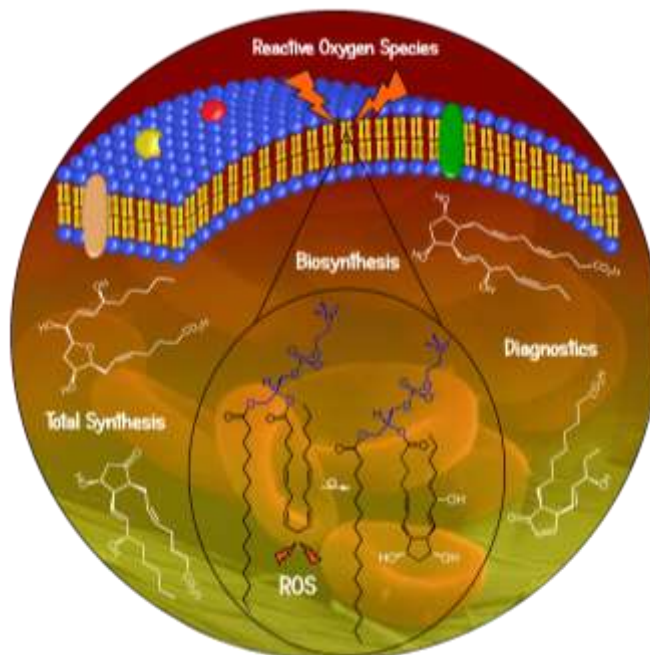




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Isoprostanes, Neuroprostanes, Phytprostanes: Marqueurs de Peroxydation Lipidique

Thierry DURAND

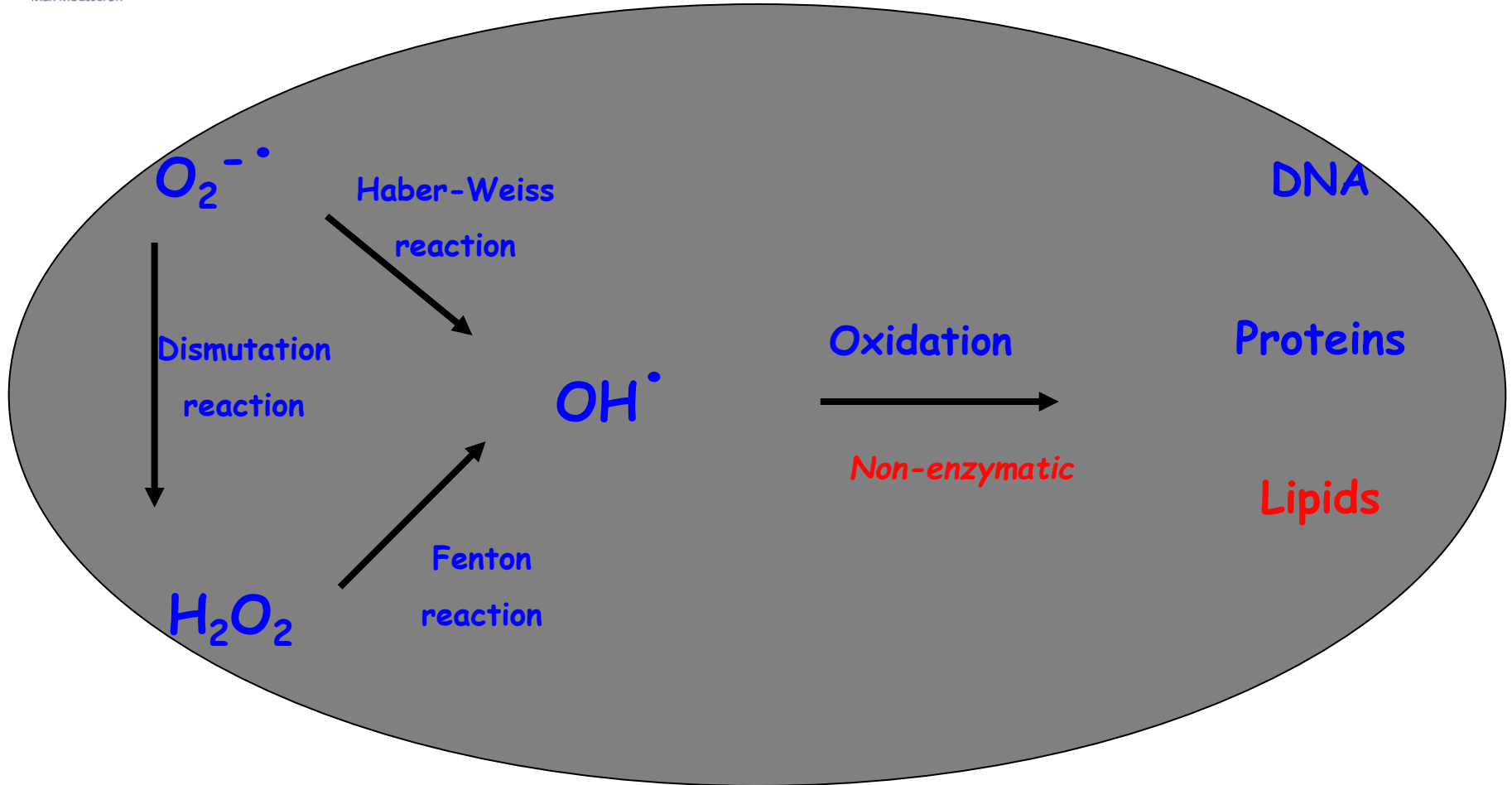


IBMM : UMR 5247 – CNRS – UM - ENSCM
Faculté de Pharmacie, Montpellier
Thierry.Durand@umontpellier.fr



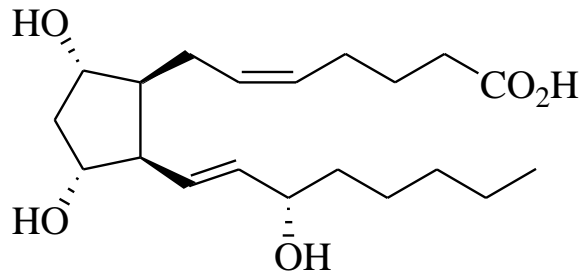


Toxicity of ROS

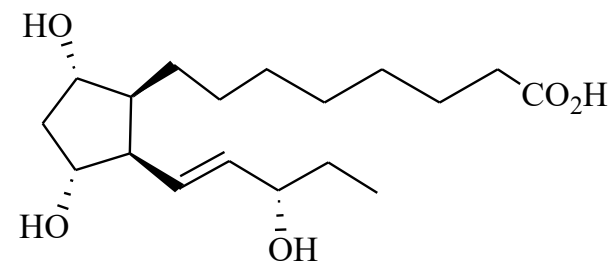




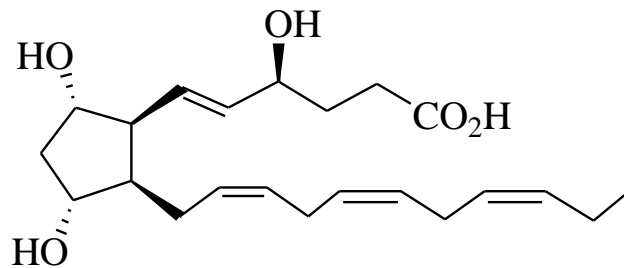
What are Isoprostanes, Neuroprostanes, Phytprostanes



15-F_{2t}-IsoP



16-F_{1t}-PhytoP



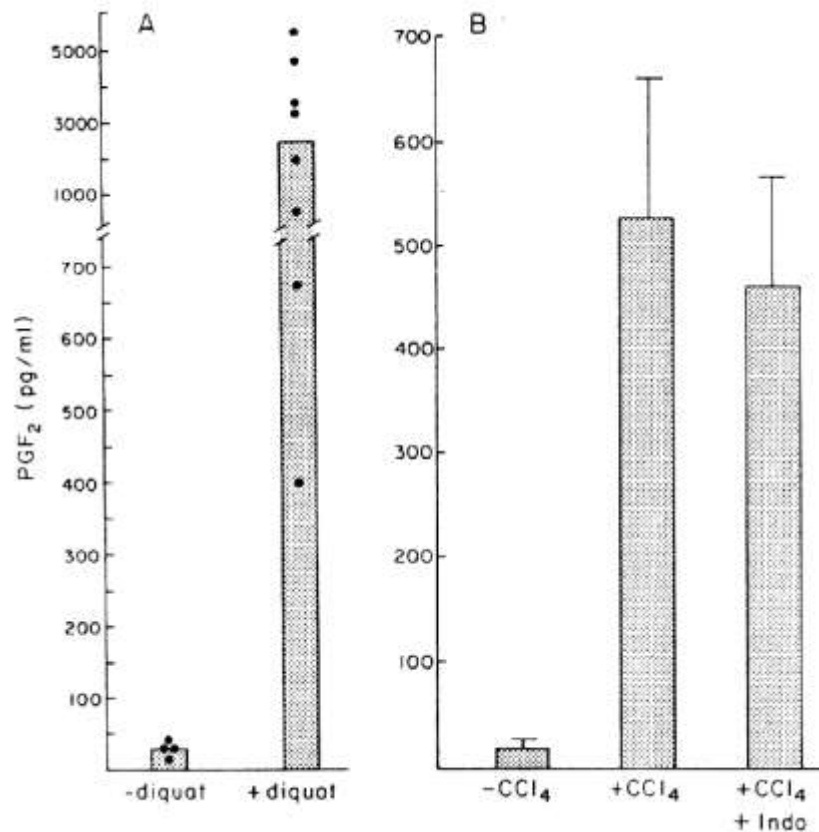
4-F_{4t}-NeuroP



Quantification

(A) Levels of PGF_2 -like prostanoids in plasma obtained from **Se-deficient rats** 90 min after administration of diquat compared with levels in **Se-deficient rats** not given diquat. Dots represent plasma levels in individual animals and the bars represent mean values.

