ConCordix®

Views on liver care and supplementation

A technical paper on Choline

The liver is one of the most important organs of the human body. Its main function is to detoxify the blood and to rid it of harmful substances including drugs, breaking down food for energy and supporting the body's defence system. Non-alcoholic fatty liver disease (NAFLD) is a disease that develops when excess fat accumulates in liver cells. Globally, NAFLD has become the most diagnosed liver disease, and is commonly associated with insulin resistance, obesity, and high levels of cholesterol and triglycerides. It has been estimated that the incidence of NAFLD increases with 50% in the next 15 years.

An essential vitamin-like nutrient known as choline has proven to prevent NAFLD development. However, the majority (90%) of the European and U.S. population is choline deficient. Choline deficiency is highly associated with increased risks for the development of NAFLD. Since choline deficiency is mainly driven by a poor diet there is a growing need of choline supplements to maintain liver and overall health. A new approach to deliver nutraceutical and pharmaceutical supplements is ConCordix which provides a different and novel oral delivery form. Both oil- and water-soluble ingredients can be combined in one supplement. Next to that, absorption of certain oil-based ingredients is significantly higher compared with usual oral delivery forms. Because many supplements have disadvantages such as size, off-taste, and ease to swallow, compliance is often hampered. ConCordix is a patented chewable oral delivery system which is formulated without the addition of sugar and enables that nutraceuticals and pharmaceuticals are easy to ingest without the need of water. Both children and people who have difficulties swallowing pills will benefit from this oral delivery form.

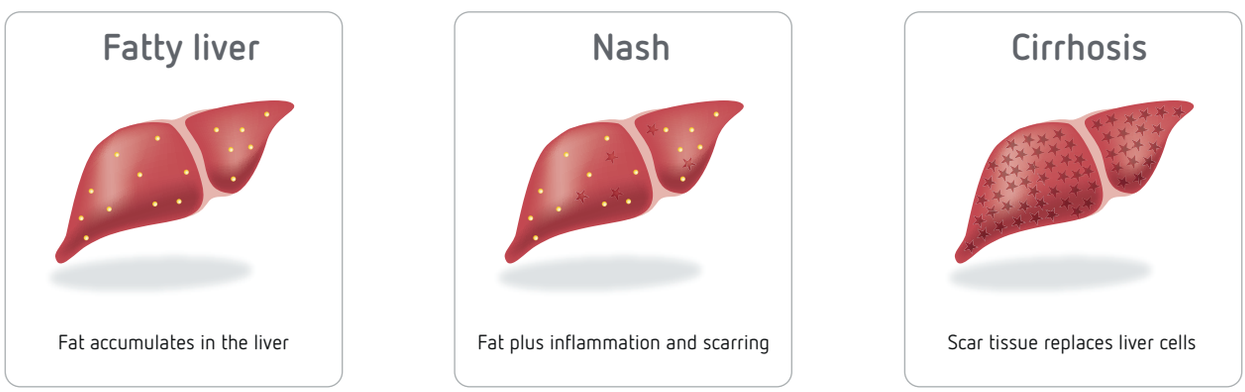
Non-alcoholic fatty liver disease

The liver is one of the most important organs of the body. A primary function is the detoxification of blood and to rid it of harmful substances including drugs and alcohol.

Furthermore, the liver is involved in the breakdown of carbohydrates into glucose, and plays a vital role in fighting infections by mobilizing the body's defence system [1]. Impairment of

liver functions gives rise to altered bodily functions and increases the risk for many (chronic) diseases such as type 2 diabetes.
Non-alcoholic fatty liver disease (NAFLD) is a liver disorder that develops when excess fat accumulates in liver cells. When more than 10% of the liver's weight is from fat, it is termed as a fatty liver [2]. The pathogenesis is not completely understood, but numerous mechanisms including metabolic, genetic, environmental and gut microbial factors play a crucial role in the development of NALFD [3, 4]. Considerable progress has been made in elucidating the mechanisms that are responsible for NALFD development. Initial theories were based on a "2-hit hypothesis" [5, 6]. The "first hit" was characterized by lipid accumulation in the liver cells, which increases susceptibility of the liver to injury mediated by "second hits," such as inflammatory cells, mitochondrial dysfunction, and oxidative stress, which in turn lead to non-alcoholic steatohepatitis (NASH) and/or cirrhosis [2, 4, 5, 7] (Figure 1).

