Influence of the Di(2-Ethylhexyl) Phthalate (DEHP) on the lipid metabolism of the detoxification organs and spleen

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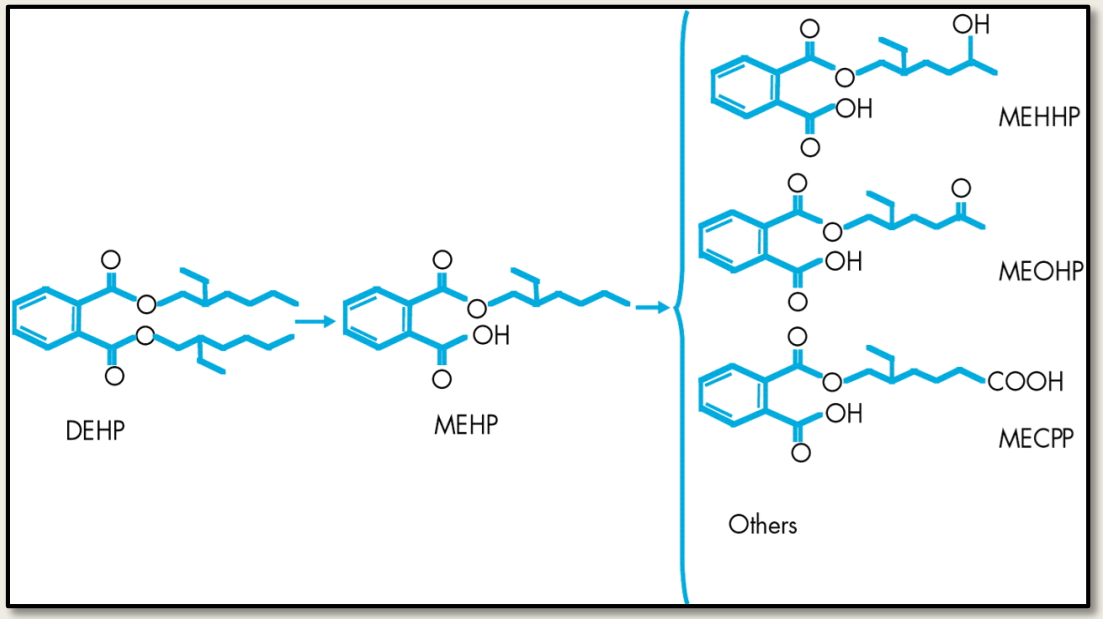
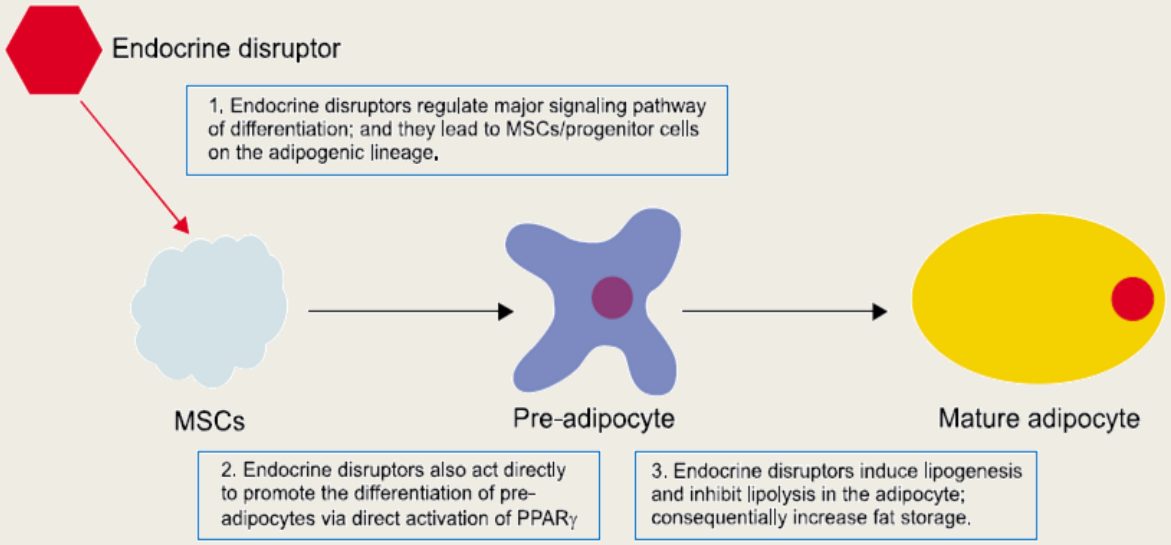
DEHP MORE THAN ENDOCRINE DISRUPTOR ?

- DEHP and MEHP are also classified as peroxisome proliferator chemicals (PPCs) causing peroxisome proliferation, malfunction in the fatty acid transport, metabolism and lipid homeostasis

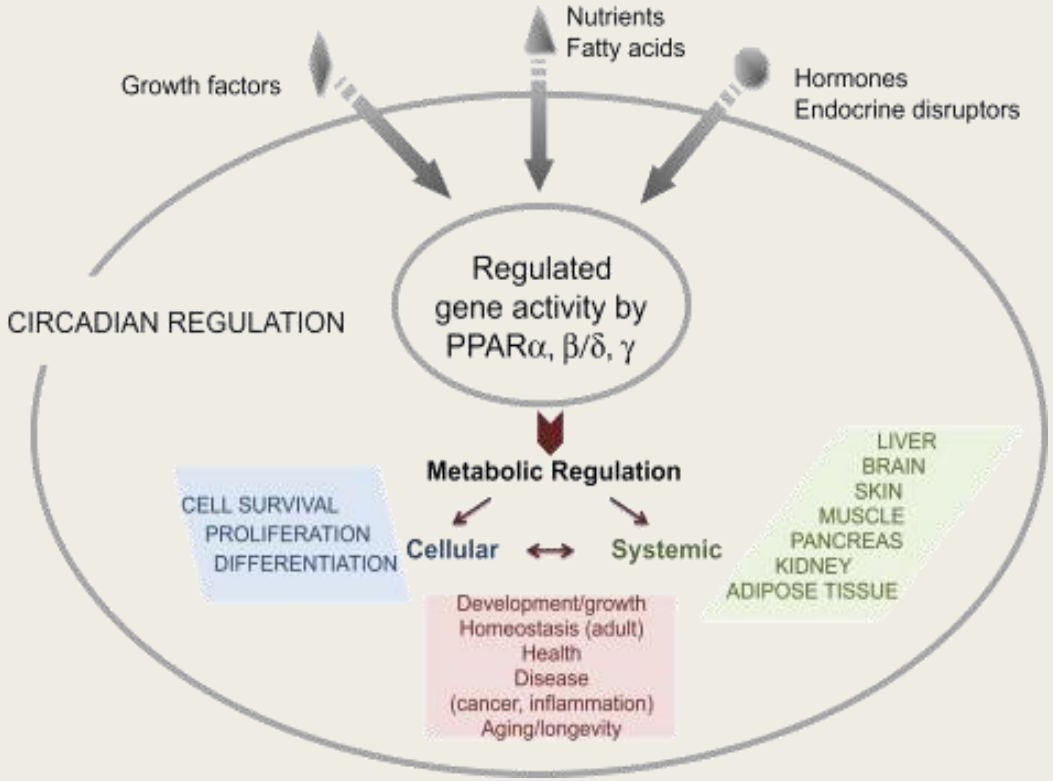
- EDCs are called as obesogens when they target adpocytes