(B) Levels of PGF_2 -like prostanoids in plasma obtained from normal rats 90 min after administration of CCl_4 with or without indomethacin (Indo) pretreatment compared with plasma levels measured in untreated rats. Results are expressed as mean SD ($n = 5$ for each group).



Morrow et al., *Proc Natl Acad Sci USA* **1990**, 87, 9383-9387

Kadiiska MB et al. *Free Radic Biol Med* **2005**; 38: 698-710.

EFSA Journal **2011**; 9(12): 2474

Vigor et al. *J. Chromatograph. B* **2014**, 964, 65-78;

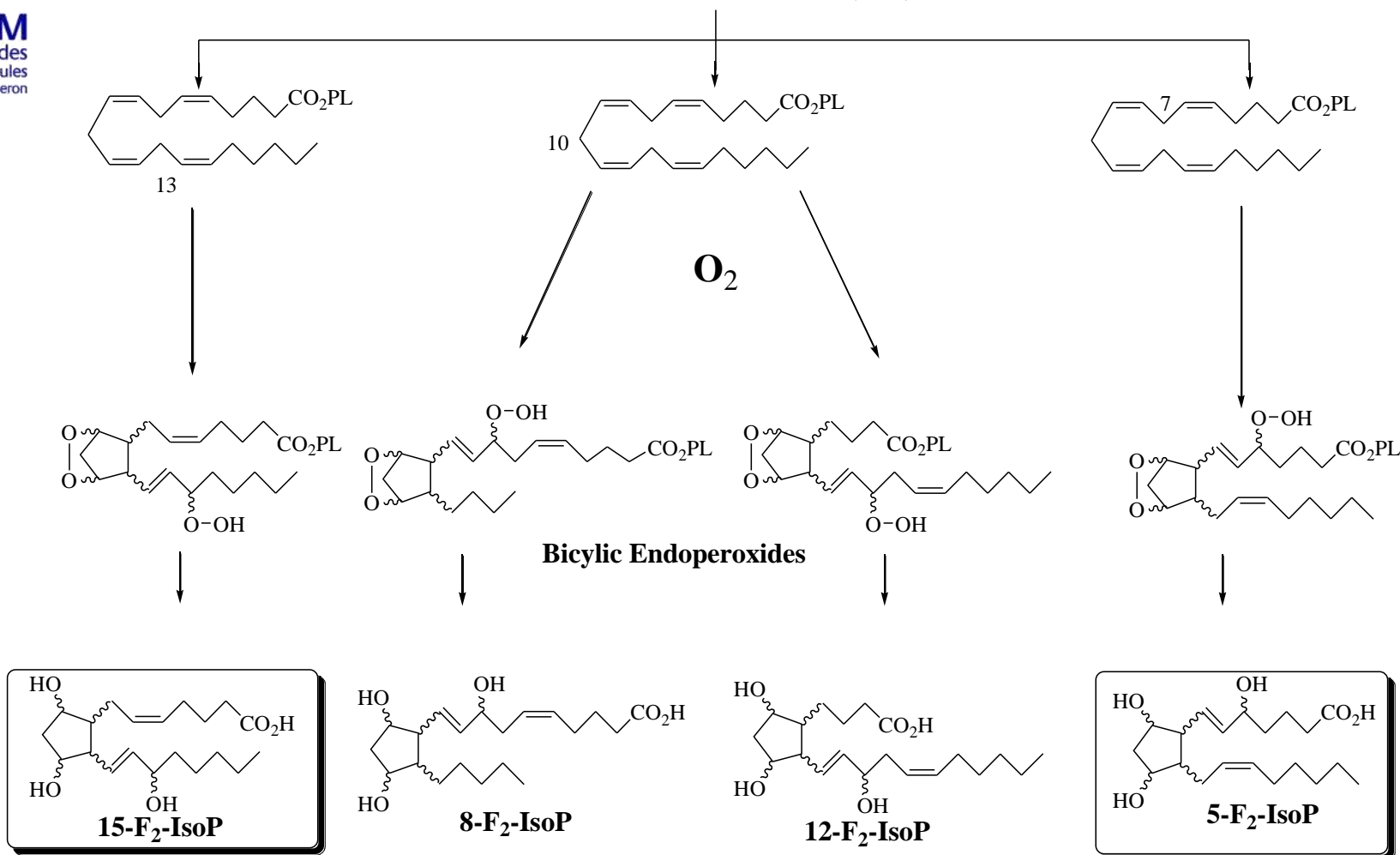
Dupuy et al *Anal Chim Acta* **2016**, 921, 46-58.



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Biosynthesis of F_2 -Isoprostanes

Arachidonic Acid (AA)



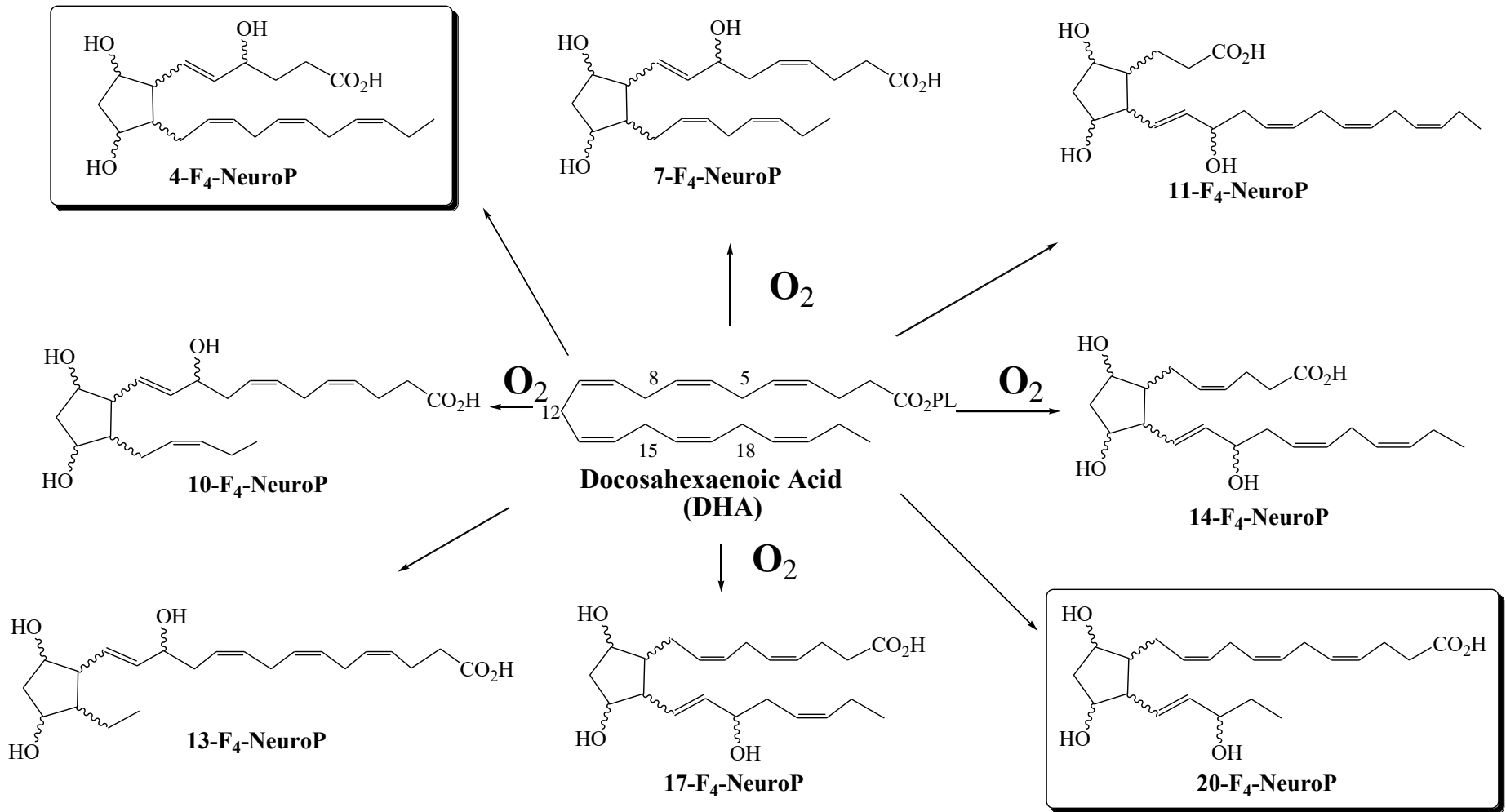
Morrow *et al.* *Proc. Natl. Acad. Sci. U.S.A.* **1990**, 87, 9383-9387.