Figure 1: Development of untreated Non-alcoholic Fatty Liver



Globally, NAFLD has become the most diagnosed liver disease in adults, and is commonly associated with insulin resistance, obesity, malnutrition, and high levels of cholesterol and triglycerides [6, 8]. Also in children aged 2 to 19 years, NAFLD is one of the most occurring liver abnormalities [7, 9]. The growing obesity epidemic is believed to be the main driver in the increase of adult and paediatric NAFLD prevalence, with studies indicating that about half of the obese children have a fatty liver [7, 9]. It has been estimated that the incidence of NAFLD ranges from 11% to 19% of the U.S. adult population, and based on the current diet, it is likely that the incidence rate increases with 50% in the next 15 years. Additional data show that overweight and obese adolescents have 4.14 and 5.98 times, respectively, the risk of NAFLD compared with adolescents of normal weight [4].

The pathogenesis of NAFLD is often not noticed by patients. Some symptoms of fatigue, malaise, or pressure in the right upper abdomen might occur. In most cases NAFLD is detected and diagnosed during routine blood tests that indicate abnormal liver function [2]. Currently there are no approved pharmacological treatments for NAFLD. Most studies have demonstrated that especially diet changes, alcohol reduction, and weight loss have a significant improvement on liver function in patients with NAFLD [3, 6]. Some nutrients, but in particular choline have proven to benefit liver health and to reduce NAFLD development [3, 10-12].

Choline

Choline is an essential vitamin-like nutrient involved in many physiological processes, including (liver) metabolism, lipid transport, cell reactions, and brain function.

Choline was officially recognized as an essential nutrient by the Institute of Medicine in 1998 [13]. In 2013 the European Food Safety Association (EFSA) approved 3 health claims that stated that choline benefits human health, including liver health [14, 15].

Choline is predominantly obtained from the diet. Foods with the highest choline concentration are: chicken meat, salmon, eggs, wheat germ, and milk [16]. Although the human body can synthesize choline itself, the amount that is produced is not sufficient to meet its essential requirements [13]. The liver is dependent on choline to function properly by transporting liver fats, maintaining liver cell health, and normal blood concentrations of toxic compounds such as homocysteine by contributing to normal homocysteine metabolism [10, 11].

Set by the Institute of Medicine the Adequate Intake (AI) of choline in the U.S. is 550 mg/day for men and 425 mg/day for women. The AI increases for pregnant women to 450 mg/day and lactating women to 550 mg/day to support the neurological development of the foetus [13, 17].

The European recommended choline intakes also depend on the AI set by the Institute of Medicine. Recently, it was published that the average choline intake of the majority of the European population was below the AI [18]. These results were well in line with previous findings from the National Health and Nutrition Examination Survey (NHANES) that demonstrated that choline intakes were far below the AI of most people (90%) living in the U.S. [17]. Data from the NHANES found a significant gap of 135 mg/d for men and 186 mg/d for women [17].

Choline deficiency is associated with increased risks of NAFLD, cardiovascular diseases, neurological and cognitional disorders, and developmental disorders in neonates [10, 11].

It has been estimated that choline deficiency is likely to get worse in the next decades because of poor diet and the obesity epidemic. One of the earliest adverse events of choline deficiency is a fatty liver [19]. Without sufficient choline levels, fat metabolism is impaired leading to fat accumulation and secondary morbidities such as insulin resistance. In rodents, choline deficient diets caused progressive liver disease much like what is seen in some humans with a fatty liver [20]. It was also demonstrated that a diet low in choline increased the risk for NALFD development of more than 50.000 healthy men and women aged between 40 and 75 years [21].

