Tridocosahexanoina-AOX®

BRUDYLAB **SCIENCE FUNDAMENTALS 2000-2020**

MEDICAL NUTRITION SPECIALISTS | BRUDYLAB®

The European Office of Patents has recently recognized the success of Brudy's science by the concession, between others, of the **patent EP1962825**. This patent has not only exceeded the most exigent novelty exams and inventive activity of this office, but also confirming its validity and efficacy by firm decision given on May 12, 2017, and with rejection of all oppositions posed by various DHA producing companies. With the trade name of **ALGATRIUM®**, Brudylab produces and markets the **only available products containing highly concentrated DHA-triglyceride (Tridocosahexanoina-AOX®) authorized for antioxidative protection in eye diseases associated to oxidative stress.** In this monograph, we present the science fundamentals giving support to the antioxidant-anti-inflammatory activity of our molecule, Tridocosahexanoina-AOX®, which has been patented as a cell antioxidant; it induces intracellular glutathione synthesis. We explain the synthesis method, our strict control of environmental pollutants, the importance of DHA for the visual and intelectual human development, and the beneficial healthy claims approved by the European Commission. We explain our *"in Vitro"* tests, of induced oxidative stress on human cell cultures, the dose-response bioavailability trials, as also our main clinicals trials done to demonstrate the antioxidant and anti-inflammatory efficacy at a clinical level. We also show a summary of all our clinical experience. Our achievements after 20 years of research efforts are the result of a private company working in close relation with the University (Biochemistry and Molecular Biomedicine Department , Biology Faculty, University of Barcelona), for the benefit of the human health.

BRUDYLAB, SL.

Abreviations

ADHD:	Attention Deficit Hyperactivity Disorder
ALA:	Alphalinolenic acid
ARA:	Arachidonic acid
ARPE-19:	Inmortalized human pigmentary epithelium cells from the retina
AOX:	Antioxidant
CG:	Control Group
DE:	Dry Eye
DHA:	Docosahexaenoic acid
DNA:	Desoxiribonucleic acid
EPA:	Eicosapentaenoic acid
ETDRS:	Early Treatment Diabetic Retinopathy Study
FA:	Fatty Acids
GPAA:	Primary Open Angle Glucoma
GPX:	Glutathine Peroxidase
GRed:	Glutathione Reductase
GSH:	Reduced Glutathione
GSSG:	Oxidized Glutathione
HIV:	Human Immunodeficient Virus
IL:	Interleukines
IMA:	Ischemic Modifyed Albumin
IOP:	Intraocular Pressure
MDA:	Malondialdehyde
MGD:	Meibomian Gland Disfunction
MUFA:	Monounsaturated fatty acids
NF-κβ:	Nuclear Factor κβ
OCT:	Optical Coherence Tomography
OMPD:	Ocular Macular Pigment Density
OSDI:	Ocular Surface Disease Index
POAG:	Primary Open Angle Glaucoma
PUFA:	Polyunsaturated fatty acids
ROX:	Oxigenated free-radicals
SFA:	Saturated fatty acids
Sn-1,2,3:	Stereospecific number-1,2,3
SOD:	Superoxide dismutase
TBUT:	Tear Break-Up Time
TG:	Triglyceride
TNF-α:	Tumor Necrosis Factor-α
TUNEL:	Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labelling
VA:	Visual Acuity

* Tridocosahexanoina-AOX®: Antioxidant DHA-Triglyceride. It is Brudy's patented DHA-Triglyceride

BRUDYLAB, SL Medical Department
Biochemistry and Molecular Biology Department, Biology Faculty, University of Barcelona

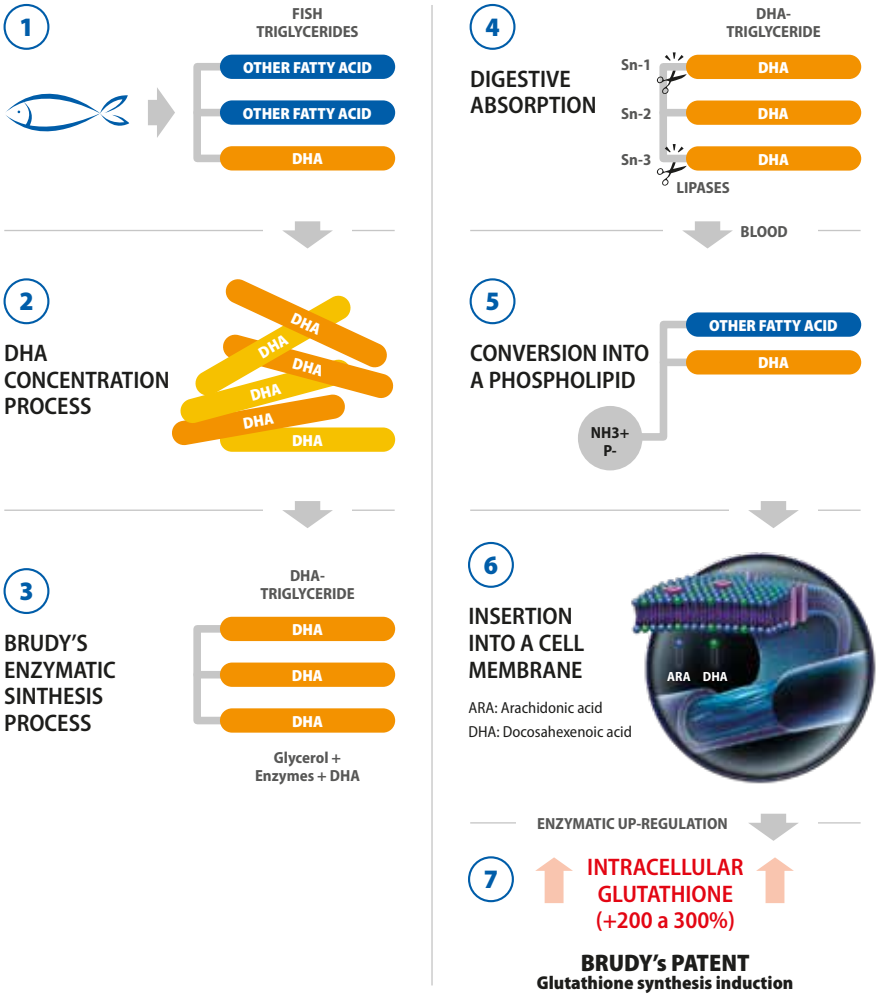
TRIDOCOSAHEXANOINA-AOX® SYNTHESIS

What is basic is to know about the DHA human physiology

Tridocosahexanoina-AOX® synthesis process

Conversion of fish-triglycerides into human-like triglycerides, **as they are found in human maternal milk**, having DHA in central position(Sn-2).

1. Departing from fish (Tuna fish and anchovies from Peru) triglycerides.
2. Cholesterol, Phytanic acid and all the fatty acids but DHA are eliminated. It is obtained a 70% concentrated DHA-ethyl ester.
3. After total extraction of ethanol, new triglycerides are enzymatically re-synthetized, having DHA in central position Sn-2 around 80% of the molecules.
4. Digestive lipases can break bonds in Sn-1 and Sn-3 positions of the triglycerides. A monoglyceride having DHA in central position is absorbed.
5. When the liver detects PUFA in central position (Sn-2), they are immediately transformed into DHA-phospholipids.
6. DHA-phospholipids are inserted into a cell membrane bilayer.
7. **BRUDY PATENT**: The larger DHA presence in the cell membrane is inducing glutathione synthesis (GSH).



We demand more than to meet the standards of environmental pollutants control, far below the allowed maximum levels[1]

Exhaustive purification process by filtration, distillation and adsorption to remove environmental contaminants, heavy metals, fish proteins, and microbial contaminants. Compliance with international quality standards, the Food Codex, the GOED and the European Pharmacopoeia. ALGATRIUM® follows an exhaustive analytical process to detect more than 250 environmental pollutants.

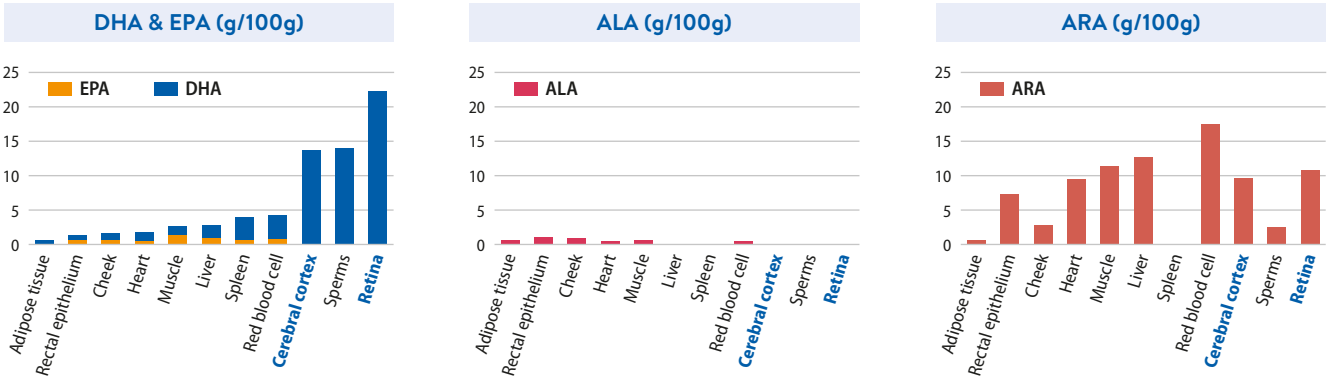
POLLUTANTS	Allowed maximum levels		Brudy batches
	European legislation	GOED	Results
Pb	0,1 ppm	0,1 ppm	< 0,02 ppm
As	-	0,1 ppm	< 0,05 ppm
Hg	0,5 ppm	0,1 ppm	< 0,005 ppm
Cd	0,1 ppm	0,1 ppm	< 0,005 ppm
Sn	-		< 0,2 ppm
Cu	-		< 0,1 ppm
Fe	-		< 0,1 ppm
Dioxins	1,75 pg/g		< 0,4 pg/g
Dioxins and similar PBC	6 pg/g		< 3,0 pg/g
PBCs	200 ng/g		< 15 ng/g
PAH (Benzopirenes)	2,0ppb		<2,0 ppb

PBCs: Polychlorinated biphenyls / GOED: Global Organization for EPA and DHA / PAH: Polycyclic Aromatic Hydrocarbons / ppm: Parts per million

DHA HUMAN NEEDS ARE A MUST

A basic need for intellectual and visual development in humans[2]