Yin *et al.* *J. Biol. Chem.* **2004**, 279, 3766-3776.



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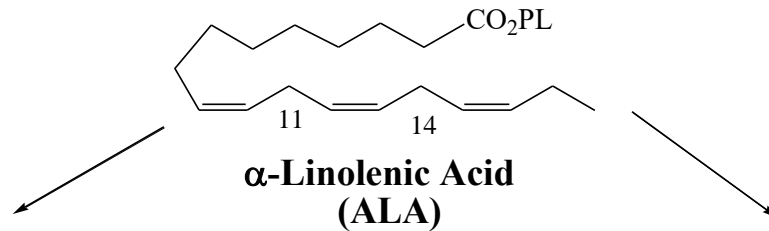
Biosynthesis of F_4 -Neuroprostanes



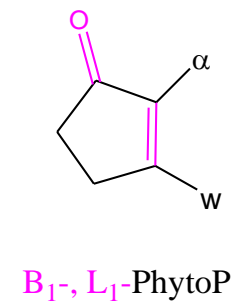
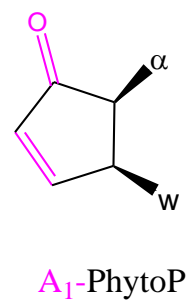
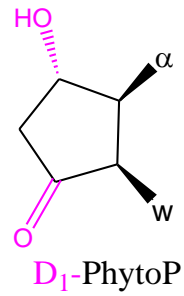
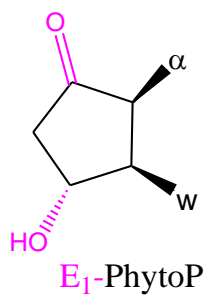
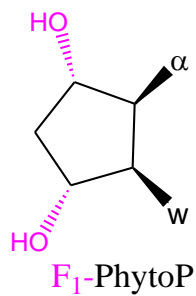
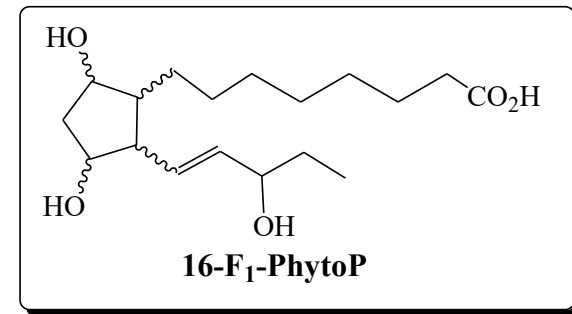
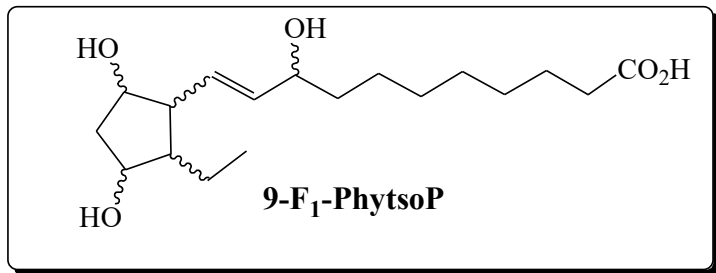
Nourooz-Zadeh *et al. Biochem. Biophys. Res. Com.*, **1998**, 242, 338. Roberts LJ 2nd *et al. J Biol Chem.* **1998**, 273, 13605. Yin *et al. J. Biol. Chem.* **2005**, 280, 2600



Biosynthesis of F₁-Phytoprostanes



O₂

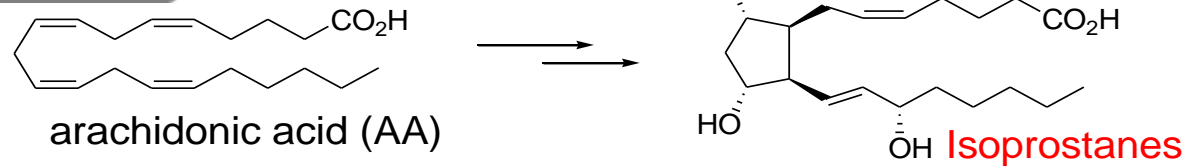


Imbuch R., Mueller M.J. *Free Radic. Biol. Med.* **2000**, 28, 720

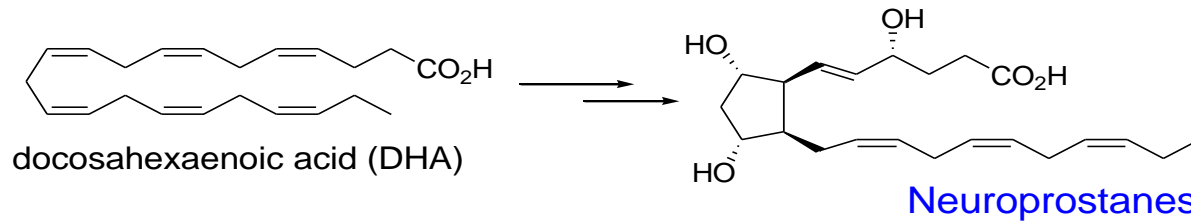
Jahn U; Galano J-M; Durand T *Prostaglandins Leukot Essent Fatty Acids*, **2010**, 82, 83–86

Isoprostanes - Classes by Precursors and Organisms

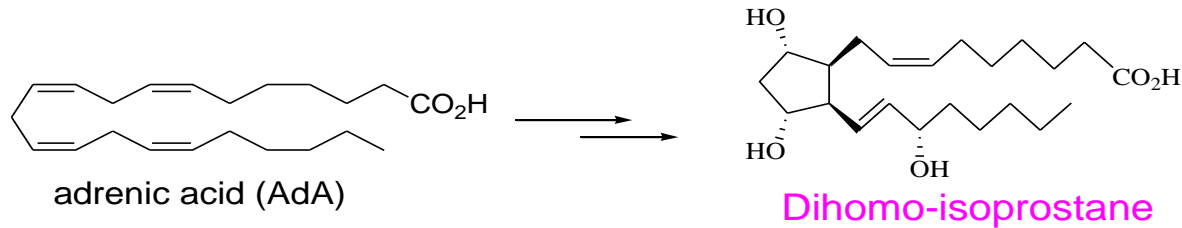
In Vertebrates:



Morrow J.D., Hill K.E., Burk R.F., Nammour T.M., Badr K.F. Roberts LJ 2nd. *Proc Natl Acad Sci USA* **1990**, 87, 9383

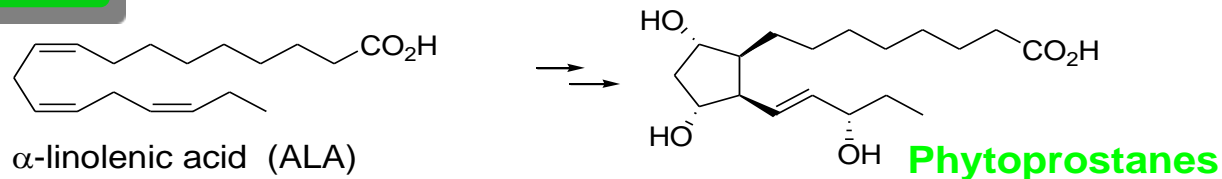


Nourooz-Zadeh J, Liu E.H, Yhlen B, Anggard E.E, Halliwell B, *J Neurochem.* **1999** , 72, 734



VanRollins, M., R. L. Woltjer, H. Yin, J. D. Morrow, and T. J. Montine *J. Lipid Res.* **2008**, 49, 995

In Plants:



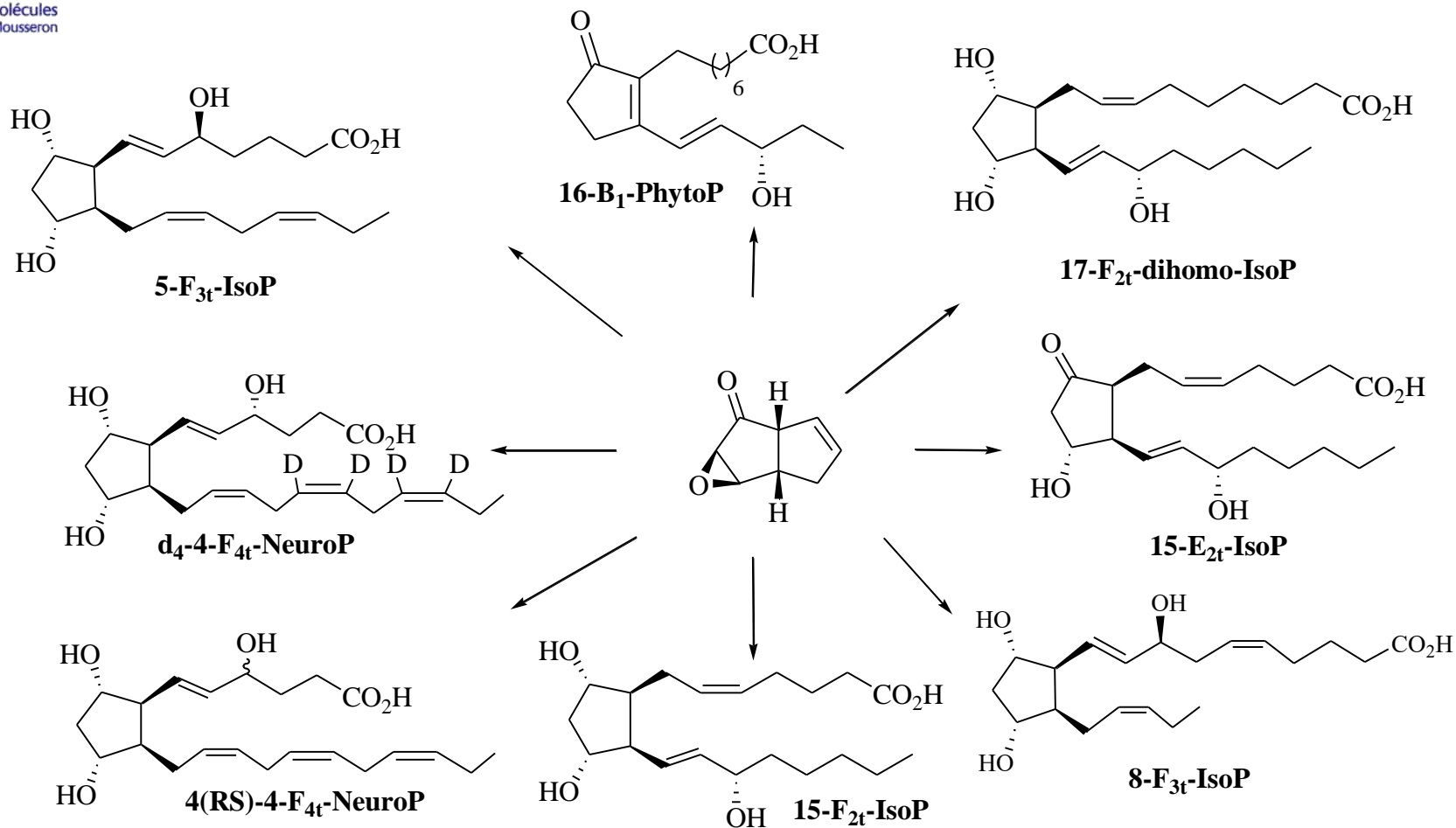
Imbuch R., Mueller M.J. *Free Radic. Biol. Med.* **2000**, 28, 720



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Chemical Synthesis

A fully flexible approach



Oger et al. *J. Org. Chem.* **2010**, 75, 2411-2414; *J. Org. Chem.* **2010**, 75, 1892-1897; *Chem. Eur. J.* **2010**, 16, 13976-13980; *Eur. J. Org. Chem.* **2012**, 2621-2634; *Chem. Rev.* **2013**, 113, 1313-1350.

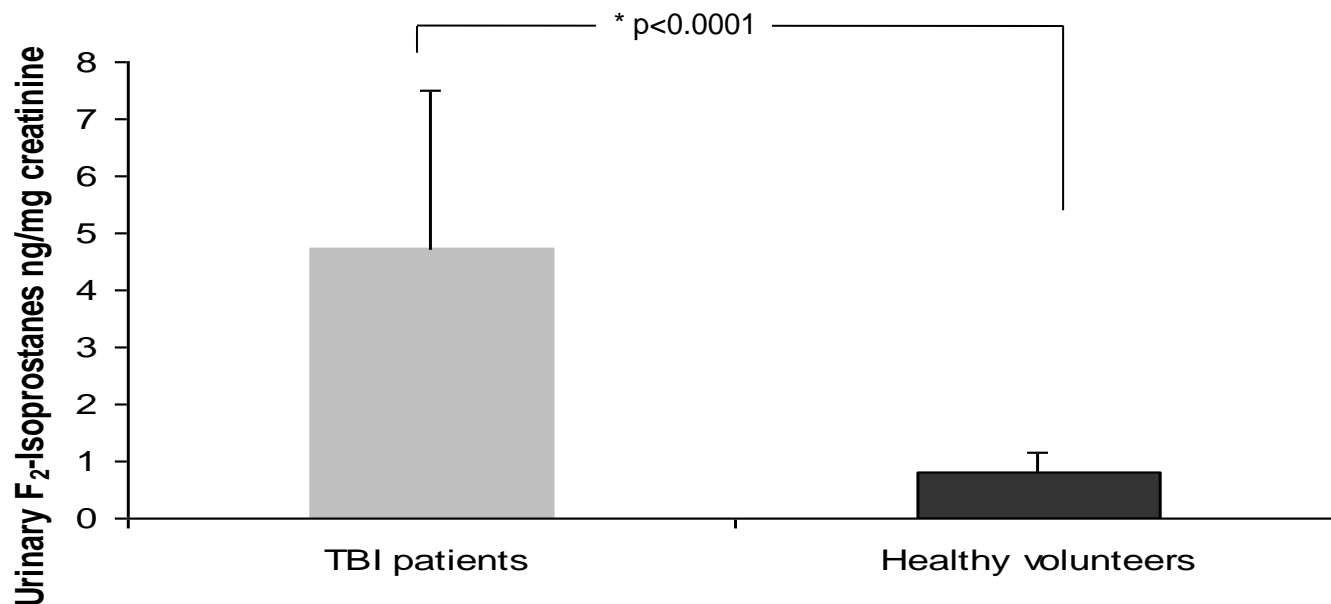
Guy et al. *Chem. Eur. J.* **2014**, 20, 6374-6380, *Front. Chem.* **2015**, 3, 41-51



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Biomarkers of Lipid Oxidative Damage

Quantification of Urinary F₂-isoPs with 4(RS)-F_{4t}-NeuroP as an IS using GC-MS.

