Clinic'n'Cell

Blood

Cells

Human data

WINNER NUTRA INGREDIENTS AWARDS 2022

Rapid Ex vivo clinical trials

linking metabolism to cellular biology

contact@clinicncell.com

Head and Co-founders of **ClinicnCell SAS**

Dr. Yohann Wittrant - CSO

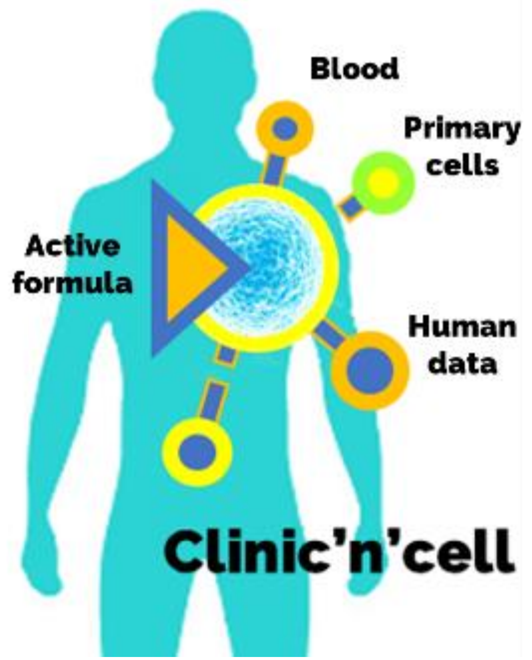
Ms. Line Boutin - COO

Dr. Fabien Wauquier - CEO

WHAT?

- ✓ **Innovative and Rapid**
- ✓ **Ex vivo Clinical approach**
- ✓ **Human health**

Solution: exclusive licence of use (Patent INRAE – Clermont Auvergne University)



Ex vivo clinical trials

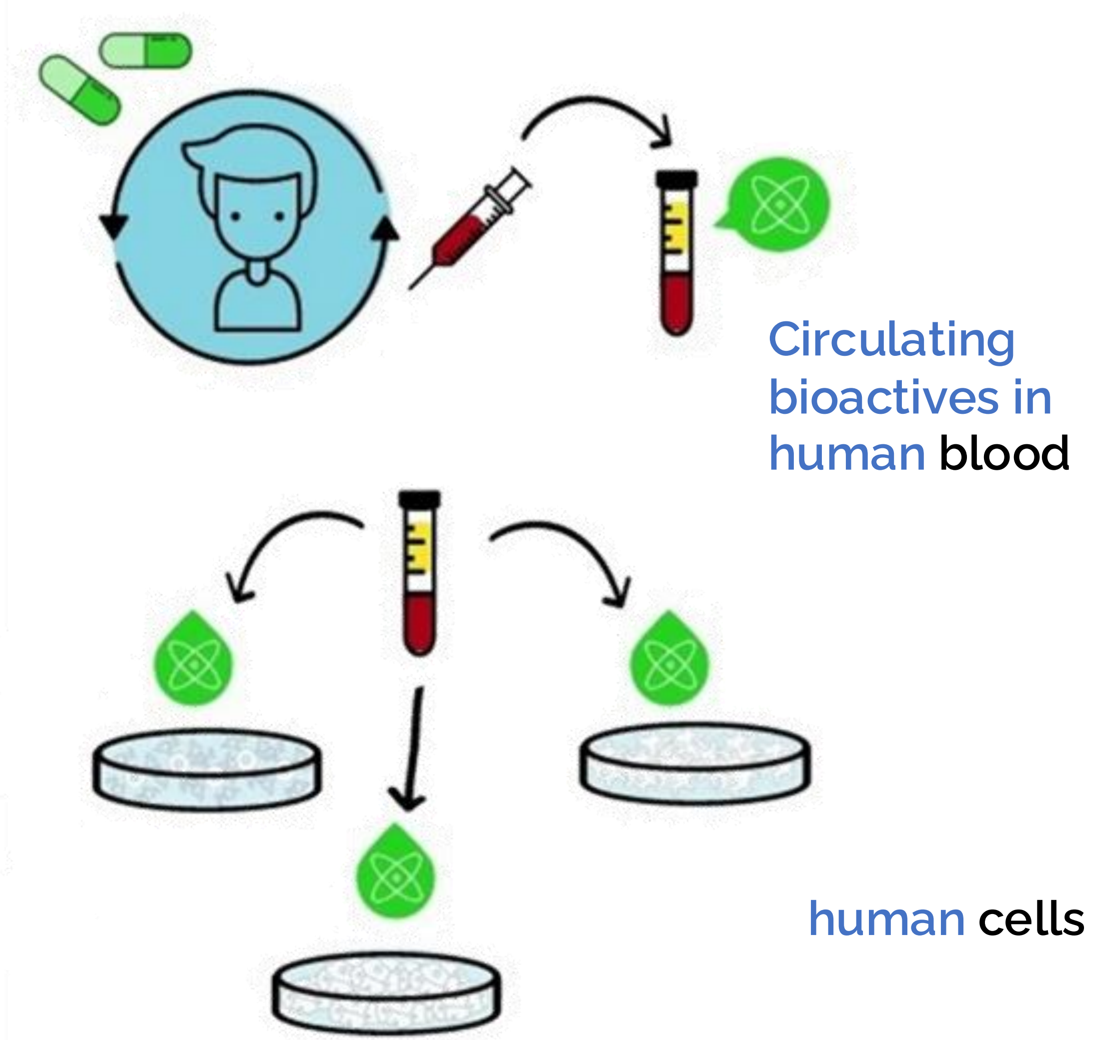
	+	
In vitro	Rapid (5X) Cost efficiency (10X-) Mode of action	Not Physiological
Animal studies		Ethical pressure Not Human (100k€)
Clinical trials	Physiological Human metabolism Human data	Time Price (1000k€)

HOW?

Conventional Clinical trial

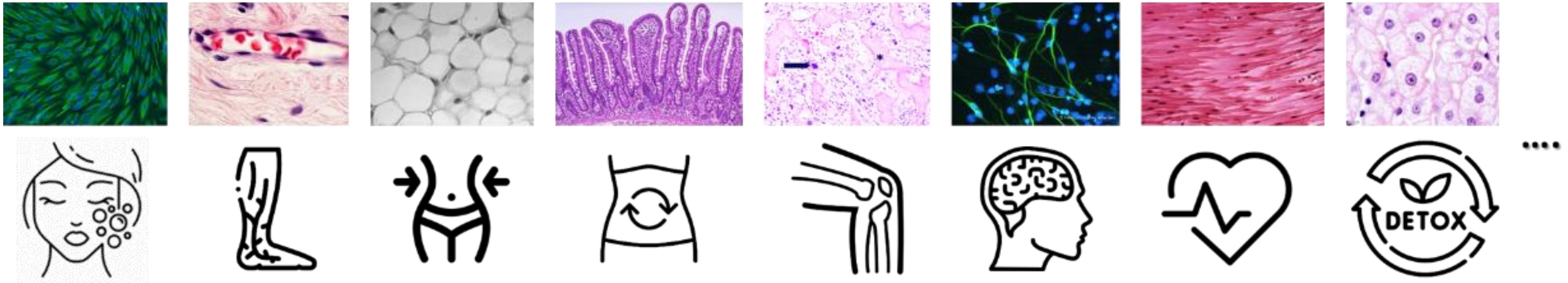
Ex Vivo Clinical trial (patented)

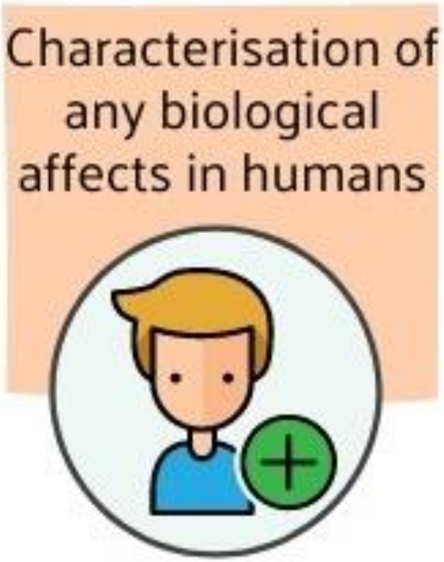
➔ **<u>We smartly go throught the outside</u>**



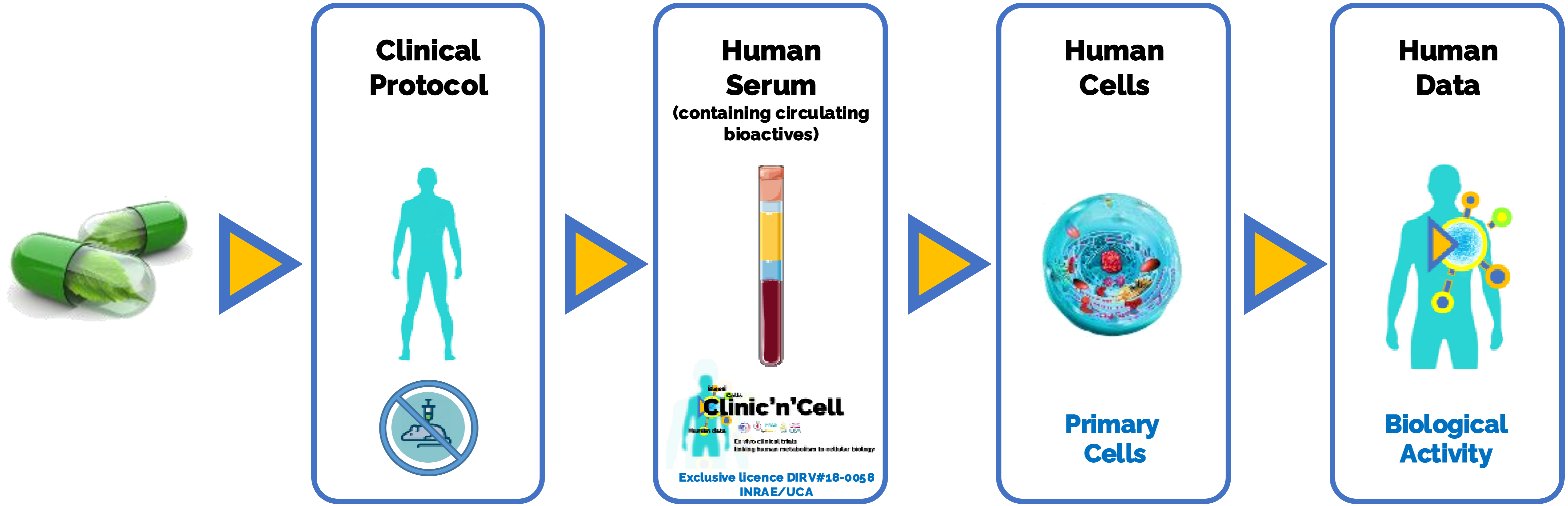
HOW?