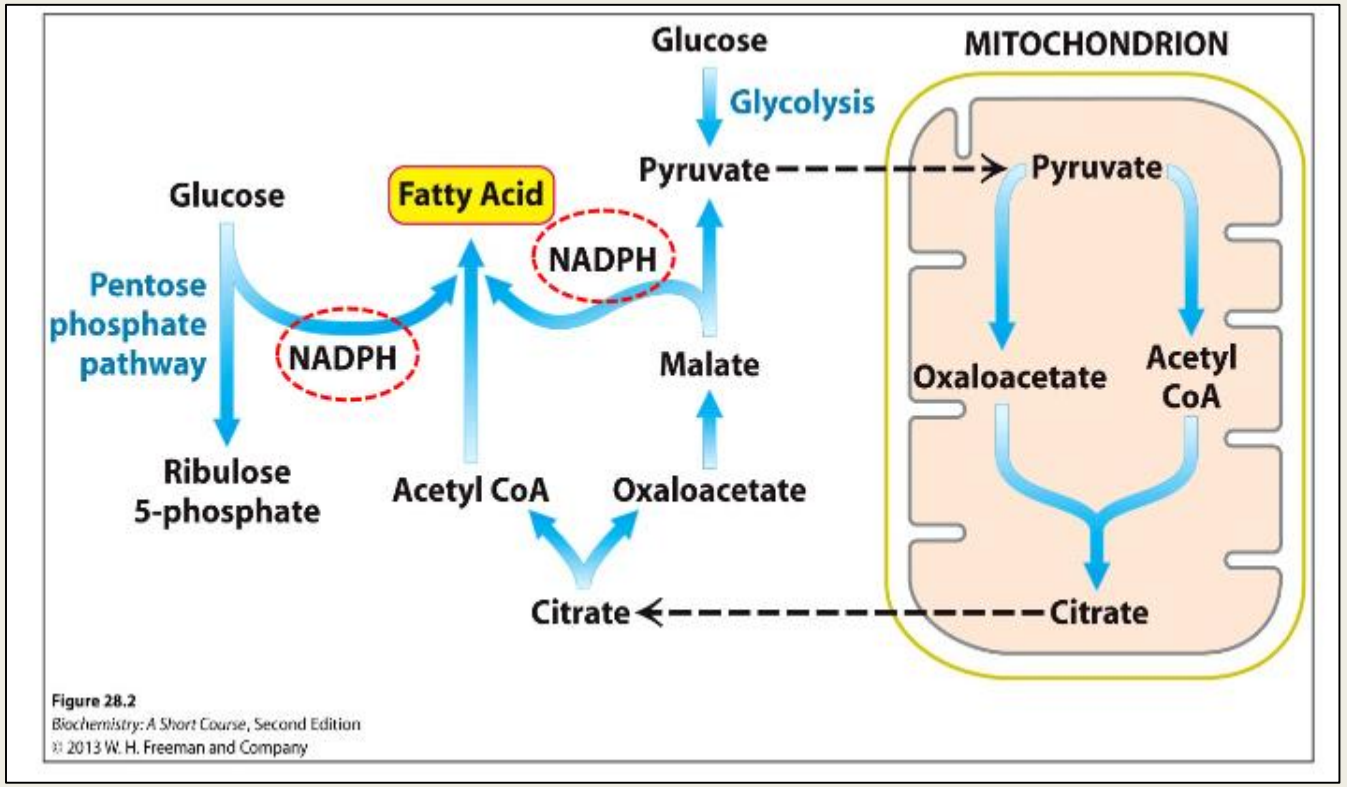




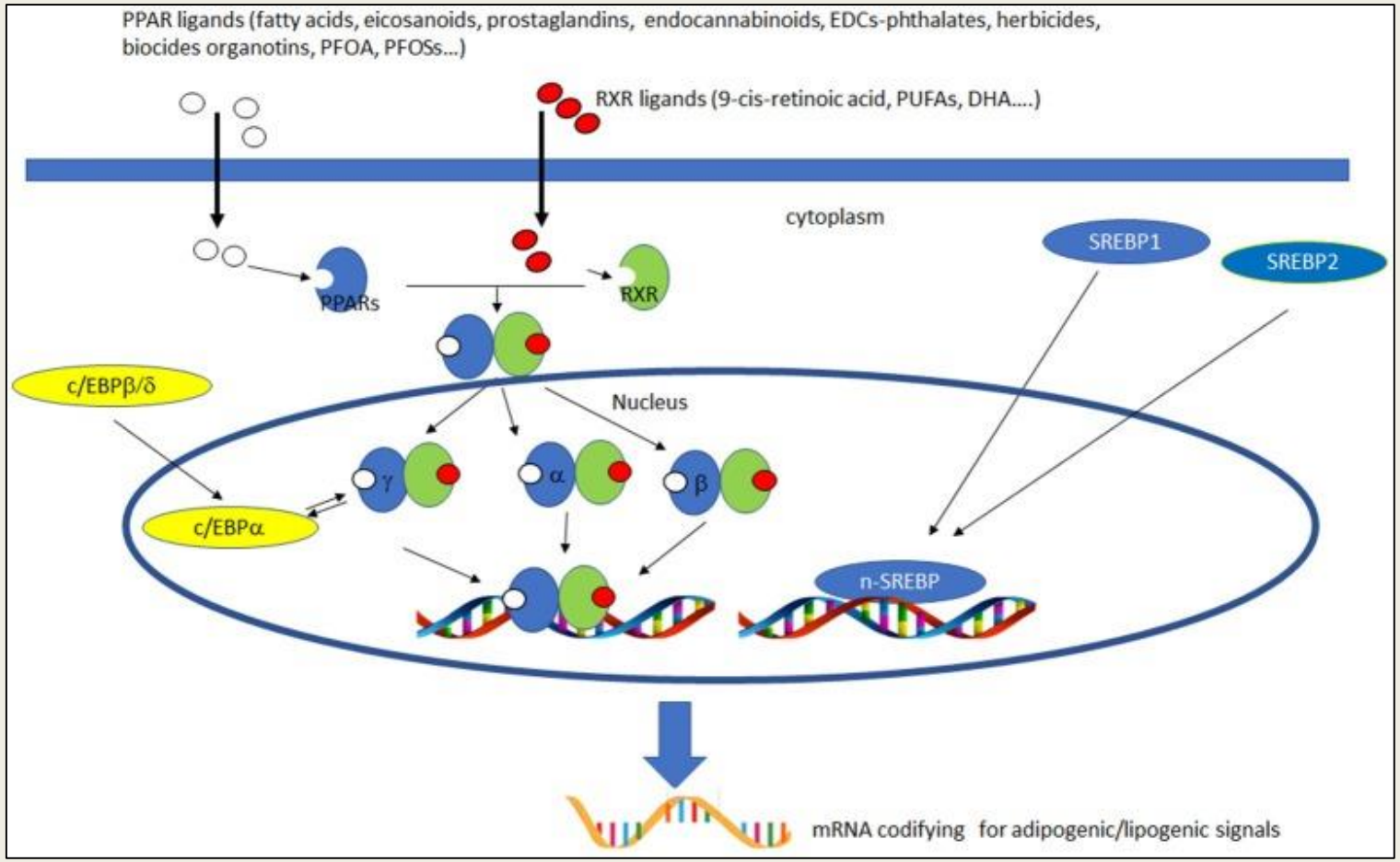
IMPACT OF DEHP ON THE LIPID METABOLISM

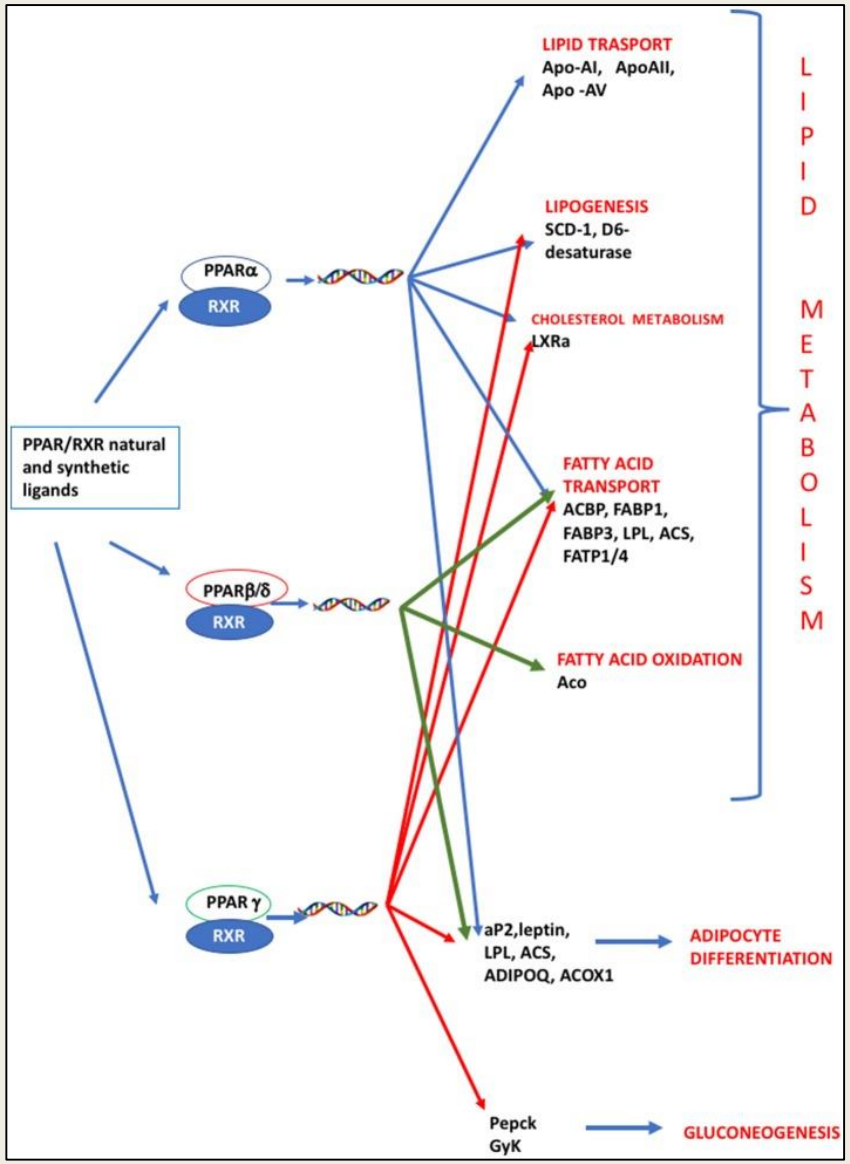
- DEHP disrupts adipogenesis via activation of peroxisome proliferator-activated receptors (PPARs) α and γ
- Fatty acid (FA) transport, FA metabolism, lipid homeostasis and catabolism are affected by DEHP





PEROXISOME PROLIFERATOR ACTIVATOR RECEPTOR (PPAR)

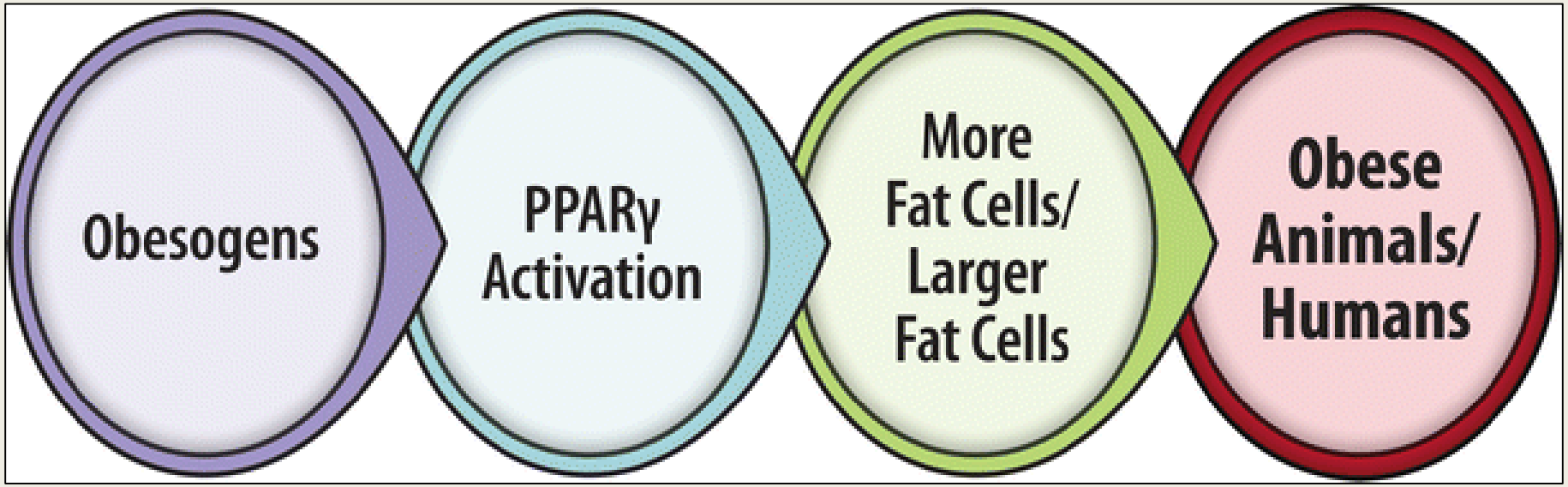




Lipid metabolism, including transport, lipogenesis, cholesterol metabolism and adipocyte differentiation.