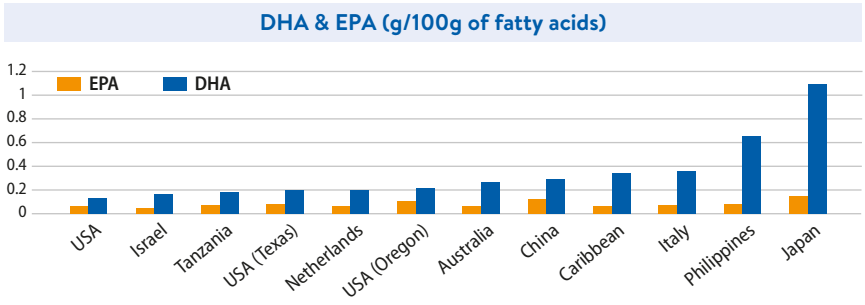
Concentration of fatty acids found in human tissues (g/100g of total fatty acids)[2]
of USA, Canada, Australia and European adults



EPA: Eicosapentaenoic acid / DHA: Docosahexaenoic acid / ALA: Alphalinolenic acid / ARA: Arachidonic acid

DHA & EPA content in human mothers milk from a diverse origin[2]
depending on their dietetic culture

The level of DHA (g/100g of fatty acids) is considered:
- Optimum: 0,8 to 1g
- Intermediate: 0,4 to 0,8g
- Suboptimal: < 0,4g



DHA Healthy Claims approved by European Comission

DHA HEALTHY CLAIMS APPROVED BY EUROPEAN COMISSION	CONSUMER SHOULD BE INFORMED THAT THE BENEFIT IS OBTAINED WITH INGESTION OF:
DHA (and also DHA+EPA) contribute to the normal function of the heart.	DHA 250mg/day (EU 432/2012) for adults. EFSA journal 2014; 12(10): 3840 for child of 2 to 18 years.
DHA contributes to maintenance of normal vision.	
DHA contributes to maintenance of normal brain function.	
DHA intake contributes to normal visual development of infants up to 12 months of age.	DHA 100mg/day (EU 440/2011).
DHA maternal intake contributes to the normal development of the eye of the fetus and breastfed infants.	(For pregnant and lactating women) DHA 200mg/day additional to 250mg/day recommended for adults (EU 440/2011).
DHA maternal intake contributes to the normal brain development of the fetus and breastfed infants.	
DHA (and also for combined DHA+EPA) contribute to the maintenance of normal blood triglyceride levels.	DHA 2g/day, also for DHA+EPA. Not to exceed a supplemental daily intake of 5g/day (EU 536/2013).
DHA and EPA contribute to the maintenance of normal blood pressure.	DHA 3g/day, also for combined DHA+EPA. Not to exceed a supplemental daily intake of 5g/day (EU 536/2013).

Consultation of European regulations should be made in: **www.eur-lex.europa.eu** (searches must be done with the year and the document number that appear in the right column of the table)

OUR PATENT

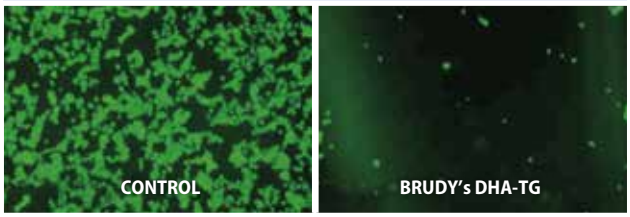
Tridocosahexanoina-AOX® cell antioxidant effect[3]

When a cell membrane is highly enriched with DHA, being DHA easily oxidized, the cell makes a genic activation of intracellular glutathione (GSH) synthesis, by means of an enzymatic up-regulation. GSH concentration is increased between 200 to 300% inside the cell cytoplasm.

GSH is the main antioxidant molecule, electron donor, in mammal cells; scavenger of oxygen free-radicals (ROX) protecting DNA, lipids and proteins from the cell organelles of being oxidized.

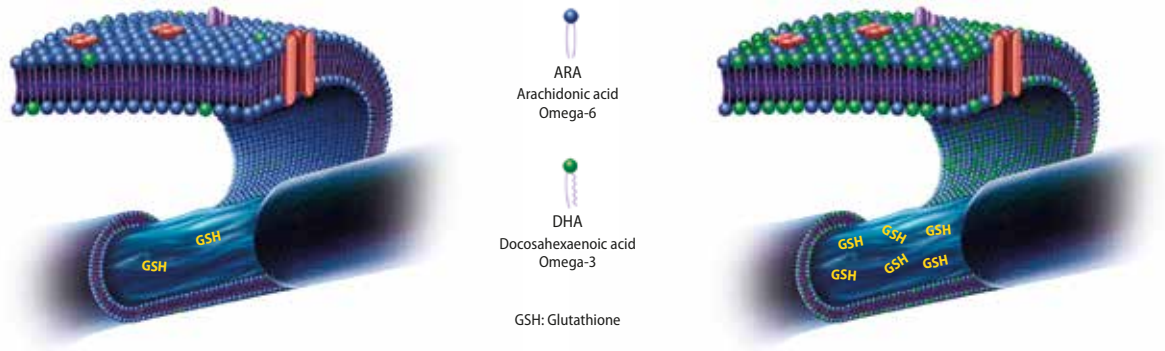
FIBROBLASTS

RETINA ARPE-19 CELLS



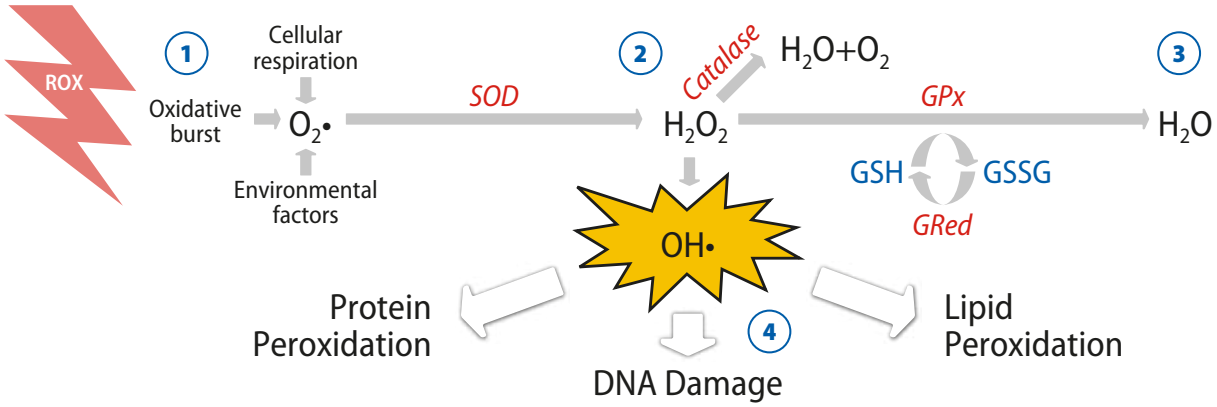
Induced ROX are reduced by 50% in human cell cultures when they are pre-incubated in Tridocosahexanoina-AOX®.

SECTION OF A NEURON MEMBRANE



Cells get shielded against any internal or external oxidation excess based on a their larger glutathione production. Glutathione is responsible of scavenging oxygen free radicals as an electron donor.

CELLULAR ENZIMATIC MECHANISMS BY WHICH OXIGENATED FREE RADICALS ARE SCAVENGED



Anion superoxide (O_2•) is converted into hydrogen peroxide (H_2O_2) by superoxide dismutase to avoid formation of the hydroxil radical (OH•). Catalase and glutathione peroxidase are converting the peroxide into molecular oxygen and water (H_20+O_2) by using the electrons given by GSH, thus avoiding oxidative harm on to the DNA, lipids and proteins of the cell.

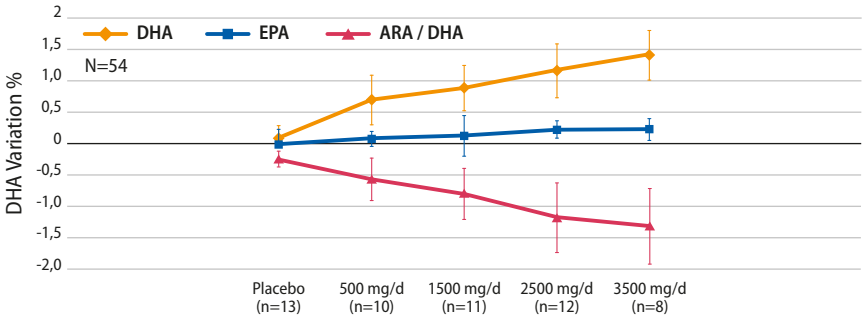
TRIDOCOSAHEXANOINA-AOX® DIGESTIVE ABSORPTION

Bioavailavility: dose-response trials

Short term[4]

DHA concentration in erythrocyte membrane, after supplementing 5 groups of healthy volunteers with variable doses of Tridocosahexanoina-AOX® or with Placebo. A dose dependent significant reduction in the Omega-6/Omega-3 index is seen.

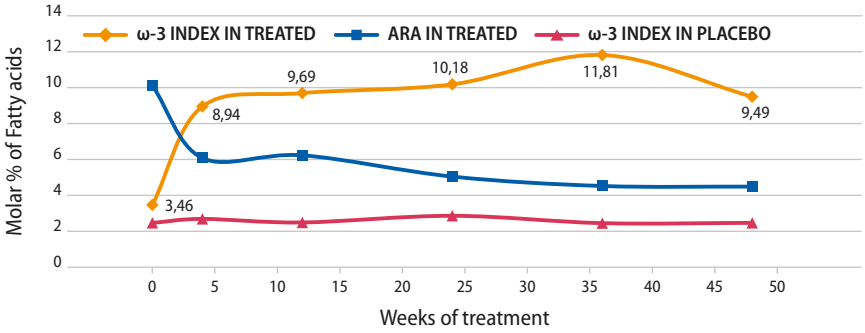
MARKER: ERYTHROCYTE MEMBRANE



Long term[5]

A controlled, randomized, double-blinded clinical trial including a sample of 84 HIV+ patients, being supplemented either with Tridocosahexanoina-AOX® 4g/day or Placebo during 1 year. PUFA concentration is detected by means of gas Chromatography. Only the active supplementation is significantly increasing DHA concentration in the erythrocyte cell membrane, and reducing the ARA levels.

MARKER: ERYTHROCYTE MEMBRANE

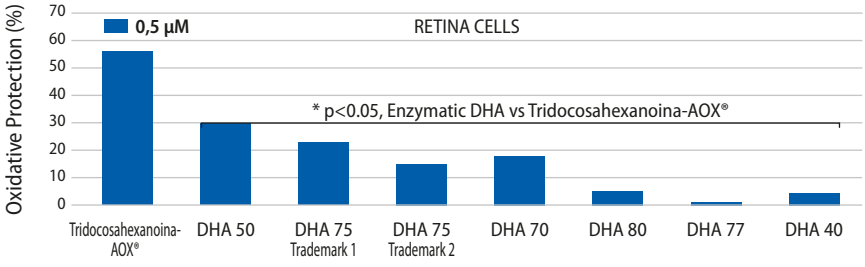


THE ANTIOXIDANT EFFICACY IS NOT RELATED WITH THE DHA CONCENTRATION IN THE TRIGLYCERIDE

The antioxidant efficacy is related with the DHA 6 double bonds integrity, but also with DHA occupying the central position in the triglyceride

Tridocosahexanoina-AOX® (ENZYMATIC DHA 70%) is reducing 60% the free radicals production when oxidative stress is induced in ARPE-19 cell cultures.[3] Significant differences with the rest of enzymatic triglycerides, from different trademarks, are seen whatever the concentration used.