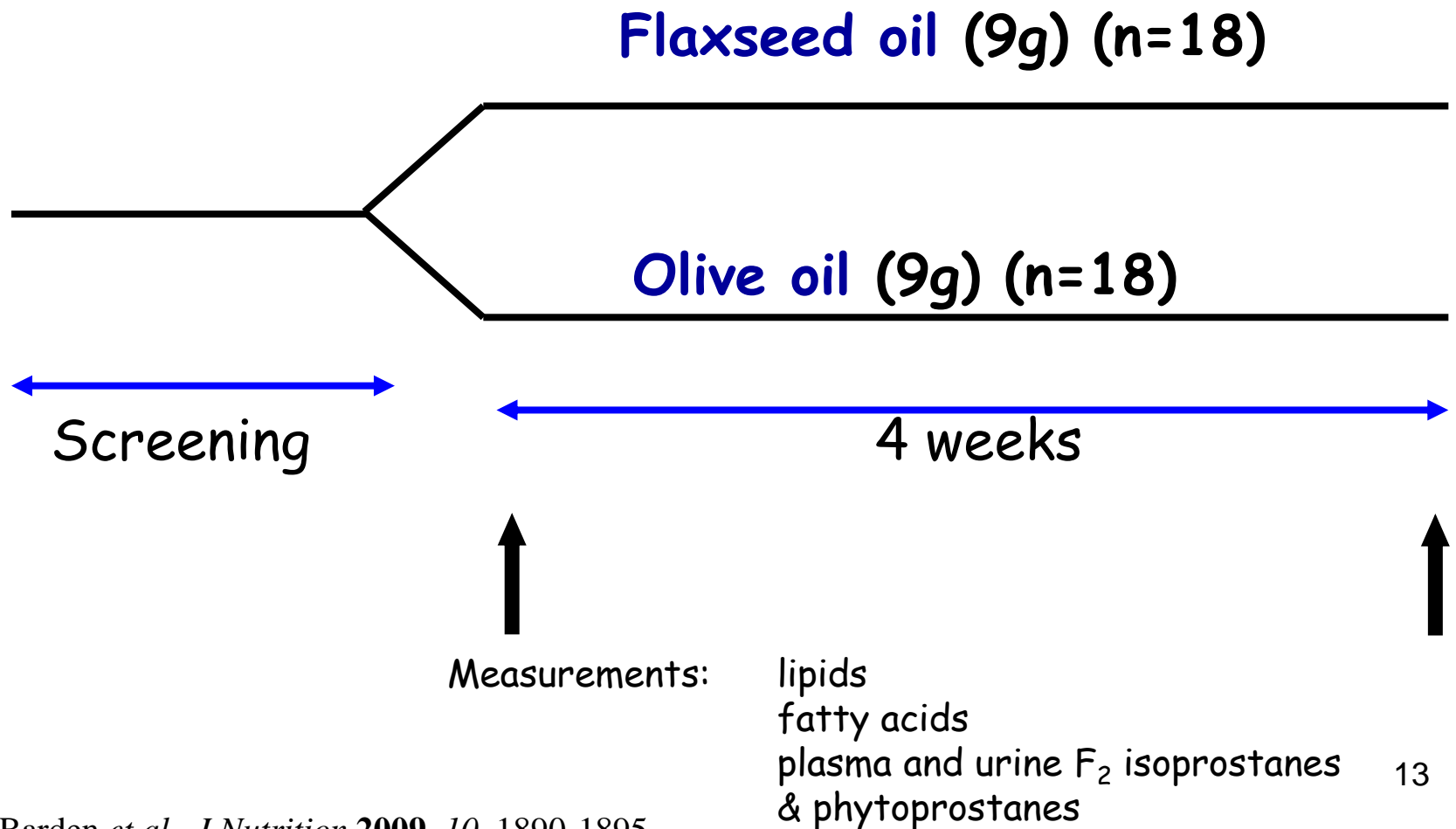


Urinary levels of F₂-Isoprostanes in traumatic brain patients (4.73 +/- 2.7 ng/mg creatinine) compare to healthy subjects (0.811 +/- 0.357 ng/mg creatinine).
Data are presented as mean +/- SD.

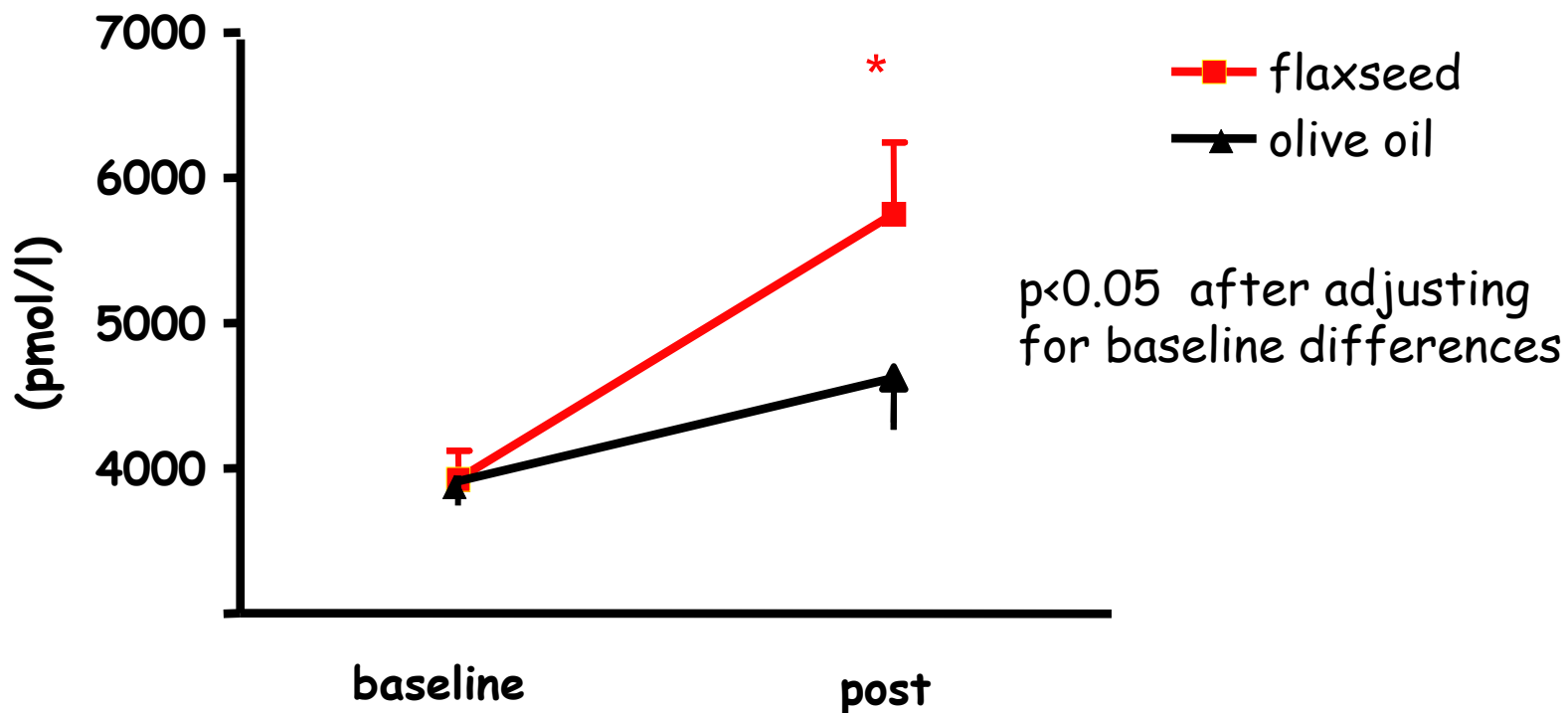


Study Design

Aim : To examine whether ALA given as flaxseed oil affects lipid peroxidation in men