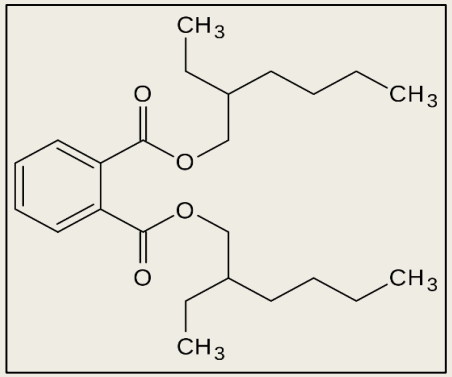
Maradona et al., 2018

IMPACT OF DEHP ON THE LIPID METABOLISM



Heidel et al., 2014

METHOD



DEHP

Oral gavage (28 days)

0, 100, 200, 400 mg/kg/day

24 prepubertal male Wistar albino rat (*Rattus norvecigus*), six weeks

Spleen, kidney and liver tissue samples were homogenized in 1 ml methanol

Overnight at -60 ^{0}C to evaporate methanol

3 ml methanol with 2% HCl or for 2 h at 80 °C

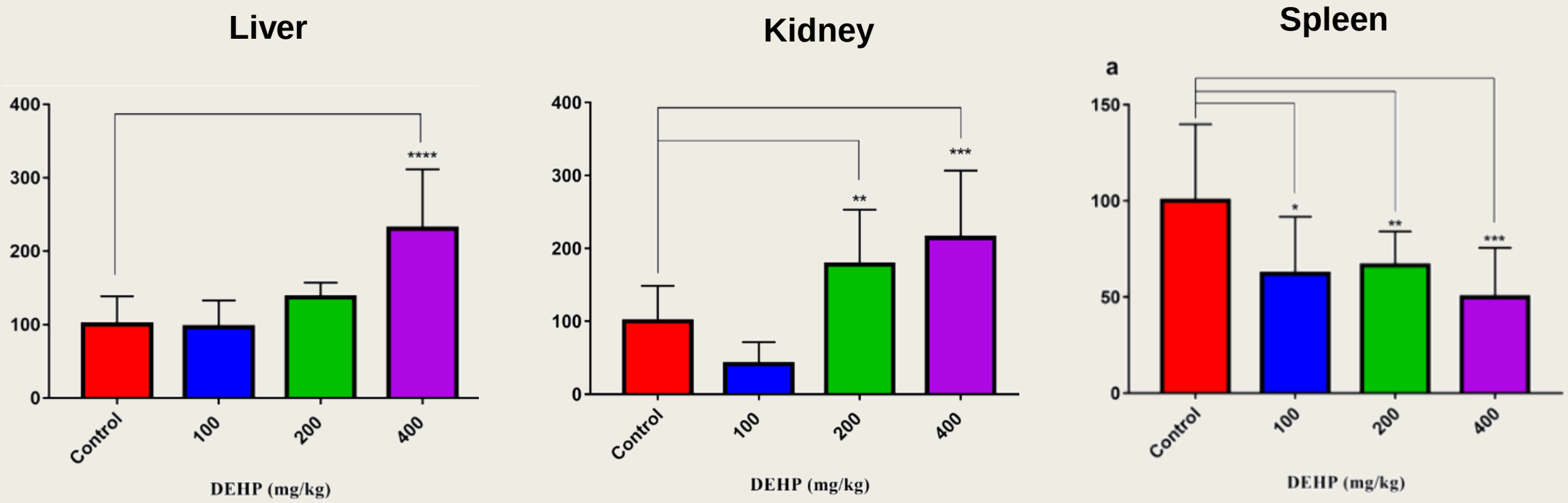
distilled water and hexane were used to separate the fatty acid methyl esters (FAMEs)