ANTIOX. EFFECT OF TRIGLYCERIDES WITH VARIABLE DHA CONCENTRATIONS



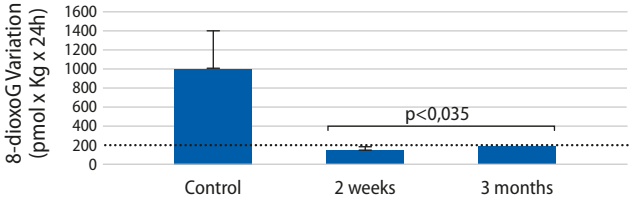
TRIDOCOSAHEXANOINA-AOX® ANTIOXIDANT EFFECT

Clinical trials

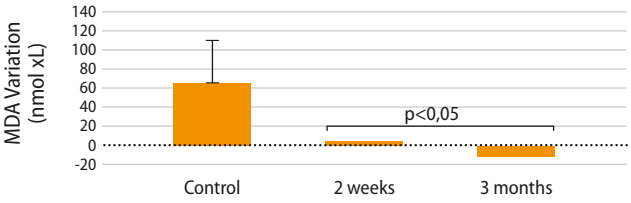
In Sport[4]

Protection against oxidative stress induced with intense physical exercise by means of a 90 minutes effort load in (n=40) healthy sportsmen. Tridocosahexanoina-AOX® is supplemented during 3 months following a randomized; placebo controlled, and crossed trial design. Significant differences versus the basal levels can be seen after 2 weeks and after 3 months in the DNA oxidation metabolites found in the 24 hours urine collection, and also in the serum lipid peroxidation levels.

OXIDIZED DNA IN 24 HOUR URINE COLLECTION



SERUM LIPID PEROXIDATION

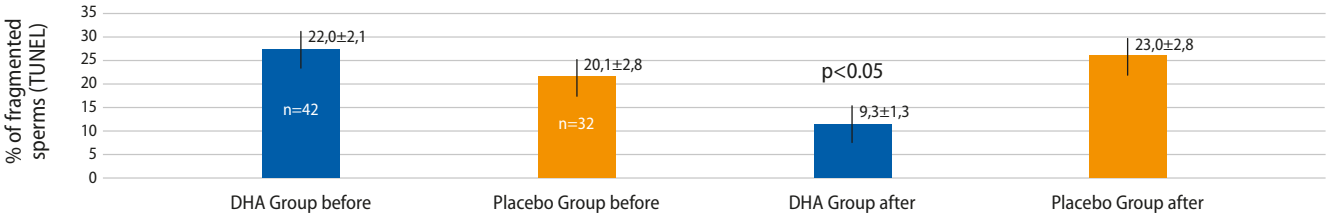


Time supplementing with Tridocosahexanoina-AOX®

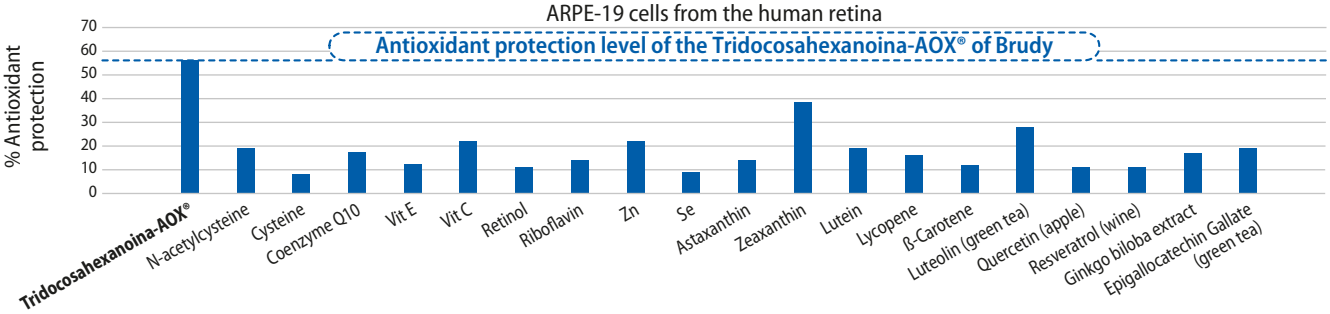
In Fertility[6]

Effects of supplementing Tridocosahexanoina-AOX® (n=42) (Brudy Plus 3 capsules/day: 1000mg/day) versus Placebo (n=32) during 10 weeks in patients with poor sperms DNA integrity, by means of TUNEL technique with fluorescent DNA markers. Significant differences can be seen in the percentage of oxidized sperms showing less fragmented DNA in the actively supplemented group versus in the Placebo group.

DNA FRAGMENTATION



OXIDATIVE PROTECTION IN ARPE-19 CELL CULTURE
Comparing the antioxidant effect of DHA with other available antioxidants



Grupo consolidado "Transporte y Vehiculación de fármacos" (2009 SGR-367). Departamento de Bioquímica y Biología Molecular, Universidad de Barcelona.

TRIDOCOSAHEXANOINA-AOX® ANTI-INFLAMMATORY EFFECT

Glutathione reduces the oxidative harm in the cell, and is the main actor controlling the inflammatory process[3,7-11]

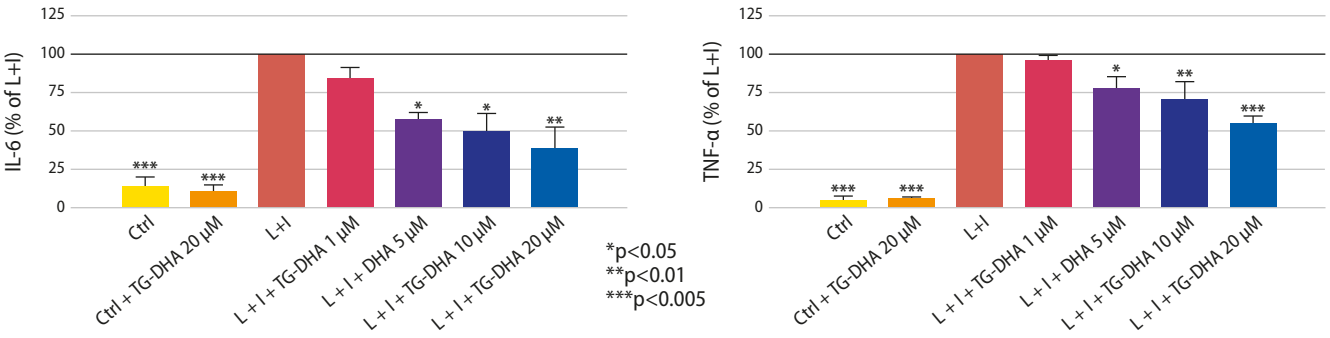
01 Stimulates the synthesis of intracellular glutathione, protector of oxidative damage (BRUDY Patent)[3]

02 It blocks synthesis of pro-inflammatory E2 Eicosanoids, and stimulates synthesis of anti-inflammatory E3 Eicosanoids (need of reducing animal meat and fat consumption).

03 It inhibits Nuclear Factor-κβ activation, blocking the synthesis of some pro-inflammatory cytokines as: IL-6, TNF-α and IL-1β.

04 It promotes resolving docosanoids: D1 Protectin plus E1 and D1 Resolvins derived from DHA and EPA, which facilitates resolution of inflammation.

TRIDOCOSAHEXANOINA-AOX® "IN VITRO" EFFECT IN A CELL CULTURE[7]

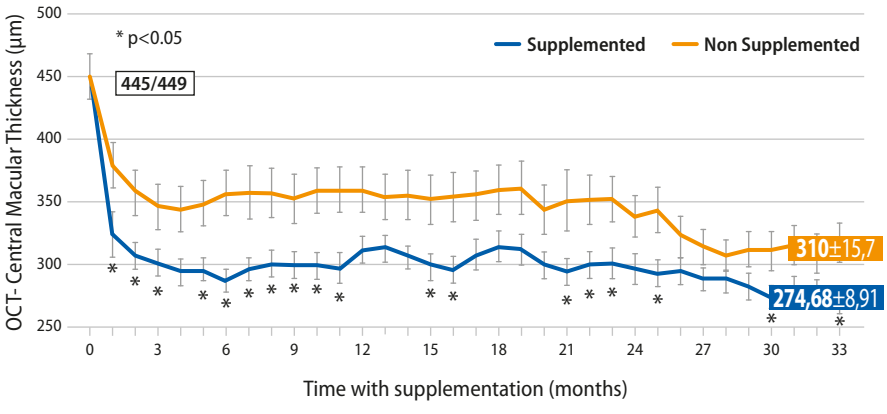


Tridocosahexanoina-AOX® inhibitory effect on the NF-κβ activation in BV2 microglia activated with bacterial lipopolysaccharide + interferon-Gamma (L+I). It can be seen a dose-dependent, significant reduction on the cytokines synthesis: IL-6 and FNT-α.

Clinical results

Antiinflamatory-Antiedema effect in central macula in (n=61) patients suffering Diabetic Macular Edema, treated all of them with intravitreal Ranibizumab, and 50% randomly assigned either to receive or not Tridocosahexanoina-AOX® supplementation for 36 months. Sustained significant differences in the central macular thickness (P<0.05), measured with Optical Coherence Tomography (OCT), in the supplemented group versus the non supplemented group.

