



# Get the Science Tre-En-En® Grain Concentrates

Get the science behind Tre-En-En® Grain Concentrates with Peer Reviewed Studies that support ingredients found in this amazing product.



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## Peer Reviewed Studies

### Cellular Health & Energy Production

#### The Plasma Membrane As A Capacitor For Energy And Metabolism

##### ABSTRACT

When considering which components of the cell are the most critical to function and physiology, we naturally focus on the nucleus, the mitochondria that regulate energy and apoptotic signaling, or other organelles such as the endoplasmic reticulum, Golgi, ribosomes, etc. Few people will suggest that the membrane is the most critical element of a cell in terms of function and physiology. Those that consider the membrane critical will point to its obvious barrier function regulated by the lipid bilayer and numerous ion channels that regulate homeostatic gradients. What becomes evident upon closer inspection is that not all membranes are created equal and that there are lipid-rich microdomains that serve as platforms of signaling and a means of communication with the intracellular environment. In this review, we explore the evolution of membranes, focus on lipid-rich microdomains, and advance the novel concept that membranes serve as “capacitors for energy and metabolism.” Within this framework, the membrane then is the primary and critical regulator of stress and disease adaptation of the cell.

*Source: Ray S, Kassan A, Busija AR, Rangamani P, Patel HH. The plasma membrane as a capacitor for energy and metabolism. Am J Physiol Cell Physiol. 2016;310(3):C181-C192. doi:10.1152/ajpcell.00087.2015*

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#### Rice Bran Oil Ameliorates Inflammatory Responses By Enhancing Mitochondrial Respiration In Murine Macrophages.

##### ABSTRACT

Previous studies have revealed the anti-inflammatory properties of rice bran oil (RBO), but the detailed mechanisms are poorly understood. Recent studies on the molecular/cellular anti-inflammatory mechanisms of dietary components have demonstrated that mitochondrial respiration plays a key role in macrophage functioning. Since dietary lipids are major substrates for mitochondrial respiration through  $\beta$ -oxidation, the current study examined whether RBO regulates inflammatory responses by modulating mitochondrial energy metabolism. Palm oil (PO), enriched with palmitic acid which are known to be effectively taken up by cells and used for oxidative phosphorylation, served as a positive control. In the in vitro model of LPS-stimulated

RAW 264.7 murine cells, the levels of pro-inflammatory cytokines (IL-6 and TNF- $\alpha$ ) in the culture supernatant were significantly reduced by RBO treatment. In contrast, secretion of the anti-inflammatory cytokine IL-10 was upregulated by RBO. Transcription of genes encoding inflammatory mediator molecules (COX-2 and iNOS) and expression of activation markers (CD80, CD86, and MHC-II) in LPS-stimulated RAW 264.7 cells were suppressed by RBO. Mitochondrial respiration (as assessed by an extra cellular flux analyzer) increased upon RBO treatment, as the basal respiration, maximal respiration, ATP production, and spare respiratory capacity were up regulated. In an in vivo study, C57BL/6 mice were fed a negative control diet containing corn oil (CO), PO, or RBO for 4 weeks, and bone marrow-derived macrophages (BMDM) were isolated from their tibias and femurs. In pro-inflammatory M1-polarized BMDM (M1-BMDM), the RBO-induced suppression of IL-6 and TNF- $\alpha$  was recapitulated in vivo. Mitochondrial respiration in M1 BMDM also increased following the RBO intervention and the PO control treatment as compared to CO fed negative control. Overall, the current study for the first time demonstrates that RBO regulates inflammatory responses in murine macrophages by upregulating mitochondrial respiration. Further clinical studies are required to validate the animal study.

*Source: Lee S, Yu S, Park HJ, Jung J, Go GW, Kim W. Rice bran oil ameliorates inflammatory responses by enhancing mitochondrial respiration in murine macrophages. PLoS One. 2019;14(10):e0222857. Published 2019 Oct 11. doi:10.1371/journal.pone.0222857*

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#### Dietary Fats And Membrane Function: Implications For Metabolism And Disease.

##### ABSTRACT

Lipids play varied and critical roles in metabolism, with function dramatically modulated by the individual fatty acid moieties in complex lipid entities. In particular, the fatty acid composition of membrane lipids greatly influences membrane function. Here we consider the role of dietary fatty acid profile on membrane composition and, in turn, its impact on prevalent disease clusters of the metabolic syndrome and mental illness. Applying the classical physiological conformer-regulator paradigm to quantify the influence of dietary fats on membrane lipid composition (i.e. where the membrane variable is plotted against the same variable in the environment - in this case dietary fats), membrane lipid composition appears as a predominantly regulated parameter. Membranes remain relatively constant in their saturated (SFA) and monounsaturated (MUFA) fatty acid levels over a wide