Supported by EFSA's health claim and evidence from many studies, intake of adequate amounts of choline benefits normal liver function and helps to prevent NAFLD. Since choline deficiency is mainly driven by a poor diet there is a growing need of choline supplements to maintain liver and overall health.

Balchem, the producer of choline constituents (VitaCholine®) is closely involved in clinical research, including in the area of liver health and NAFLD [22]. VitaCholine® consists of scientifically substantiated choline-salts that are produced with superior quality. For example, VitaCholine® bitartrate is solely made of a natural form of L+tartaric acid present in grapes. Although most supplements with choline are delivered in large tablets and capsules, VitaCholine® is delivered in a unique form that is easy to take without the need for water.

ConCordix

A unique oral delivery form is ConCordix produced by Vitux AS. Vitux is a leader in contract manufacturing for the nutraceutical and pharma industry.

ConCordix is a patented oral delivery system and offers a new approach to administering nutraceuticals and pharmaceuticals. It disables many of the issues consumers and manufactures come across when taking or producing a common oral delivery form as displayed below.

Table 1: ConCordix benefits compared to common oral delivery forms

	Liquid forms		Solid forms					
Characteristics oral delivery forms	Suspension (drinkable)	Elixirs (drinkable)	Tablet/ hard capsule	Oro-dispersal	Soft capsule	Gummies	CCx Delivery System	CCx Techno-logy Platform
Water soluble ingredients –in form of solution	Yes	Yes	No	No	No	Yes	Yes	Yes
Lipid soluble ingredients –in form of solution	Restricted	Restricted	No	No	Yes	Yes	Yes	Yes
Particulate materials	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Pre-emulsified	Possible	No	No	No	No	Possible	Yes	Yes
Protection from oxidation	Only until opened	Only until opened	Extra packing step	Extra packing step	Extra packing step	No	Yes	Yes
Allowed water content	Yes	Yes	No	No	Max. 10%	Yes	Yes	Yes
Chewable form	-	-	No	Yes	Possible	Yes	Yes	Yes
Taste masking/ flavouring	Yes	Yes	Restricted	Possible	Possible	Restricted*	Yes	Yes
Easy to swallow / no water needed	Yes	Yes	No	Yes	No / patient dependent	Yes	Yes	Yes

*due to oxidation factor

In summary, ConCordix assists to overcome hurdles as:

- Off-taste of tablets, powders or capsules;
- Swallowing large tablets or capsules;
- Product compliance;
- Absorption of the ingredient;
- Combining oil- and water-soluble ingredients.

An important feature of this oral delivery system is its ability to combine both oil-and water-soluble ingredients that opens new possibilities for manufacturers and consumers. For instance, choline is a hydrophilic ingredient, which makes it very easy to add to the ConCordix matrix that contains a water phase. In addition, the ConCordix matrix makes it easy to combine choline with various nutrients that have a synergetic effect such as essential fatty acids (EPA and DHA), vitamin E and various B vitamins.

Figure 3: Oil- and water-soluble fraction ConCordix

Moreover, it has been demonstrated that short-term absorption of fish oil delivered by ConCordix was significantly increased compared with normal soft gel capsules (Figure 4) [23]. As a consequence, more effective health benefits are accomplished with the same concentration of ingredients.