7890-B Agilent GC equipped with a 5977A Agilent MSD detector and DB-23 column

WHY KIDNEY, LIVER AND SPLEEN

- DEHP is categorized as peroxisome proliferator chemicals (PPCs) responsible for lipid metabolism, immune system, glucose homeostasis, cellular differentiation and apoptosis.
- DEHP is metabolized in the liver and kidney
- Spleen play main role in the immune system for instance it produces pro-inflammatory cytokines.
- Impairment in the immune system contributes to the formation of various diseases including diabetes, obesity, cardiovascular diseases and cancer

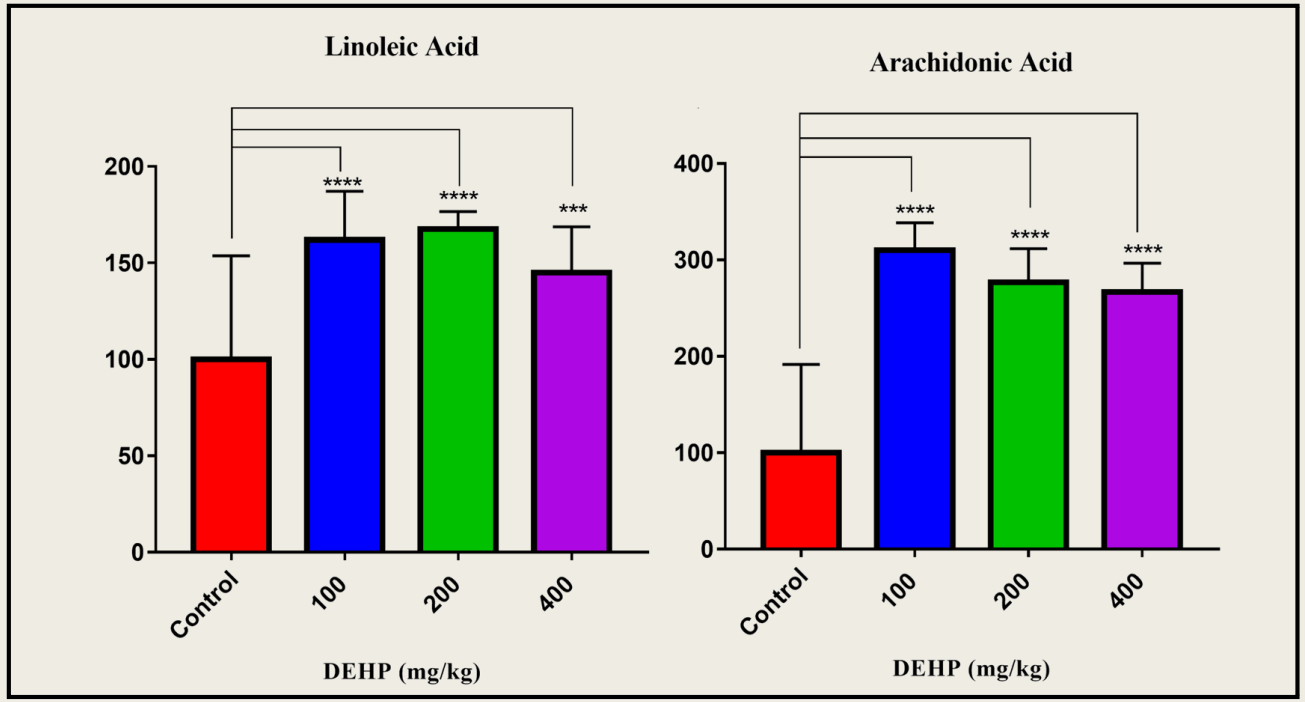
RELATIVE TOTAL FATTY ACID CONTENT

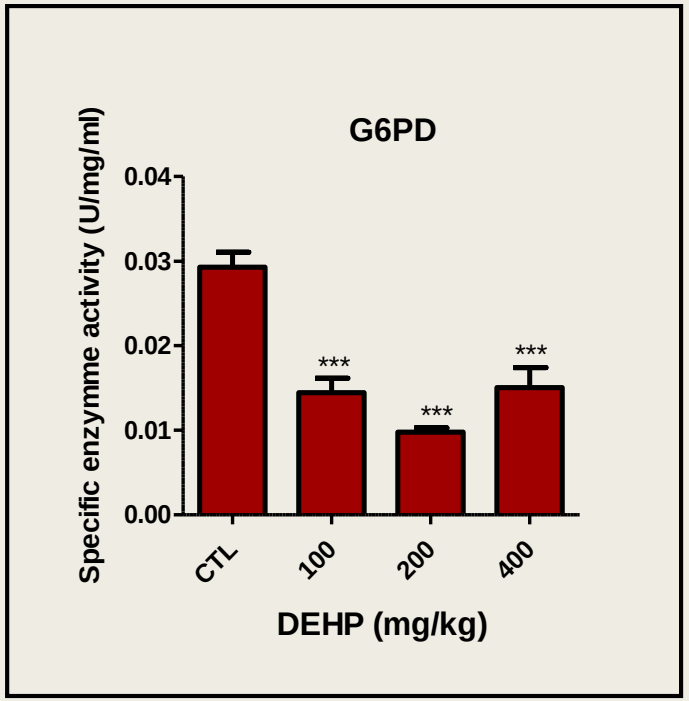


- Elevated fatty acid levels are correlated with the insulin resistance, inflammation and obesity
- DEHP induces lipid accumulation in the liver cells

Relative fatty acids content of liver tissue. Total peak areas and FAME composition (% of total FAME) of samples were measured. First, the fold change was calculated between control and DEHP treated samples, and then the percentage change for each was calculated after setting the amount in control as 100%. Notes: *$p \leq 0.05$, ** $p \leq 0.01$ and *** $p \leq 0.001$ indicate different from control group