range of dietary variation for these fatty acids. Membrane composition was found to be more responsive to n-6 and n-3 polyunsaturated fatty acid (PUFA) levels in the diet and most sensitive to n-3 PUFA and to the n-3/n-6 ratio. These differential responses are probably due to the fact that both n-6 and n-3 PUFA classes cannot be synthesised de novo by higher animals. Diet-induced modifications in membrane lipid composition are associated with changes in the rates of membrane-linked cellular processes that are major contributors to energy metabolism. For example, in the intrinsic activity of fundamental processes such as the Na<sup>+</sup>/K<sup>+</sup> pump and proton pump-leak cycle. Equally, dietary lipid profile impacts substantially on diseases of the metabolic syndrome with evidence accruing for changes in metabolic rate and neuropeptide regulation (thus influencing both sides of the energy balance equation), in second messenger generation and in gene expression influencing a range of glucose and lipid handling pathways. Finally, there is a growing literature relating changes in dietary fatty acid profile to many aspects of mental health. The understanding of dietary lipid profile and its influence on membrane function in relation to metabolic dysregulation has exciting potential for the prevention and treatment of a range of prevalent disease states.

*Source: Hulbert AJ, Turner N, Storlien LH, Else PL. Dietary fats and membrane function: implications for metabolism and disease. Biol Rev Camb Philos Soc. 2005;80(1):155-169. doi:10.1017/s1464793104006578*

## Immune Health

### Exogenous Fatty Acids Are The Preferred Source Of Membrane Lipids In Proliferating Fibroblasts.

#### ABSTRACT

Cellular proliferation requires the formation of new membranes. It is often assumed that the lipids needed for these membranes are synthesized mostly de novo. Here, we show that proliferating fibroblasts prefer to take up palmitate from the extracellular environment over synthesizing it de novo. Relative to quiescent fibroblasts, proliferating fibroblasts increase their uptake of palmitate, decrease fatty acid degradation, and instead direct more palmitate to membrane lipids. When exogenous palmitate is provided in the culture media at physiological concentrations, de novo synthesis accounts for only a minor fraction of intracellular palmitate in proliferating fibroblasts as well as proliferating HeLa and H460 cells. Blocking fatty acid uptake decreased the proliferation rate of fibroblasts, HeLa, and H460 cells, while supplementing media with exogenous palmitate resulted in decreased glucose uptake and rendered cells less sensitive to glycolytic inhibition. Our results suggest

that cells scavenging exogenous lipids may be less susceptible to drugs targeting glycolysis and de novo lipid synthesis.

*Source: Yao CH, Fowle-Grider R, Mahieu NG, et al. Exogenous Fatty Acids Are the Preferred Source of Membrane Lipids in Proliferating Fibroblasts. Cell Chem Biol. 2016;23(4):483-493. doi:10.1016/j.chembiol.2016.03.007*

## Metabolic Health

### Association Of Erythrocyte Membrane Fatty Acids With Changes In Glycemia And Risk Of Type 2 Diabetes.

#### ABSTRACT

**Background:** The significance of erythrocyte membrane fatty acids (EMFAs) and their ratios to predict hyperglycemia and incident type 2 diabetes is unclear. **Objective:** We investigated EMFAs as predictors of the worsening of hyperglycemia and incident type 2 diabetes in a 5-y follow-up of a population-based study. **Design:** We measured EMFAs in 1346 Finnish men aged 45–73 y at baseline [mean  $\pm$  SD age: 55  $\pm$  6 y; body mass index (in kg/m<sup>2</sup>): 26.5  $\pm$  3.5]. Our prospective follow-up study included only men who were nondiabetic at baseline and who had data available at the 5-y follow-up visit (n = 735). **Results:** Our study showed that, after adjustment for confounding factors, palmitoleic acid (16:1n-7; P = 2.8  $\times$  10<sup>(-7)</sup>), dihomo g-linolenic acid (20:3n-6; P = 2.3  $\times$  10<sup>(-4)</sup>), the ratio of 16:1n-7 to 16:0 (P = 1.6  $\times$  10<sup>(-8)</sup>) as a marker of stearoyl coenzyme A desaturase 1 activity, and the ratio of 20:3n-6 to 18:2n-6 (P = 9.4  $\times$  10<sup>(-7)</sup>) as a marker of D6-desaturase activity significantly predicted the worsening of hyperglycemia (glucose area under the curve in an oral-glucose-tolerance test). In contrast, linoleic acid (18:2n-6; P = 0.0015) and the ratio of 18:1n-7 to 16:1n-7 (P = 1.5  $\times$  10<sup>(-9)</sup>) as a marker of elongase activity had opposite associations. Statistical significance persisted even after adjustment for baseline insulin sensitivity, insulin secretion, and glycemia. Palmitoleic acid (P = 0.010) and the ratio of 16:1n-7 to 16:0 (P = 0.004) nominally predicted incident type 2 diabetes, whereas linoleic acid had an opposite association (P = 0.004), and n-3 polyunsaturated fatty acids did not show any associations. **Conclusion:** EMFAs and their ratios are associated longitudinally with changes in glycemia and the risk type 2 diabetes.

