The role of essential phospholipids in the NAFLD continuum

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Disclosures

- Consultant to many pharmaceutical companies: Abbott, Novo Nordisk, Lunatus, MSD, Julphar, Sanofi, Takeda, Janssen, BMS, AstraZeneca, Sandoz, Tabouk, Al 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 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 **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

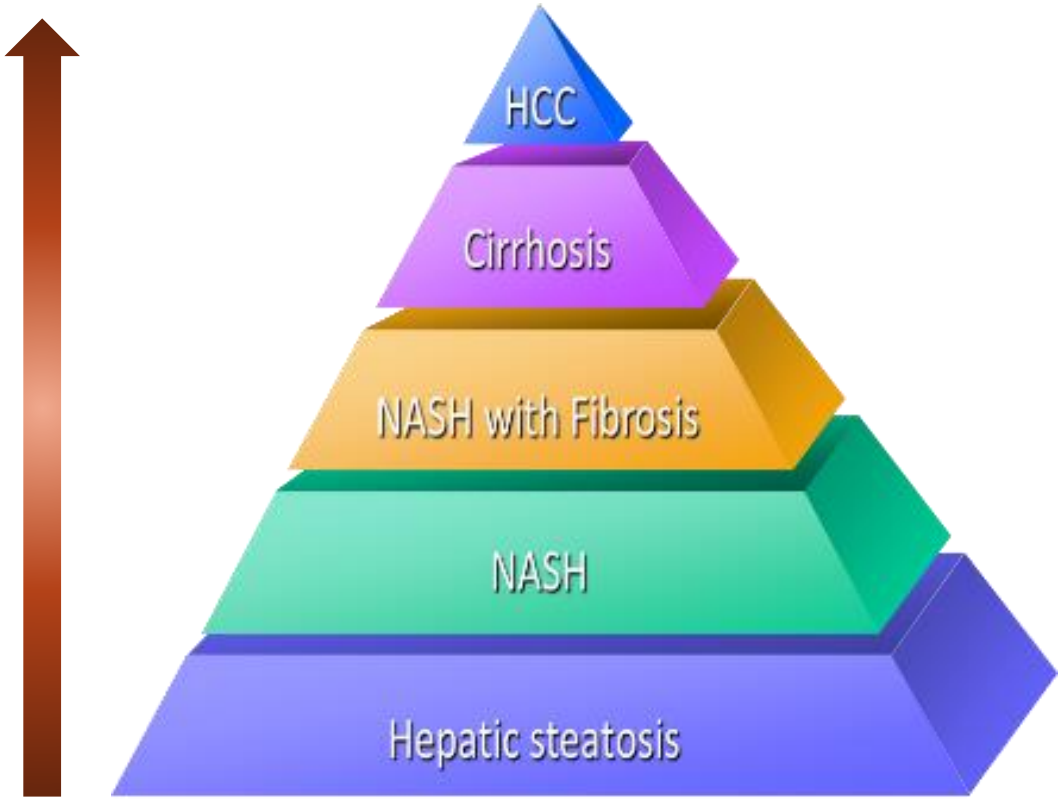
EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease

Treating NAFLD patients… Why?

Long term outcomes for patients with NAFLD and NASH:

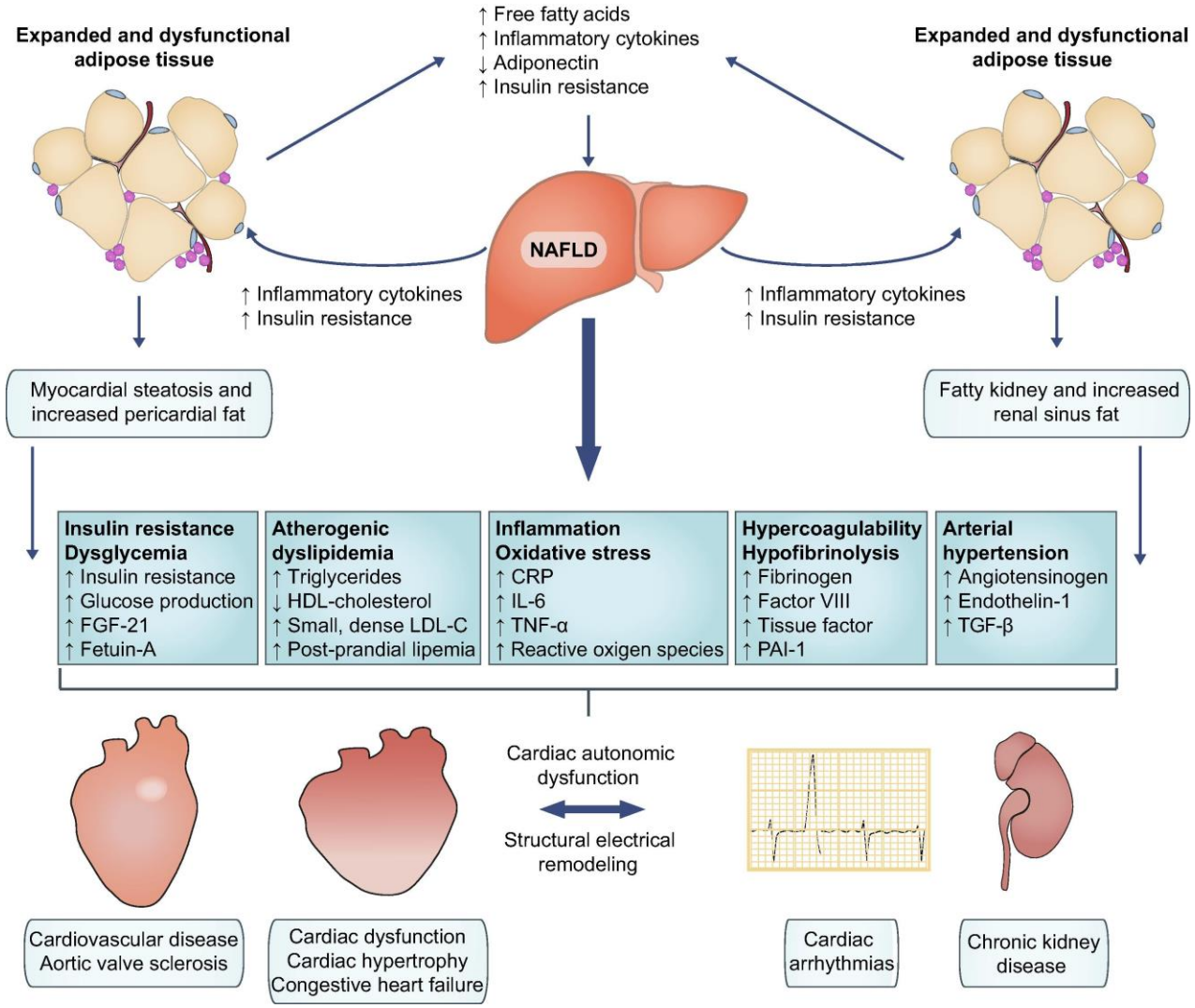
- Increased overall mortality versus matched control populations[1,2]
- NAFLD may pose a risk of CVD above and beyond traditional CVD risk factors[2,3]
  - NAFLD increases the risk of hypertension in children[4]
  - NAFLD increases the risk of atherosclerosis[3]
- NAFLD and T2DM may pose a greater risk of hypertension than T2DM alone[5]
- NAFLD may be a risk factor for CKD, colorectal cancer, endocrinopathies including thyroid dysfunction, and osteoporosis[6,7]
- Patients with NASH have an increased rate of liver-related mortality[1,2]
- Patients with NAFLD and advanced fibrosis and cirrhosis are at increased risk for HCC[2,8]

Defining the need for therapy



CKD, chronic kidney disease; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus

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



CRP, C-reactive protein; FGF-21, fibroblast growth factor 21; HDL, high-density lipoproteins; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; NAFLD, non-alcoholic fatty liver disease; PAI-1, plasminogen activator inhibitor-1; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha

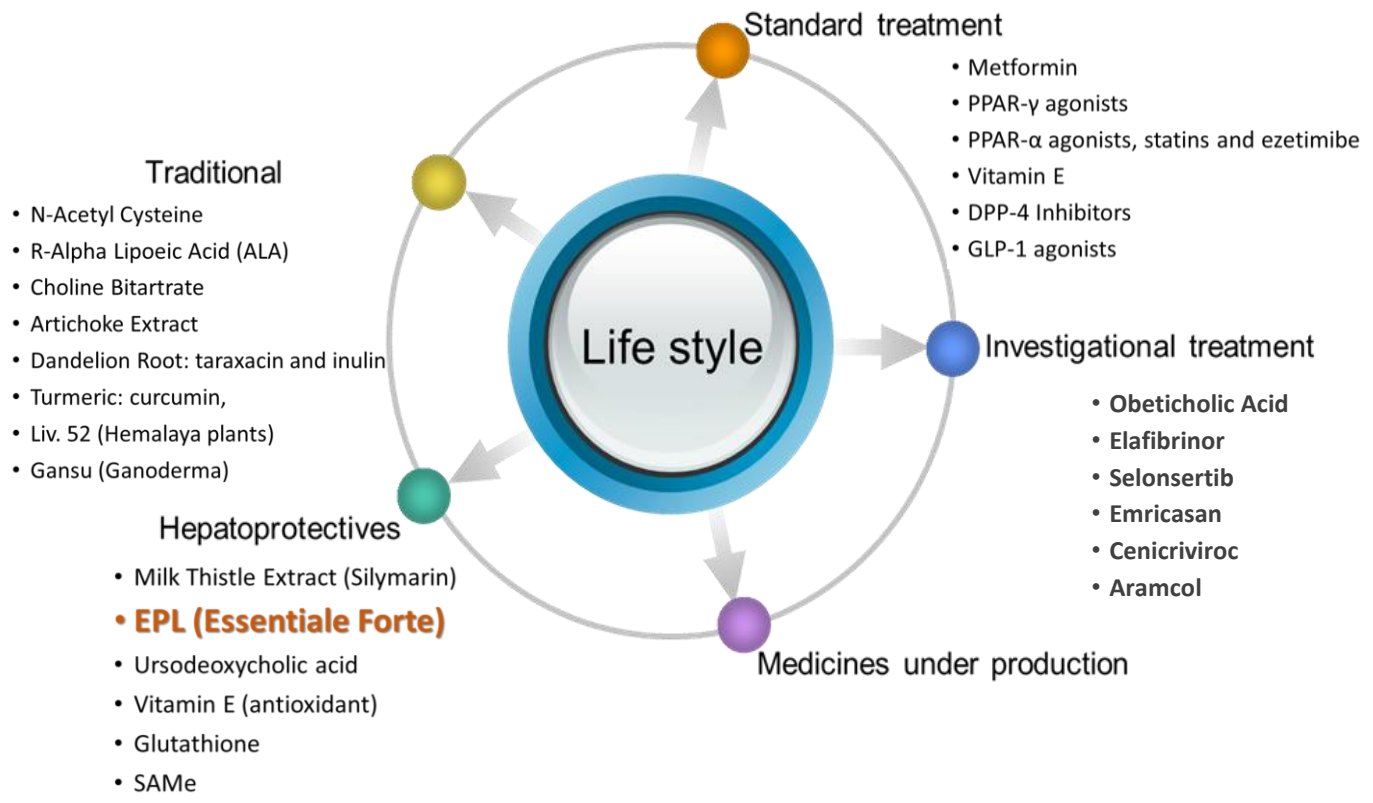
Byrne CD & Targher G. J Hepatol 2015;62 (suppl 1):S47–64

Current medical treatments are experimental

The facts

- Inconsistent evidence base for the standard medications used for comorbid conditions
- Traditional agents lack supportive research
- Hepatoprotective agents remain an important, reliable part of the protocol for adjunctive therapies

The tools



DPP-4, dipeptidyl peptidase-4; EPL, essential phospholipids; GLP-1, glucagon-like peptide-1; PPAR, peroxisome proliferatory-activated receptor; SAMe, S-adenosylmethionine

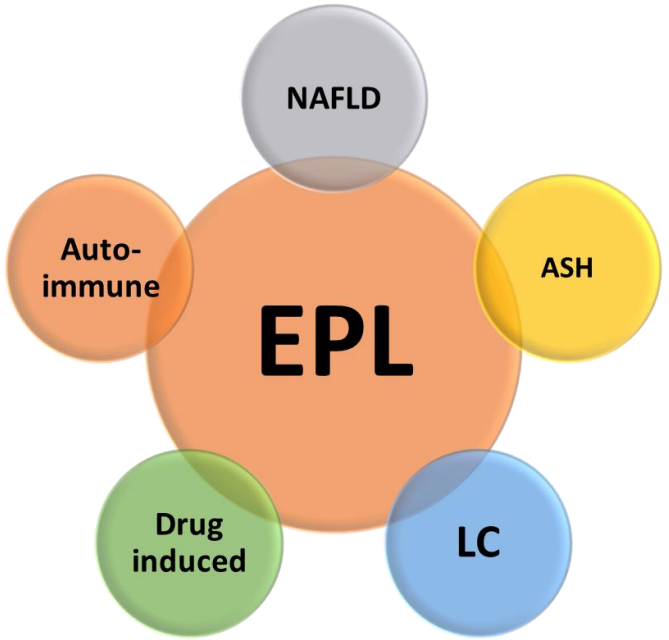
Dajani A & AbuHammour A. Saudi J Gastroenterol 2016;22:91–105

Phospholipids are essential components of mammalian cells

Role: 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



ASH, alcoholic steatohepatitis; EPL, essential phospholipids; LC, cirrhosis of the liver; NAFLD, non-alcoholic fatty liver disease

Gundermann KJ, et al. Pharmacol Rep 2011;63:643–59

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EPL as a supportive medication for NAFLD

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Evaluation of response to EPL in patients with NAFLD

Open label, randomized observational study

- Method – three arms:
  1. **Patients with lone NAFLD** (N=113)
  2. **Patients diabetic NAFLD:** patients with T2DM on metformin and/or pioglitazone (N=107)
  3. **Patients with hyperlipidemic NAFLD:** patients with mixed-type hyperlipidemia on atorvastatin and/or ezetimibe (N=104)
- Standard inclusion and exclusion criteria
- 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)

End points: 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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Treatment procedure

- Counselling provided to advise on a standard diet and exercise
- **Study drug: EPL**
  - 1800 mg (6 capsules) a day in 3 divided doses for 24 weeks then;
  - 900 mg (3 capsules) a day in 3 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

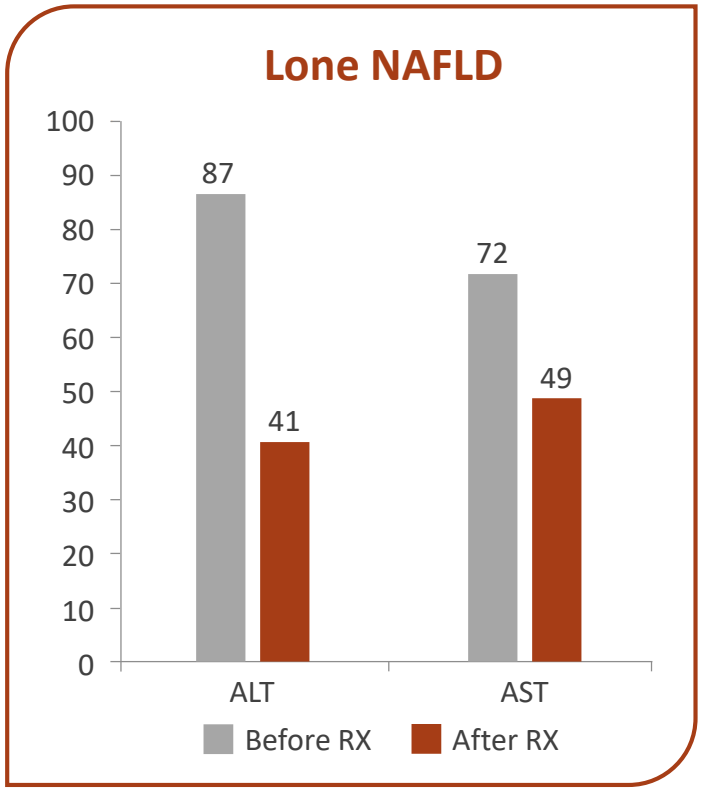
DPP-4, di[peptidyl peptidase 4; EPL, essential phospholipids; GLP-1, glucagon-like peptide 1
Dajani Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