Skin cells | Endothelial cells | Adipocytes | Enterocytes | Chondrocytes | Neurons | Smooth muscle cells | Hepatocytes





HOW ? / Protocol at a glance: rapid ex vivo clinical trial

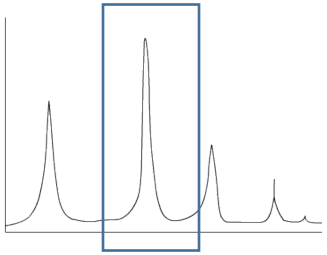


Clinic'n'Cell: A Relevant Clinical Approach

<u>Protocol : phase 1</u>

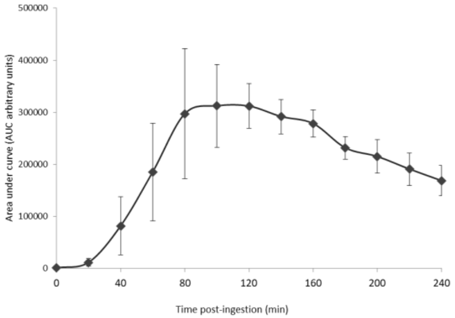
product to be tested

Absorption kinetic



Absorption peak

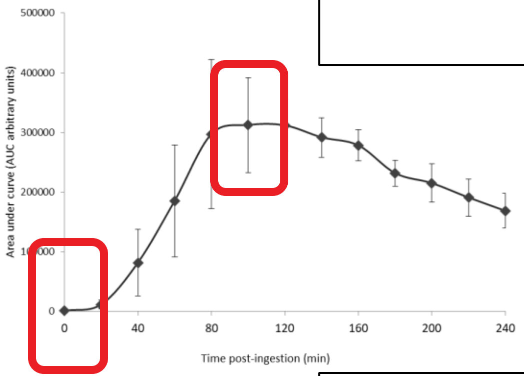
- ✓ *Characterization of human circulating bioactive metabolites*
- ✓ *Optimum metabolites enrichement of the serum for phase 2*



Clinic'n'Cell: A Relevant Clinical Approach

Protocol : phase 2

product to be tested



Baseline (T0)+ Absorption peak (Tp)

Whole signal / metabolites

➔Totum effect investigation
➔Synergistic properties preservation

✓ ***Enriched and naive sera collection***

Clinic'n'Cell: A Relevant Clinical Approach

Protocol : phase 3

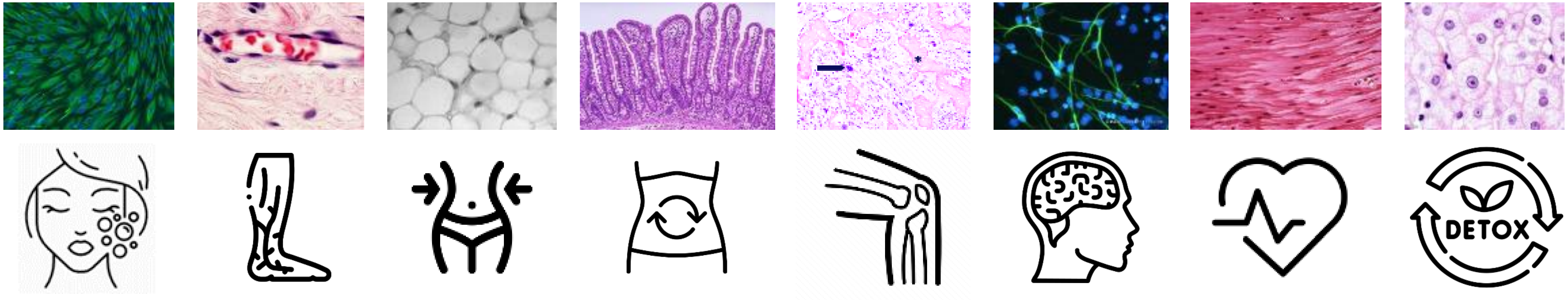
Human serum
(containing circulating bioactives)

(Processing: Exclusive methodology Clinic'n'Cell SAS)

↓

Incubation with targeted human cells (primary cultures)

Skin cells | Endothelial cells | Adipocytes | Enterocytes | Chondrocytes | Neurons | Smooth muscle cells | Hepatocytes



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Determination of biological activities

Advantage of ex vivo over regular clinical trials

Clinical Trials	Relevance	Focus	Time	Placebo	Volunteers (number)	Statistical power
Ex vivo	**Human metabolism**	**Molecular mechanism**	**Weeks to Months**	**NO**	**+**	**High**
Regular	Human metabolism	Biomarkers / Symptoms	Months to Years	YES	++++	Low

➔ Efficient, predictive, significant, cheaper and more rapid

Blood
Cells
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Human data

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➔ Study #1 (ALE alone)

nutrients

MDPI

Article

Metabolic and Anti-Inflammatory Protective Properties of Human Enriched Serum following Artichoke Leaf Extract Absorption: Results from an Innovative Ex Vivo Clinical Trial

Fabien Wauquier [1,†], Line Boutin-Wittrant [1,†], Aurélien Viret [2], Laure Guilhaudis [2], Hassan Oulyadi [2], Asma Bourafai-Aziez [3], Gwladys Charpentier [3], Guillaume Rousselot [3], Emmanuel Cassin [3], Stéphane Descamps [4], Véronique Roux [5], Nicolas Macian [5], Gisèle Pickering [5] and Yohann Wittrant [6,7,*]

2.3. Artichoke Leaf Extract

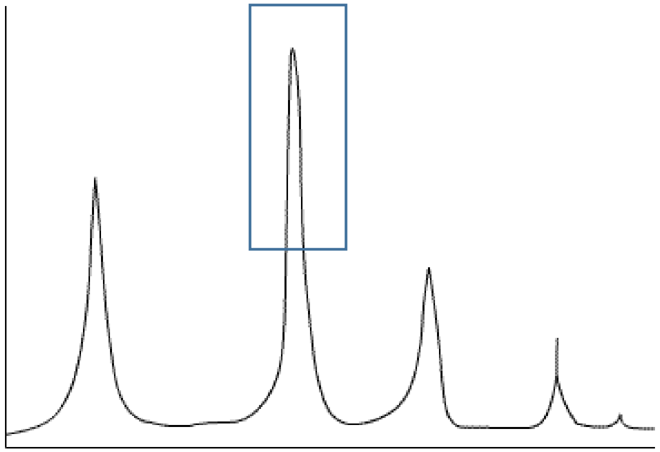
The artichoke leaves (Cynara scolymus) were collected in France (Coutures) and processed by Evear Extraction. The aqueous extract of artichoke leaves was obtained from fresh leaves. The resulting liquor is concentrated and then vacuum oven dried to produce the artichoke leaf extract powder used in this study. The final product was characterized for its total phenolic content using a Folin–Ciocalteu method.

Clinic'n'Cell:

Protocol : phase 1

Artichoke Leaf Extract (ALE)

Absorption kinetic



Kinetic of Apparition of Circulating Metabolites Resulting from ALE Ingestion in Humans

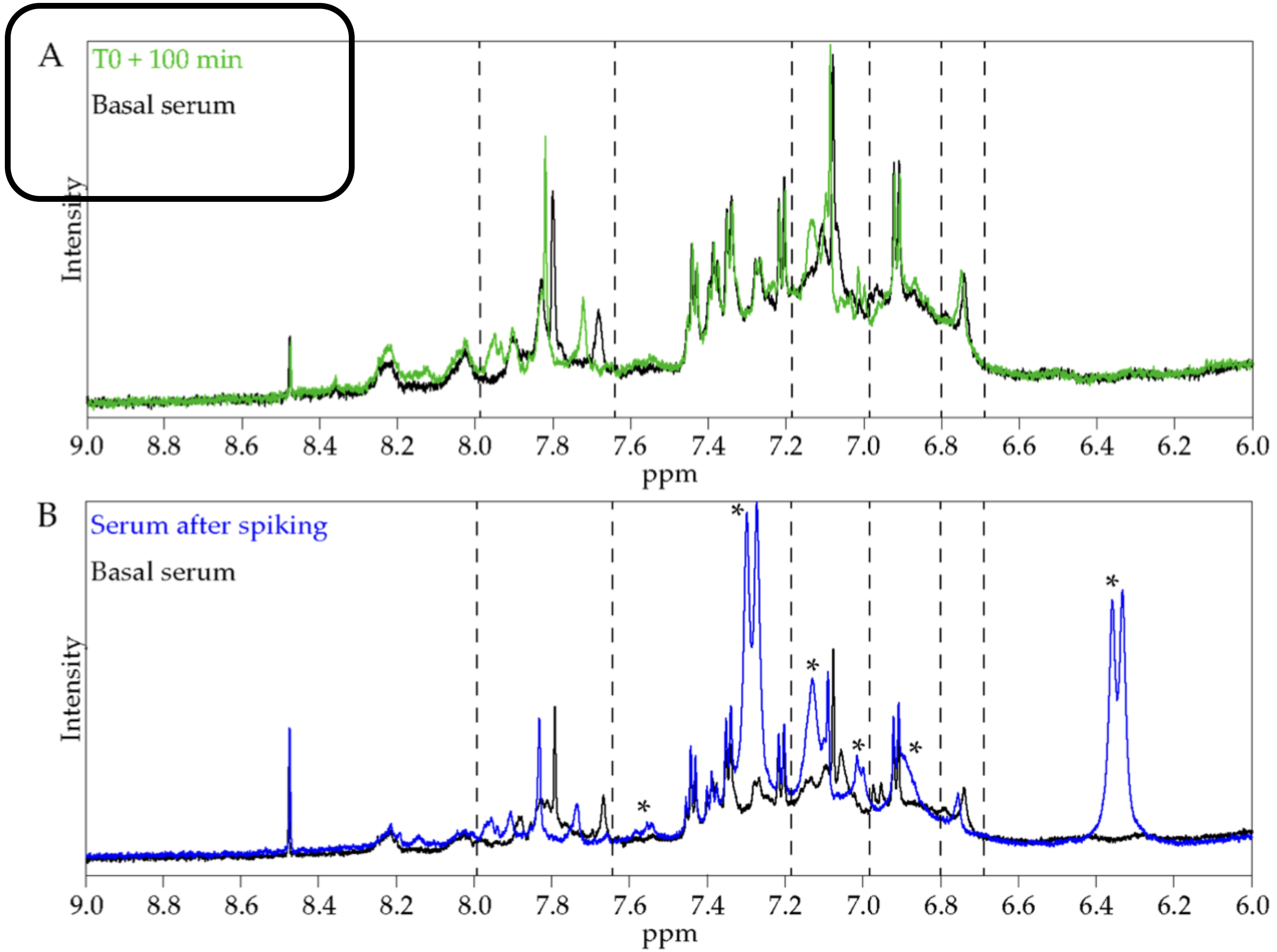


Figure 3. Expansion of the phenolic region of ^{1}H NMR spectra of serum. (**A**) Expansion of the phenolic region of ^{1}H NMR spectra of serum collected at T0 (black) and T0+100 min (green). (**B**) Expansion of the phenolic region of ^{1}H NMR spectra of a basal serum (black) and after spiking with caffeic and quinic acids (blue). *: caffeic acid signals.

