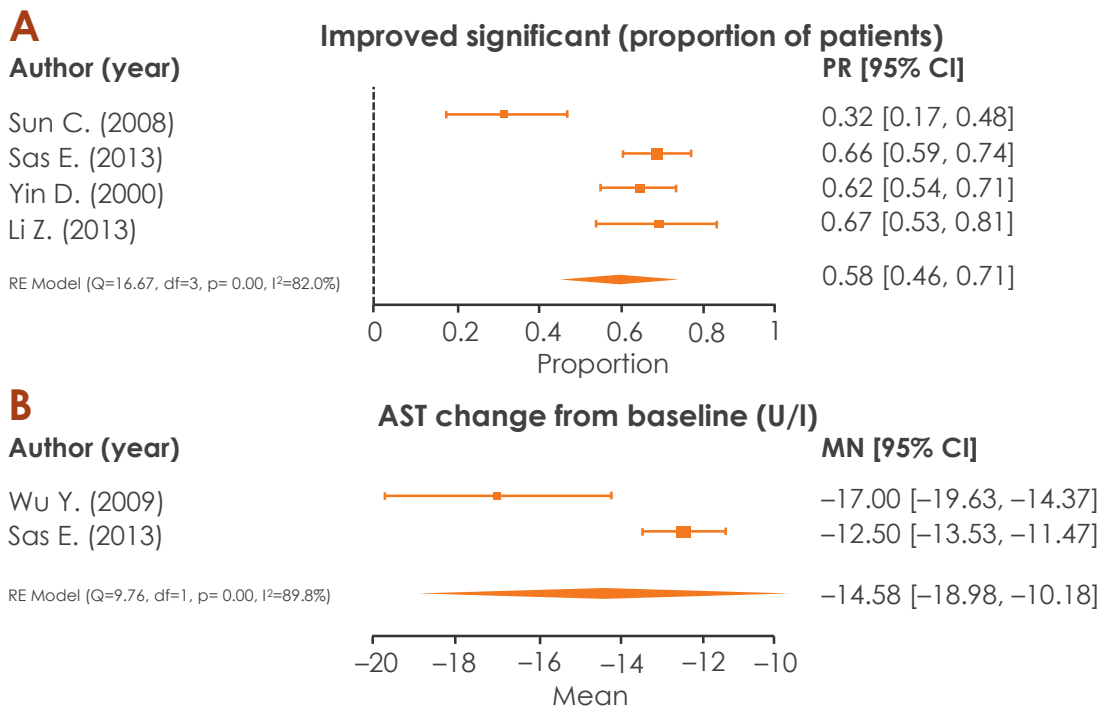
EPL for NAFLD associated with metabolic syndrome: a systematic review and network meta-analysis (2/2)

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

Significant clinical improvement (ultrasonography) and AST levels[6]



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

1. Sun C, et al. Clin Focus 2008;23:1272–3; 2. Sas E, et al. J Hepatol 2013;58(Suppl 1):S549; 3. Yin D & Kong L. Med JQ illu, 2000;15:277–8; 4. Li Z. J Tradit Chinese Med 2013;31:10–1; 5. Wu Y. J TCM Univ. Hunan 2009;29:41–2; 6. Dajani A, et al. Poster presented at APASAL 2020; PO-7-84

SANOFI

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:[1]

- 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**[2,3]

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

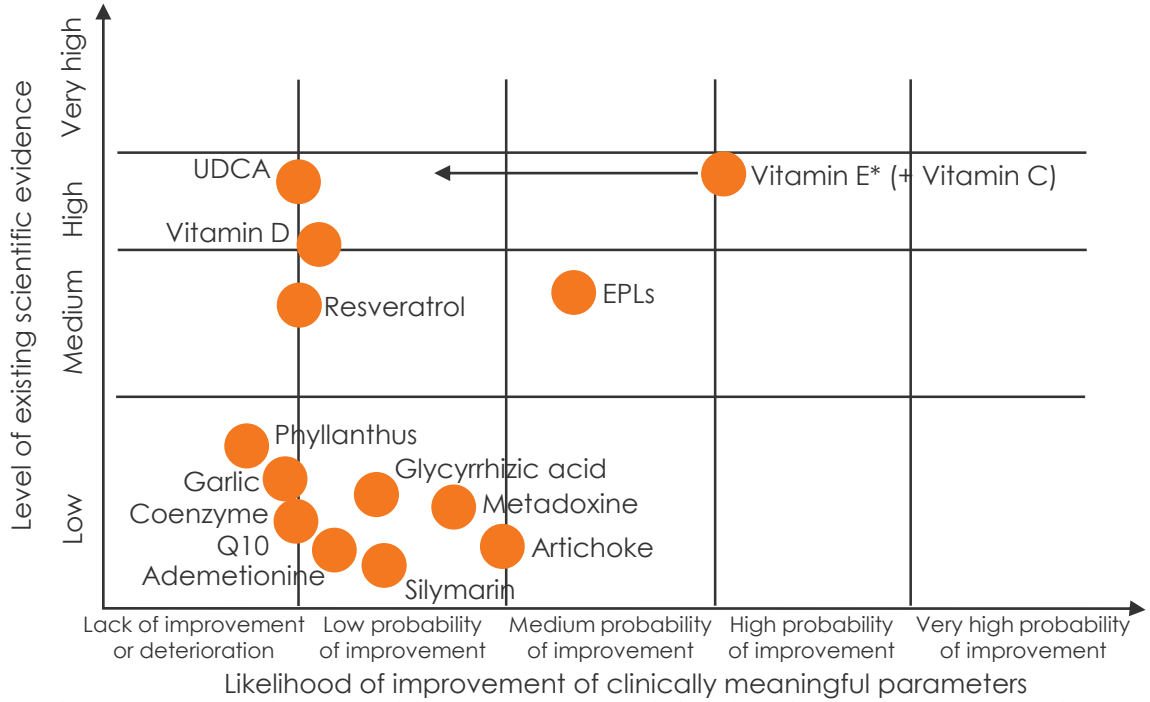
1. Jiang JZ. Drugs & Clinic 2015;30:176–80; 2. Lu XY, et al. Chin J Clin Pharmacol 2016;32:1370–5; 3. Wu Y. Journal of TCM University of Hunan 2009;29:41–2
Dajani A, et al. Drugs Ther Perspect 2020;37:249–64

SANOFI

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



*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

Dajani A, et al. Drugs Ther Perspect 2020;37:249–64

SANOFI

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

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