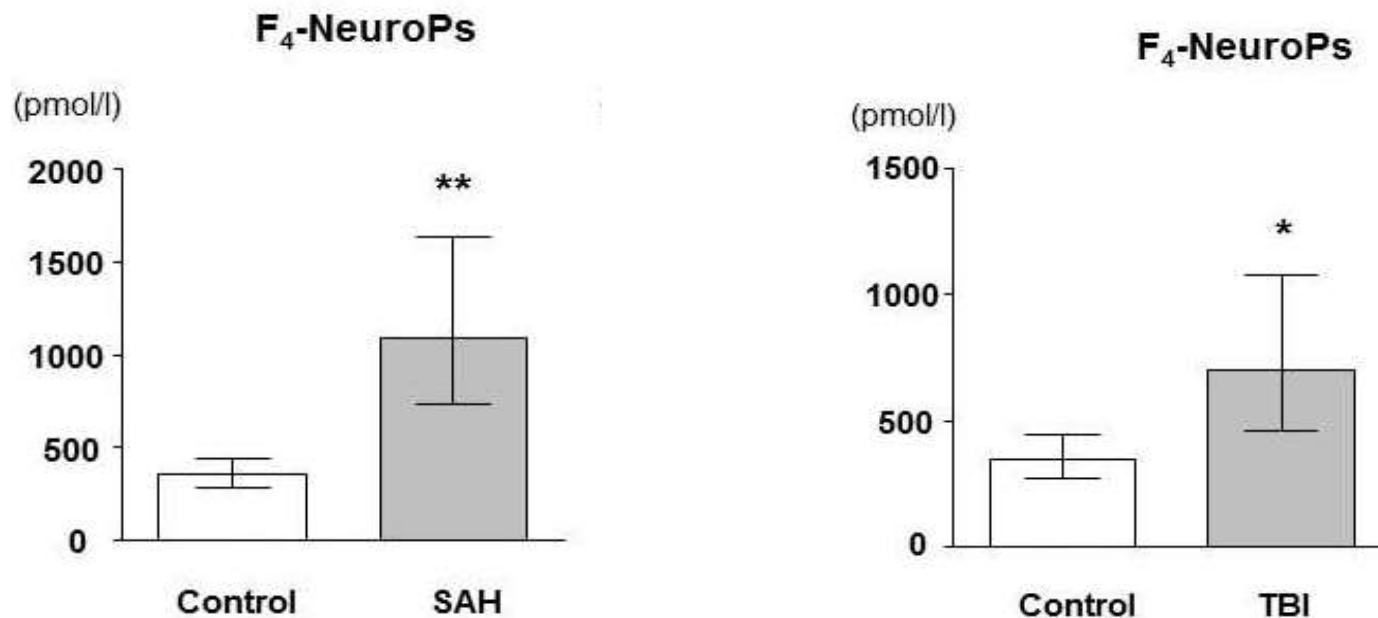


Plasma PPF₁ concentration





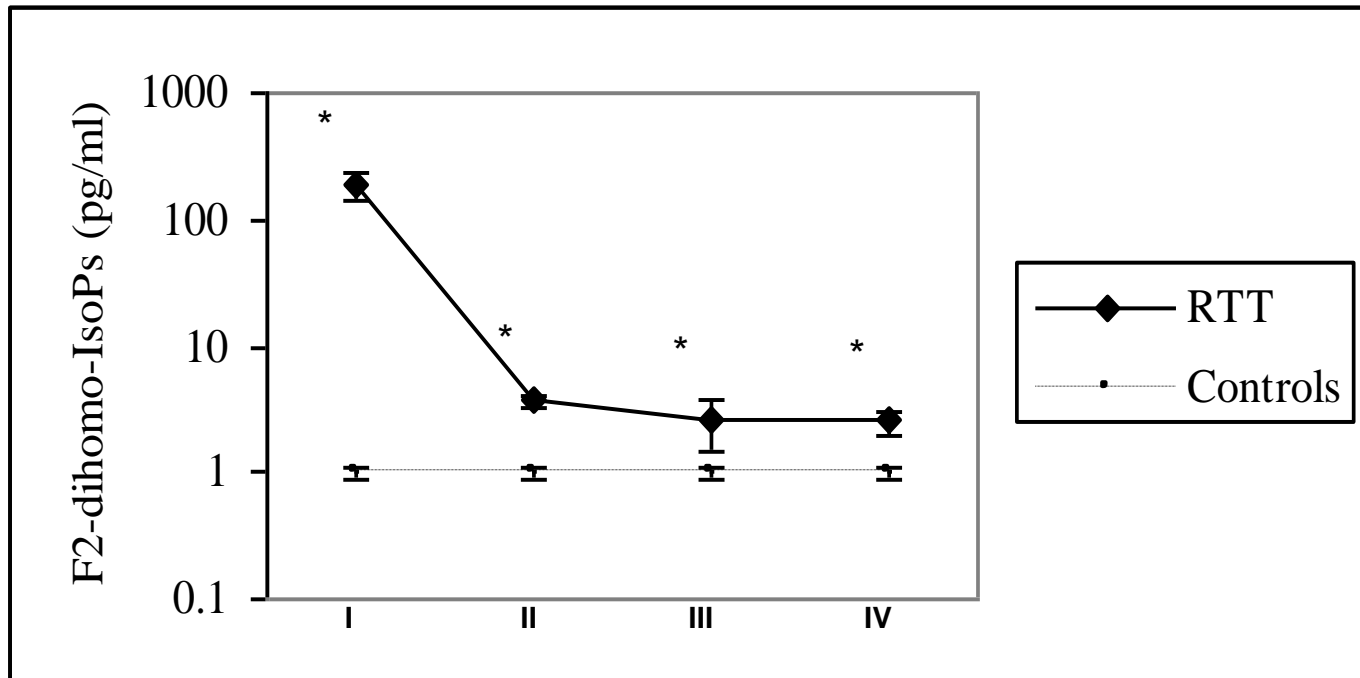
CSF F₄-NeuroPs in SAH and TBI patients



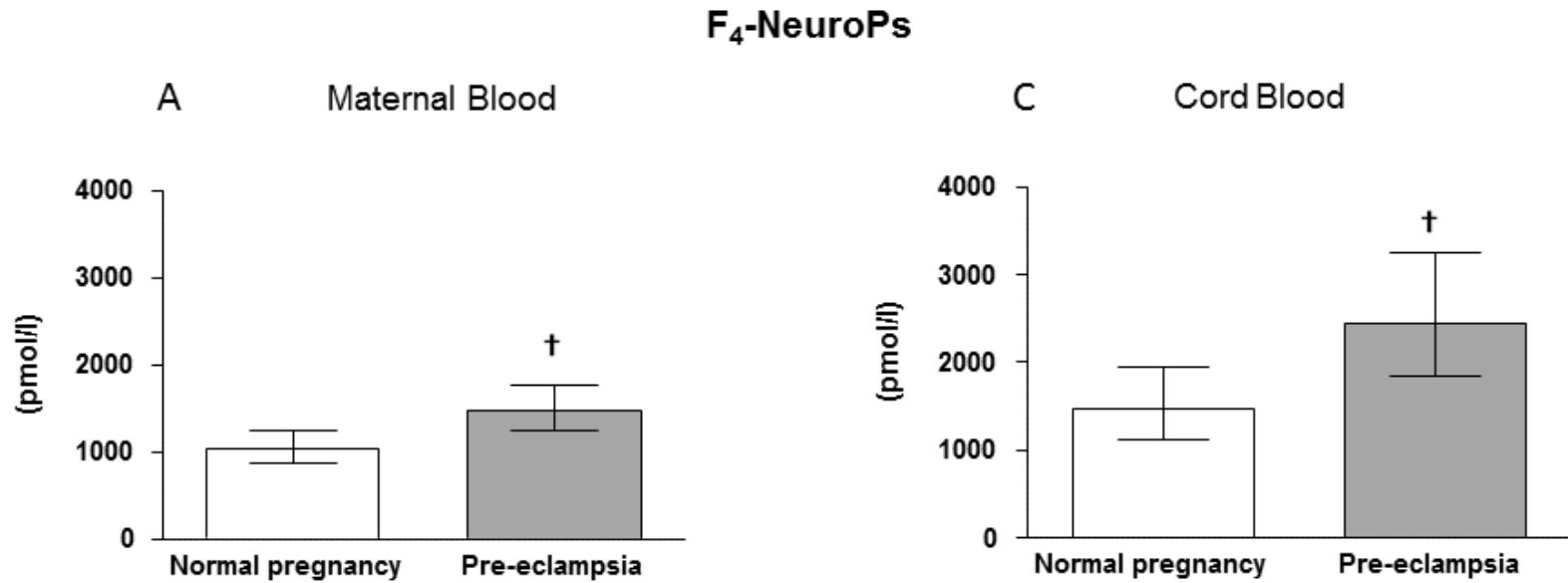
Values are geometric mean and 95%CI, * $P \leq 0.05$, ** $P \leq 0.001$

TB Corcoran, E Mas, AE Barden, T Durand, JM Galano, LJ Roberts II, M Phillips, TA Mori *Antioxid Redox Signal* **2011**, *15*, 2663-2667.

Plasma F₂-dihomo-IsoPs are related to diseases stage for RTT patients with the classical form of the disease.



Plasma F₄-NeuroPs in Normal Pregnancy and Pre-Eclampsia



AE Barden, TB Corcoran, E Mas, T Durand, JM Galano, LJ Roberts II, M. Paech, N.A. Muchatuta, M Phillips, TA Mori *Antioxid Redox Signal* **2012**, *16*, 165-169.



DHA dose-dependently reduces atherosclerosis: a putative Role for its peroxidation metabolites F₄-NeuroPs

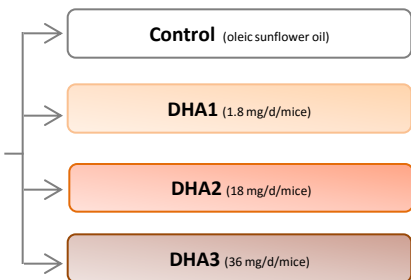
Methods & Results

Experimental design



LDL^r-/- mice
(♂, 8 wks, n=30/group)

20 weeks, diet rich in lard (10%, w/w)
& cholesterol (0.045%, w/w)
Oral gavage with oils 5 days/wk

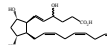


Phenotypic effects of DHA

	Control	DHA1	DHA2	DHA3	R ²
Plasma TG (mM)	1.1 ± 0.1 ^a	1.1 ± 0.1 ^{ab}	13.9 ± 0.5 ^b	0.8 ± 0.1 ^{bc}	0.97**
Plasma Chol. (mM)	13.2 ± 0.5 ^{ab}	-3 ± 3 ^a	11.2 ± 0.6 ^{bc}	9.5 ± 0.3 ^c	0.96**
Δsystolic BP (mmHg)	-2 ± 2 ^a	24 ± 1 ^a	-4 ± 2 ^a	-16 ± 3 ^b	15 ± 0.84
ΔPlaque area (%)	22 ± 1 ^{ab}		18 ± 1 ^{bc}	1 ^c	0.97*

(Mean ± SEM, ANOVA and Tukey-Kramer post-hoc analysis, ^{a, b, c} significantly different at p<0.05)
(R²=Pearson correlation coefficient between the phenotypic variables and the dose of DHA, ** p<0.01 and * p<0.05)

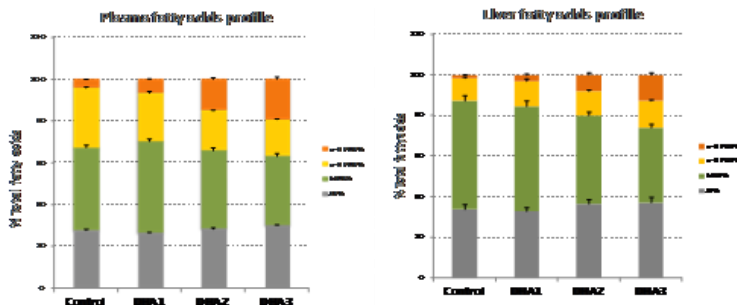
→ DHA dose-dependently reduced cardiovascular risk factors and atherosclerosis



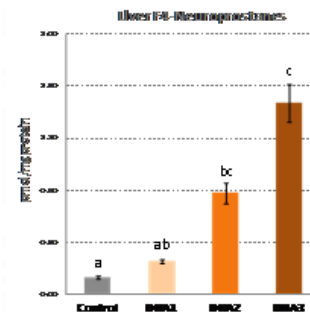
Profiles of fatty acids and oxygenated metabolites

Profiles of fatty acids and oxygenated metabolites

Fatty acids (GC/FID and GC/MS)



Oxygenated metabolites (LC-MS and GC-MS/MS)