Clinic'n'Cell

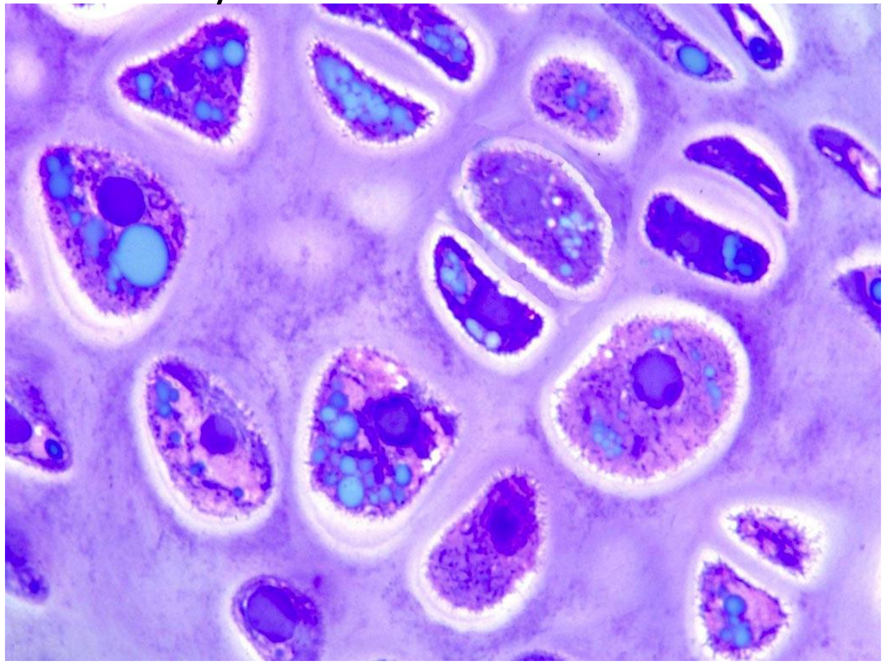
Ex vivo clinical trials
linking human metabolism to cellular biology

Blood (serum)
(containing circulating bioactives)

Patented methodology Clinic'n'Cell SAS (INRAE/UCA)

Incubation settings

Chondrocytes



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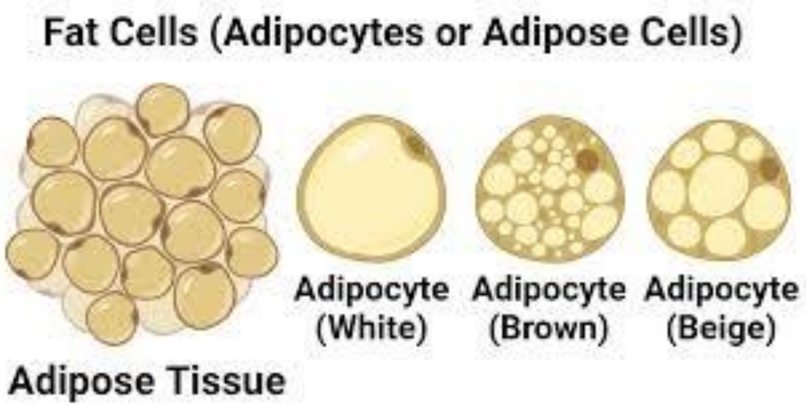
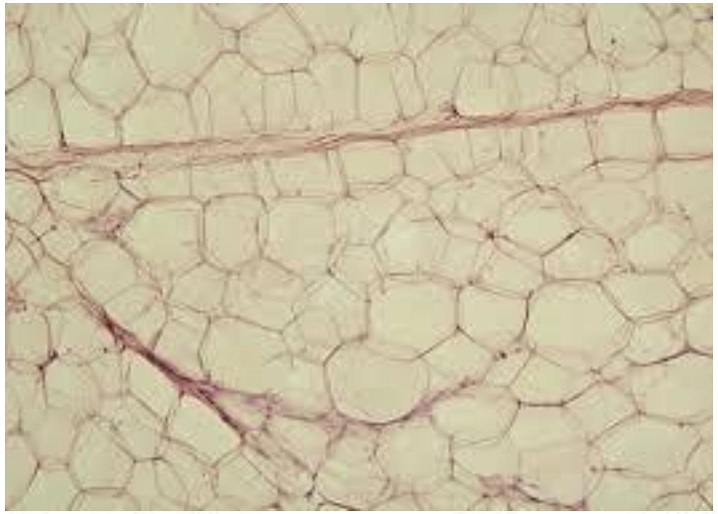
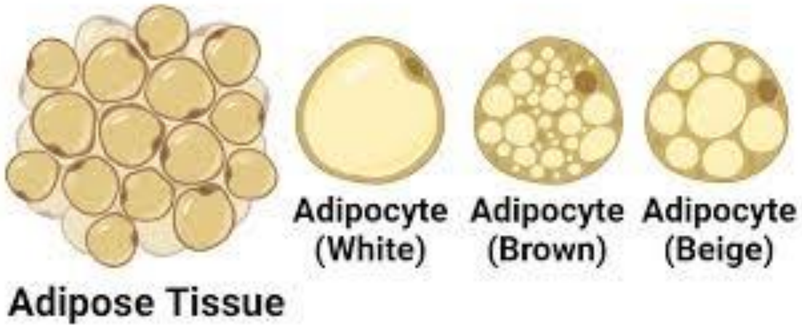


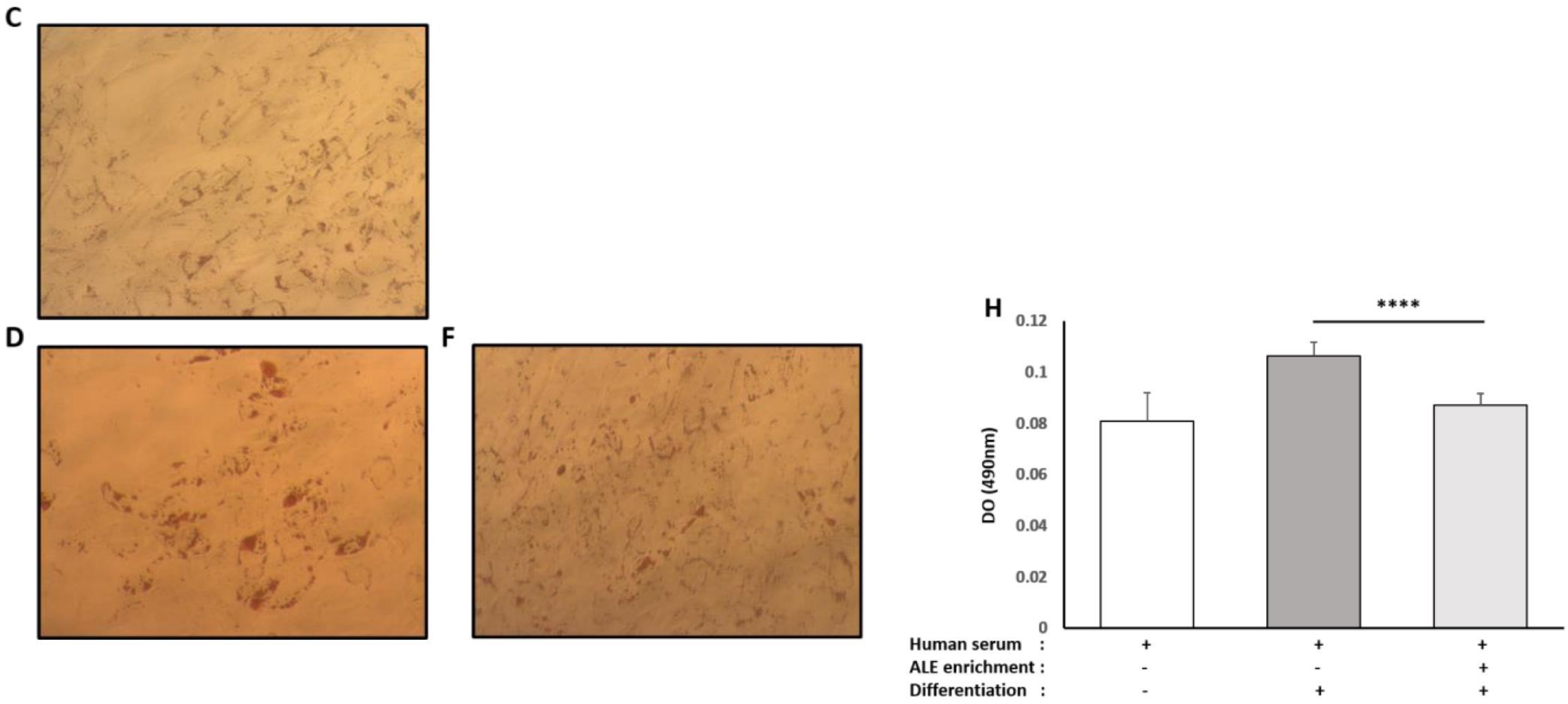
➔ Ex#1: Adipocytes and lipid metabolism



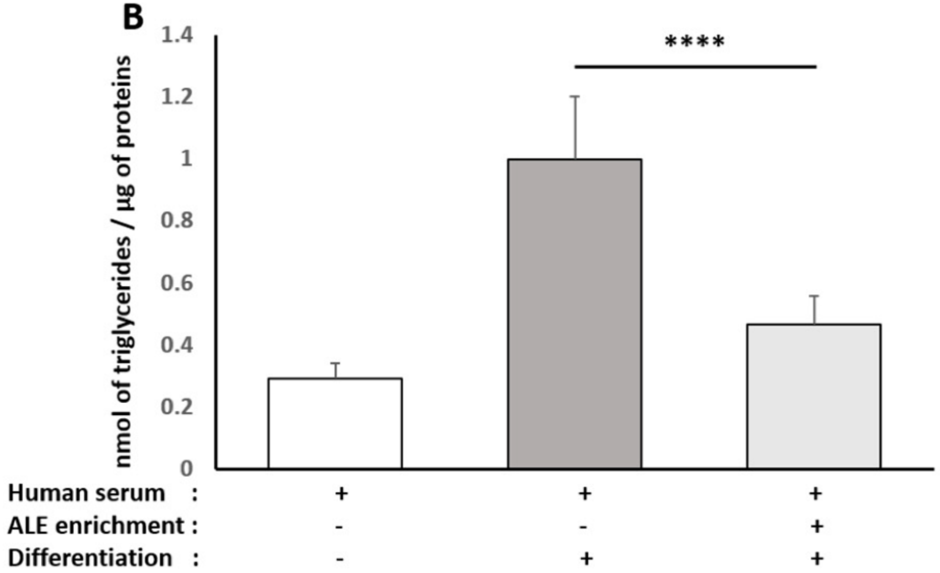
Fat Cells (Adipocytes or Adipose Cells)



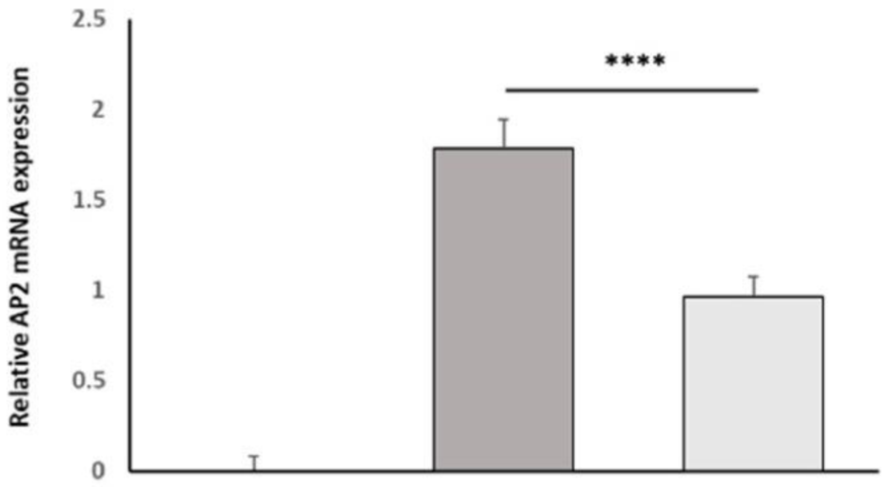
ALE limits fat deposit in human adipocytes