Clinical assessment

	Lone NAFLD		Diabetic NAFLD		Hyperlipidemic NAFLD	
	Subjects	**After treatment**	**Subjects**	**After treatment**	**Subjects**	**After treatment**
Asymptomatic	(n=70) 61.9%	(n=92) 81.4%	(n=64) 59.8%	(n=85) 79.4%	(n=55) 52.9%	(n=80) 76.9%
Symptomatic	(n=43) 38.1%	(n=21) 18.6%	(n=43) 40.2%	(n=22) 20.6%	(n=49) 47.1%	(n=24) 23.1%
General symptoms						
Asthenia	(13/43) 30.2%	(3/21) 14.3%	(19/43) 44.2%	(4/22) 18.2%	(19/49) 44.2%	(13/24) 30.2%
Sleeping disorder	(13/43) 30.2%	(2/21) 9.5%	(13/43) 30.2%	(3/22) 13.6%	(13/49) 30.2%	(8/24) 18.6%
Irritability	(14/43) 32.6%	(3/21) 14.3%	(21/43) 48.8%	(6/22) 27.3%	(21/49) 48.8%	(6/24) 13.9%
GI symptoms						
Postprandial distress	(12/43) 27.9%	(4/21) 19.0%	(21/43) 48.8%	(6/22) 27.3%	(21/49) 42.9%	(9/24) 20.9%
Flatulence	(13/43) 30.2%	(6/21) 28.6%	(21/43) 48.8%	(8/22) 36.4%	(21/49) 42.9%	(18/24) 41.9%
RUQ pain	(9/43) 20.9%	(2/21) 9.5%	(9/43) 20.9%	(4/22) 18.2%	(9/49) 18.3%	(4/24) 9.3%
Nausea	(8/43) 18.6%	(2/21) 9.5%	(8/43) 18.6%	(3/22) 13.6%	(8/49) 16.3%	(7/24) 16.3%
Heartburn	(5/43) 11.6%	(3/21) 14.3%	(5/43) 11.6%	(2/22) 9.1%	(5/49) 10.2%	(2/24) 4.65%
Clinical finding						
Jaundice	(4/43) 9.3%	(2/21) 9.5%	(5/43) 11.6%	(2/22) 9.1%	(5/49) 10.2%	(3/24) 6.97%
Hepatomegaly	(9/43) 20.9%	(4/21) 19.0%	(13/43) 30.2%	(2/22) 9.1%	(13/49) 26.5%	(11/24) 25.6%
		P<0.01		P<0.01		P<0.01

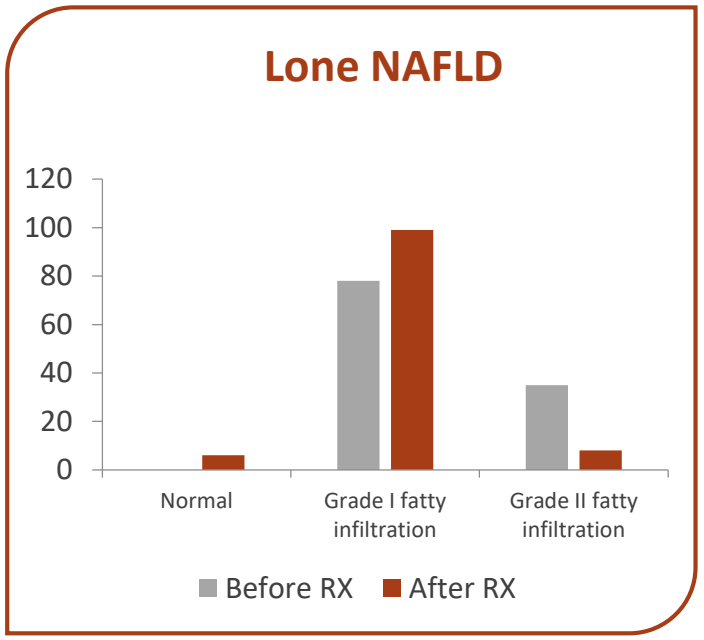
GI, gastrointestinal; NAFLD, non-alcoholic fatty liver disease
Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

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

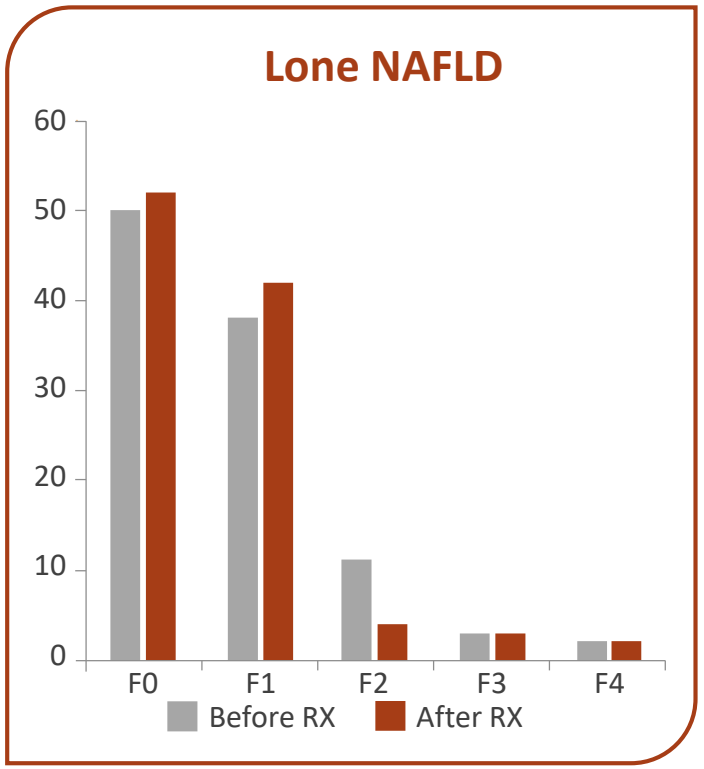
Ultrasonography findings



Overall improvement in echography 29.2%

ALT. alanine aminotransferase; AST, aspartate aminotransferase
Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

Elastography findings



Overall improvement in elastography 14.2%

F, fibrosis stage

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

Summary of results

Variable	Lone NAFLD	T2DM	Hyperlipidemia
Clinical	Significant improvement of clinical symptoms and signs	Significant improvement of clinical symptoms and signs	Significant improvement of clinical symptoms and signs
Transaminases	Significant reduction	Significant reduction	Significant reduction
Ultrasonography	Improvement in 29.2% of patients	Improvement in 23.4% of patients	Improvement in 20.2% of patients
Elastography	Change in liver stiffness measurement in 14.2% of patients	Change in liver stiffness measurement in 26.1% of patients	Change in liver stiffness measurement in 20.2% of patients

T2DM, type 2 diabetes mellitus
Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

According to current evidence, EPL as a supportive treatment option in NAFLD have demonstrated improvement in which symptoms?

1. Asthenia
2. Sleeping disorder
3. Nausea
4. All
5. None

EPL, essential phospholipids; NAFLD, non-alcoholic associated fatty liver disease

Clinical evidence for EPL

Liver steatosis in NAFLD

- EPL reduces lipid accumulation in the liver[1]
  - Recent studies in rats fed a HFD indicate that treatment with EPL (550 mg/kg/day orally) for 4 weeks **reduces lipid content of liver tissue**
  - This effect was associated with increased expression of the leptin gene as shown by **increased levels of leptin mRNA**
- EPL alleviates HFD-induced hyperlipidemia[2]
- Suggested metabolic effects of EPL in steatosis reduction: increased TG oxidation, decreased TG synthesis and increased lipoprotein secretion[3–6]

Early stage NAFLD is characterized by liver steatosis

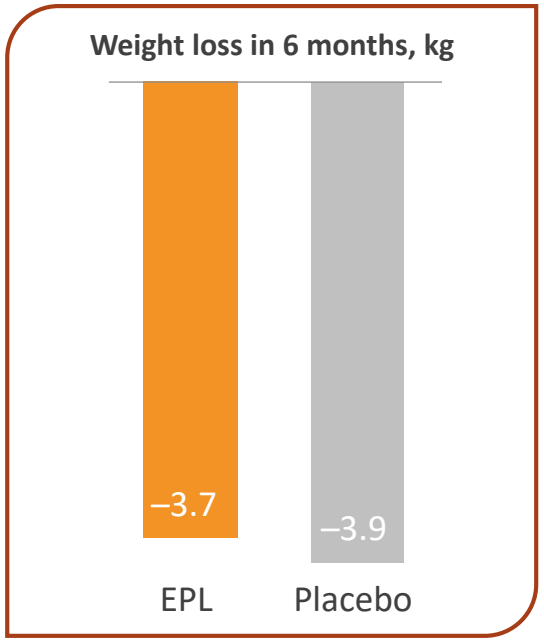
Treatment with Essentiale® Forte has shown to reduce liver steatosis in animal model studies[1,2]