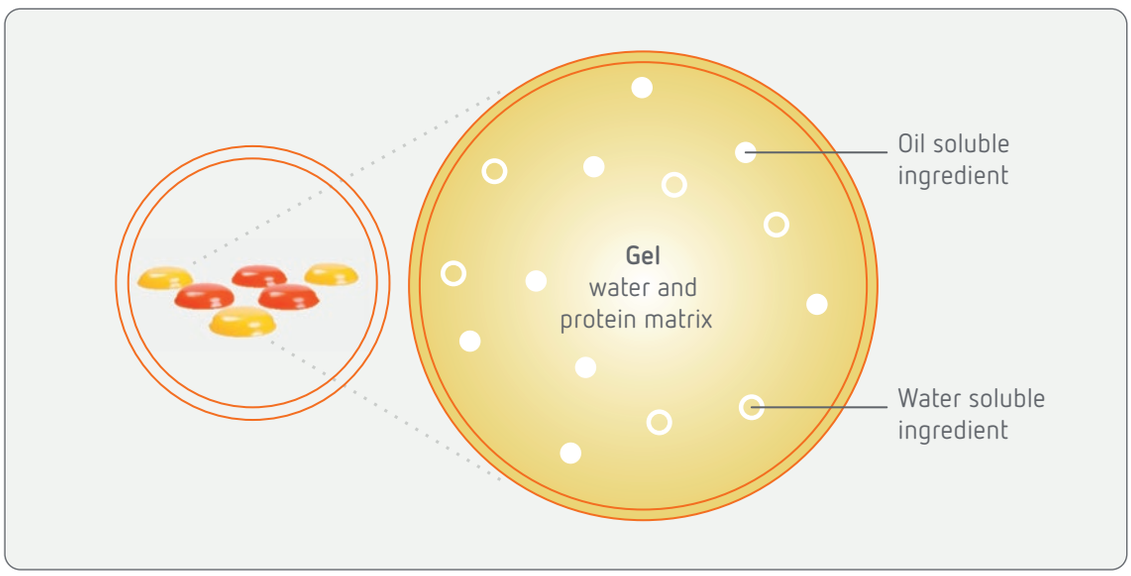
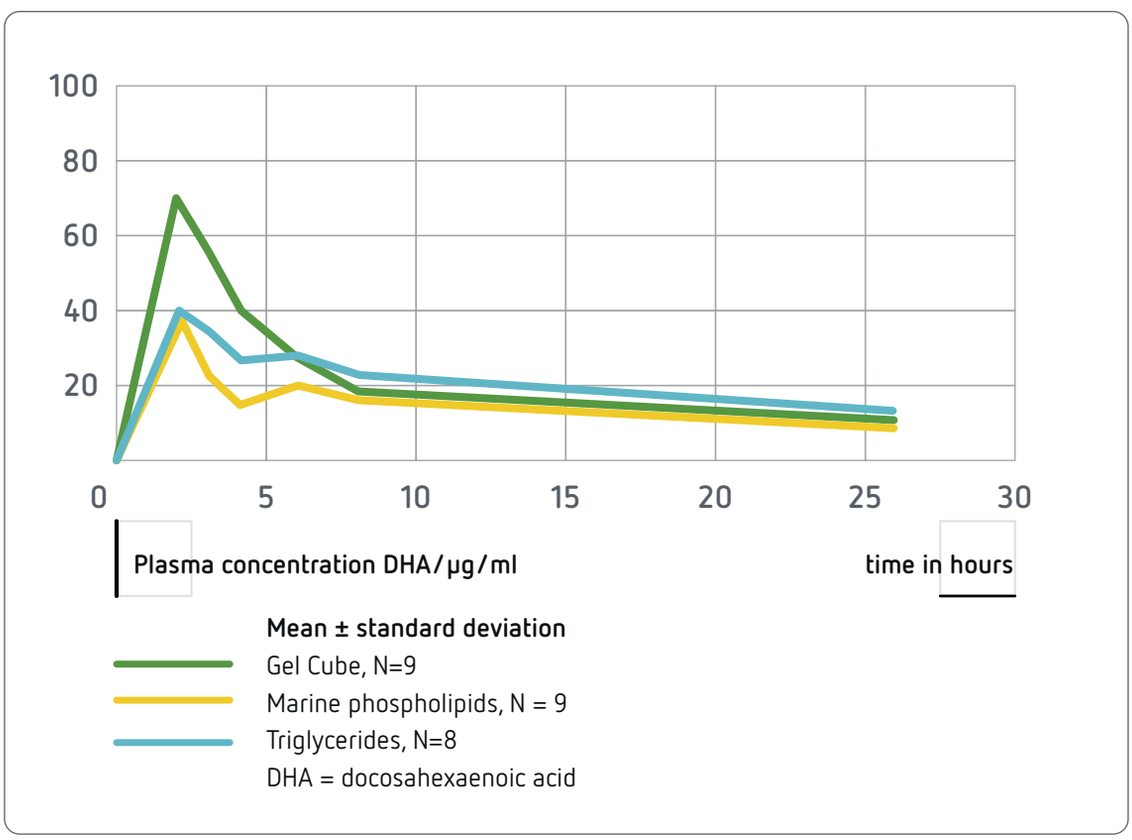