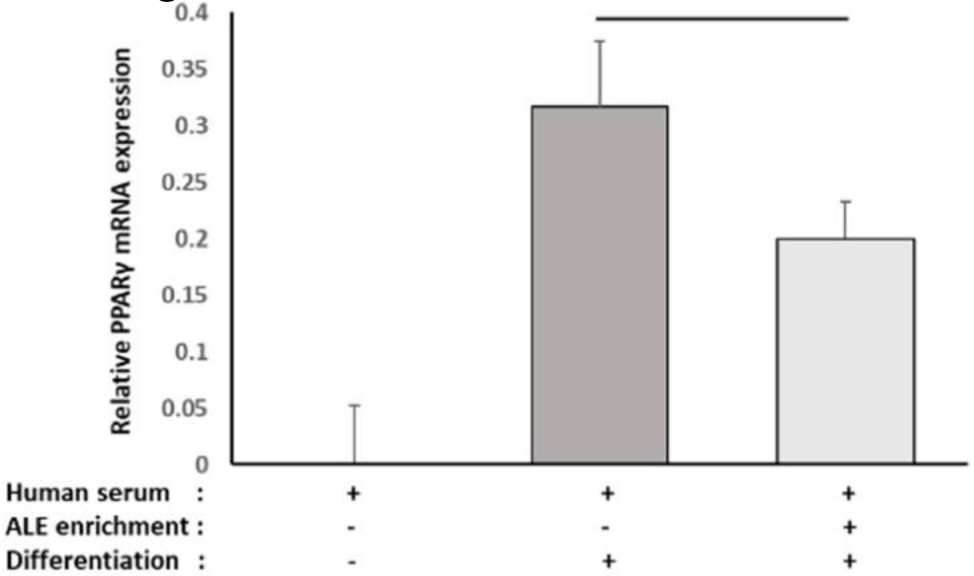
Triglycerides



AP2



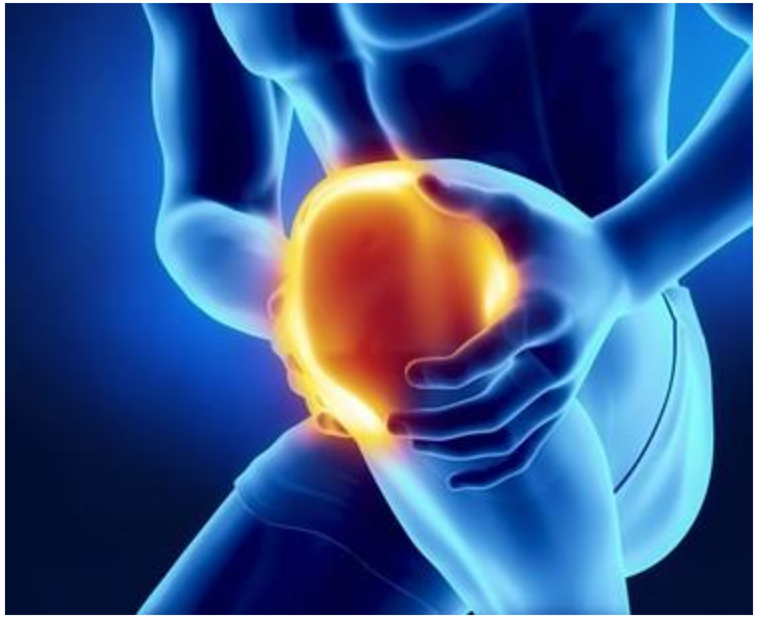
PPARg



ALE limits human adipocyte differentiation

➔ Ex#2: Chondrocytes and osteoarthrosis

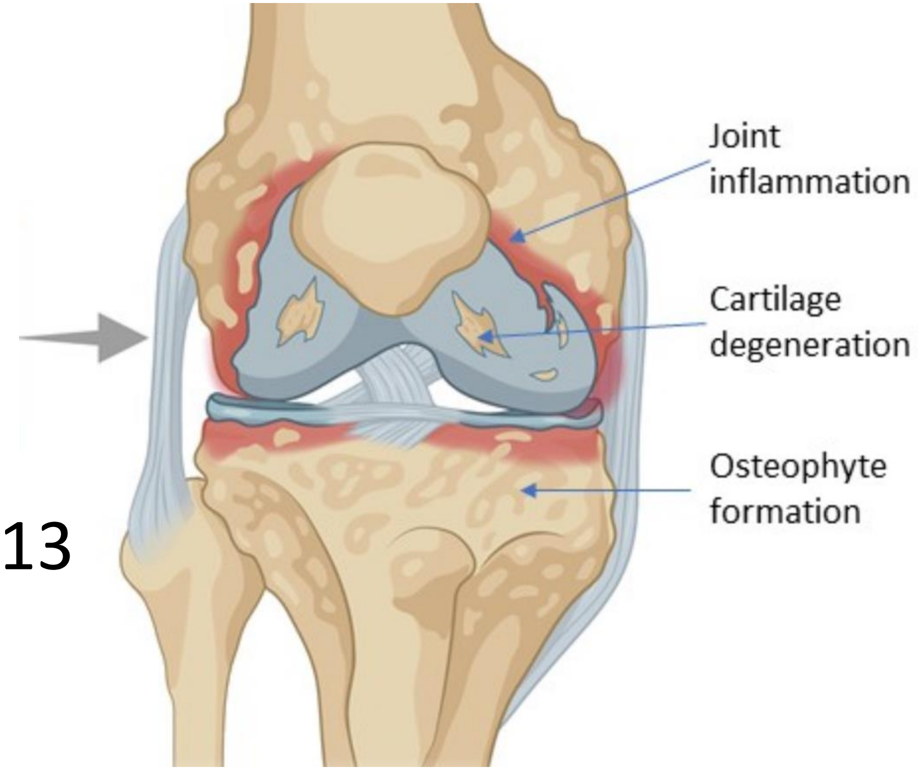
VS

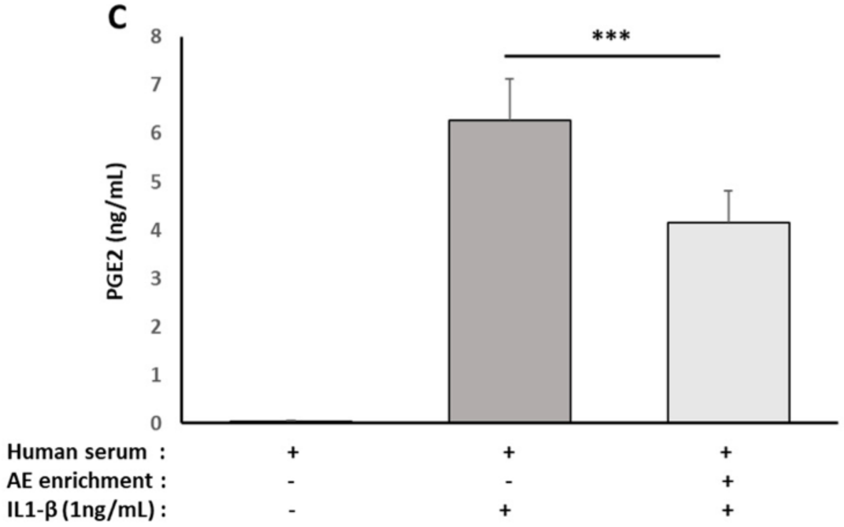


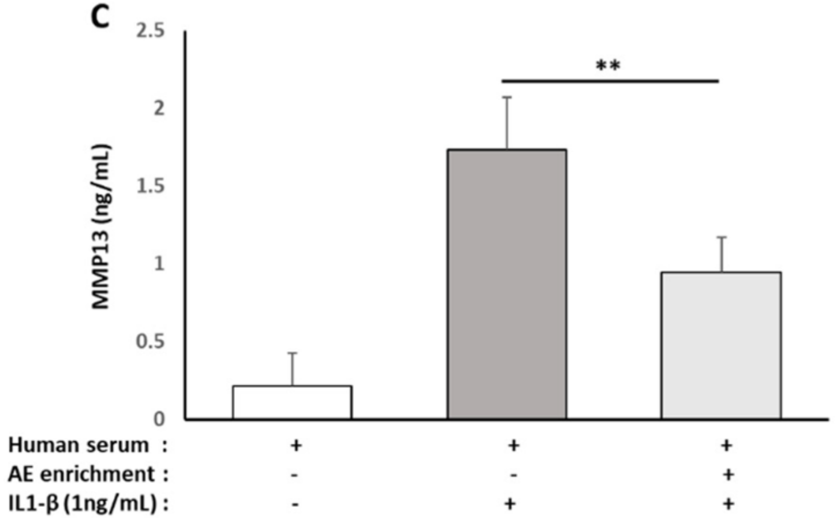
ALE limits IL-1b induced inflammation

IL-1b

↗ PGE2
↗ MMP13



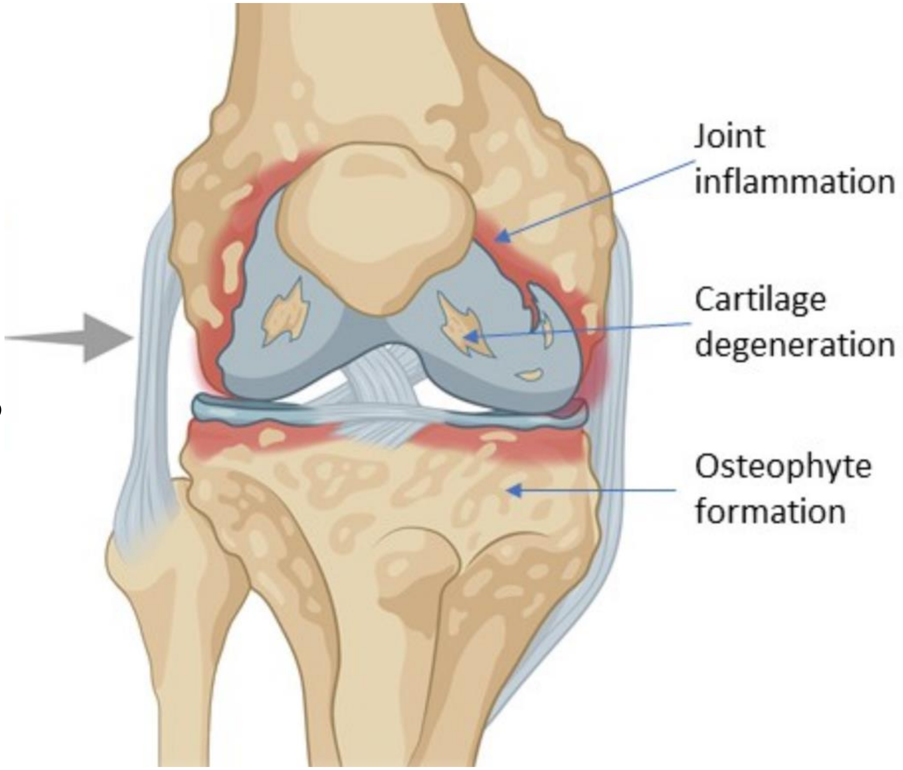


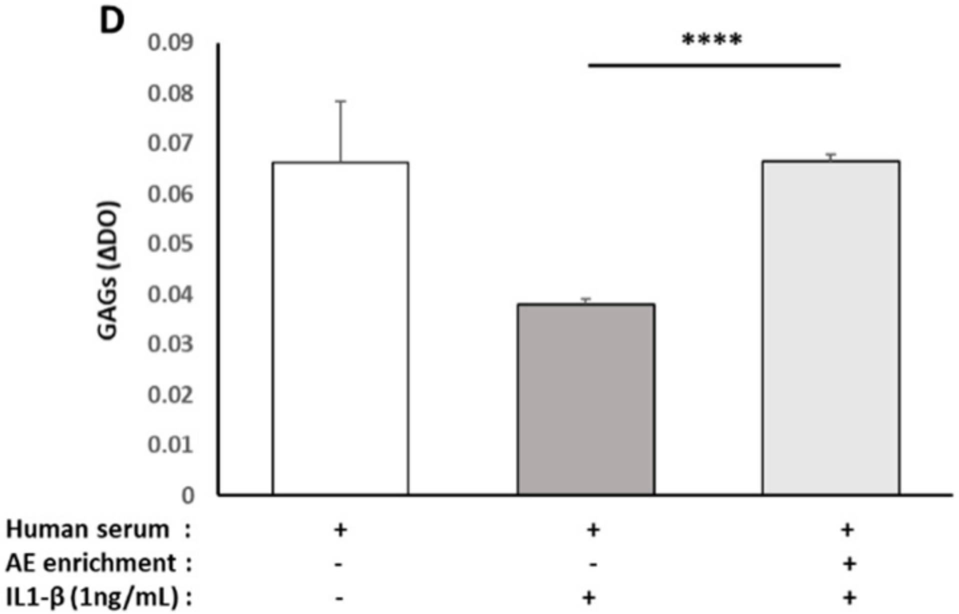


ALE prevent IL-1b induced GAGs loss

IL-1b

↘ GAGs





More interesting than NSAIDs

➔ Study #2 (ALE in combination)