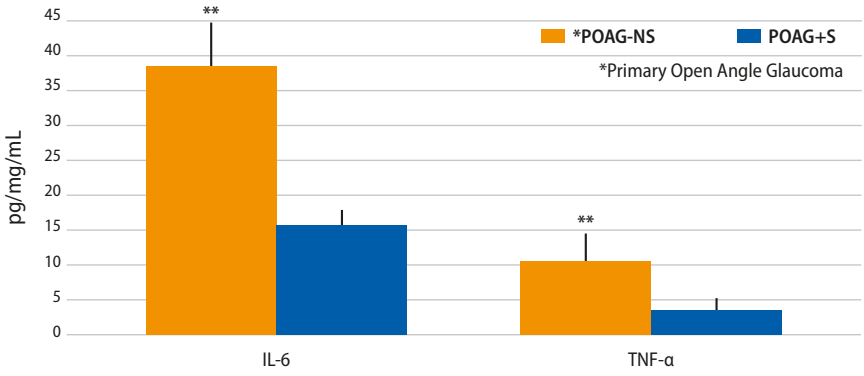
ANTI-INFLAMMATORY EFFECT AT CENTRAL MACULAR LEVEL[11,22]



EXPRESSION OF CYTOKINES IN TEARS AFTER SUPPLEMENTATION[8-10]

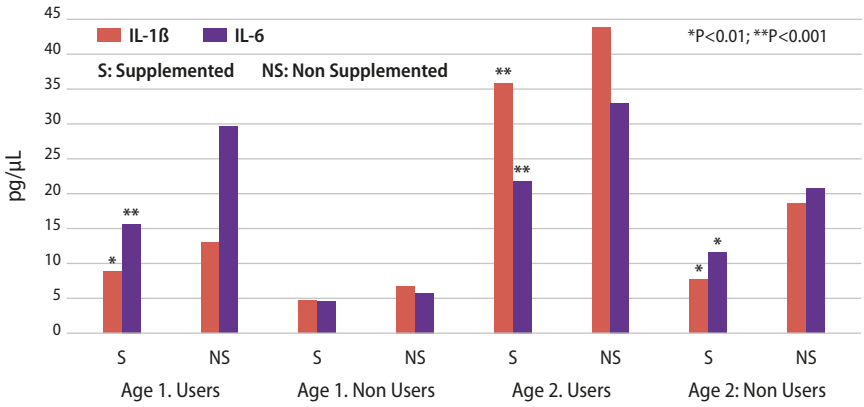
Inhibitory effect on the cytokines produced in the tears in (n=31) patients suffering Primary Open Angle Glaucoma (POAG) being users of topical anti-glaucoma eye-drops. Patients are 50% supplemented or not with Tridocosahexanoina-AOX® at random during 90 days. Significant lower levels of IL-6 and FNT-α can be seen in the supplemented POAG group of patients versus the non-supplemented POAG group of patients. There is a significant improvement of all the studied clinical variables: BUT, Schirmer, OSDI.

CYTOKINES IN TEARS (Glaucoma)[9]

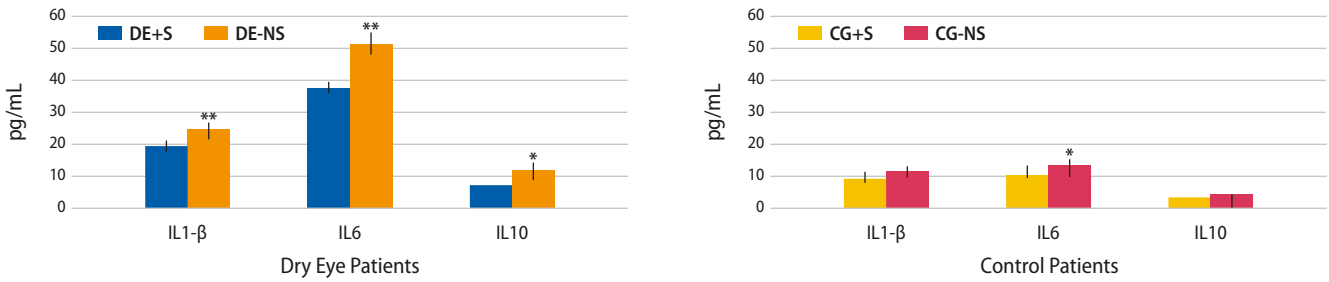


Expression of inflammatory markers (IL-6 and IL-1B) in reflex tears of n=83 women intensive users of computer screens, and in n=65 women non users (Controls). They are analyzed in two different age ranks (Age 1: 40-52 years; Age 2: 53-65 years), 50% randomly assigned either to receive or not supplementation with Tridocosahexanoina-AOX® during 90 days. *P<0.01; **P<0.001
Active supplementation had a positive influence on the ocular surface pathology, showing evident and significant improvement of the clinical signs and symptoms derived from the abusive use of screen computers: BUT, Schirmer, OSDI.

CYTOKINES IN TEARS (Intensive users of computer screens)[10]



EFFECT OF ORAL SUPPLEMENTATION ON THE CYTOKINES EXPRESSED IN TEARS[8]



Synthesis of Tear cytokines is significantly reduced in (n=30) patients suffering moderate dry eye, and in (n=36) healthy controls, 50% of them being Supplemented or not at random with Tridocosahexanoina-AOX® during 90 days. A statistical significant lower tear levels of IL-6, IL-1B, and IL-10 are detected in the actively supplemented Dry Eye patients (DE+S) and in the actively supplemented Controls (CG+S) than in the non supplemented Dry Eye patients (DE-NS) and in the non supplemented group of Controls (CG-NS). (*P<0.01, **p<0.001). A significant improvement of all clinical variables are also detected (p<0.005): BUT, Schirmer, OSDI.

EXPRESSION OF CYTOKINES AT SYSTEMIC LEVEL (SERUM) AFTER SUPPLEMENTATION, AND LEVEL OF ANTIOXIDANT PROTECTION[20-22]

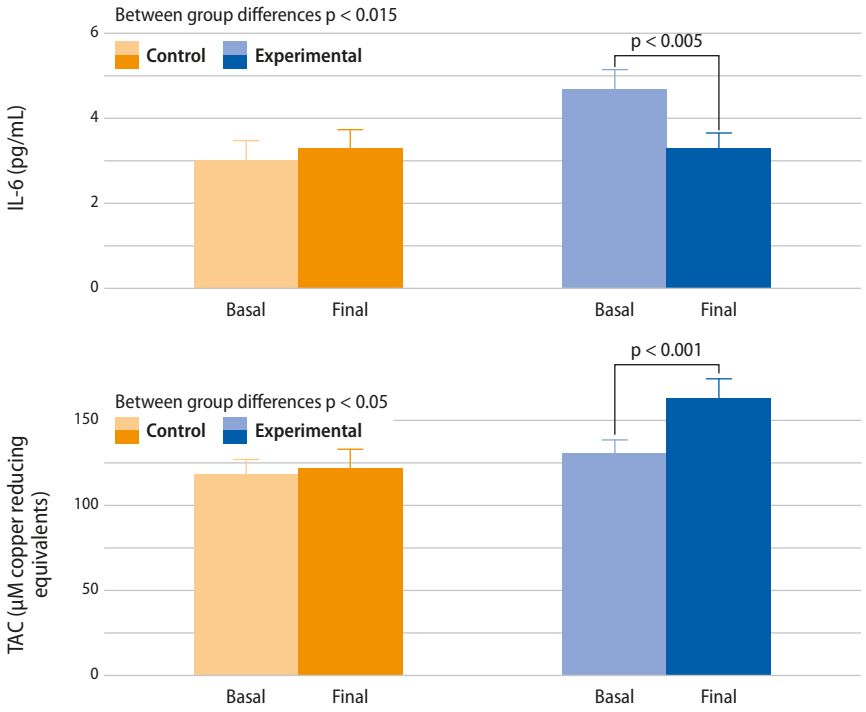
Tridocosahexanoina-AOX® shows a clear inhibiting effect on IL-6 synthesis at systemic level, but also an increase in the Total Antioxidant Capacity at short, medium and long term, in patients suffering Diabetic Retinopathy and Pseudoexfoliation Glaucoma.

At short term: 90 days[20]

N=24 patients suffering Non Proliferative Diabetic Retinopathy. 50% being supplemented with Tridocosahexanoina-AOX® 1000mg/day (BrudyRetina, 3 capsules/day) during 90 days. Control group not being supplemented.

Significant reduction in the IL-6 blood levels is only seen in the actively supplemented group, also showing between group significant differences. A worsening is seen in the control group. A significant increase of the Total Antioxidant Capacity is only seen in the actively supplemented group[20].

IL-6: Interleukin-6
TAC: Total Antioxidant Capacity

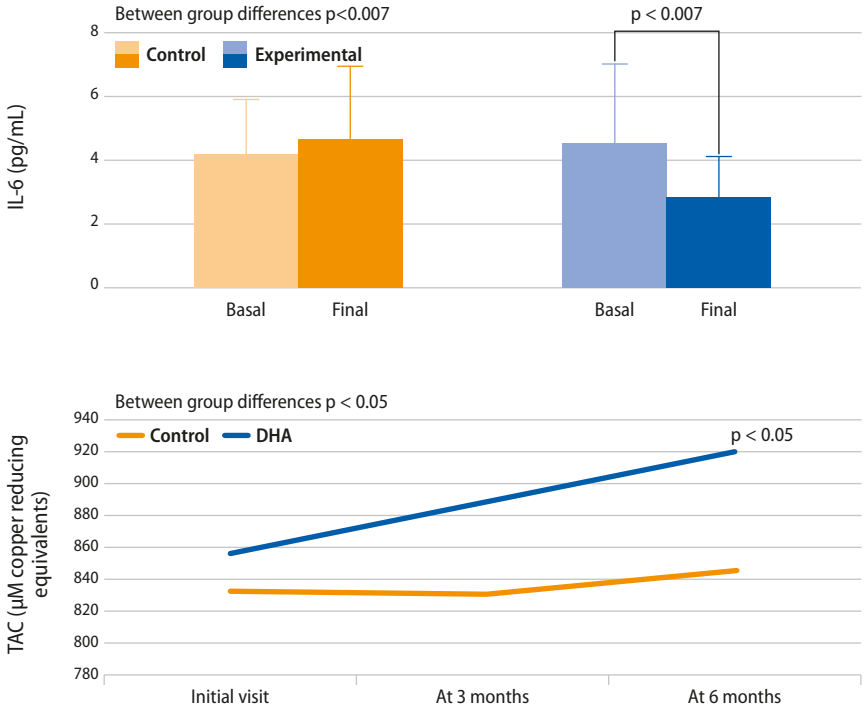


At mid term: 6 months[21]

N=47 patients suffering pseudoexfoliation glaucoma. 50% of the patients are supplemented with Tridocosahexanoina-AOX®. 1000mg/day (BrudyPio 3 capsules/day) during 6 months; control group not being supplemented.

Significant reduction in the IL-6 blood levels is only seen in the actively supplemented group, also showing between group significant differences. A worsening is seen in the control group. A significant increase in the Total Antioxidant Capacity is only seen in the actively supplemented group[21].