DHA supplementation **substantially modified** both the profiles of **fatty acids** and of **oxygenated metabolites**
DHA might be preferentially and **readily peroxidized** into **F₄-Neuroprostanes**

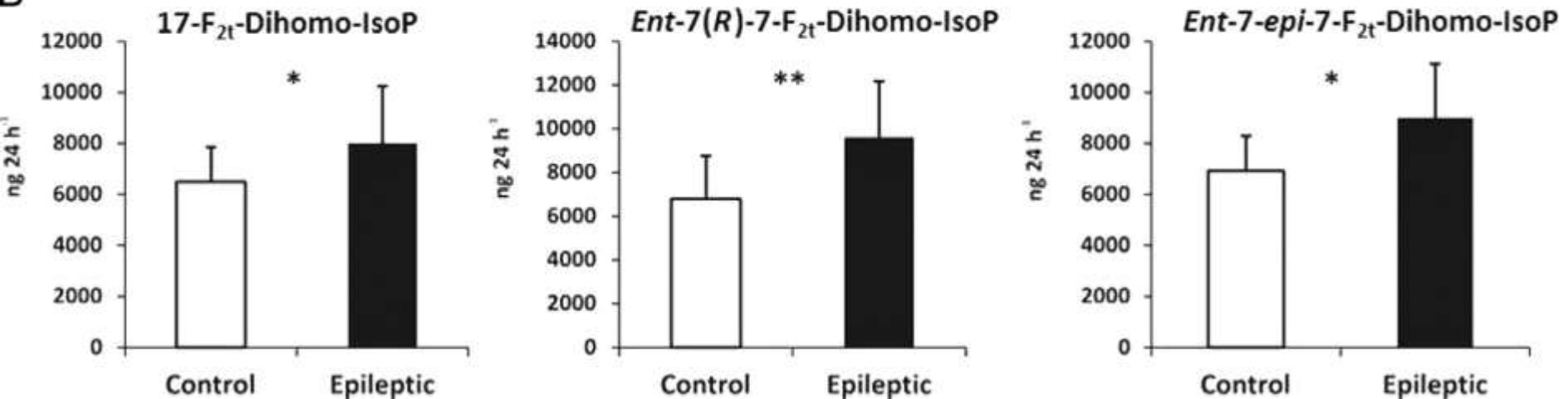
* C. Gladine, J-W. Newman, T. Durand, T. L. Pedersen, J-M. Galano, C Demouget, O. Berdeaux, E. Pujos-Guillot, A. Mazur, B. Comte *PloS One* **2014**, 9(2), e89393

* A. Dupuy, P. Le Faouder, C. Vigor, C. Oger, J-M. Galano, C. Dray, J. C. Y. Lee, P Valet, C. Gladine, T. Durand, J. Bertrand-Michel *Anal Chim Acta*. **2016**, 921, 46-58.



Urinary F₂-dihomo-IsoPs in epileptic patients

B

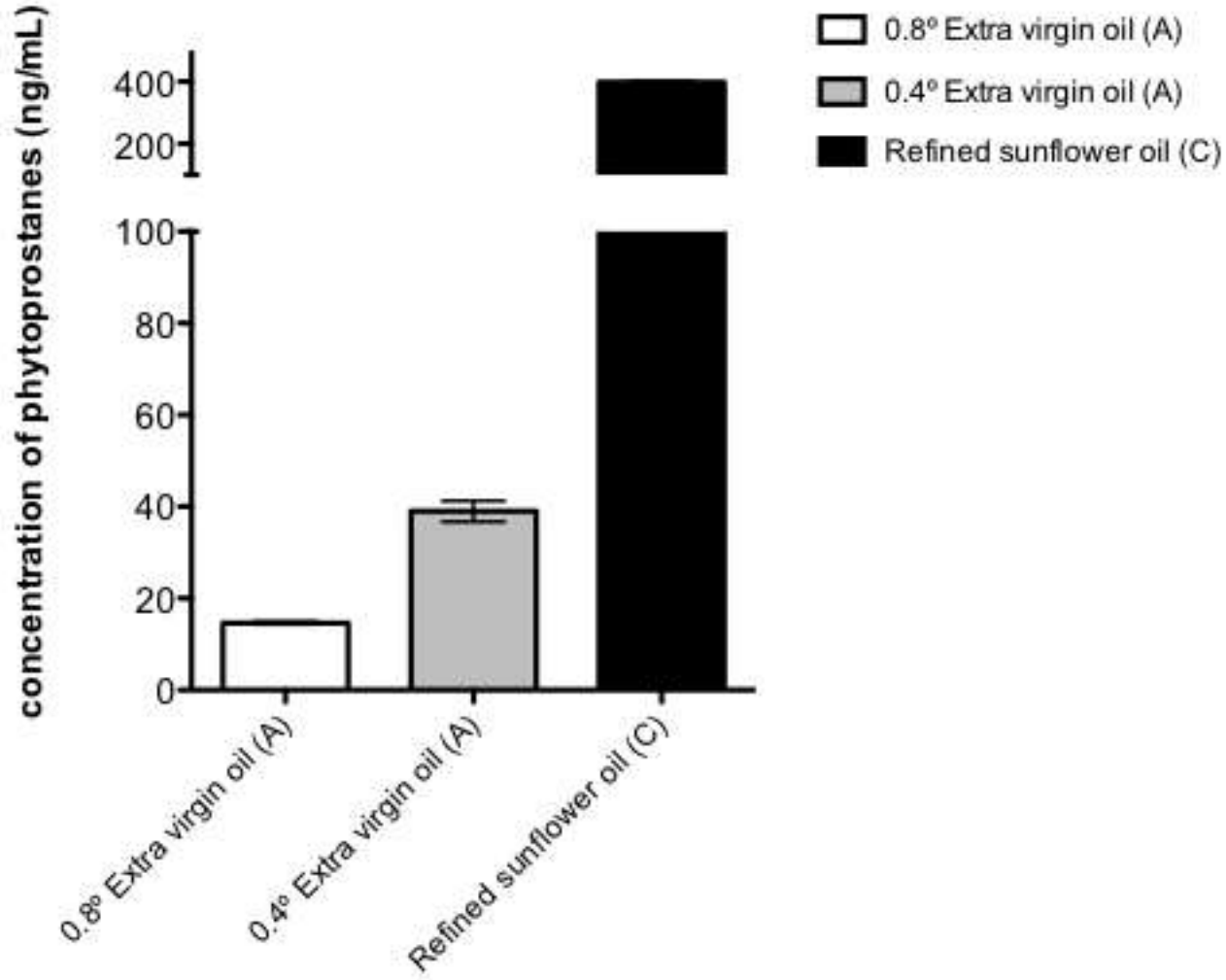


Urinary Dihomo-isoprostanes (17-F_{2t}-Dihomo-IsoP, Ent-7(RS)-7-F_{2t}-Dihomo-IsoPs, and Ent-7-epi-7-F_{2t}-Dihomo-IsoPs) (ng/24h) determined in epileptic patients (n $\frac{1}{4}$ 15) and the control group (n $\frac{1}{4}$ 15). Bars with asterisks are statistically different at *P < 0.05 or ** P < 0.01.

S Medina, I de Miguel-Elizaga, C Oger, J-M Galano, T Durand, M Martinez-Villanueva, M L Gil-del-Castillo, I Villegas-Martinez, F Ferreres, P Martinez-Hernandez, A Gil-Izquierdo
Free Radic. Biol. Med. **2015**, 79, 154-163



Total content of PhytoPs determined by UHPLC/MS-MS on commercial olive and sunflower oils

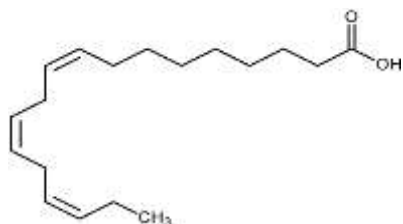


Water deficit during pit hardening enhances PhytoP content in EVOO

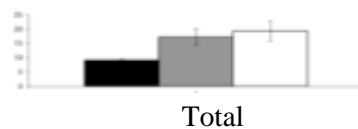
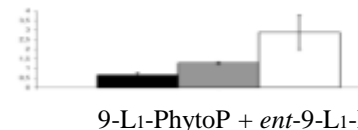
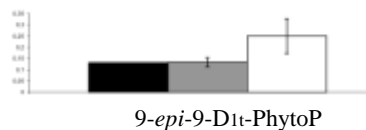
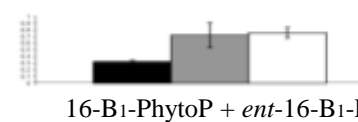
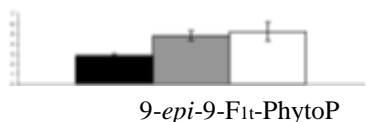
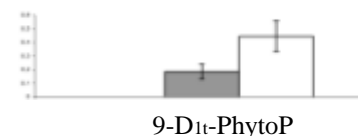
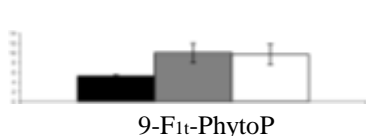
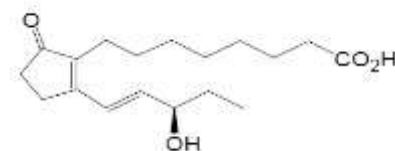
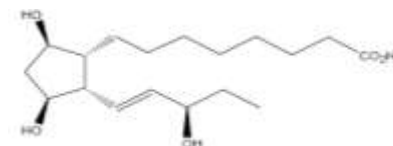
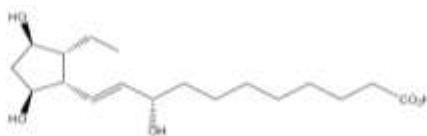