nutrients

MDPI

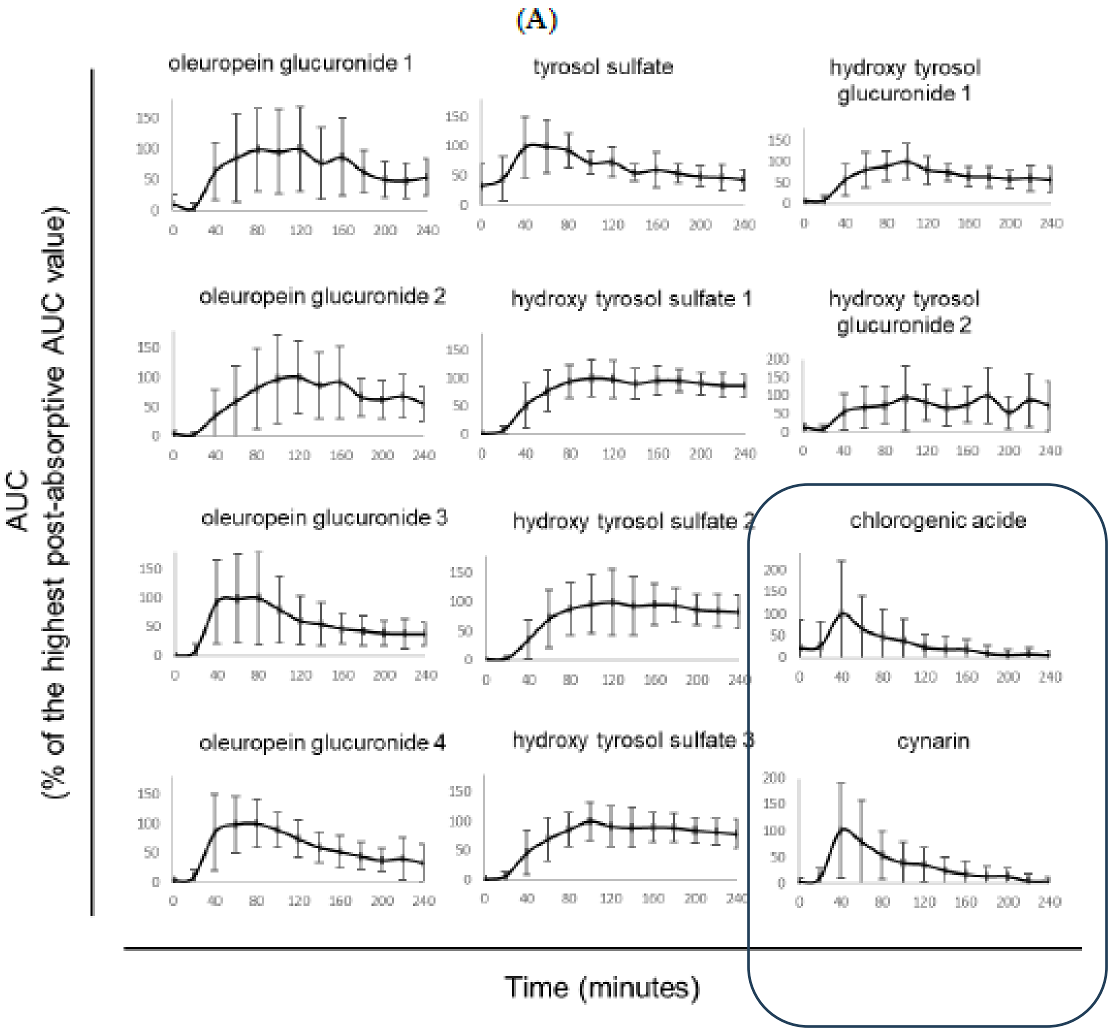
Article

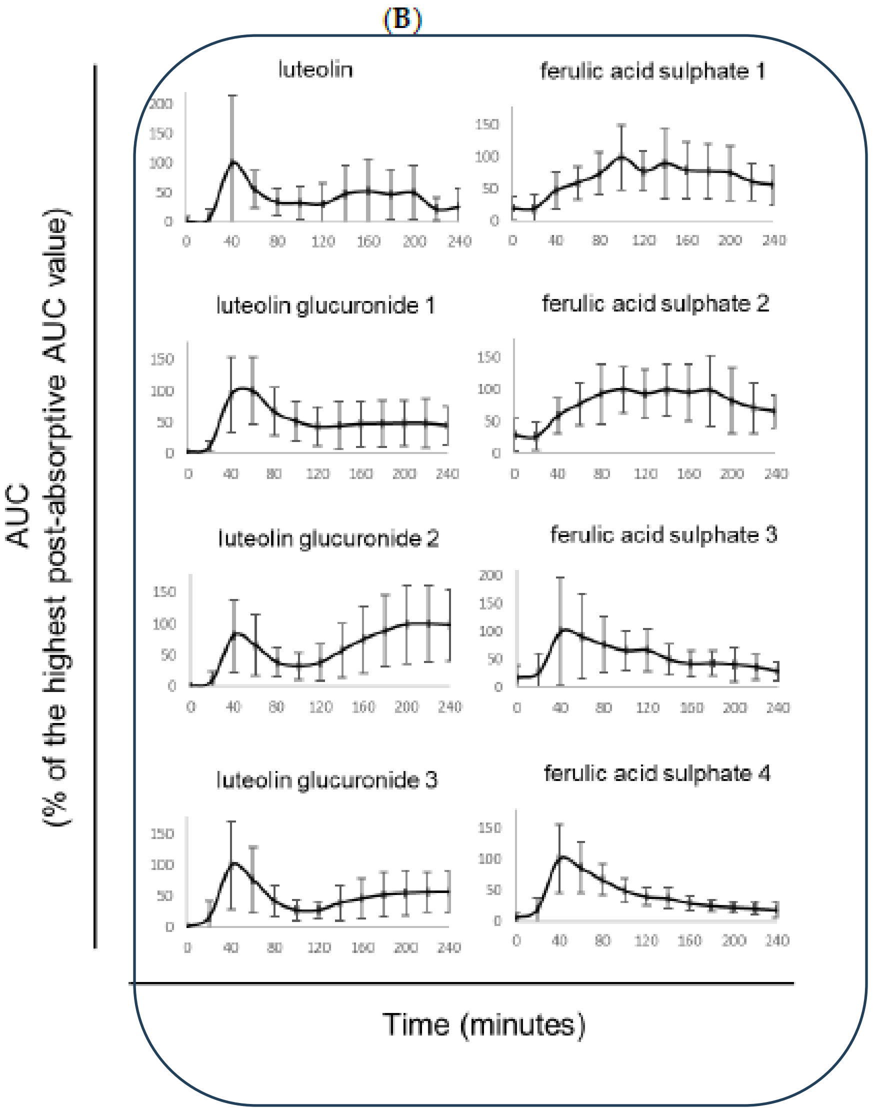
Circulating Human Metabolites Resulting from TOTUM-070 Absorption (a Plant-Based, Polyphenol-Rich Ingredient) Improve Lipid Metabolism in Human Hepatocytes: Lessons from an Original Ex Vivo Clinical Trial

Fabien Wauquier [1], Line Boutin-Wittrant [1], Stéphanie Krisa [2], Josep Valls [2,3], Cedric Langhi [4], Yolanda F. Otero [4], Pascal Sirvent [4], Sébastien Peltier [5], Maxime Bargetto [5], Murielle Cazaubiel [5], Véronique Sapone [5], Annie Bouchard-Mercier [6], Véronique Roux [7], Nicolas Macian [7], Gisèle Pickering [7] and Yohann Wittrant [8,9,*]

2.1. Study Product

VALBIOTIS has developed TOTUM-070 (priority French patent: FR1559965), a food ingredient composed by the combination of different plant extracts. The extracts were initially selected on the basis of published clinical data and/or traditional use for their possible effectiveness in reducing LDL-c.


(A)
oleuropein glucuronide 1
tyrosol sulfate
hydroxy tyrosol glucuronide 1
oleuropein glucuronide 2
hydroxy tyrosol sulfate 1
hydroxy tyrosol glucuronide 2
oleuropein glucuronide 3
hydroxy tyrosol sulfate 2
chlorogenic acide
oleuropein glucuronide 4
hydroxy tyrosol sulfate 3
cynarin
AUC
(% of the highest post-absorptive AUC value)
Time (minutes)


(B)
luteolin
ferulic acid sulphate 1
luteolin glucuronide 1
ferulic acid sulphate 2
luteolin glucuronide 2
ferulic acid sulphate 3
luteolin glucuronide 3
ferulic acid sulphate 4
AUC
(% of the highest post-absorptive AUC value)
Time (minutes)

Blood
Cells
Clinic'n'Cell
Human data
Ex vivo clinical trials
linking human metabolism to cellular b

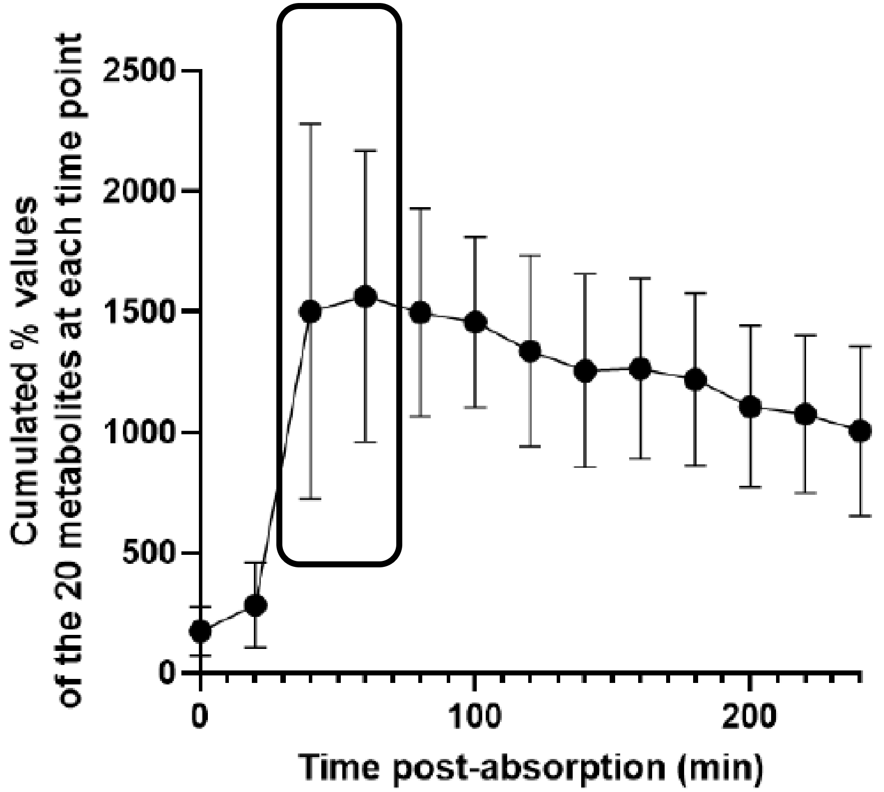
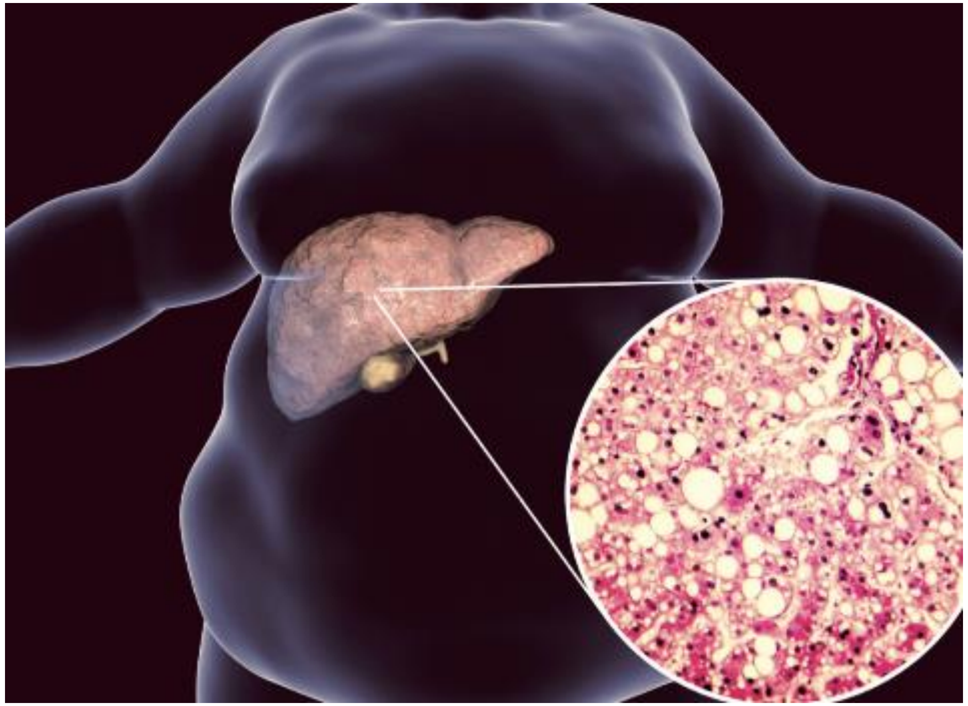


Figure 2. Absorption profile. (**A**,**B**) Circulating polyphenol metabolites resulting from human absorption and metabolization of TOTUM-070. For each metabolite, 100% is the highest post-absorptive AUC value. (**C**) Metabolites diversity per time point following TOTUM-070 ingestion (cumulated percentage values of the 20 metabolites at each time point ± SD).