IL-6: Interleukin-6
TAC: Total Antioxidant Capacity

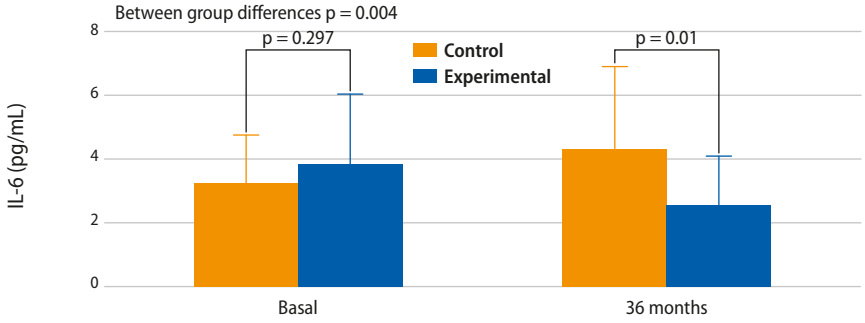


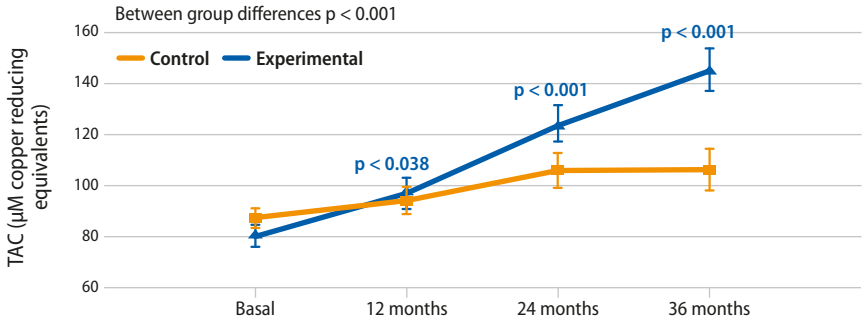
At long term: 3 years[22]

N=60 patients with type 2 diabetes, suffering Diabetic Macular Edema. 50% of patients being supplemented with Tridocosahexanoina-AOX® 1000mg/day (BrudyRetina 3 capsules/day) during 36 months. Control group not being supplemented. All patients are treated with intravitreal injections of Ranibizumab.

Significant reduction in the IL-6 levels is only seen in the actively supplemented group, also showing between group differences. A worsening is seen in the control group. A significant increase in the Total Antioxidant Capacity is only seen in the actively supplemented group[22].

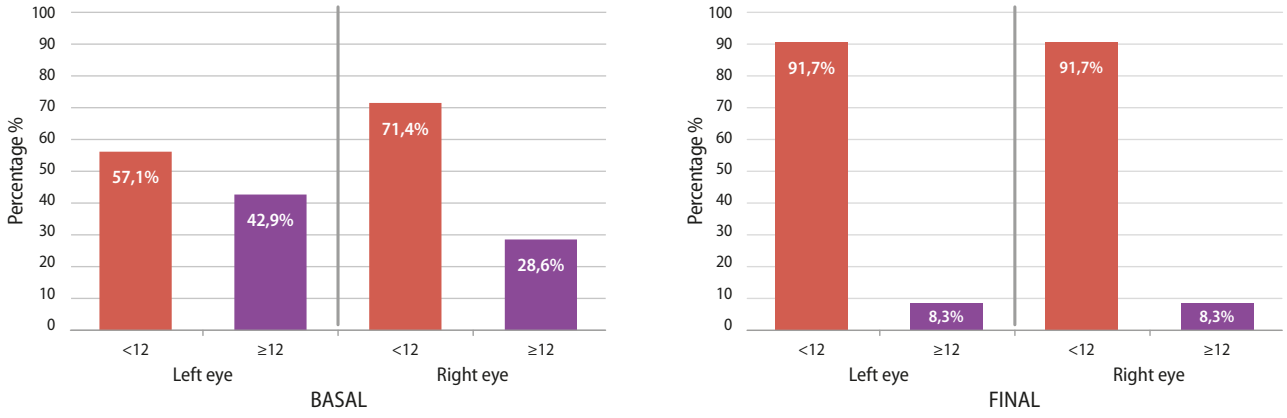
IL-6: Interleukin-6
TAC: Total Antioxidant Capacity





TOPICAL EYELID APPLICATION OF A GEL-CREAM WITH TRIDOCOSAHEXANOINA-AOX®[25]

CLDEQ-8 QUESTIONNAIRE (Index>12 indicates risk of suffering dry eye)



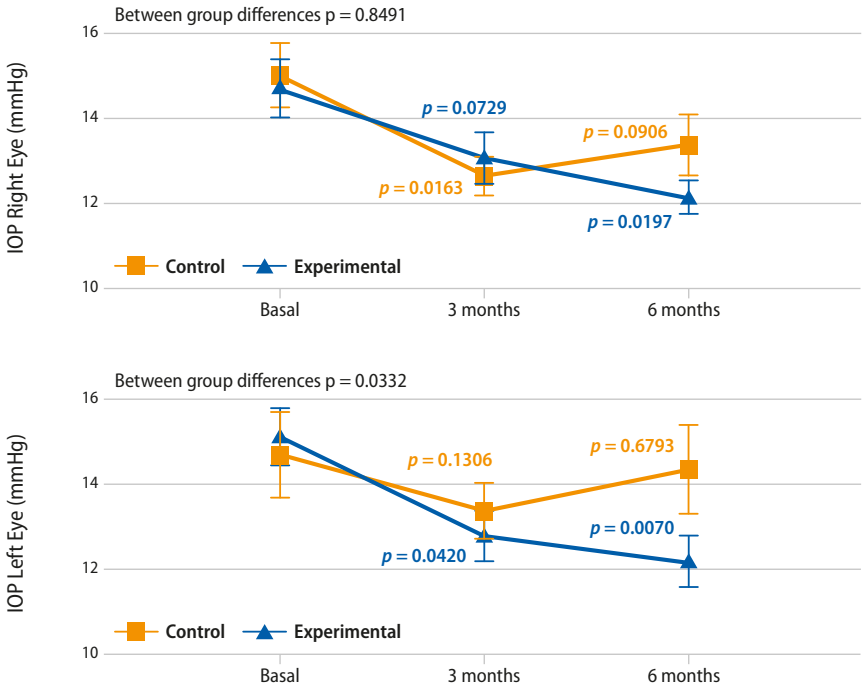
Risk of suffering dry eye is evaluated in N=30 healthy volunteers wearers of soft contact lenses after repeated night time eyelid application for 2 weeks. Scoring >12 identifies contact lens wearers being in risk. CLDQ = Contact Lens Dry Eye Questionnaire). BrudyDerm Dry Eye Gel-Cream for eyelid application incorporates Tridocosahexanoina-AOX®, Hyaluronic acid, and Aloe Vera leaf juice. Risk of suffering dry eye is reduced in both eyes.

EFFECT OF TRIDOCOSAHEXANOINA-AOX® ON THE IOP AND ON THE PEROXIDATION OF PLASMATIC LIPIDS[21]

N=47 patients suffering pseudoexfoliation glaucoma randomized 50% (1:1) to receive or not 1000mg/day of Tridocosahexanoina-AOX® (BrudyPio 3 caps/day) during 6 months.

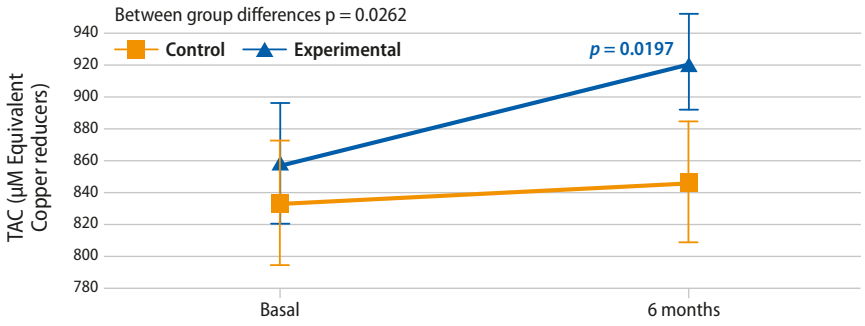
Both groups are showing a controlled level of IOP (15mmHg aprox). The actively supplemented group shows a significant additional IOP reduction in both eyes after 6 months (RE: p<0.02; LE:p<0.007).

CHANGES IN IOP LEVELS



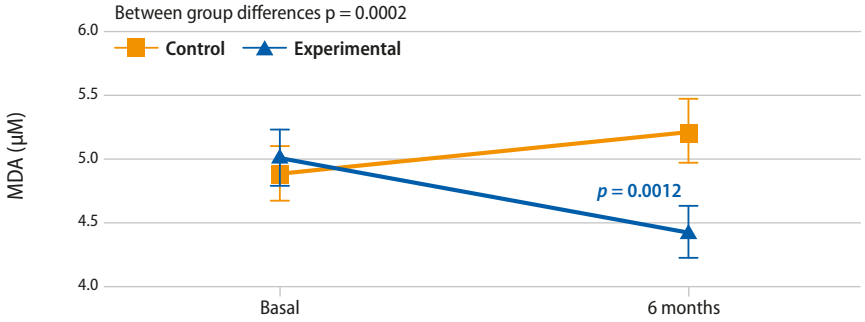
A significant (P<0.02) elevation in the Total Antioxidant Capacity (TAC) is also seen.

CHANGES IN TOTAL ANTIOXIDANT CAPACITY



As well as a significant reduction (p <0.01), only in the actively supplemented group, in the plasma lipid peroxidation levels (MDA).

CHANGES IN PLASMA LIPID PEROXIDATION LEVELS



TRIDOCOSAHEXANOINA-AOX® IN ATTENTION DEFICIT HYPERACTIVITY DISORDER[23]

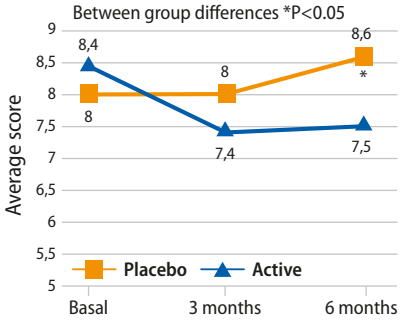
Prospective, intervention, placebo-controlled study. N = 66 children with a diagnosis of ADHD in any of its 3 modalities, which are randomized to 50% (1: 1) to receive 1000mg / day of Tridocosahexanoina-AOX® (1 sachet per day of Brudy NEN Emulsion) or Placebo, for 6 months

The D2 Test of successes and errors, with pencil and paper. Measure the ability to concentrate and maintain attention. There is a significant improvement for both treatment options, but the results are better in the experimental group.

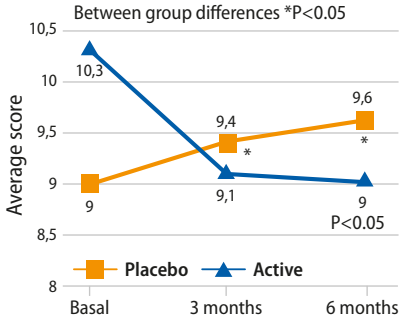
In the EDAH test, a registry that evaluates the frequency of behaviors, there is significant improvement ($p < 0.05$) in favor of the group supplemented with DHA versus those with Placebo, either in Hyperactivity, in Attention Deficit, as well as in Attention Deficit with Hyperactivity.