*Source: Mahendran Y, Ågren J, Uusitupa M, et al. Association of erythrocyte membrane fatty acids with changes in glycemia and risk of type 2 diabetes. Am J Clin Nutr. 2014;99(1):79-85. doi:10.3945/ajcn.113.069740*

## Low Percentage Of Vegetable Fat In Red Blood Cells Is Associated With Worse Glucose Metabolism And Incidence Of Type 2 Diabetes.

### ABSTRACT

The identification of nutritional patterns associated with the development of type 2 diabetes (T2D). Our study is aimed at evaluating the association between fatty acids (FA) in red blood cell (RBC) membranes, as a quantitative biomarker of regular dietary fat intake, and incident type 2 diabetes in a Spanish population. We included 1032 adult Spaniards (57% women, age 49 +/- 15 years, 18% prediabetes), without diabetes at study entry, from the Di@bet.es cohort. Incident diabetes was diagnosed at the end of the study follow-up. The FA percentage in RBC was determined at baseline by gas chromatography. Participants were followed on average 7.5 +/- 0.6 years. Lower percentages of linoleic acid (LA), alpha-linolenic acid (ALA), and eicosapentaenoic acid (EPA), and higher percentages of docosahexaenoic acid (DHA) in RBC membranes were associated, independently of classical risk factors, with worse glucose metabolism at the end of the study follow-up. In addition, higher percentages of ALA and EPA, and moderate percentages of DHA, were associated with lower risk of diabetes. No significant associations were found for LA and diabetes risk. Dietary patterns rich in vegetables are independently associated with lower risk of both deterioration of glucose regulation and incident diabetes, and should be reinforced for the prevention of diabetes.

Source: Chiva-Blanch G, Giró O, Cofán M, et al. Low Percentage of Vegetable Fat in Red Blood Cells Is Associated with Worse Glucose Metabolism and Incidence of Type 2 Diabetes. *Nutrients*. 2022;14(7):1368. Published 2022 Mar 25. doi:10.3390/nu14071368

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## Heart Health

### Biomarkers Of Dietary Omega-6 Fatty Acids And Incident Cardiovascular Disease And Mortality: And Individual-Level Pooled Analysis Of 30 Cohort Studies.

#### ABSTRACT

**Background:** Global dietary recommendations for and cardiovascular effects of linoleic acid, the major dietary omega-6 fatty acid, and its major metabolite, arachidonic acid, remain controversial. To address this uncertainty and inform international recommendations, we evaluated how in vivo circulating and tissue levels of linoleic acid (LA) and arachidonic acid (AA) relate to incident cardiovascular disease (CVD) across multiple international studies. **Methods—**We performed harmonized, de novo,

individual-level analyses in a global consortium of 30 prospective observational studies from 13 countries. Multivariable-adjusted associations of circulating and adipose tissue LA and AA biomarkers with incident total CVD and subtypes (coronary heart disease (CHD), ischemic stroke, cardiovascular mortality) were investigated according to a prespecified analytical plan. Levels of LA and AA, measured as the % of total fatty acids, were evaluated linearly according to their interquintile range (i.e., the range between the mid-point of the first and fifth quintiles), and categorically by quintiles. Study-specific results were pooled using inverse-variance weighted meta-analysis. Heterogeneity was explored by age, sex, race, diabetes, statin use, aspirin use, omega-3 levels, and fatty acid desaturase 1 genotype (when available). **Results—**In 30 prospective studies with medians of follow-up ranging 2.5 to 31.9 years, 15,198 incident cardiovascular events occurred among 68,659 participants. Higher levels of LA were significantly associated with lower risks of total CVD, cardiovascular mortality, and ischemic stroke, with hazard ratios per interquintile range of 0.93 (95% CI, 0.88–0.99), 0.78 (0.70–0.85), and 0.88 (0.79–0.98), respectively, and nonsignificantly with lower CHD risk (0.94; 0.88–1.00). Relationships were similar for LA evaluated across quintiles. AA levels were not associated with higher risk of cardiovascular outcomes; comparing extreme quintiles, higher levels were associated with lower risk of total CVD (0.92; 0.86–0.99). No consistent heterogeneity by population subgroups was identified in the observed relationships.

#### CONCLUSION

In pooled global analyses, higher in vivo circulating and tissue levels of LA and possibly AA were associated with lower risk of major cardiovascular events. These results support a favorable role for LA in CVD prevention.

Source: Marklund M, Wu JHY, Imamura F, et al. Biomarkers of Dietary Omega-6 Fatty Acids and Incident Cardiovascular Disease and Mortality. *Circulation*. 2019;139(21):2422–2436. doi:10.1161/CIRCULATIONAHA.118.038908