→ Ex#3: Hepatocytes and lipid metabolism

VS



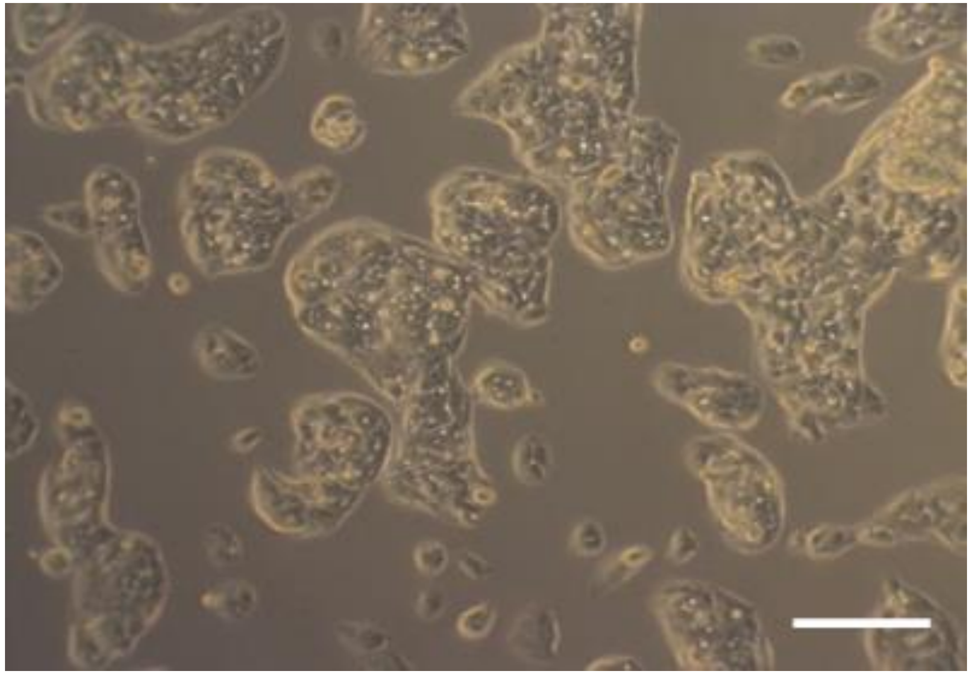
Clinic'n'Cell

Ex vivo clinical trials
linking human metabolism to cellular biology

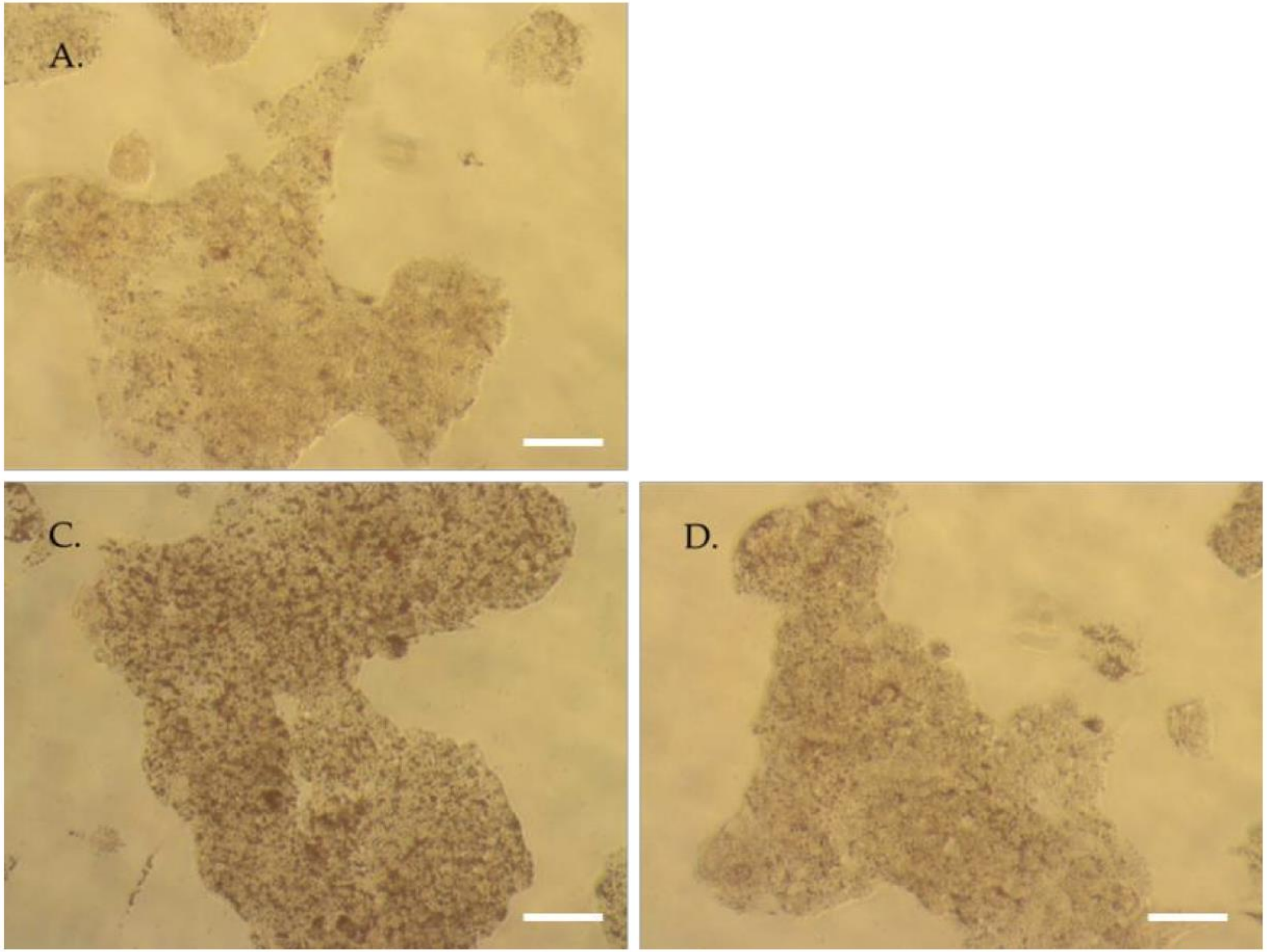
Blood (serum)
(containing circulating bioactives)

Patented methodology Clinic'n'Cell SAS (INRAE/UCA)

Incubation settings



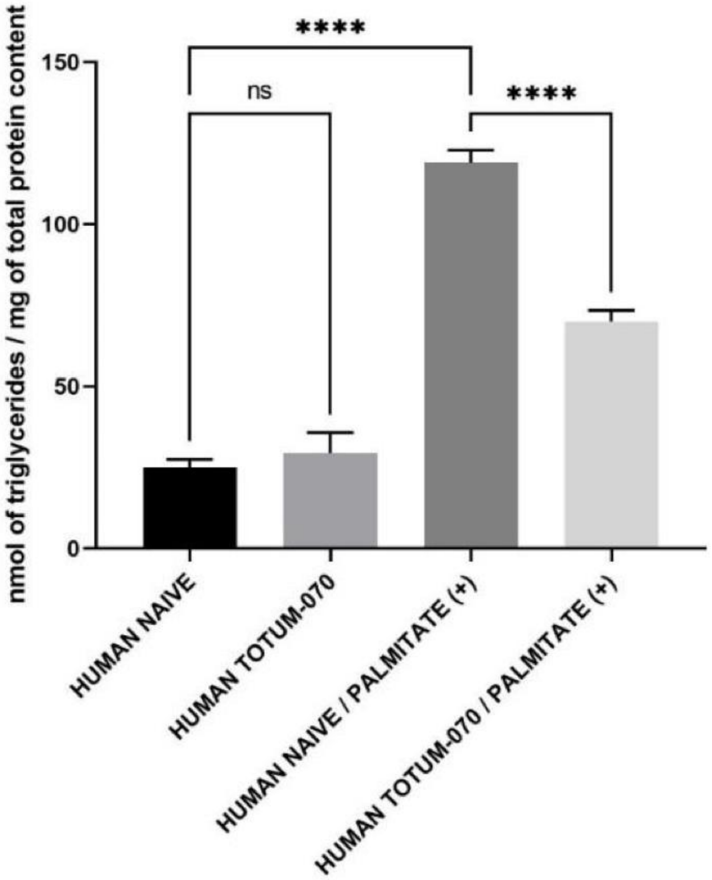
Limitation of palmitate-induced lipid accumulation



Artichoke leaves metabolites Limit Triglycerides and Fully Abolish Palmitate-induced Cholesterol storage

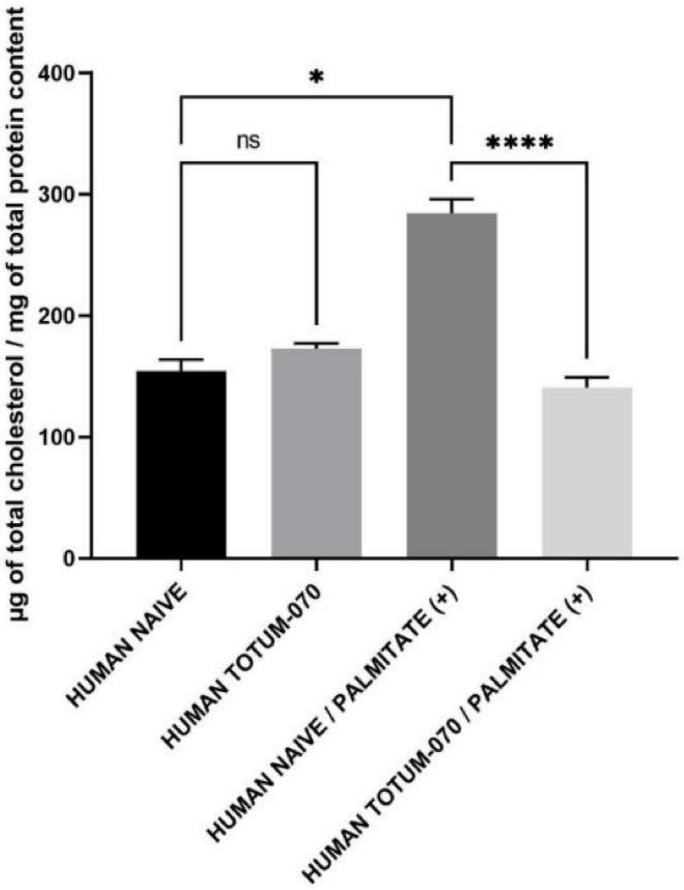
Triglycerides

(A)