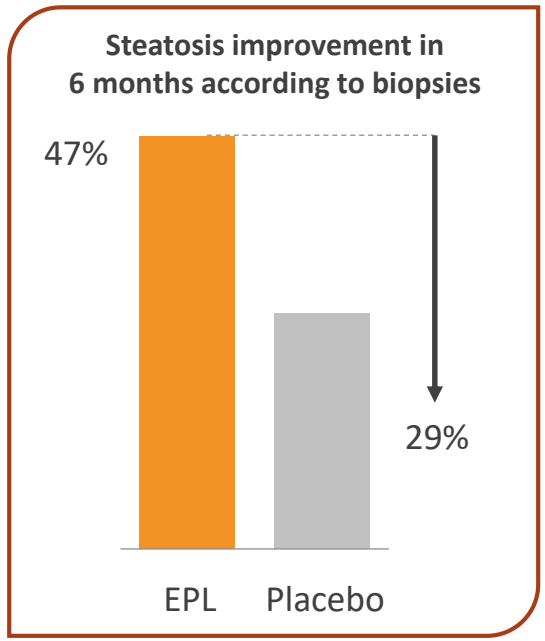
EPL, essential phospholipids; HFD, high-fat diet; NAFLD, non-alcoholic fatty liver disease; TG, triglyceride

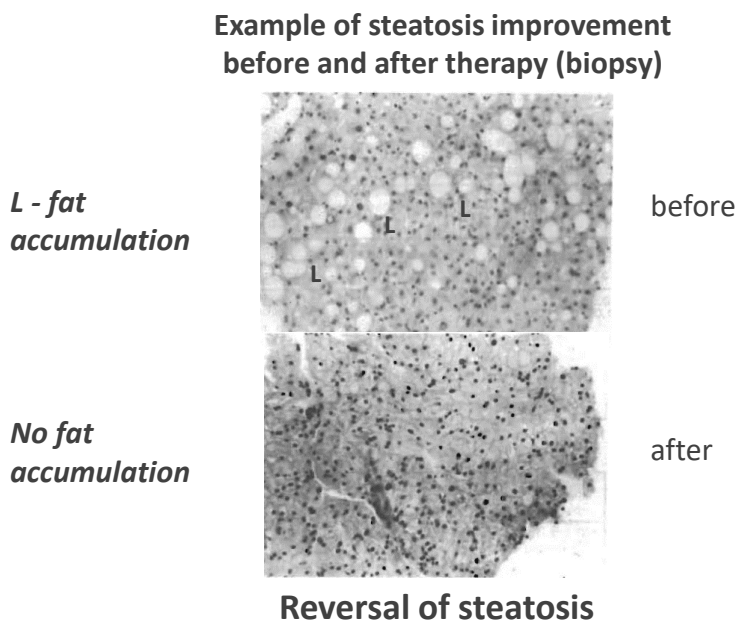
1. Jiang Q, et al. Acad J Guangzhou Med Coll 2008;37; 2. Lee HS, et al. Life Sciences 2014;118:7–14; 3. Csak T, et al. PLoS ONE 2015;10:e0129251; 4. Yao ZM, et al. J Biol Chem 1988;263:2998–3004; 5. Jacobs RL, et al. J Biol Chem 2004;279:47402–10; 6. Matías Caviglia J, et al. J Lipid Res 2004;45:1500–9

Effects of EPL in steatosis: Biopsy changes

- Double-blind, placebo-controlled clinical study of **30 patients with histology-proven NAFLD, T2DM** and HBsAg negative receiving EPL **[Essentiale® forte*] 1800 mg/d** 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
d, Day; EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus. Gonciarz Z, et al. Med Chir Digest 1988;17:61–5

Study: Yin & Kong, 2000

- **Study design:** Prospective, randomized, controlled, parallel-group study
- **Objective:** To assess the efficacy of Essentiale® Forte
- **Patients:** Patients with NAFLD associated with diabetes (N=185)
  - 125 patients received Essentiale® Forte, 1800 mg/day (2 capsules tid) + standard care for 12 weeks
  - 60 patients received standard care for 12 weeks
- **Standard care:** Diabetic treatment + diet + exercise
- **Outcomes:** Response rates, blood lipids, ALT and fasting blood glucose

ALT, alanine aminotransferase; NAFLD, non-alcoholic fatty liver disease; tid, three times a day

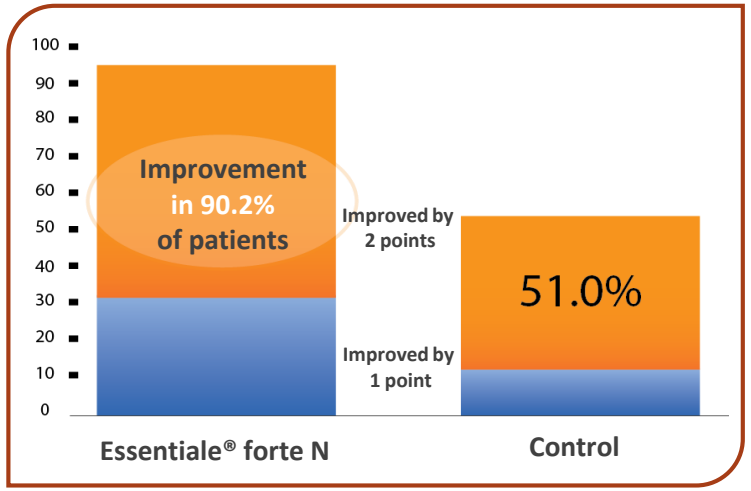
Yin D, et al. Med J Q ilu 2000;15:277–8

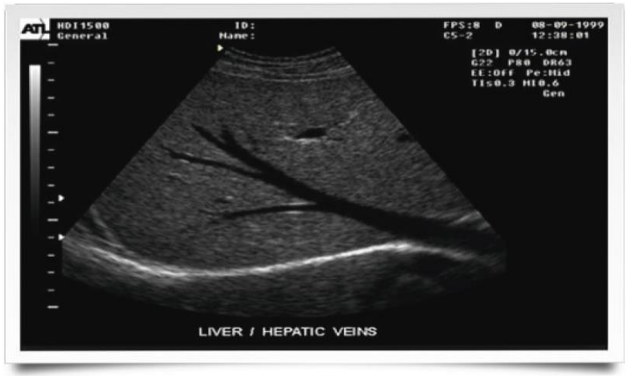
Study: Yin & Kong, 2000

Results

- Response rates were significantly higher with Essentiale® Forte

		Standard care (N = 60)	Essentiale® Forte (N = 125)
Response rate [n (%)]	Significant (improved by 2 points)	3 (5.0%)	78 (62.4%)*
	Effective (improved by 1 point)	28 (46.7%)	35 (28.0%)*
	Non-effective	29 (48.3%)	12 (9.6%)*





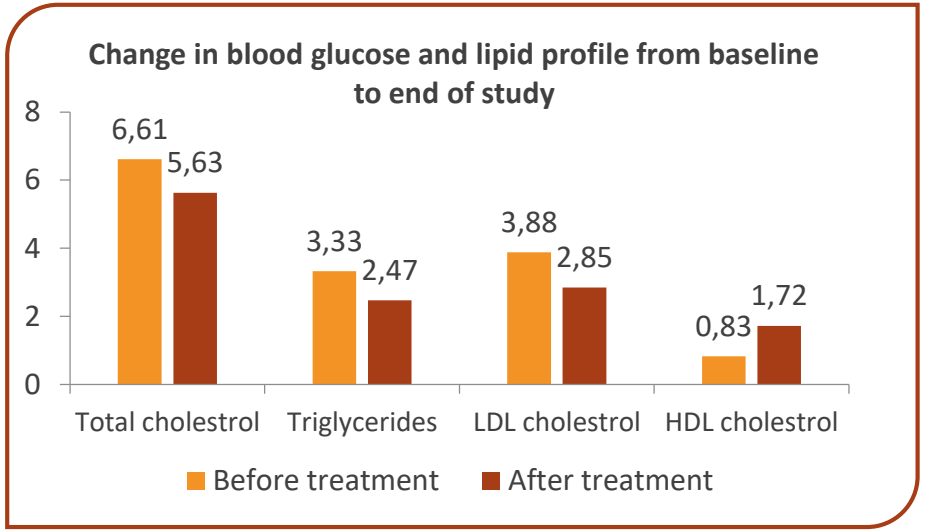
* P<0.05 between treatments; Data are n(%)
Yin D, et al. Med J Q ilu 2000;15:277–8

Study: Yin & Kong, 2000

Results (continued)

- Reductions in ALT were significantly higher with Essentiale® Forte

		Standard care (N = 60)	Essentiale® Forte (N = 125)
ALT (µmol•s-1/l)	Baseline	0.7 ± 0.1	0.8 ± 0.1
	12 weeks	512 ± 0.1	0.3 ± 0.04*
(mean ± SD)	P value (baseline vs. 12 weeks)	P>0.05	P<0.01