RELATIVE FATTY ACID CONTENT OF LIVER



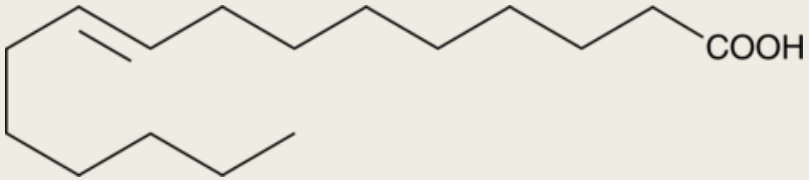


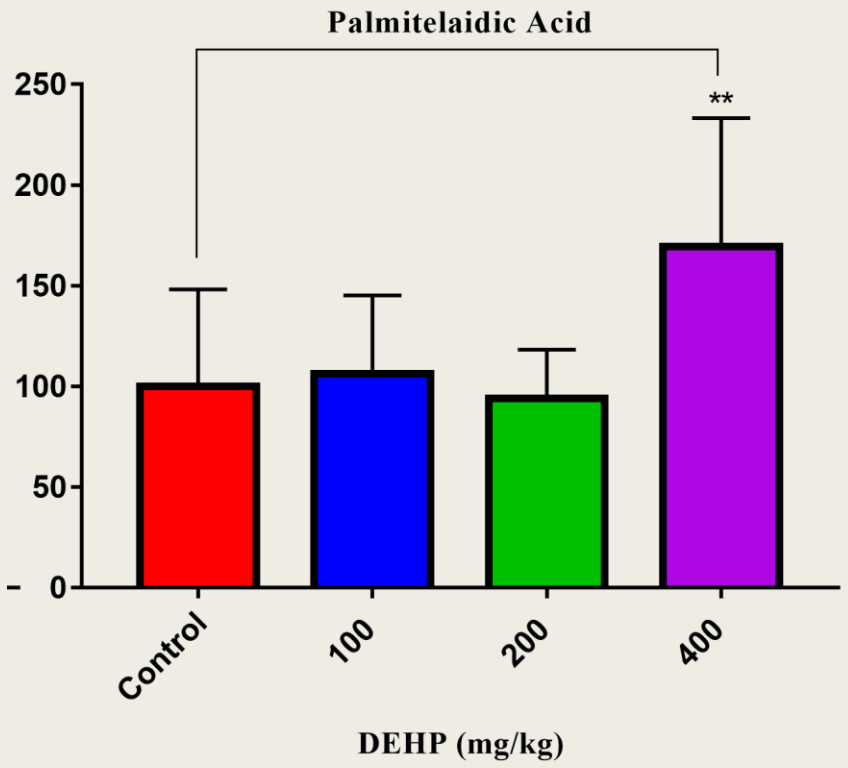
- Linoleic acid and arachidonic acid are polly unsaturated fatty acids (PUFAs)
- Arachidonic acid is produced by the metabolism of linoleic acid
- Immune system, cardiovascular diseases, liver health and diabetes
- High levels of linoleic acid increases insulin resistance
- Arachidonic acid is associated with impairment of the lipid metabolism, leptin sensitivity and hepatic energy homeostasis
- Arachidonic acid is categorized as the negative regulator of the glucose-6 phosphate dehydrogenase (G6PD)

Relative fatty acids content of liver tissue. Total peak areas and FAME composition (% of total FAME) of samples were measured. First, the fold change was calculated between control and DEHP treated samples, and then the percentage change for each was calculated after setting the amount in control as 100%. Notes: *$p \leq 0.05$, ** $p \leq 0.01$ and *** $p \leq 0.001$ indicate different from control group

RELATIVE FATTY ACID CONTENT OF LIVER

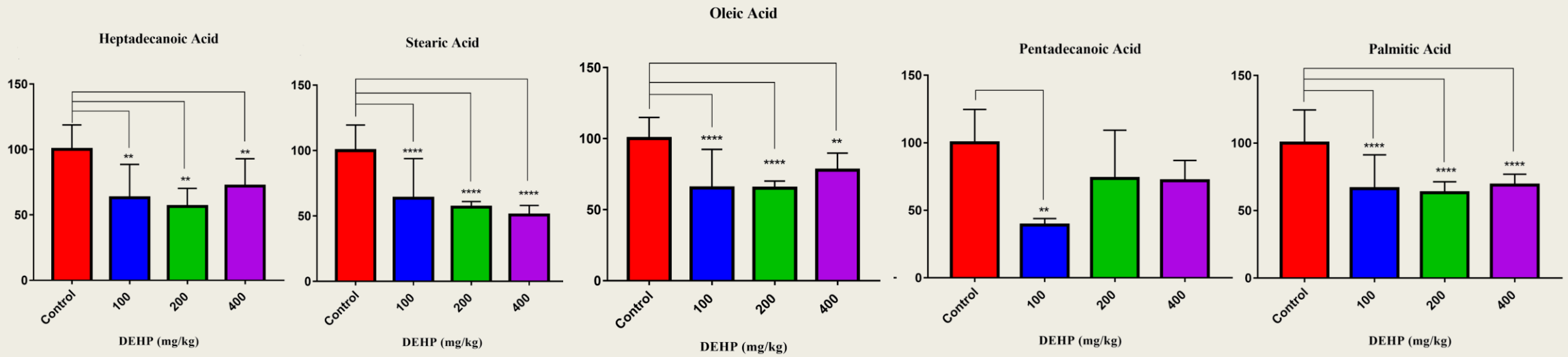
- Trans fatty acid
- Involved in the unsaturated lipid structure
- Increased trans fatty acid is correlated with the coronary heart diseases





Relative fatty acids content of liver tissue. Total peak areas and FAME composition (% of total FAME) of samples were measured. First, the fold change was calculated between control and DEHP treated samples, and then the percentage change for each was calculated after setting the amount in control as 100%. Notes: *p ≤ 0.05, ** p ≤ 0.01 and *** p ≤ 0.001 indicate different from control group