Figure 4: Absorption of fish oil (docosahexaenoic acid)



To achieve a better compliance to supplement intake, ConCordix comes in a chewable formulation that can be manufactured in many different flavours without the addition of sugar.

A chewable supplement can be taken everywhere and anytime and does not need water for ingestion which most common oral delivery forms (tablets, capsules or powders) need. This unique feature will benefit many people who have difficulties swallowing or dislike the taste of usual pills.

For example, many usual oral delivery systems have an off-taste or trigger gastric reflux. Intake of fatty acids extracted from fish oil supplements often leads to gastric reflux that causes people to quit taking more supplements. A recent randomized placebo-controlled double-blind study demonstrated that omega-3 fatty acids (fish oil) supplements delivered by ConCordix did not affect the compliance of supplement intake in children. Of the 413 children (aged 8.5 years), 204 children received omega-3 fatty acids delivered in ConCordix, the rest of the subjects received a placebo also delivered in ConCordix. After the intervention period of 3 months it became clear that only 5.4% of children in the intervention group, and 4.3% in the placebo group quit taking omega-3 fatty acid supplements before the study was ended. As there were no differences between the intervention and the placebo group these findings indicated that the fish oil taste was surprisingly well hidden using the ConCordix technology and indicates that it has the potential to increase compliance [24].

Conclusion

A healthy liver is crucial for staying healthy. Choline has proven to benefit and protect the liver against the development of NALFD.

Since the majority of people consume a diet that lacks sufficient amounts of choline, the risk for NALFD development is increased and will grow in the next decades in both adults and children. Therefore supplementation with choline is an excellent way to prevent NALFD development and comorbidities such as type 2 diabetes and high cholesterol levels. The novel oral delivery form ConCordix is a unique way to combine both oil- and water-soluble ingredients and provides a solution for many nutraceutical and pharmaceutical manufacturers. An example is VitaCholine that is easy to add to the ConCordix matrix.
A larger health effect of certain ingredients is established by the increased absorption due to emulsified ingredients. Next to that, the chewable formulation offers easy ingestion of supplements with essential ingredients and the different flavours without the addition of sugar makes that people are more likely to adhere to their supplement routine.
Vitux uses state-of-the-art manufacturing methods and only the freshest ingredients in producing turnkey products and customized dietary supplements of the highest quality.
For more information about ConCordix or any of our other products, we invite you to visit our website at http://www.concordix.com or contact one of our experts.

vitux AS
Brynsveien 11
NO-0667 Oslo
Norway
www.concordix.com
info@concordix.com
+47 77 75 99 00