- **Fasting blood glucose** levels were reduced with Essentiale® Forte versus standard care
- Reductions in **triglycerides and cholesterol** were significantly higher with Essentiale® Forte versus standard care
- **HDL-C levels** were significantly higher with Essentiale® Forte versus standard care

P<0.05 between treatments; Data are mean ± SD
ALT, alanine aminotransferase s; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; SD, standard deviation
Yin D, et al. Med J Q ilu 2000;15:277–8

Study: Sas et al, 2013

- **Study design:** Randomized, prospective, blinded clinical trial
- **Objective:** Evaluate the efficacy of EPL
- **Patients:** Patients with NASH and T2D controlled by diet and metformin (N=215)
  - Investigational group: 178 patients received EPL + standard of care for 6 months
  - Control group: 37 patients received standard of care for 6 months
  - Standard of care: Diet, metformin and physical activity regimen
    - 114 patients in the EPL group and 37 patients in the control group were followed for up to 7 years
- **Outcomes:** Liver function markers and ultrasound results

EPL, essential phospholipids; NASH, non-alcoholic steatohepatitis; RCTs, randomised controlled trials; T2D, type 2 diabetes
Sas E, et al. J Hepatol 2013;58:S409–S566

Study: Sas et al, 2013

Results

- All liver enzymes were significantly reduced with Essentiale® Forte versus standard of care

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

	Study Endpoints	Essentiale® (N=178)
ALT	Baseline 6 months P value	56.5 ± 28.6 IU/L 35.2 ± 18.4 IU/L P=0.02
AST	Baseline 6 months P value	39.0 ± 9.0 IU/L 26.5 ± 7.2 IU/L P=0.04
γ-GT	Baseline 6 months P value	38.2 ± 11.4 IU/L 27.5 ± 8.6 IU/L 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
Sas E, et al. J Hepatol 2013;58:S409–S566

Study: Sas et al, 2013

Results (continued)

- Hepatic echo-texture was significantly improved with EPL versus standard of care
- Sonographic signs of fatty liver significantly decreased with EPL versus standard of care

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 to control (P=0.03)

*P=0.02; **P<0.05. Data shown as n(%)
EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; RCTs, randomized controlled trials
Sas E, et al. J Hepatol 2013;58:S409–S566

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EPL as adjunctive therapy

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At what stage in the NAFLD continuum would you first consider the place of EPL?

1. Hepatic steatosis
2. NASH
3. NASH with fibrosis
4. All

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

EPL and Metformin in NAFLD

	Metformin + EPL vs metformin alone[1,2]
Number of patients	74/86
Overall response, TG and LDL	78.4% vs 5 4.1% / 86% vs 65%
ALT/AST	Improved in both studies
Ultrasound	Significant improvement

Adding EPL to metformin significantly improved efficacy compared with metformin alone

ALT, alanine aminotransferase, AST, aspartate aminotransferase; LDL, low-density lipoprotein; TG, triglycerides

1. Sun C, et al. Clinical Focus 2008;23:1272–3; 2. Li, et al 2013

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EPL and probiotics

	EPL	EPL + Probiotics
Number of patients	200	200
AST, ALT, Lipid profiles	Reduced	Greater reduction
TNFα	Reduced	Greater reduction
Fatty liver	Significant improvement	Comparable P<0.05

Adding EPL to probiotics in treatment of NAFLD increases efficacy of both

ALT, alanine aminotransferase, AST, aspartate aminotransferase; EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; TNFα, tumor-necrosis factor alpha
Wang W, et al. Zhonghua Nei Ke Za Zhi 2018;57:101–6

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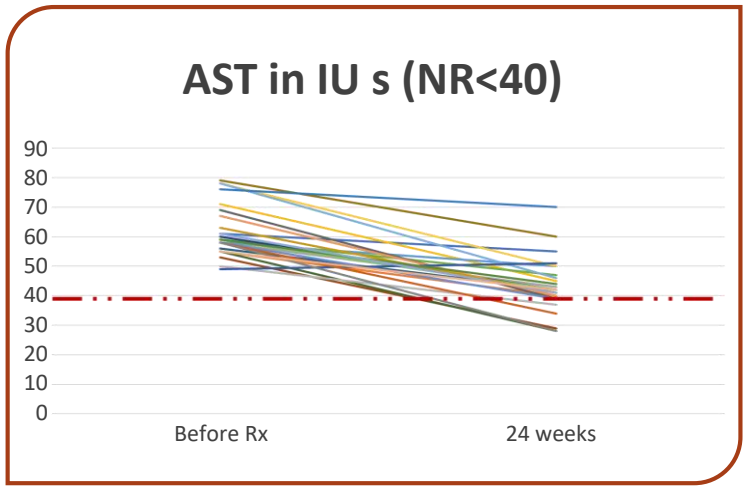
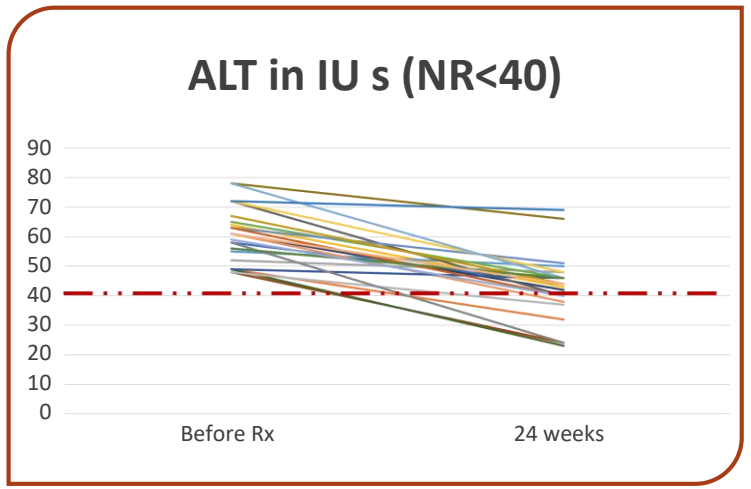
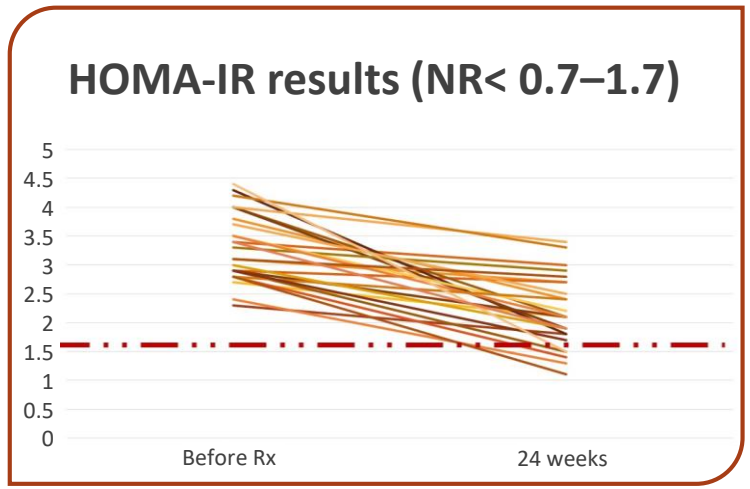
EPL & Bacillus Clausii in NAFLD

A prospective pilot study to evaluate the effect of adding the probiotic, Bacillus Clausii, to patients with moderate to severe NAFLD who are on Essentiale® forte treatment (N=38)*







*Study included patients with NAFLD (primary or with co-morbid states) who 1) were on treatment with Essential® forte for the previous six months; 2) were still receiving treatment with EPL; or 3) had an elastography fibrosis score of ≥F1 (>4.0 kPa). Inclusion/exclusion criteria applied. 26 people completed the study and 12 dropped out

ALT, alanine aminotransferase; AST, aspartate transaminase; EPL, essential phospholipids; F, fibrosis stage; HOMA-IR. Homeostatic Model Assessment of Insulin Resistance; kPa, kilopascal; NAFLD, non-alcoholic fatty liver disease; NR, normal range

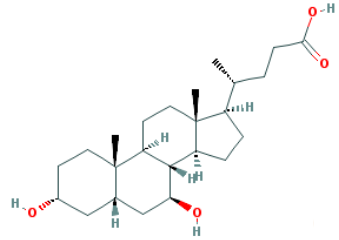
Please note, this information is preliminary data and is currently unpublished – provided by speaker

EPL versus comparator agents

Ursodeoxycholic acid (UDCA)