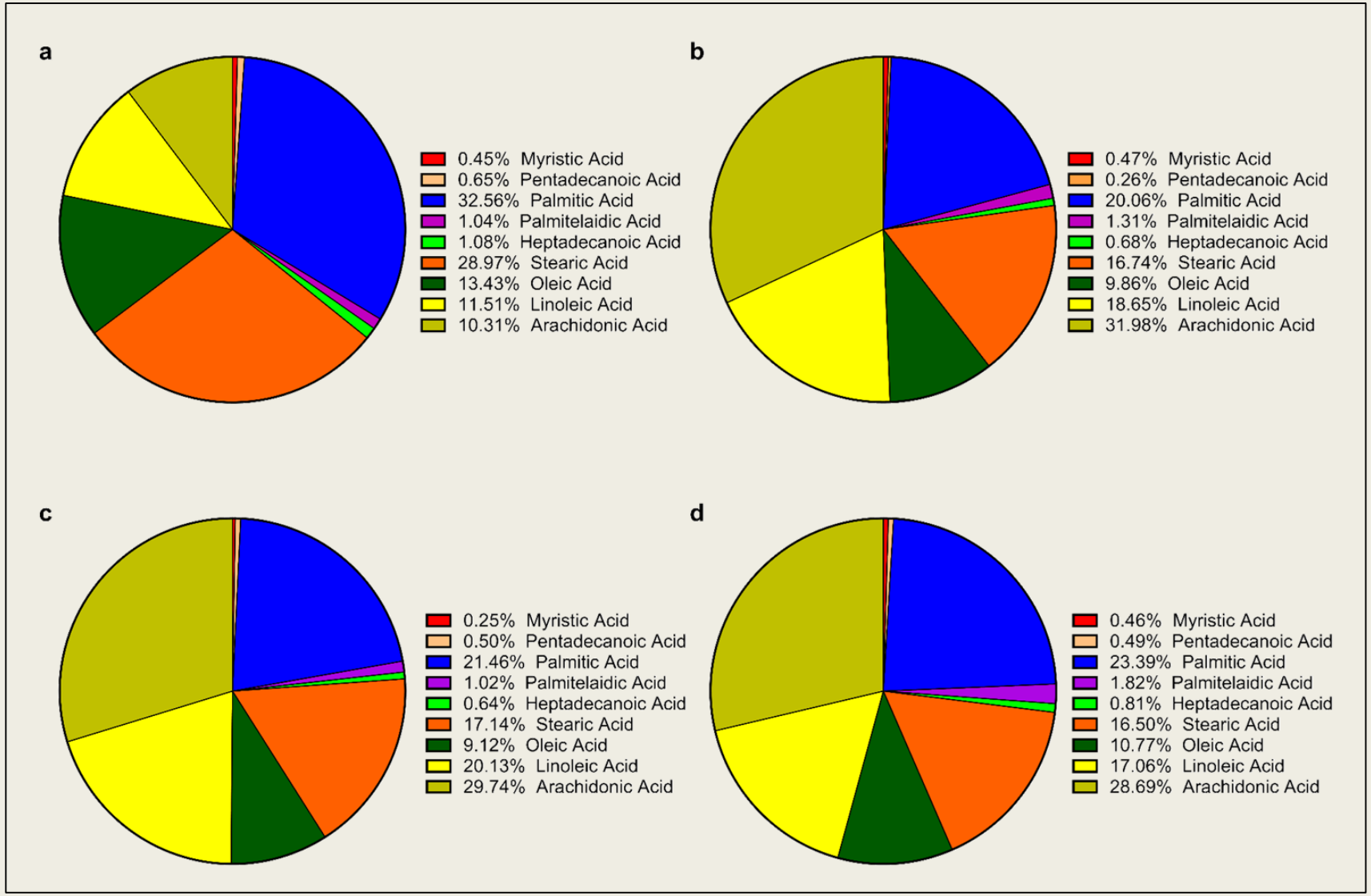
RELATIVE FATTY ACID CONTENT OF LIVER



- Oleic acid prevents inflammation, diabetes and cardiovascular diseases and responsible for wound healing
- Heptadeconic acid and pentadeconic acid biomarkers for coronary heart disease (CHD) risk and type II diabetes
- Stearic acid is nutritional long chain fatty acid and has anti-inflammatory effects. The third most abundant fatty acid in the liver and responsible for lipoprotein biogenesis and cholesterol metabolism

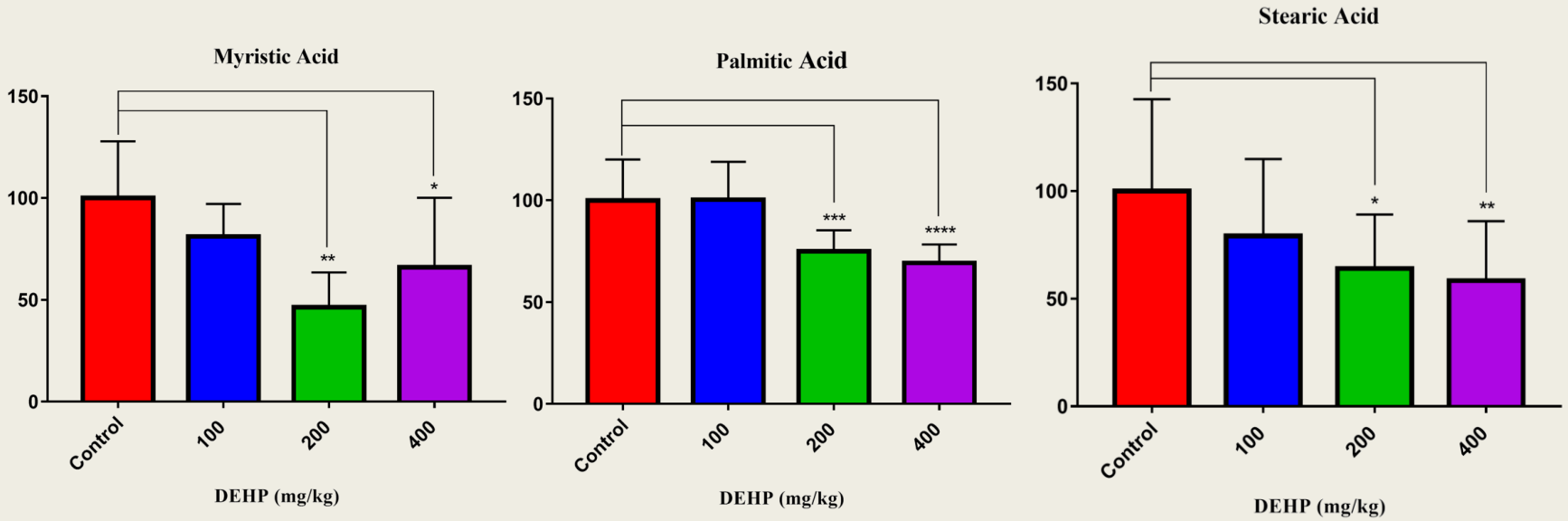
Relative fatty acids content of liver tissue. Total peak areas and FAME composition (% of total FAME) of samples were measured. First, the fold change was calculated between control and DEHP treated samples, and then the percentage change for each was calculated after setting the amount in control as 100%. Notes: *$p \leq 0.05$, ** $p \leq 0.01$ and *** $p \leq 0.001$ indicate different from control group

RELATIVE FATTY ACID CONTENT OF LIVER



FAME composition (% of total FAME) in liver tissue of a) control, b) 100 mg/kg DEHP, c) 200 mg/kg DEHP and d) 400 mg/kg DEHP

RELATIVE FATTY ACID CONTENT OF KIDNEY

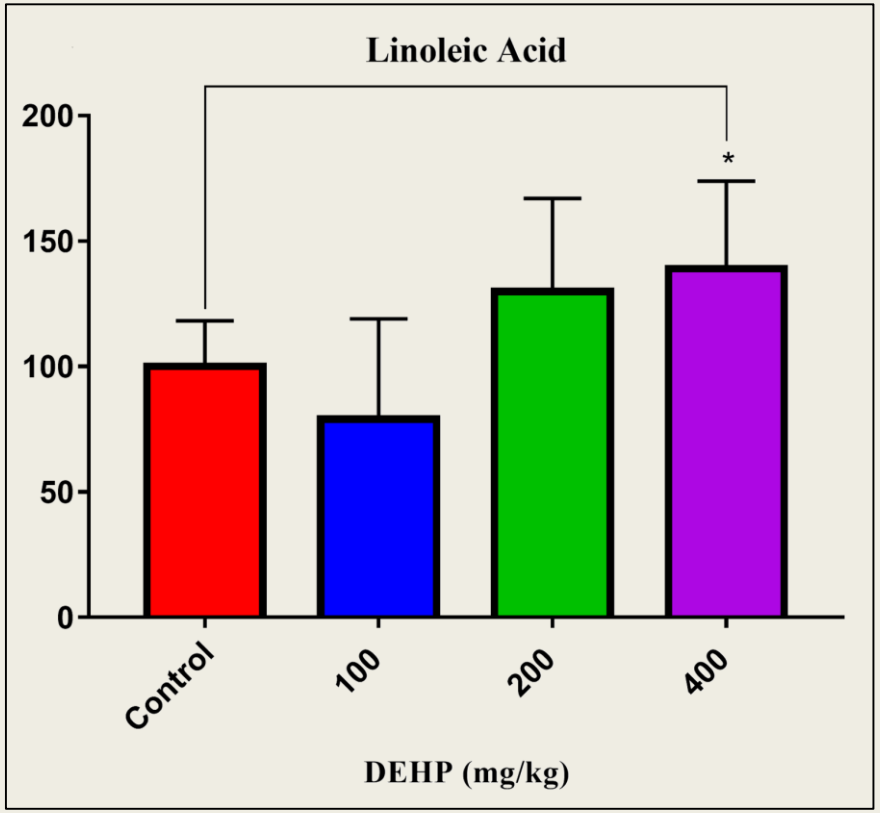


- Lower stearic acid levels were observed in the kidney damage
- Myristic acid is saturated fatty acid and has protective effect on renal damage
- That may cause kidney to be more vulnerable against DEHP-induced damage

Relative fatty acids content of kidney tissue. Total peak areas and FAME composition (% of total FAME) of samples were measured. First, the fold change was calculated between control and DEHP treated samples, and then the percentage change for each was calculated after setting the amount in control as 100%.