RESULTS EDAH

EVOLUTION OF BEHAVIOR HYPERACTIVITY

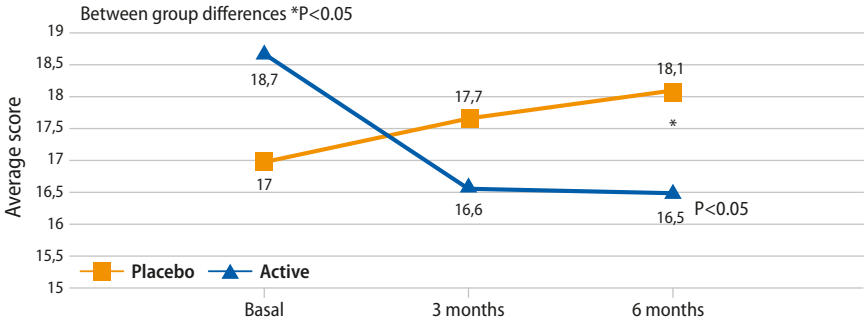


EVOLUTION OF BEHAVIOR ATTENTION DEFICIT



The Active group experiences a significant improvement in the variables: Hyperactivity, Attention Deficit, and ADHD, with a reduction in symptoms as treatment progresses.

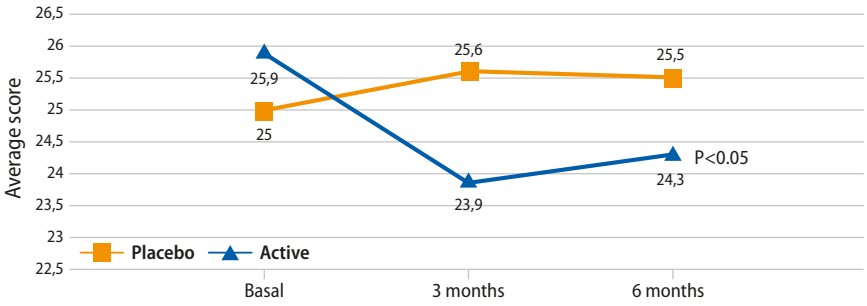
EVOLUTION BEHAVIOR: ATTENTION DEFICIT AND HYPERACTIVITY



The Conner's scale for parents shows significant improvement in the Attention Deficit in favor of the actively supplemented group ($p < 0.05$).

CONNER'S SCALE RESULTS

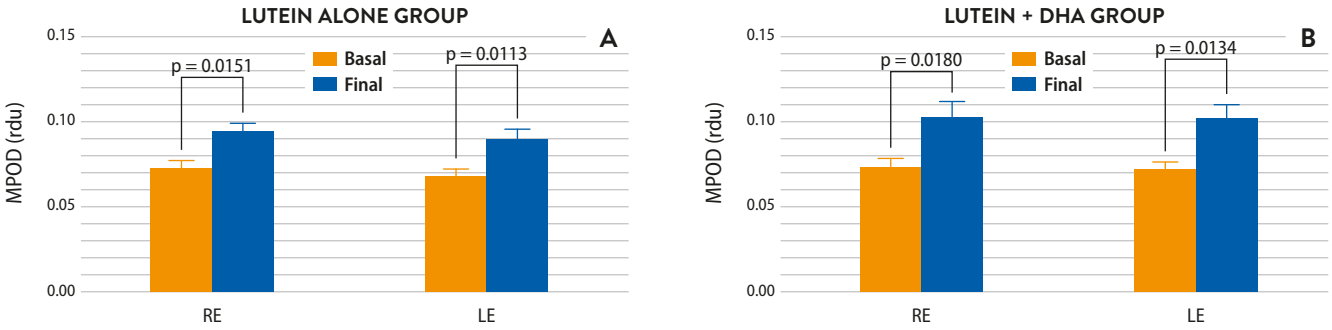
EVOLUTION OF GENERAL BEHAVIOR ON THE CONNER'S SCALE



Significant differences are observed in the Actively supplemented group, with a decrease in symptoms between the initial and the final test. This is not the case in the Placebo group

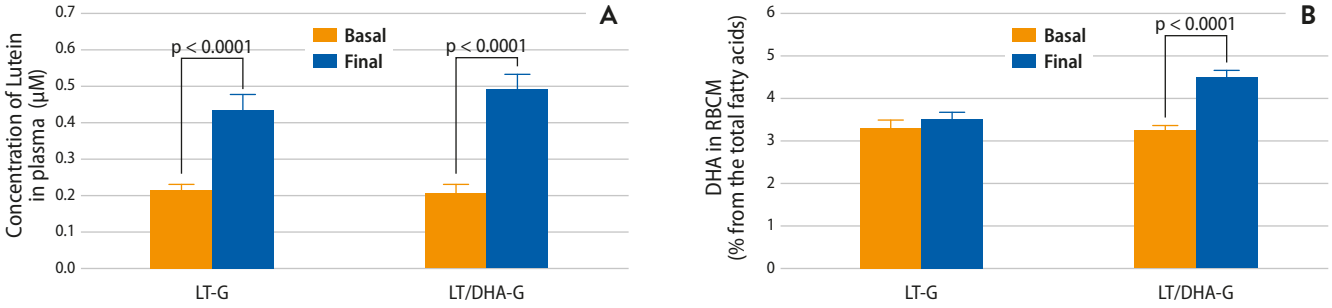
EFFECTS OF TRIDOCOSAHEXANOINA-AOX® ON THE MACULAR PIGMENT OPTICAL DENSITY[27]

Prospective, intervention study on 100 healthy volunteers supplemented for 3 months with 6mg / day of lutein + vitamins and minerals (Group-LT), or with 6mg / day of lutein + vitamins and minerals + 700mg of DHA triglyceride (Group-LT / DHA) (BrudyRetina 2 capsules / day). Changes in the Macular Pigment Optical Density (Visucam retinograph), in plasma lutein, and in DHA in erythrocyte membrane are evaluated.



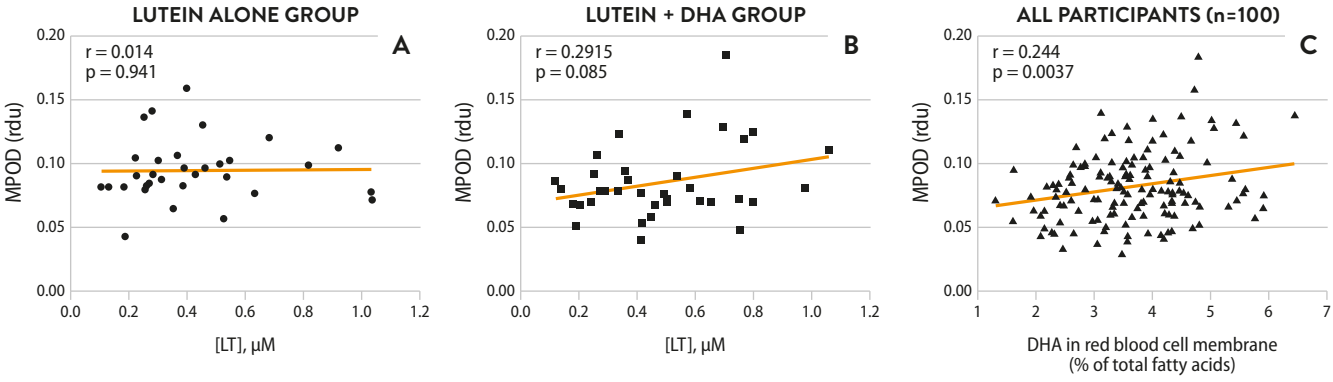
MPOD: Macular Pigment Optical Density; RDU: Relative Densitometry Units; RE: Right Eye; LE: Left Eye; LT-G: Lutein Group; LT/DHA-G: LT/DHA Group.

At 3 months there is significant improvement of the MPOD with both formulations, (A and B) but with a significant difference in favor of the LT/DHA-G (B).



LT-G: Lutein Group; LT/DHA-G: LT/DHA-Group; RBCM: Red Blood Cell Membrane.

The achieved plasmatic concentration of lutein is higher in LT/DHA-G (A). The concentration of DHA in erythrocyte membrane grows only in LT/DHA-G, and there are no changes in LT-G (B).



MPOD: Macular Pigment Optical Density; RDU: Relative Densitometry Units; LT-G: Lutein Group; LT/DHA-G: LT/DHA Group; [LT], µM: Concentration of lutein in plasma

There is no correlation between the level of plasma lutein and the MPOD in the LT-G (A). but very close to the significance in the LT/DHA-G (B, p <0.085), which reaches significance (C, p <0.0037) by extending the analysis to all participants.

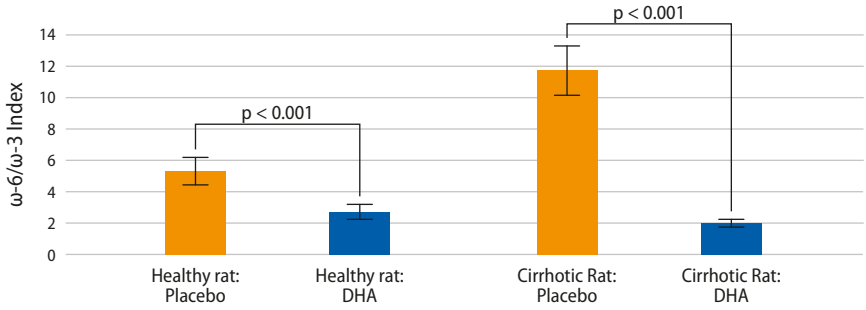
Conclusión: when supplementing with lutein, the addition of DHA-triglyceride it favors a significant increase in the macular pigment optical density.

TRIDOCOSAHEXANOINA-AOX® IN ADVANCED CHRONIC LIVER DISEASE[28]

Study in preclinical rat model.[28] After comparing cirrhotic rats treated with placebo (standard vehicle) and those receiving DHA (500mg / Kg) for 2 weeks:

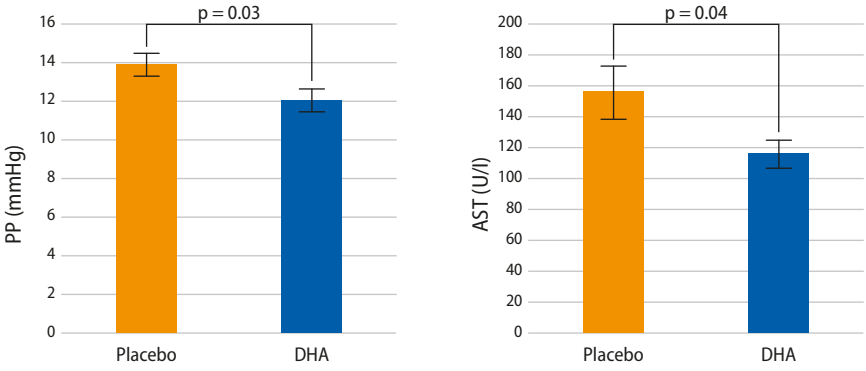
1. Rats treated with DHA normalize the healthy liver profile of fatty acids:

EFFECT ON LIPID PROFILE IN LIVER TISSUE[28]



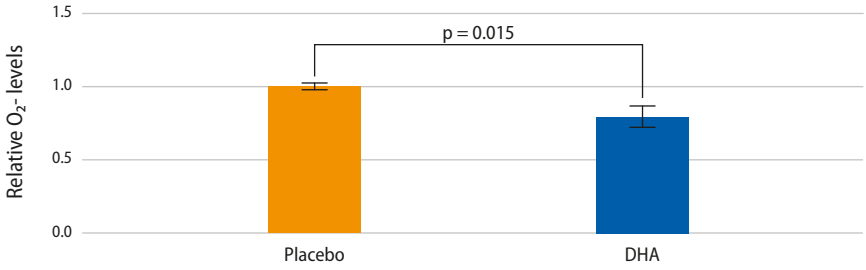
2. This is associated with a significant reduction in portal hypertension (-13.37%) (P = 0.03) that suggests a reduction in intrahepatic vascular resistance (-24.57%). There is also a significant improvement in Aspartate Aminotransferase (AST) (-25.67%), which indicates an improvement in liver inflammation (p = 0.04).