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**α -linolenic acid
(ALA)**

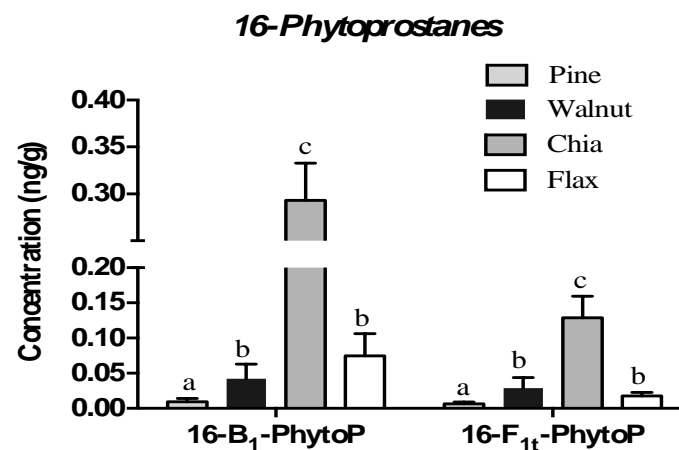
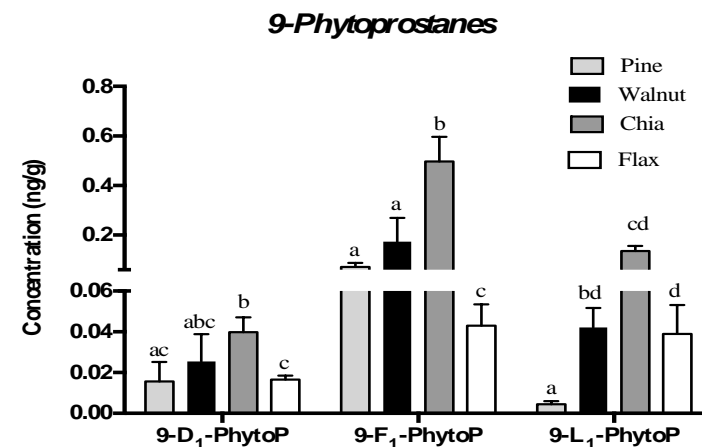
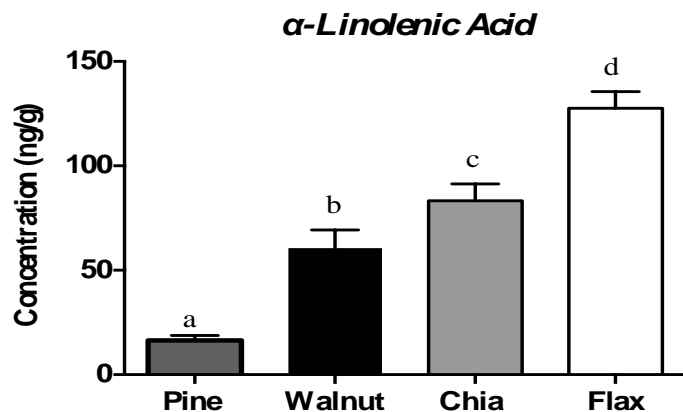


**Phytosteranes
(PhytoPs)**



- Control treatment
- Mild water deficit (T1 treatment)
- Severe water deficit (T2 treatment)

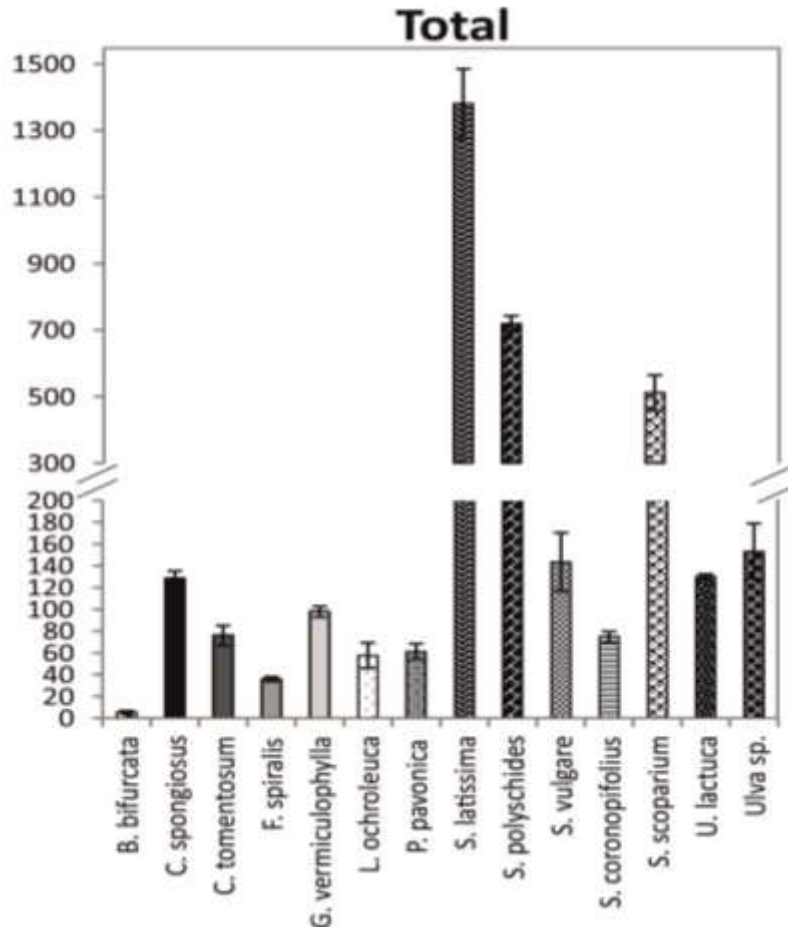
PhytoPs determined by LC/MS-MS in Nuts and Seeds



The lipid component was isolated by soxhlet reaction prior to LC-MS/MS measurement. Values of the column in graphical display is annotated as mean±SD, n=4. Columns sharing different alphabetical superscripts in each graph are significantly different (p<0.05).



Total content of PhytoPs on macroalgae species belonging to Chlorophyta, Phaeophyta and Rhodophyta



- ▣ B. bifurcata
- C. spongiosus
- C. tomentosum
- F. spiralis
- G. vermiculophylla
- L. ochroleuca
- ▣ P. pavonica
- ▣ S. latissima
- ▣ S. polyschides
- ▣ S. vulgare
- ▣ S. coronopifolius
- ▣ S. scoparium
- ▣ U. lactuca
- ▣ Ulva sp.



Dr Justine Bertrand-Michel



Pr Jetty Lee



Pr Claudio de Felice



Pr Angel Gil-Izquierdo



Pr Maria Fedorova



Thank you for your attention and for your kind invitation

57th International Conference on the Bioscience of Lipids (ICBL)

Chamonix - Mont Blanc, France

from September 4-8, 2016

The thematic of this edition will be « Lipidomics: from Structures to
Functions »

Please see the link for the Conference website: <http://icbl.chamonix.com/>





SFEL Satellite Symposium

Lipids and Brain: Antioxidants and Brain Health

Scientific Committee: Pr Stephen CUNNANE (Université Sherbrooke, Canada), Dr Bernadette DELPLANQUE (Université Paris Sud, Orsay), Pr Thierry DURAND (CNRS, Montpellier), Dr Philippe GUESNET (PG Consulting, Versailles), Pr Joseph VERCAUTEREN (Université, Montpellier)

Tentative programme

*** Keynote Lecture by Pr Joseph Vercauteren (Université de Montpellier, France)**

Antioxydants: new insights in brain protection

*** Pr Fulvio Mattivi (FEM, S Michele all'Adige, Italy)**

Is the brain a target of polyphenol metabolites?

*** Pr David Vauzour (University of East Anglia, UK)**

Flavonoids and brain health: physiological and molecular mechanisms underpinning their beneficial effects

*** Pr David Sinclair (Harvard Medical School, Boston, USA)**

Effects of resveratrol and sirtuin activation on brain health?

*** Dr Lionel Bertillon (INRA, Dijon, France)**

Carotenoids under the spotlight: from diet to the retina

*** Round Table : D Sinclair, F Mattivi, L Bertillon, Ph Guesnet, D Vauzour, J Vercauteren**

Prospects in human nutrition/supplementation