Medical information

- **Historical background:** UDCA – hydrophilic bile acid indicated for the treatment of cholestatic liver diseases[1,2]
- Oral, less bile acid therapy requires the existence of radiolucent cholesterol-enriched gallstones more than 2 cm in diameter[3,4]
- Monitoring of serum values is recommended upon initiation and during treatment[3]
- Contrainidications: acute cholestasis



Clinical trials

- Some trials assessed the effects of UDCA in NAFLD/NASH patients – proof-of-concept studies only due to their design, small size sample and surrogate endpoints
- Results of 2 large RCTs show that UDCA is not more efficacious than placebo in patients with NASH
  - Lindor et al: Double-blind RCT, 166 patients with liver biopsy–proven NASH received 13–15 mg/kg/d of UDCA (n=80) or placebo (n=86) for 2 years[5]
  - Leuschner et al : Double-blind RCT, patients with liver biopsy–proven NASH received 23–28 mg/kg/d of UDCA (n=94) or placebo (n=91) for 18 months. **No significant differences in the liver histology could be detected between the groups in comparison with placebo[6]**

Clinical practice guidelines

- UDCA can reduce the level of AST, ALT but no data exists regarding long-term effect on fibrosis in patients with NAFLD[7]
- Demonstrates some biochemical but no histological improvements[8]
- **Not recommended for the treatment of NAFLD/NASH[9]**
  - Based on relevant scientific data, for the treatment of NAFLD/NASH, UDCA does not demonstrate higher efficacy vs placebo

ALT, alanine aminotransferase; AST, aspartate transaminase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RCT, randomized controlled trial

1. Trauner M & Graziadei IW. Aliment Pharmacol Ther. 1999 Aug;13:979–96; 2. Kumar D, et al. J Gastroenterol Hepatol 2001;16:3–14; 3. Ursofalk SmPC; Available at https://www.medicines.org.uk/emc/product/145/pil#gref (Last accessed: October 2020); 4. Ilyas Tuncer, et al. Gastroenterol Res Pract 2012;2012:159438; 5. Lindor KD, et al. Hepatology 2004;39:770–8; 6. Leuschner UFH, et al. Hepatology 2010;52:472–9; 7. Российское общество по изучению печени. Методические рекомендации для врачей. Диагностика и лечение неалкогольной жировой болезни печени. Под редакцией академика РАН, профессора В. Т. Ивашкина. Москва 2015;
8. .EASL-EASD-EASO. J Hepatol 2016;64:1388–402; 9. . Chalasani N, et al. Hepatology 2018;67

UDCA and Essentiale® forte: Comparative study

Comparative, double-blind study to compare the efficacy of UDCA and Essentiale® forte in patients with early-stage NAFLD (N=40)

Results

- A trend towards improved symptoms and ultrasound findings was observed in the EPL group versus the UDCA group
- More consistent improvements in liver function tests were found in the EPL group versus 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, 2 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 transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; EPL, essential phospholipids; UDCA, ursodeoxycholic acid
Arvind N, et al. IJCP 2006;16:10:21–4

SANOFI

Silymarin: Meta-analysis 2017

World Journal of Gastroenterology

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META-ANALYSIS

Effect of silymarin on biochemical indicators in patients with liver disease: Systematic review with meta-analysis

Camila Ribeiro de Avelar, Emile Miranda Pereira, Priscila Ribas de Farias Costa, Rosângela Passos de Jesus, Lucivalda Pereira Magalhães de Oliveira

Does silymarin influence on serum levels of ALT, AST, γGT in patients with liver diseases?

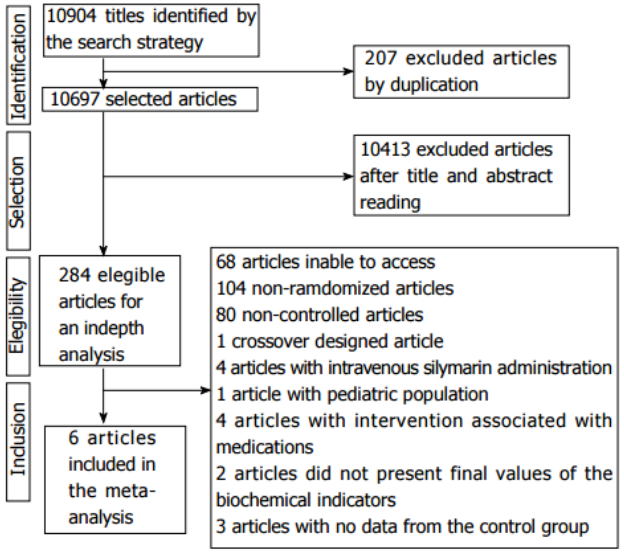


Table 2 Results of selected studies for meta-analysis

Ref.	Used Indicators	Results
Loguercio *et al*[39], 2007	ALT, γGT	There were no adverse events in either group. The intervention group presented a significant reduction of hepatic steatosis in the ultrasonography score (change from 2-3 to 1-2) after 6 mo and 12 mo ($P < 0.01$). Significant reduction of ALT and γGT after 6 mo and 12 mo only in the intervention group ($P < 0.01$). Treatment affected the levels of ALT and γGT Range independent of changes in BMI of the participants. We did not evaluate data from the group with HCV patients
Hashemi *et al*[38], 2009	ALT, AST	There was a significant reduction in the average of ALT levels only in the intervention group (113.54 IU/mL *vs* 73.14 IU/mL) ($P < 0.001$). The percentage of patients with normalization (ALT < 40) was 32% after 3 mo and 52% after 6 mo in the intervention group and the difference in these percentage between control and intervention group was significant ($P = 0.001$). There was also a significant reduction in AST averages only in the intervention group (71.42 IU/mL *vs* 49.66 IU/mL) ($P = 0.006$). The percentage of patients with normalization (AST < 40) was 46% after 3 mo and 62% after 6 mo in the intervention group and the difference in these percentages between control group and intervention was also significant ($P = 0.0001$)
Massodi *et al*[59], 2013	ALT, AST	There were no serious adverse events and the side effects were similar in frequency and uncommon in both groups. There was a significant reduction in the average of ALT levels only in the intervention group (84.06 IU/mL *vs* 68.54 IU/mL) ($P < 0.001$) and in the average AST levels only in the intervention group (71.94 IU/mL *vs* 54.70 IU/mL) ($P < 0.001$)
Solhi *et al*[28], 2014	ALT, AST	There was a significant difference in the mean values of ALT levels only in the intervention group (91.3 IU/mL *vs* 38.4 IU/mL) ($P = 0.026$) and in the AST levels only in the intervention group (62.8 IU/mL *vs* 30.5 IU/mL) ($P = 0.038$).
Aller *et al*[34], 2015	ALT, AST, γGT	There were no adverse events in both groups. There was a significant improvement in the fibrosis score in both groups ($P < 0.05$). There was a significant difference in the reduction of the average γGT levels (81.5 IU/L *vs* 46.2 IU/L) ($P < 0.05$) in the intervention group and also in the control group (80.5 IU/L *vs* 50.3 IU/L) ($P < 0.05$). There was a significant reduction only in the average of ALT levels (70.8 IU/L *vs* 54.7 IU/L) ($P < 0.05$) and AST (41.6 IU/L *vs* 36 IU/L) ($P < 0.05$) in the control group.
Sorrentino *et al*[35], 2015	ALT, AST, γGT	No adverse events were reported in both groups. Mean levels of ALT, AST and γGT were within normal limits at the baseline. There was a significant reduction only in the average values of right lobe size of the liver by the USG (17.24 cm *vs* -0.96 cm) ($P = 0.044$)

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; γGT: Gamma glutamyl transpeptidase.