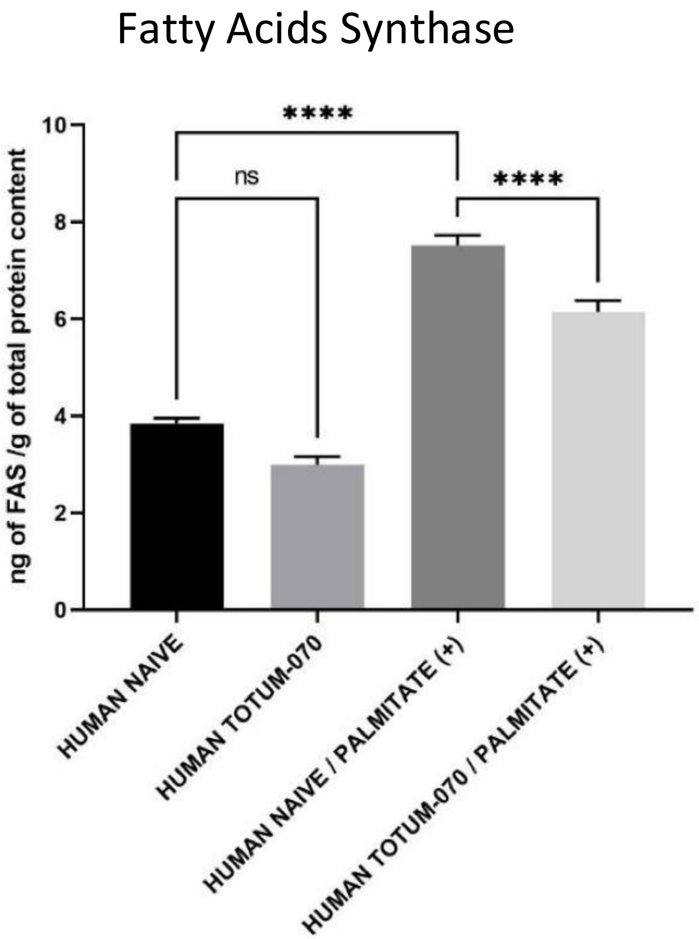


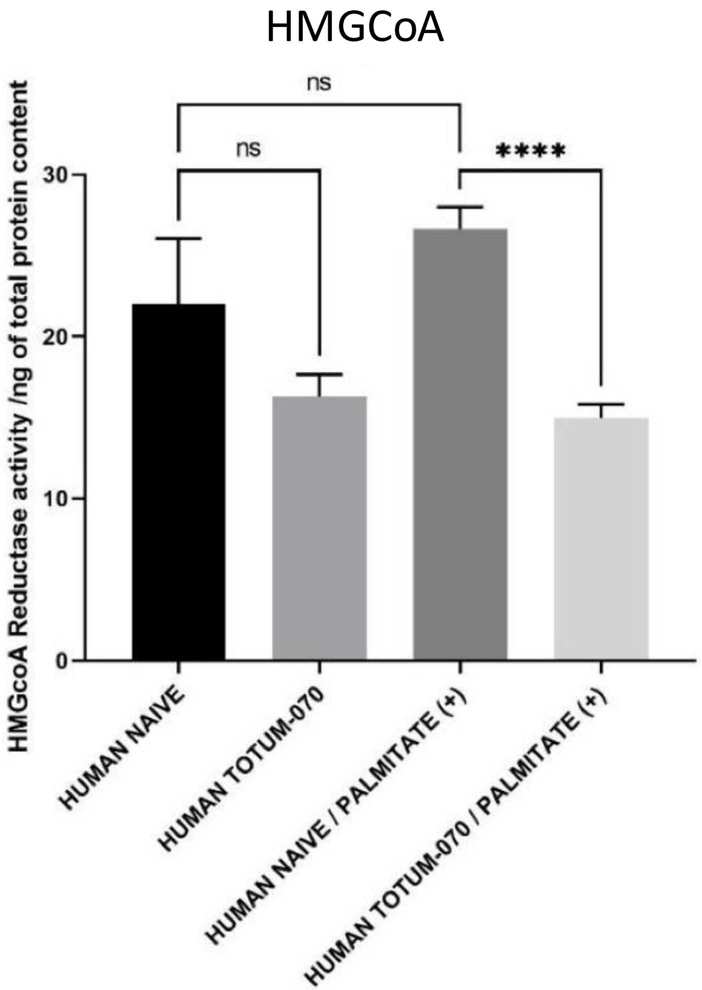
Cholesterol

(B)



Artichoke leaves Derived Metabolites Limit Lipid Synthesis





Hepatoprotective effects upon a lipotoxic stress

➔ Study #3 (ALE in combination)

nutrients

MDPI

Article

TOTUM-854 Human Circulating Bioactives Preserve Endothelial Cell Function

Fabien Wauquier [1], Doriane Ripoche [2], Line Boutin-Wittrant [1], Yolanda F. Otero [2], Stéphanie Krisa [3], Josep Valls [4], Mahéva Maura [5], Florian Le Joubioux [5], Thierry Maugard [6], Gaëtan Bolea [7], Grégory Meyer [7], Cyril Reboul [7], Véronique Roux [8], Nicolas Macian [8], Gisèle Pickering [8], Bruno Pereira [9], Maxime Bargetto [5], Véronique Sapone [5], Murielle Cazaubiel [5], Sébastien Peltier [5], Pascal Sirvent [2] and Yohann Wittrant [1,10,*]

2.1. Study Product

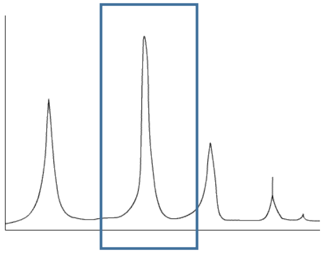
VALBIOTIS has formulated TOTUM-854 (Patent: FR1460064), a food supplement resulting from the combination of six plant extracts (chrysanthellum indicum, artichoke leaves (*Cynara scolymus* L.), olive leaves (*Olea europaea* L.), blueberry (*Vaccinium myrtillus* L.), *Piper nigrum* L., and garlic (*Allium sativum* L.)). The blend was formulated according to previously described clinical data and the traditional uses for their supposed benefits in preventing hypertensive conditions. The formulation of the product meets the requirements of the European regulations relating to food supplements (European directive n°2002/46/EC and French decree n°2006-352 of 20 March 2006, which transposes it).

Clinic'n'Cell:

Protocol : phase 1

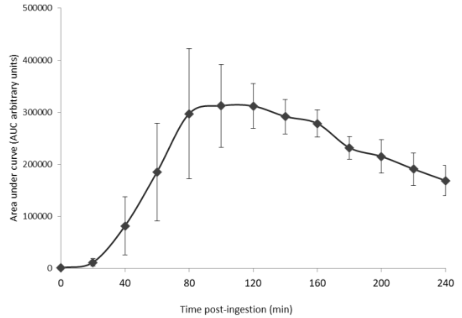
TOTUM 854

Absorption kinetic

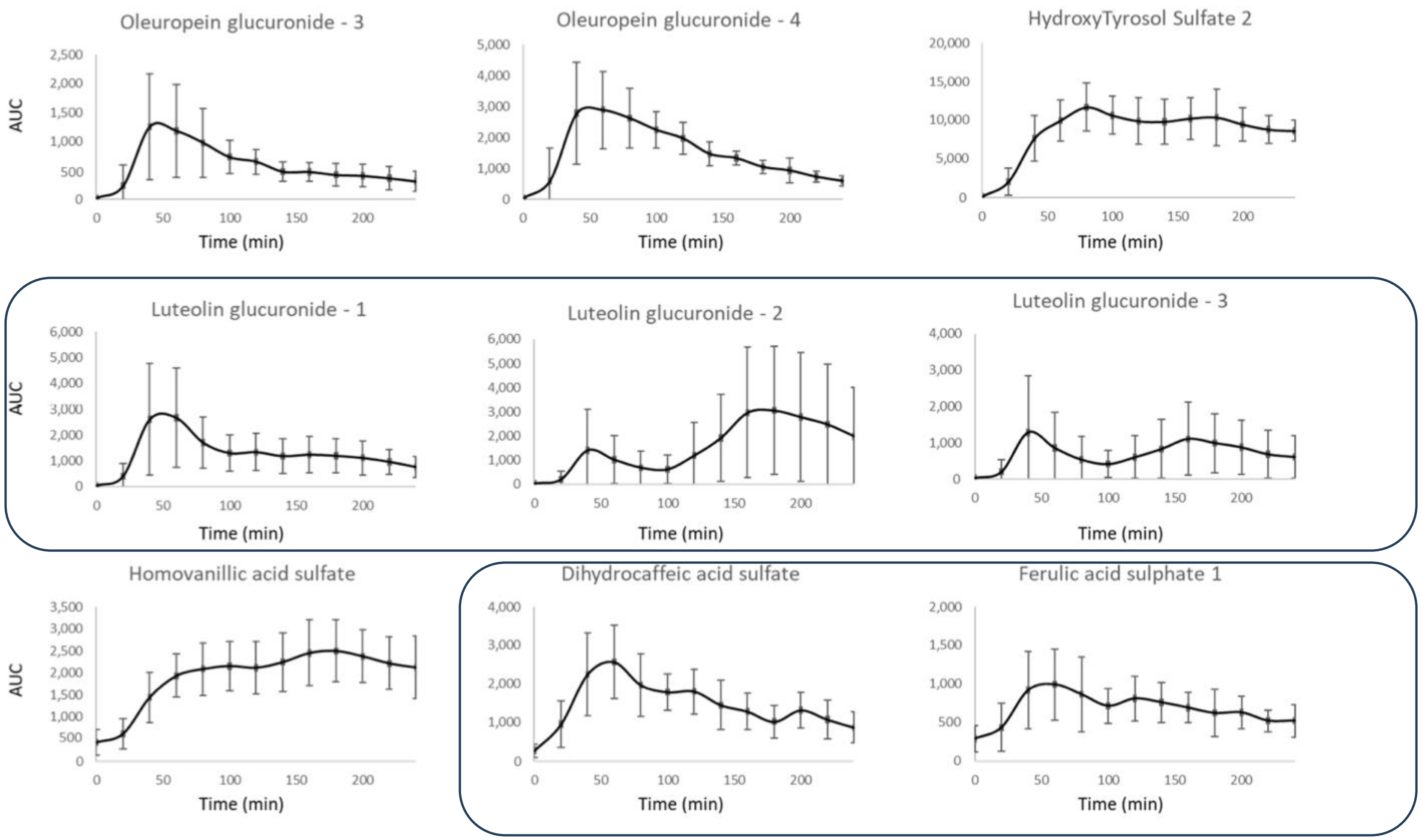


Absorption peak

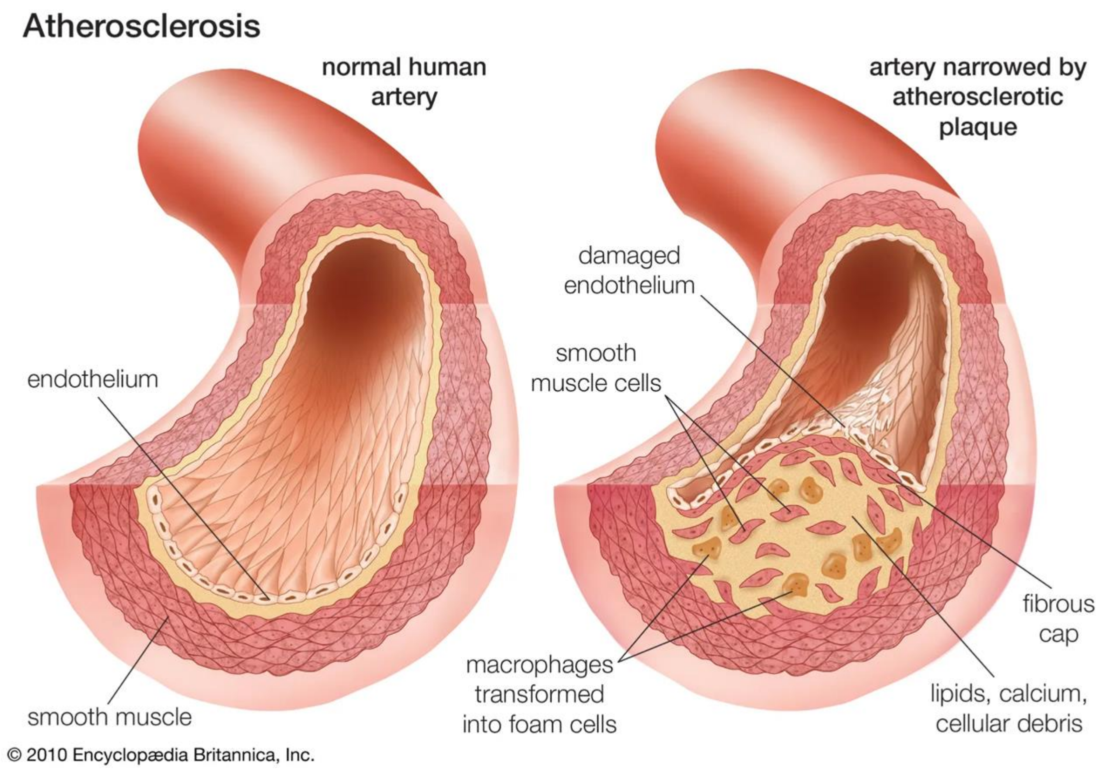
- ✓ ***Characterization of human circulating bioactive metabolites***
- ✓ ***Optimum metabolites enrichement of the serum for phase 2***