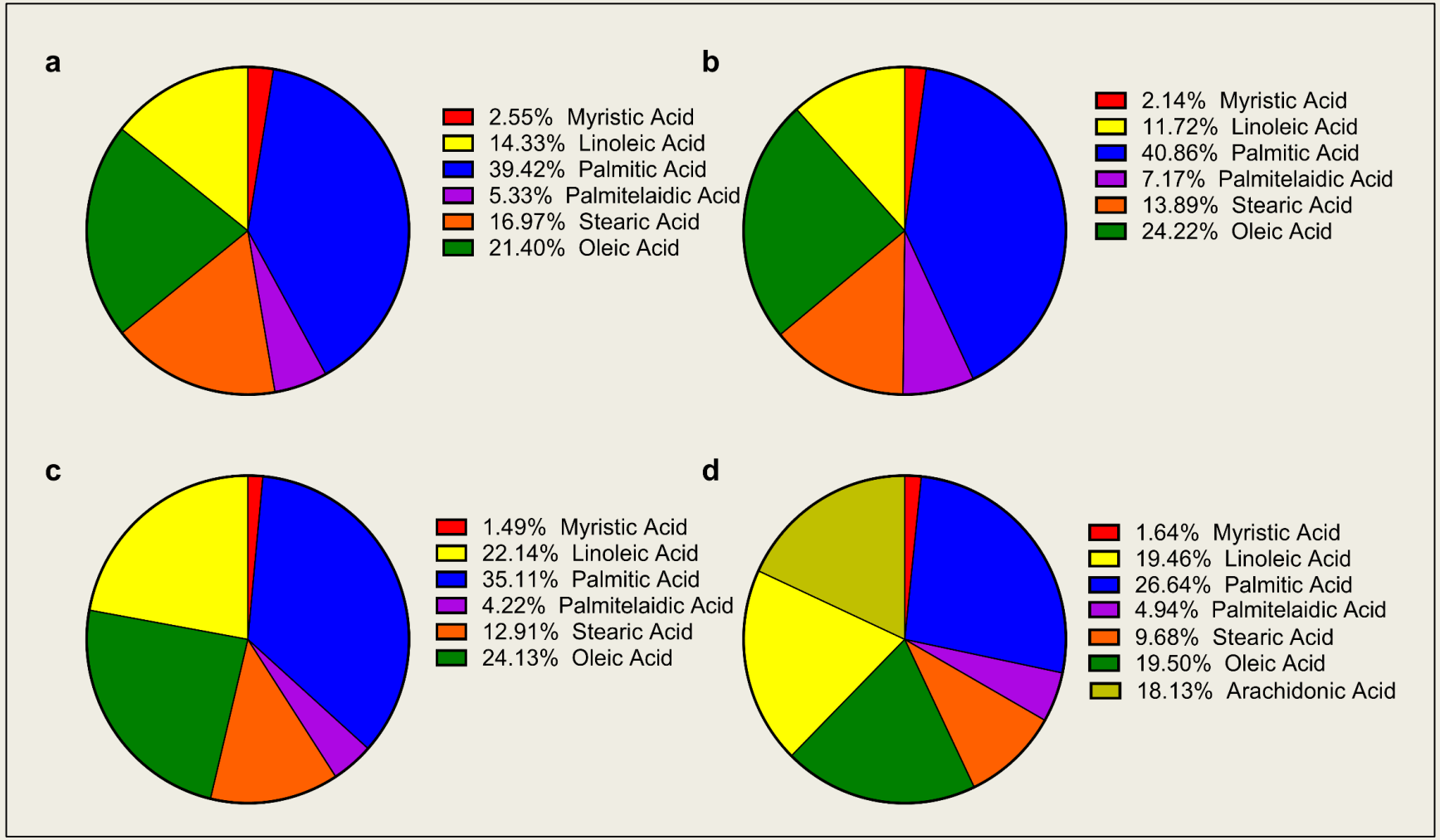
RELATIVE FATTY ACID CONTENT OF KIDNEY

- Linoleic acid is an essential fatty acid
- High levels of linoleic acid increases insulin resistance
- Hypertension, obesity, diabetes and coronary heart disease



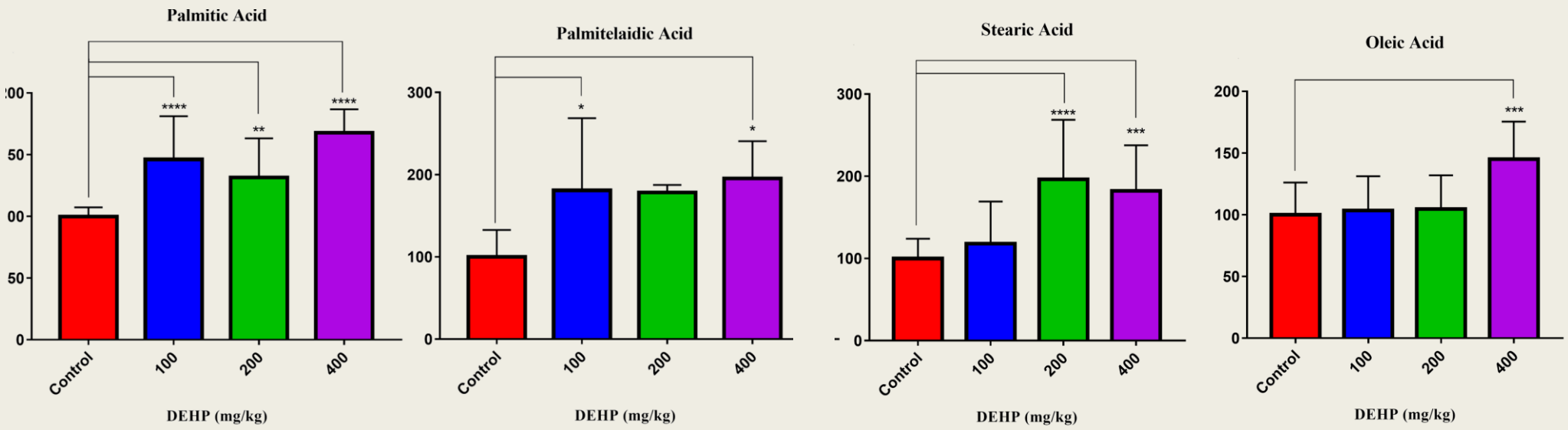
Relative fatty acids content of liver tissue. Total peak areas and FAME composition (% of total FAME) of samples were measured. First, the fold change was calculated between control and DEHP treated samples, and then the percentage change for each was calculated after setting the amount in control as 100%. Notes: *p ≤ 0.05, ** p ≤ 0.01 and *** p ≤ 0.001 indicate different from control group

RELATIVE FATTY ACID CONTENT OF KIDNEY



FAME composition (% of total FAME) in kidney tissue of a) control, b) 100 mg/kg DEHP, c) 200 mg/kg DEHP and d) 400 mg/kg DEHP