ConCordix®

a product by the Vitux group vitux

References

1. Corbin, K.D. and S.H. Zeisel, Choline metabolism provides novel insights into nonalcoholic fatty liver disease and its progression. Curr Opin Gastroenterol, 2012. 28(2): p. 159-65.
2. Rinella, M.E., Nonalcoholic fatty liver disease: a systematic review. JAMA, 2015. 313(22): p. 2263-73.
3. Adams, L.A. and P. Angulo, Treatment of non-alcoholic fatty liver disease. Postgrad Med J, 2006. 82(967): p. 315-22.
4. Angulo, P. and K.D. Lindor, Non-alcoholic fatty liver disease. J Gastroenterol Hepatol, 2002. 17 Suppl: p. S186-90.
5. Dowman, J.K., J.W. Tomlinson, and P.N. Newsome, Pathogenesis of non-alcoholic fatty liver disease. QJM, 2010. 103(2): p. 71-83.
6. Weiss, J., M. Rau, and A. Geier, Non-alcoholic fatty liver disease: epidemiology, clinical course, investigation, and treatment. Dtsch Arztebl Int, 2014. 111(26): p. 447-52.
7. Widhalm, K. and E. Ghods, Nonalcoholic fatty liver disease: a challenge for pediatricians. Int J Obes (Lond), 2010. 34(10): p. 1451-67.
8. McCarthy, E.M. and M.E. Rinella, The role of diet and nutrient composition in nonalcoholic Fatty liver disease. J Acad Nutr Diet, 2012. 112(3): p. 401-9.
9. Feldstein, A.E., et al., The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. Gut, 2009. 58(11): p. 1538-44.
10. Counsel, C.I. Liver Health. 2016 2016 [cited 2016 7 April]; Available from: http://www.cholinecouncil.com/health_professional/liver_health.php.
11. Zeisel, S.H. and K.A. da Costa, Choline: an essential nutrient for public health. Nutr Rev, 2009. 67(11): p. 615-23.
12. Dowman, J.K., et al., Current therapeutic strategies in non-alcoholic fatty liver disease. Diabetes Obes Metab, 2011. 13(8): p. 692-702.
13. Board, F.a.N., Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B-6, Vitamin B012, Pantothenic Acid, Biotin, and Choline. , I.o. Medicine, Editor. 1998, National Academy of Sciences: Washington D.C. p. 390-422.
14. Union, E., Register of claims: No 432/2012 Article 13.1, in Official Journal of EU, EU, Editor. 2012.
15. EFSA, Scientific Opinion on the substantiation of health claims related to choline and contribution to normal lipid metabolism (ID 3186), maintenance of normal liver function (ID 1501), contribution to normal homocysteine metabolism (ID 3090), maintenance of normal neurological function (ID 1502), contribution to normal cognitive function (ID 1502), and brain and neurological development (ID 1503) pursuant to Article 13(1) of Regulation (EC) No 1924/20061. EFSA Journal, 2011. 9(4).
16. USDA, Choline database. 2016.
17. Jensen HH Batres-Marquez P, C.A., Schalinske KL, Choline in the diets of the US population: NHANES, 2003-2004. The FASEB Journal, 2007. 21: p. 219.
18. Vennemann, F.B., et al., Dietary intake and food sources of choline in European populations. Br J Nutr, 2015. 114(12): p. 2046-55.
19. Fischer, L.M., et al., Sex and menopausal status influence human dietary requirements for the nutrient choline. Am J Clin Nutr, 2007. 85(5): p. 1275-85.
20. da Costa, K.A., et al., Effects of prolonged (1 year) choline deficiency and subsequent re-feeding of choline on 1,2-sn-diradylglycerol, fatty acids and protein kinase C in rat liver. Carcinogenesis, 1995. 16(2): p. 327-34.
21. Yu, D., et al., Higher dietary choline intake is associated with lower risk of nonalcoholic fatty liver in normal-weight Chinese women. J Nutr, 2014. 144(12): p. 2034-40.
22. Belchem. Choline Science. 2016 2016 [cited 2016 7 April]; Available from: http://www.cholinecouncil.com/health_professional/liver_health.php.
23. Haug IJ, S.L., Zeiss D, Olsen IC, Draget KI, Bioavailability of EPA and DHA delivered by gelled emulsions and soft gel capsules. Eur. J. Lipid. Sci. Technol, 2011. 113: p. 113-145.
24. Danielsson P, M.C., Study STOP 8 OM3: evaluation of compliance of omega-3 oil intake or placebo in gel-tablets. 2015, Karolinska Institu.