Silymarin minimally reduced the serum levels of ALT and AST; however, this effect is not clinically relevant It is necessary to carry out studies with more appropriate methodological designs

ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; EPL, essential phospholipids; γGT, gamma-glutamyl transpeptidase

Ribeiro de Avelar C, et al. World J Gastroenterol 2017;23:5004–17

EPL vs other comparator agents

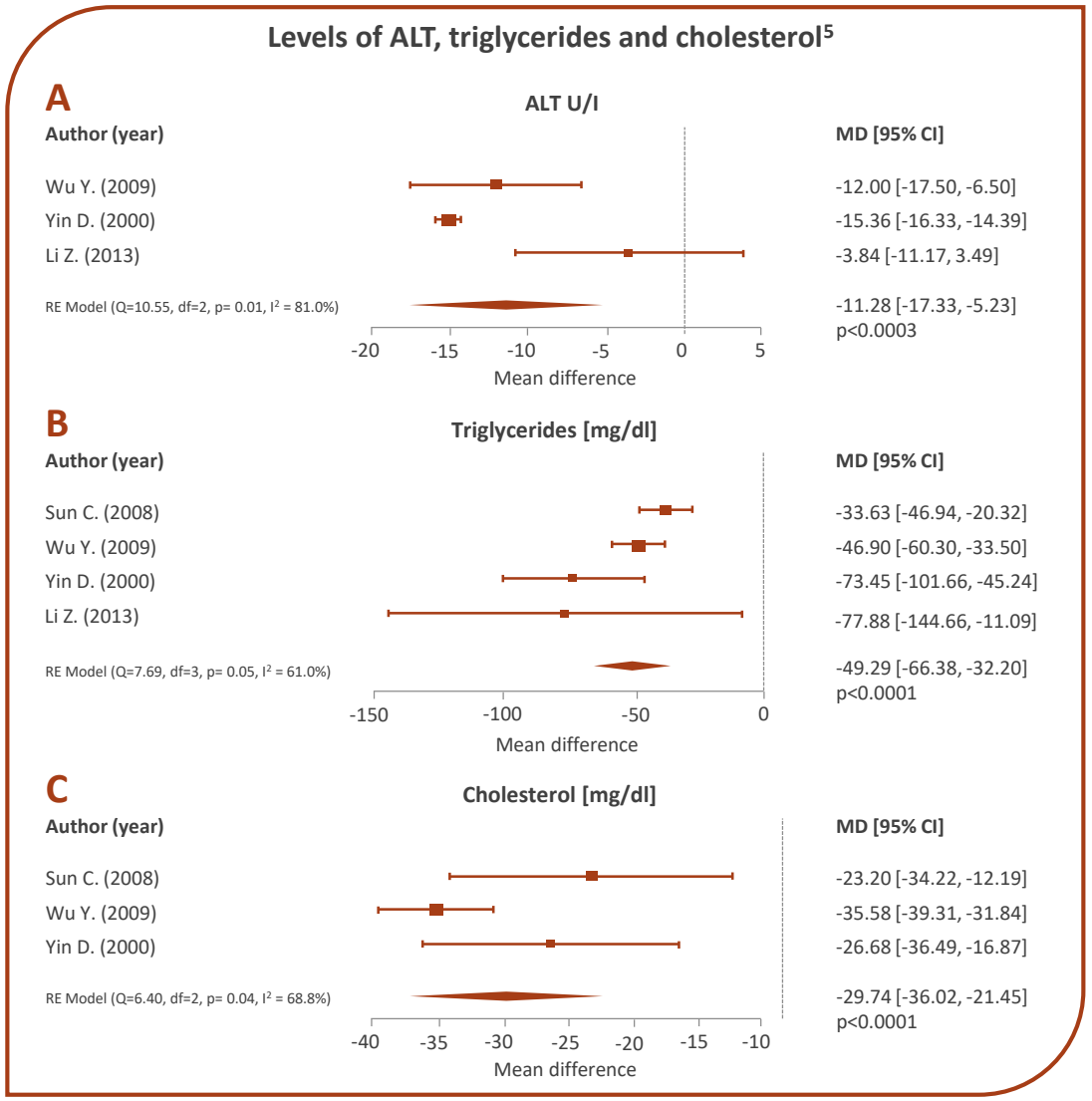
	N	Clinical	ALT/AST/GGT	Overall
EPL vs UDCA (in diabetic, obese patients)[1]	40	>EPL	>EPL (US: 20% for EPL vs 10% for UDCA)	Symptom reduction: 45% for EPL vs 30% for UDCA
EPL/sibutramine vs sibutramine[2]	80	>EPL	>EPL (reduction in HOMA-IR and steatosis)	US improvement in 92% of EPL/sibutramine treated patients vs no change in 23% of patients
EPL/silymarine vs EPL/glutathione[3]	150	Same	**Severe FL:** 17 cases pre-treatment vs 4 post-treatment, in the control group; 16 cases pre-treatment vs 0 cases post-treatment in the treatment group **Moderate FL:** 34 cases pre-treatment vs 14 post-treatment, in the control group; 36 cases pre-treatment vs 4 cases post-treatment in the treatment group	Response rate: 93.4% in the treatment group vs 82.4% in the control group
EPL vs vitamins/inosine[4]	52	>EPL	>EPL	>EPL

EPL, essential phospholipids; FL, fatty liver; HOMA-IR, homeostatic model assessment of insulin resistance; UDCA, ursodeoxycholic acid; US, ultrasound

1. Arvind N, et al. IJCP 2006;16:10:21–4; 2. Sas E, et al. Gut 2012;61(Suppl 2):A216–A217; Jiang JZ. Drugs Clinic 2015;30:176–80; 4. Du Q. Chin J Gastro Hepa 2004;13

EPL for NAFLD associated with metabolic syndrome: A systematic review and network meta-analysis (1/3)

- Results of a direct meta-analysis of RCTs comparing the effect of treatment with EPL plus AD vs AD therapy:
  - **A:** Change in ALT, three studies[1–3] (total n=371), mean treatment 1.97 months
  - **B:** Change in triglyceride levels, four studies[1–4] (total n=445), mean treatment 2.1 months
  - **C:** Change in total cholesterol levels, three studies[1,2,4] (total n=359), mean treatment 2.27 months



AD anti-diabetic treatment; ALT, alanine aminotransferase; CI, confidence interval; EPL, essential phospholipids; MD, mean difference; RCTs, randomised controlled trials; RE, random effects

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

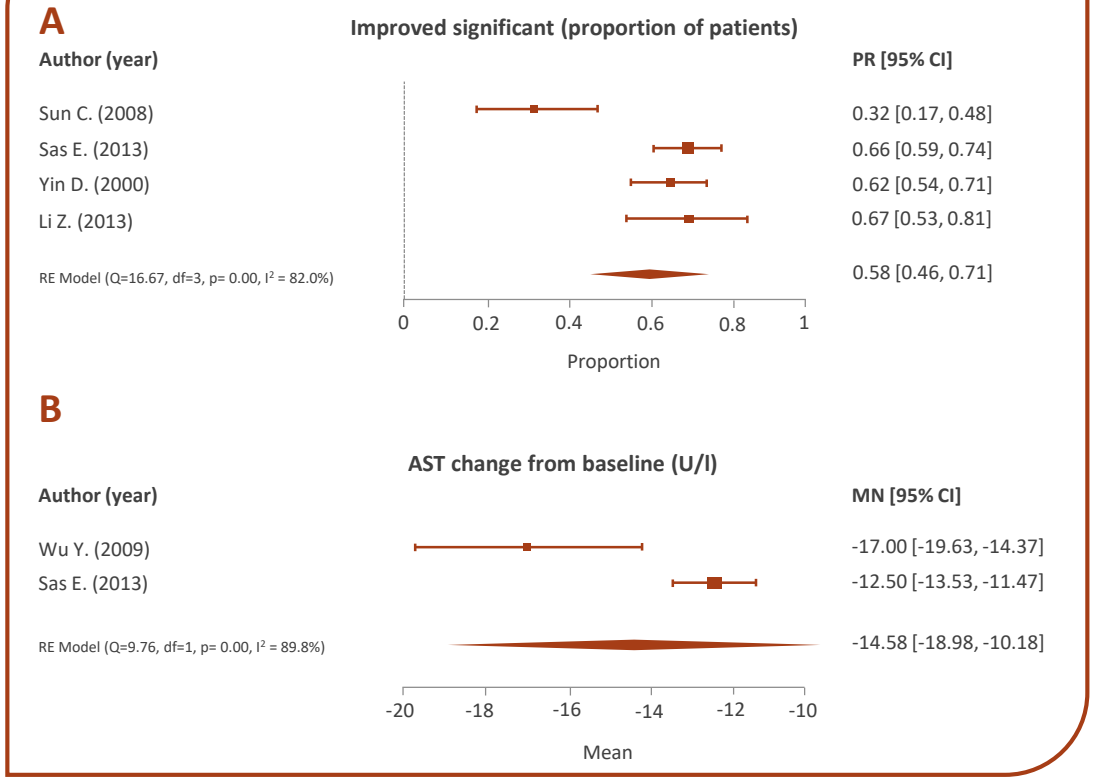
EPL for NAFLD associated with metabolic syndrome: A systematic review and network meta-analysis (2/3)

- Results of a direct meta-analysis of RCTs comparing the effect of treatment with EPLs plus AD vs AD therapy (continued):

  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]