EFFECT ON LIVER PORTAL HYPERTENSION AND IN AST IN SERUM



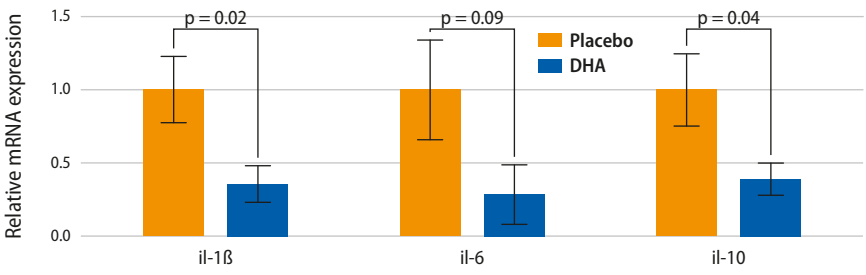
3. The mechanisms associated with this hemodynamic improvement included a reduction of oxidative stress in liver tissue (P = 0.015).

EFFECT ON OXIDATIVE STRESS IN LIVER TISSUE



4. There is also a reduction in the expression of pro-inflammatory cytokines, with significance in the case of IL-1ß (P = 0.02) and IL-10 (P = 0.04), and very close to the significance in the case of IL-6 (P = 0.09).

EFFECT ON INFLAMMATION OF THE LIVER TISSUE



The results confirm that there is a suppression in the activation of the hepatic stellate cell mediated by inflammation and oxidative stress, which is also confirmed in human hepatic stellate cell.

TRIDOCOSAHEXANOINA-AOX® IN DRY EYE.[8,10,12-16] CLINICAL EXPERIENCE

Prospective, controlled, interventional, randomized clinical trials[8,10,12]

TRIAL ARTICLE	TITLE / THEME	MATERIAL & METHODS	RESULTS	P VALUE
Pinazo-Duran, MD, et al; Clinical Int Aging 2013; 8:139-148	Supplementation effect in moderate dry eye and on the inflammatory markers present in reflex tears	30 moderate Dry Eye patients and 36 healthy controls 50% randomized to receive or not 2 caps/day x 90 days	Schirmer B.U.T. OSDI: -64% Cytokines expression: IL-1β, IL-6, IL-10	<0.05 <0.05 <0.01 <0.001
Ribelles A, et al; BioMed Research Int 2015; 467039 Id 467039. doi: 10.1155/Epub 2015 Oct 18	Supplementation effects in women intensive computer screen users and on the inflammatory markers present in reflex tears	Non Users, 50% randomized to receive or not 3 caps/day x 90 days	Schirmer OSDI Tear Volume (µl) Cytokines expression: IL-1β y IL-6	<0.0002 <0.05 +25% <0.001
Galbis-Estrada C, et al; Molecular Vision 2015; 21:555-567	Supplementation effect on Tears metabolomics of mild and moderate Dry Eye	22 patients with mild Dry Eye and 33 patients with moderate Dry, and 33 healthy controls 50% randomized to receive or not 3 caps/day x 90 days	Schirmer: Mild group Moderate group BUT: Mild group Moderate group OSDI Metabolomic profile Dry Eye vs Control G Metabolomic profile Before vs After Supplementation	 <0.034 <0.039 <0.001 <0.000 <0.05 <0.05

Prospective, double-blinded, randomized, placebo-controlled trial in Meibomian Gland Dysfunction[13,14]

TRIAL ARTICLE	TITLE / THEME	MATERIAL & METHODS	RESULTS	P VALUE
Oleñik A, et al; Clinical Int Aging 2013; 8:1133-1138	Supplementation effects in Meibomian Gland Dysfunction patients	60 M.G.D. patients, 50% randomized either to active supplementation or to Placebo 3 caps/day x 90 days	Schirmer BUT OSDI Lid margin redness Meibom expression Oxford grading test	<0.01 <0.001 <0.001 <0.01 <0.01 NS
Oleñik A, et al; Clinical Ophthalmol 2014; 8:831-836	Supplementation effects on the quality of life of M.G.D. patients	60 M.G.D. patients, 50% randomized either to active supplementation or to Placebo 3 caps/day x 90 days	Physical component Mental component Placebo	<0.000 <0.0002 NS

TRIDOCOSAHEXANOINA-AOX® IN DRY EYE.[8,10,12-16] CLINICAL EXPERIENCE

Prospective, interventional, open-label[15,16]

TRIAL ARTICLE	TITLE / THEME	MATERIAL & METHODS	RESULTS	P VALUE
Oleñik A, and DECSG; Clinical Ophthalmol 2014:8 169–76	Efficacy and Digestive tolerability in moderat Dry Eye patients	905 Moderate Dry Eye patients supplemented with 3 caps/day x 90 days	Symptoms improvement Average drops/day Satisfyed+Very Satisfyed Large+Very L clin improv 24 h lasting symptoms GI Adverse effects: None Some Fishy taste regurgitation Nausea Vomiting Diarrhea	<0.001 <0.001 82,1% 87,8% -19,4% 80% 20% 13,5% 4,9% 0,3% 1,3%
Gatell-Tortajada J, et LDECSG; Clin Int Aging 2016; 11:571-578	Efficacy and Digestive tolerability in moderat Dry Eye patients	1419 Moderate Dry Eye patients supplemented with 3 caps/day x 90 days	Improv individual sympt Oxford grading test Tear B.U.T. Schirmer Test Hyperemia Conjunctiva Satisfyed+Very Satisfyed Large+Very L clin improv GI Adverse effects: None Some Fishy taste regurgitation Nausea Diarrhea Vomiting	<0.001 <0.001 <0.001 <0.001 <0.001 85,7% 91,6% 79,2% 20,8% 14,6% 4,6% 2,7% 0,4%

Taking a sample from the reflex tears from the inferior lacrimal meniscus with a capillary tube. Measuring cytokines by means of flux cytometry with the Multi-Plex System (Luminex R-200, Human Cytokine/Chemokine Panel)

TRIDOCOSAHEXANOINA-AOX® IN RETINA AND IN DIABETIC RETINOPATHY.[11,20,22,27] CLINICAL EXPERIENCE

TRIAL ARTICLE	TITLE / THEME	MATERIAL & METHODS	RESULTS	P VALUE
Elena Rodríguez González-Herrero, et al; Communication at the XXI Congress of the Spanish Society of Retina & Vitreous, Madrid, Mars 3, 2017. Clinical Ophthalmology 2018; 12: 1011-1020	DHA supplementation in Non Proliferative Diabetic Retinopathy. Prospective, interventional, and controlled trial of the macular function by means of macular microperimetry	N=24 NPDR patients, randomized 50% (1:1) to receive or not 1g/day of Tridocosahexanoina-AOX® (BrudyRetina 3 caps/day) during 3 months	VA Changes Macular Sensitivity Macular Integrity Index OCT Macular Thickness Total Antiox. Capacity DHA in RBC Membrane NEI-VFQ 25 Serum Reduced IL-6 expression	NS <0.05 <0.05 NS <0.001 <0.05 <0.04 <0.005
Vicente Zanón Moreno, et al; *Sent for publication*	Effects of DHA on the Macular Pigment Optical Density when supplementing with lutein	N=100 healthy volunteers randomized 50% (1:1) either to 6mg/day of lutein+vitamins, or to 6mg/day of lutein+ vitamins+700mg day of DHA, during 90 days	Both groups show improvement in MPOD MPOD significantly higher in the L+DHA (+39,6%) Serum Lutein significantly higher in the Lutein+DHA Positive correlation between RBC DHA and MPOD	P<0.05 P<0.05 P<0.085 P=0.0037
Lafuente María, et al; RETINA 2017; 37:1277-1286	Effects of DHA supplementation in patients suffering Diabetic Macular Edema being treated with intravitreal Ranibizumab Two year outcomes	N=62 (76 eyes) Type 2 Diabetic patients suffering DME treated with Ranibizumab, 50% (1:1) randomly assigned to DHA supplementation 1000mg/day, or not. Preliminary data at 24 months follow-up	OCT intragroup: With supplement Without supplement OCT intergroup EDTRS-VA intergroup >5 Letters DHA group >10 Letters DHA group DHA in RBC membrane ω6/ω3 Index RBC membrane Total Antiox Capacity	 <0.001 <0.024 <0.05 <0.066 <0.044 <0.044 <0.01 <0.05 <0.001
Lafuente M, et al; Communication at the XXI Congress of the Spanish Society of Retina & Vitreous; Madrid, Mars 4, 2017. RETINA 2019; 39: 1083-1090	Effects of DHA supplementation in patients suffering Diabetic Macular Edema being treated with intravitreal Ranibizumab Three year outcomes	N=60 (74 eyes) Type 2 Diabetic patients suffering DME treated with Ranibizumab, 50% (1:1) randomly assigned to DHA supplementation 1000mg/day, or not. Final results at 36 months follow-up	Central Macular Thickness BCVA Metabolic Control HbA1c Total Antiox. Capacity DHA in RBC membrane IL-6 expression (serum)	<0.035 NS <0.035 <0.001 <0.001 <0.004

TRIDOCOSAHEXANOINA-AOX® IN EYELID AREA.[25] CLINICAL EXPERIENCE

TRIAL ARTICLE	TITLE / THEME	MATERIAL & METHODS	RESULTS	P VALUE
Zanón-Moreno V et al; Accepted in Journal of Optometry 2020	Effects on the eyelid skin integrity and on the ocular surface of a repeated night-time application of a Gel-cream containing Tridocosahexanoina-AOX®	N=60 healthy volunteers, n=30 contact lens users and n=30 non contact lens users with one night-time application during 2 weeks	Evident CLDEQ-8 improvement OSDI improvement Schirmer T. improvement TBUT Improvement: Right Eye Left Eye VEGF expression in tears Cosmetic improvement	 NS NS NS =0.008 =0.005 NS 54-86%