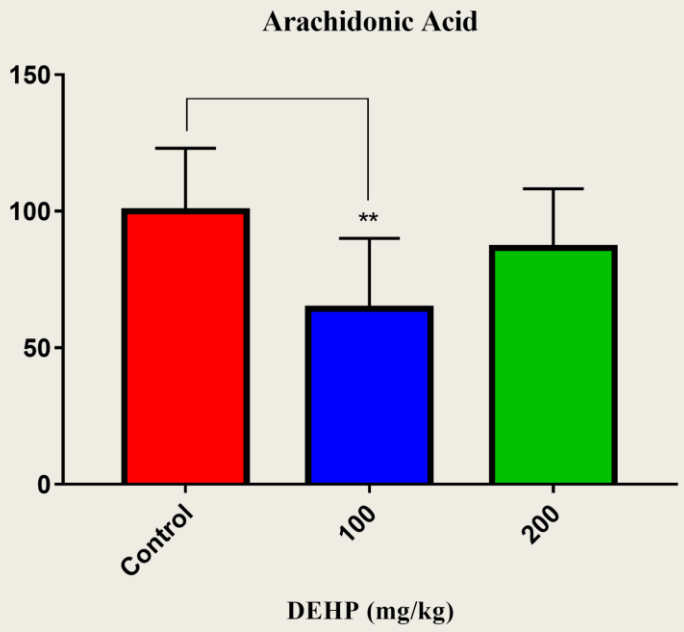
RELATIVE FATTY ACID CONTENT OF SPLEEN

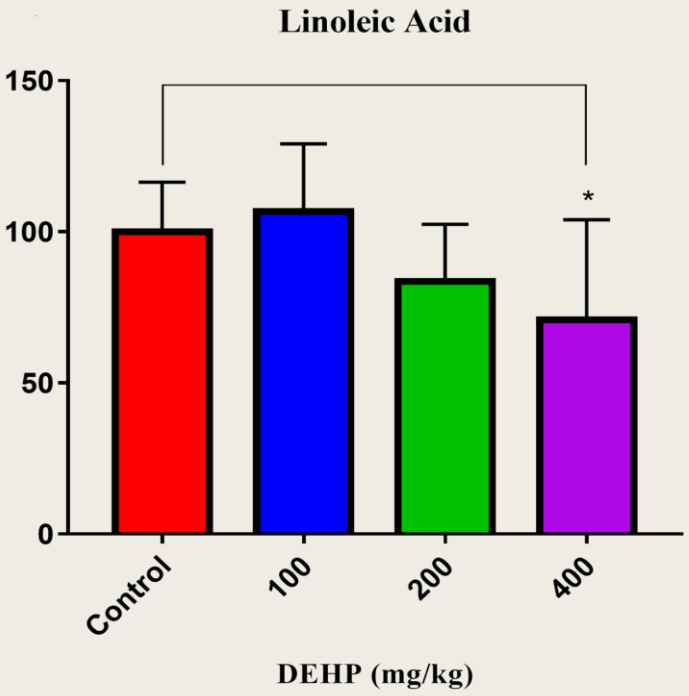


- Palmitic acid induces inflammation
- Cardiovascular diseases, diabetes, obesity

Relative fatty acids content of spleen tissue. Total peak areas and FAME composition (% of total FAME) of samples were measured. First, the fold change was calculated between control and DEHP treated samples, and then the percentage change for each was calculated after setting the amount in control as 100%. Notes: *p ≤ 0.05, ** p ≤ 0.01 and *** p ≤ 0.001 indicate different from control group

RELATIVE FATTY ACID CONTENT OF SPLEEN

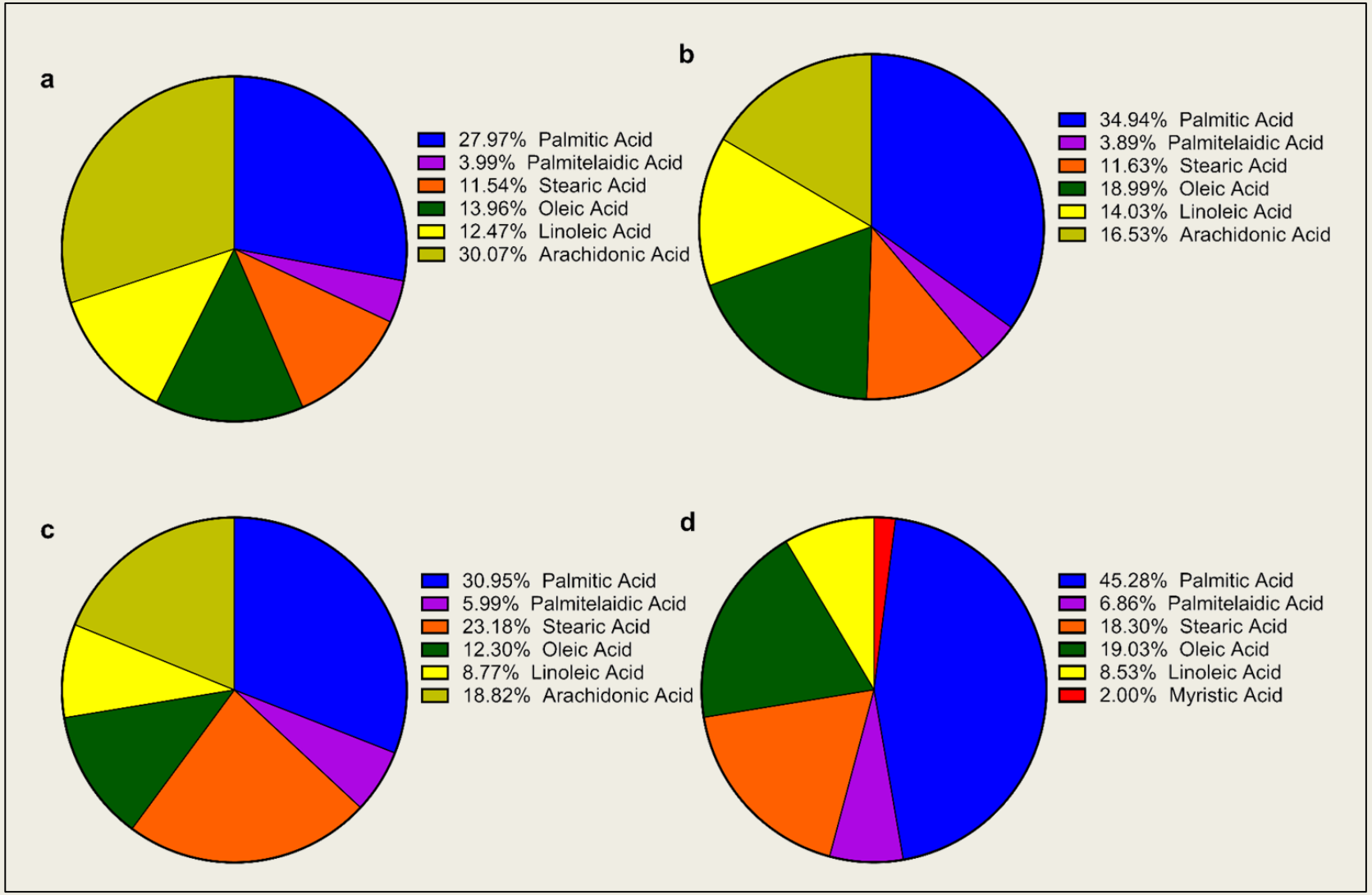




- Linoleic acid is an essential fatty acid and metabolized into arachidonic acid for the derivatization full benefit
- Essential fatty acid metabolism is impaired in various diseases such as hypertension, obesity, diabetes and coronary heart disease

Relative fatty acids content of lspleen tissue. Total peak areas and FAME composition (% of total FAME) of samples were measured. First, the fold change was calculated between control and DEHP treated samples, and then the percentage change for each was calculated after setting the amount in control as 100%. Notes: *$p \leq 0.05$, ** $p \leq 0.01$ and *** $p \leq 0.001$ indicate different from control group

RELATIVE FATTY ACID CONTENT OF SPLEEN



FAME composition (% of total FAME) in spleen tissue of a) control, b) 100 mg/kg DEHP, c) 200 mg/kg DEHP and d) 400 mg/kg DEHP

CONCLUSION

- Endocrine disrupting chemicals (EDCs) and peroxisome proliferator chemicals (PPCs) are known for their contribution to the formation of various diseases including diabetes, infertility, obesity, cancer, cardiovascular diseases etc.
- DEHP belongs to the both EDCs and PPCs families and according to various studies, it may impair developmental, reproductive and endocrine system.
- However, impact of the DEHP on the fatty acid metabolism on the detoxification organs have not been widely studied.
- Therefore, in our study we aimed to investigate influence of the DEHP on the lipid and fatty acid metabolism of liver, kidney and spleen. In conclusion, our data may help to reveal possible mechanisms behind DEHP-induced diseases.

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thank you