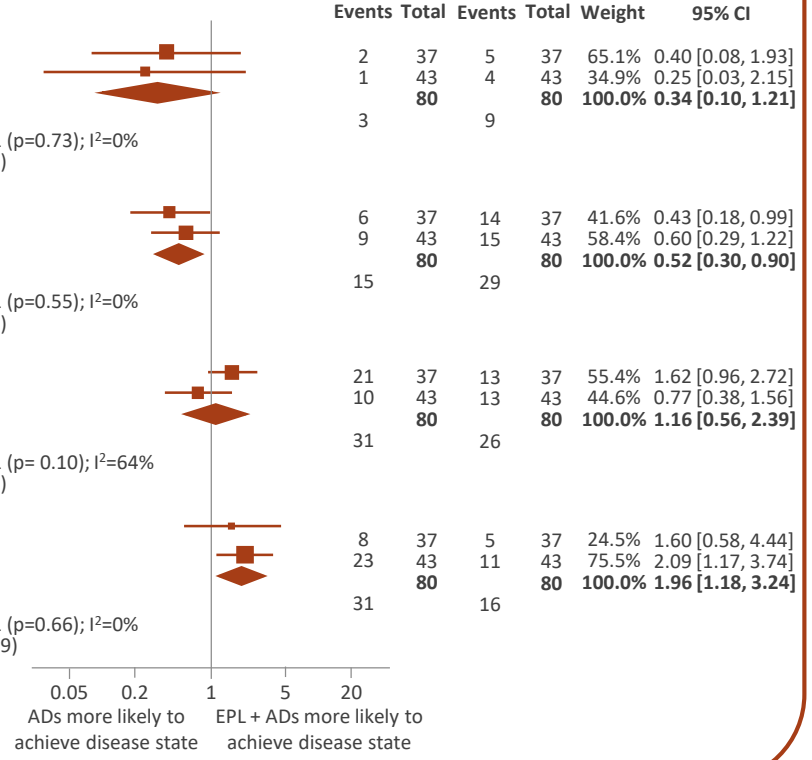


AD anti-diabetic treatment; AST, aspartate aminotransferase; CI, confidence interval; EPL, essential phospholipids; MN, raw mean; PR, proportion of responders; RCTs, randomised controlled trials; RE, random effects

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

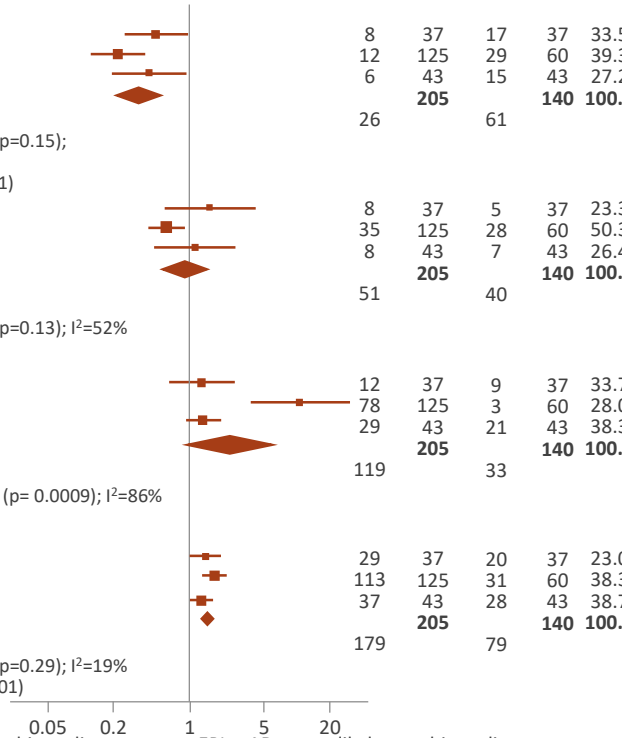
EPL for NAFLD associated with metabolic syndrome: A systematic review and network meta-analysis (3/3)

Disease severity



Study or subgroup	EPL + ADs Events	EPL + ADs Total	ADs Events	ADs Total	Weight	Risk ratio IV, Random, 95% CI
Severe						
Cunxu (2008)	2	37	5	37	65.1%	0.40 [0.08, 1.93]
Zhiguo (2013)	1	43	4	43	34.9%	0.25 [0.03, 2.15]
Subtotal (95% CI)		**80**		**80**	**100.0%**	**0.34 [0.10, 1.21]**
Total events	3		9			
Heterogeneity: τ^2=0.00; χ^2=0.12, df=1 (p=0.73); I^2=0%						
Test for overall effect: Z=1.67 (p=0.10)						
Moderate						
Cunxu (2008)	6	37	14	37	41.6%	0.43 [0.18, 0.99]
Zhiguo (2013)	9	43	15	43	58.4%	0.60 [0.29, 1.22]
Subtotal (95% CI)		**80**		**80**	**100.0%**	**0.52 [0.30, 0.90]**
Total events	15		29			
Heterogeneity: τ^2=0.00; χ^2=0.36, df=1 (p=0.55); I^2=0%						
Test for overall effect: Z=2.35 (p=0.02)						
Mild						
Cunxu (2008)	21	37	13	37	55.4%	1.62 [0.96, 2.72]
Zhiguo (2013)	10	43	13	43	44.6%	0.77 [0.38, 1.56]
Subtotal (95% CI)		**80**		**80**	**100.0%**	**1.16 [0.56, 2.39]**
Total events	31		26			
Heterogeneity: τ^2=0.17; χ^2=2.74, df=1 (p= 0.10); I^2=64%						
Test for overall effect: Z=0.41 (p=0.69)						
None						
Cunxu (2008)	8	37	5	37	24.5%	1.60 [0.58, 4.44]
Zhiguo (2013)	23	43	11	43	75.5%	2.09 [1.17, 3.74]
Subtotal (95% CI)		**80**		**80**	**100.0%**	**1.96 [1.18, 3.24]**
Total events	31		16			
Heterogeneity: τ^2=0.00; χ^2=0.20, df=1 (p=0.66); I^2=0%						
Test for overall effect: Z=2.61 (p=0.009)						

Disease response



Study or subgroup	EPL + ADs Events	EPL + ADs Total	ADs Events	ADs Total	Weight	Risk ratio IV, Random, 95% CI
Unchanged						
Cunxu (2008)	8	37	17	37	33.5%	0.47 [0.23, 0.95]
Yin (2000)	12	125	29	60	39.3%	0.20 [0.11, 0.36]
Zhiguo (2013)	6	43	15	43	27.2%	0.40 [0.17, 0.93]
Subtotal (95% CI)		**205**		**140**	**100.0%**	**0.32 [0.18, 0.56]**
Total events	26		61			
Heterogeneity: τ^2=0.12; χ^2=3.82, df=2 (p=0.15); I^2=48%						
Test for overall effect: Z=3.94 (p<0.0001)						
Partial improvement						
Cunxu (2008)	8	37	5	37	23.3%	1.60 [0.58, 4.44]
Yin (2000)	35	125	28	60	50.3%	0.60 [0.41, 0.89]
Zhiguo (2013)	8	43	7	43	26.4%	1.14 [0.45, 2.87]
Subtotal (95% CI)		**205**		**140**	**100.0%**	**0.89 [0.48, 1.67]**
Total events	51		40			
Heterogeneity: τ^2=0.16; χ^2=4.15, df=2 (p=0.13); I^2=52%						
Test for overall effect: Z=0.35 (p=0.72)						
Significant improvement						
Cunxu (2008)	12	37	9	37	33.7%	1.33 [0.64, 2.78]
Yin (2000)	78	125	3	60	28.0%	12.48 [4.11, 37.92]
Zhiguo (2013)	29	43	21	43	38.3%	1.38 [0.95, 2.00]
Subtotal (95% CI)		**205**		**140**	**100.0%**	**2.53 [0.87, 7.35]**
Total events	119		33			
Heterogeneity: τ^2=0.74; χ^2=13.95, df=2 (p= 0.0009); I^2=86%						
Test for overall effect: Z=1.70 (p=0.09)						
Any improvement						
Cunxu (2008)	29	37	20	37	23.0%	1.45 [1.03, 2.04]
Yin (2000)	113	125	31	60	38.3%	1.75 [1.36, 2.25]
Zhiguo (2013)	37	43	28	43	38.7%	1.32 [1.03, 1.70]
Subtotal (95% CI)		**205**		**140**	**100.0%**	**1.50 [1.26, 1.79]**
Total events	179		79			
Heterogeneity: τ^2=0.00; χ^2=2.47, df=2 (p=0.29); I^2=19%						
Test for overall effect: Z=4.53 (p<0.00001)						

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

Conclusions

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

2. Evidence from **RCTs** support the role of EPL in the treatment of NAFLD/NASH and comorbid conditions

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; RCTs, randomized controlled trials; RWE, real-world evidence