TRIDOCOSAHEXANOINA-AOX® IN GLAUCOMA.[9,17,21]

CLINICAL EXPERIENCE

TRIAL ARTICLE	TITLE / THEME	MATERIAL & METHODS	RESULTS	P VALUE
Galbis-Estrada C, et al; Clinical Int Aging 2013; 8:711-719	Effect of supplementation on Dry Eye due to Glaucoma and on inflammatory markers in tears	31 Glaucoma+Dry Eye patients, 31 healthy controls, and 30 Dry Eye patients with no Glaucoma, 50% supplemented at random with 2 caps/day x 90 days	Schirmer Test Tear BUT OSDI (-68%) Rose Bengal staining VA Cytokines in tears: IL-6 TNF-α	<0.002 <0.02 <0.05 NS NS <0.05 <0.001
Tellez-Vázquez J, and the DEIGSG; Clin Ophthalmol 2015; 10: 617-626	Effect of supplementation in a large series of patients with Dry Eye suffering POAG	1255 POAG+Dry Eye patients being supplemented with 3 caps/day x 90 days	Symptoms Hyperemia conjuntiva Oxford grading Test Tear BUT Schirmer Test IOP Average tear drops Satisfyed+Very Satisfyed Large+Very L clin improv GI Adverse effects: None Some Fishy taste regurgitation Nausea Diarrhea Vomiting	<0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 81,9% 87,7% 76,5% 23,5% 16,9% 4,7% 1,0% 0,3%
Ongoing Trial	Supplementation of Tridocosahexanoina-AOX® alone versus Vitamins, versus Citicoline, versus Tridocosahexanoina-AOX®+Citicoline together	N=80 patients diagnosed of primary Glaucoma, randomized to each one of the 4 arms of supplementation	*Trial is still in process*	
Stéphanie Romeo, et al; Communication at the European Glaucoma Society Congress 2018 in Florence, Italy; Journal of Ophthalmology 2018; Article ID 8259371; 8 pages	Influences of DHA-TG Supplementation in Exfoliation Glaucoma	N=47 patients suffering Exfoliation Glaucoma being 50% supplemented with Tridocosahexanoina-AOX® 1000mg/day (BrudyPio 3 caps/fday) during 6 months; Control group is not supplemented	BCVA Papillary diameters IOP Right Eye IOP Left Eye OCT thickness DHA in RBC membrane membrane n-6/n-3 Index Total Antioxidant Capacity IL-6 expression in serum	NS NS <0.02 <0.007 NS <0.0001 <0.0005 <0.02 <0.006

TRIDOCOSAHEXANOINA-AOX® IN FERTILITY.[6,19,24] CLINICAL EXPERIENCE

TRIAL ARTICLE	TITLE / THEME	MATERIAL & METHODS	RESULTS	P VALUE
Martinez-Soto JC, et al; Fertility & Sterility 2010; 94:S235-S236	Supplementation influence in Sperm DNA integrity (DNA oxidative fragmentation)	46 patients 50% supplemented at random either to active or placebo 1g/day x 10 weeks	% reduction of DNA sperms fragmentation Improved seminal fluid Antioxidant capacity	<0.01 <0.01
Popova A Yu, et al; Andrology & Genital Surgery 2015; 16(2): 51-55	Effect of supplementation on the % of sperms DNA fragmentation >15%	40 Pathozoospermic patients, 20 with Tridocosahexanoina-AOX® and 20 with antiox vitamins and minerals x 45 days	Reduction in the % of fragmented sperms (TUNEL) Active supplemented group Basal 25,8% Control group basal 25,3%	 13,7% <0.05 19,8%
Martinez-Soto JC, et al; Syst Biol Reproductive Med 2016; 62(6):387-395	Improved seminal fluid antiox cap. and sperm DNA fragmentation. Double blind, placebo-controlled	74 males randomized to: 32 with Placebo 42 with Active 1g/day x 10 weeks	DNA Sperms fragmentation analyzed with TUNEL technique Seminal fluid antiox capacity DHA levels in seminal fluid	<0.01 <0.01 <0.01

TRIDOCOSAHEXANOINA-AOX® IN NEUROPROTECTION.[38]
CLINICAL EXPERIENCE

TRIAL ARTICLE	TITLE / THEME	MATERIAL & METHODS	RESULTS	P VALUE
M. Gómez-Soler, et al; Frontiers in Neuroscience 2018; 12: article 604	DHA in neuroprotection of Parkinsonism	N=12 mice	DHA reduces neurotoxicity of 6HODA versus vehicle *In vitro* *Ex vivo* DHA increases in plasma DHA increases in membrane Index ω6/ω3 decreases DHA in cortex increases DHA in striatum increases Motor coordination	 P<0.001 P<0.001 P<0.001 P<0.001 P<0.001 NS NS P<0.001

TRIDOCOSAHEXANOINA-AOX® IN SPORT.[4,18,26] CLINICAL EXPERIENCE

TRIAL ARTICLE	TITLE / THEME	MATERIAL & METHODS	RESULTS	P VALUE
Guzman JF, et al; Journal of Sports Sci Med 2011;10:301-5	Tridocosahexanoina-AOX® improves complex reaction time in elite women soccer players	24 elite women soccer players 50% randomized to Active or Placebo 3,5g/day x 4 weeks	Complex reaction time Precision efficiency Improvement in neuromotor function is shown	<0.004 <0.003
Contreras CJ, Tesis Doctoral 2014, Universidad Católica Murcia	Supplementation effect on the oxidative protection of intense exercise	40 young healthy cyclist with a controlled efford load; 2g x 3 months	DNA oxidative metabolites in urine at 2 weeks / 3 months: Lipid Peroxidation at 2 weeks / 3 months:	<0.05 <0,05
Antonio J Luque, et al; *Pending Publication*	Tridocosahexanoina-AOX® versus Placebo in the inflammatory response and muscular harm in Triathletes	N=35 Triathletes randomized to Active or Placebo x 12 weeks, wash-up priod of 30 days and crossing supplements for an other 12 weeks period	*Analysing statistical results*	
Francisco J. López-Román, et al; Gazzetta Medica Italiana 2019; 178(6):411-6	DHA and differences in performance of endurance exercise in cyclists in aerobic conditions	N = 13 cyclists; n = 6 professional cyclists and n = 7 non-professional cyclists. Endurance test before and after supplementing 2.1g / day of DHA x 3 months	Beneficial effect on VO_2 in VT2 Output power to reach VO_2 There are no differences regarding the level of competitiveness	P=0.019 P=0.032 NS

TRIDOCOSAHEXANOINA-AOX® IN ADHD.[23] CLINICAL EXPERIENCE

TRIAL ARTICLE	TITLE / THEME	MATERIAL & METHODS	RESULTS	P VALUE
Celestino Rodriguez, et al; Neuropsychiatric Disease and Treatment 2019; 15: 1193-1209	Influence of DHA in pediatric ADHD. A randomized, double blinded, Placebo controlled trial	N=66 ADHD affected kids, n=32 on DHA, n=34 on Placebo, Brudy NEN Emulsion, sachets containing 1000mg of DHA-TG versus Placebo (olive oil), follow-up 6 months	Attention Test D2 and Aula Nesplora with better scoring in DHA group EDAH Test: Attention Deficit Hyperactivity Attention Deficit+Hyperact Conner's Scale: Behavior	NS NS <0.05 <0.05 <0.01 <0.05

TRIDOCOSAHEXANOINA-AOX® IN EXPERIMENTAL RESEARCH.[3,7,28]
CLINICAL EXPERIENCE

TRIAL ARTICLE	TITLE / THEME	MATERIAL & METHODS	RESULTS	P VALUE
Bogdanov P, et al; IOVS ARVO Journals, May 2008, Vol 49, 5932	Influence of Tridocosahexanoina -AOX® in oxidative protection of human retinal pigmentary epithelium cells (ARPE-19)	Influence of DHA-TG on the intracellular process of Glutathione synthesis	Supplementation is significantly stimulating glutathione production in the cytoplasm, protecting the DNA of cells	<0.05
Mancera P, et al; Nutrients 2017; 9:681, doi: 10.3390/nu9070681	Influence of Tridocosahexanoina -AOX® in the microglia activation and on the improvement of the induced encephalomielitis in mice	Incubation of BV-2 microglia in DHA-TG is significantly reducing cytokines synthesis in a concentration dependent manner. Is also significantly reducing the clinical symptoms of encephalomielitis comparing with placebo	BV-2 Cells: IL-6 expression Expression of TNF-α Nitrites levels Induced encephalomielitis in mice: Clinical Scoring Weight gain	 <0.05-0.001 <0.05-0.005 <0.005 <0.05 <0.01
Zoe Boyer-Díaz, et al, Nutrients 2019; 11, 2358; doi: 10.3390/nu11102358	Effect of DHA supplementation on Portal Hypertension in a rat model of liver cirrhosis	2 weeks of supplementation (500mg/Kg) in healthy rats (n=5) versus cirrhotic rats (n=11)	DHA versus Vehicle: Improved ω6/ω3 index Portal Hypertension (-13,4%) Anion Superoxide Oxidation Esteatosis Inflammation: Liver Enzymes AST Cytokines: IL-1B, IL-10 IL-6 Liver Stellate cell deactivation	 P<0.001 P<0.03 P<0.015 P<0.01 P<0.04 P<0.04 P<0.05 P<0.09 P<0.01

TRIDOCOSAHEXANOINA-AOX® IN DISLIPEMIAS AND SYSTEMIC INFLAMMATION.[5,37] CLINICAL EXPERIENCE

ESTUDIO ARTÍCULO	TÍTULO / TEMA	MATERIAL Y MÉTODO	RESULTADOS	VALOR DE P
Domingo P; Clinical Nutrition 2017 http://dx.doi.org/10.1016/j.clnu.2017.05.032	Supplementation of Tridocosahexanoina -AOX® versus Placebo in HIV active patients suffering dislipemia. Randomized, double-blinded, placebo controlled trial	N=84 patients HIV active randomized to either supplementation with DHA-TG 4,9g/day or Placebo during 48 weeks	Reduction in triglyceridemia: Week 4 (44% vs 3%): Week 12 (44% vs 3%): Week 48: Week 4 correlated with DHA in the RBC membrane:	 <0.0001 <0.05 <0.03 r =0.7110, < 0.0001

TRIAL ARTICLE	TITLE / THEME	MATERIAL & METHODS	RESULTS	P VALUE
Domingo P, et al; Cytokine 2018; 105:73-79	DHA versus Placebo in systemic inflammation of HIV infected patients	N=39; n=18 DHA supplemented patients (4g/day) versus n=21 Placebo controlled patients; follow-up of 48 weeks	High sensibility Reactive Protein ARA levels decrease Changes on expression of Adipogenesis Genic expression of the inflammation on the subcutaneous adipose tissue: TNF-α MCP1	 P<0.04 P<0.0007 NS p<0.024 p<0.033

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