Kinetic of Apparition of Circulating Metabolites Resulting from TOTUM-854 Ingestion in Humans



→ Ex#4: Endothelial cells and atherosclerosis

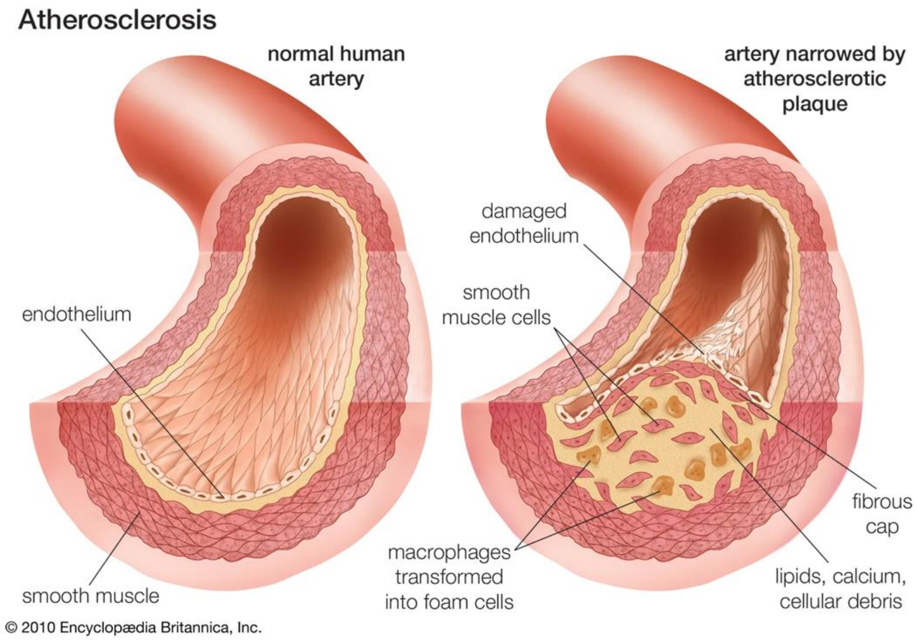


Clinic'n'Cell
Blood Cells Human data
Ex vivo clinical trials
linking human metabolism to cellular biology

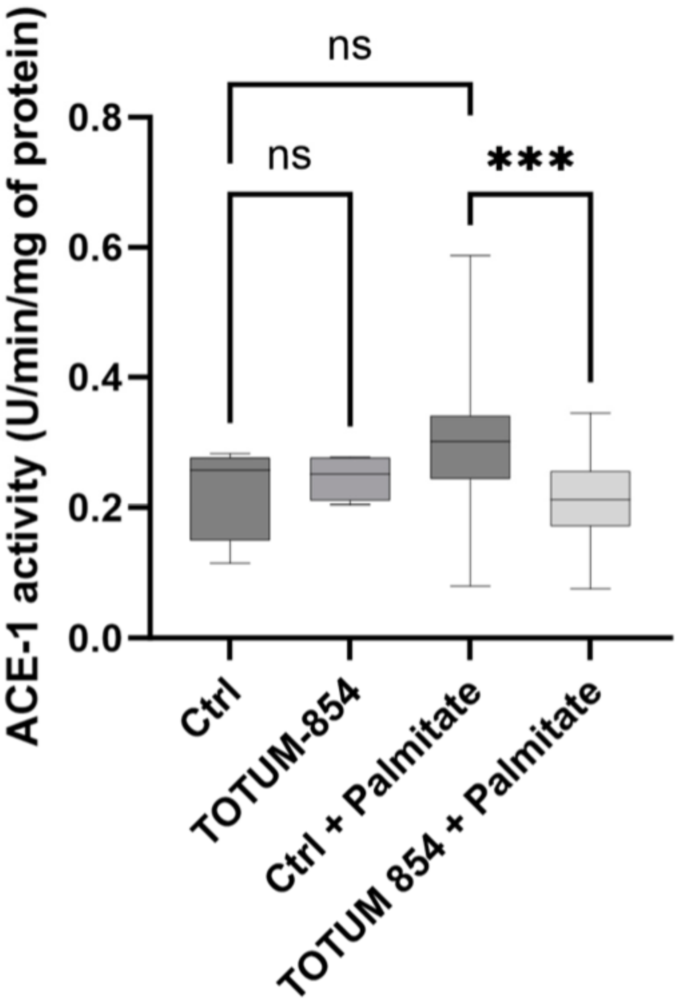
Blood (serum)
(containing circulating bioactives)

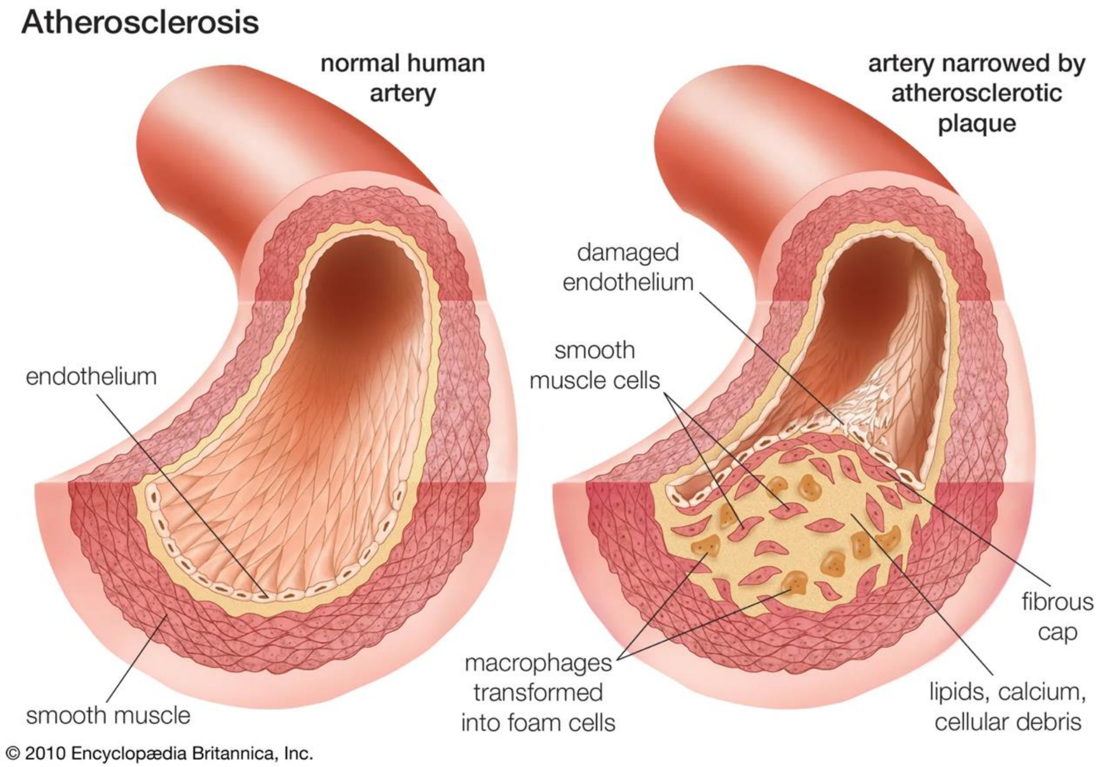
Patented methodology Clinic'n'Cell SAS (INRAE/UCA)

Incubation settings

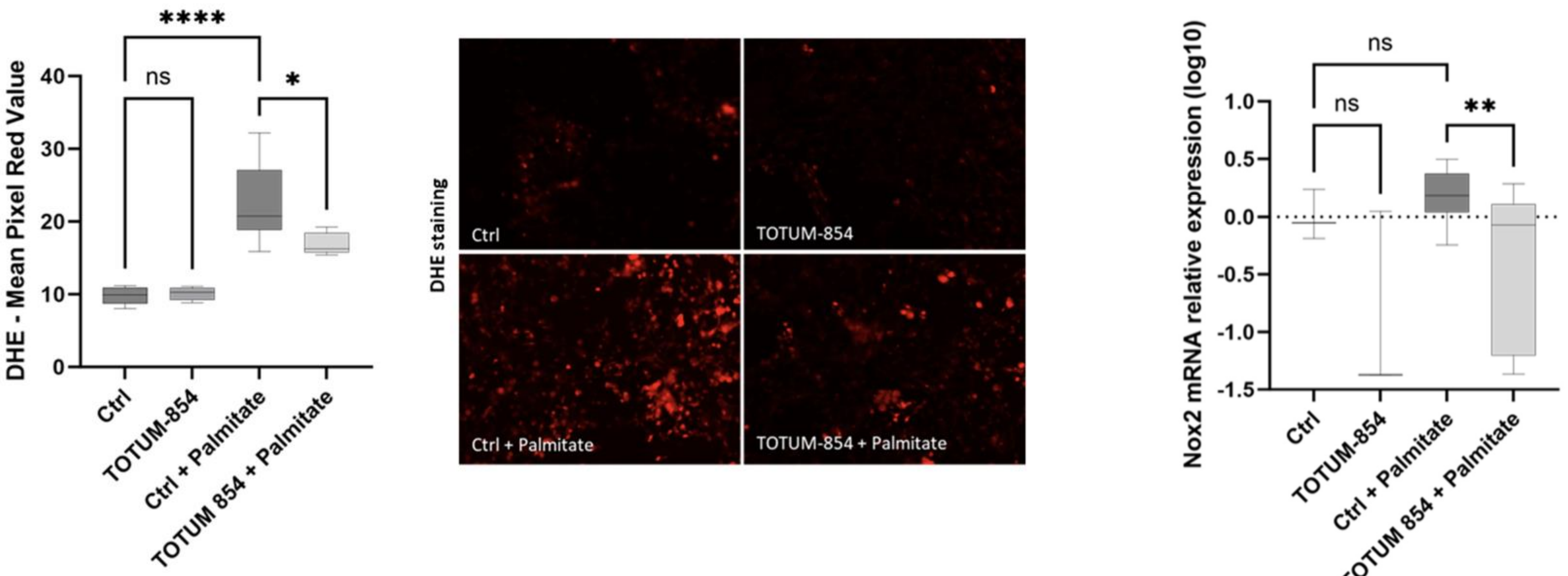


TOTUM-854 Human Metabolites Decrease Angiotensin-Converting Enzyme 1 Activity Under Palmitate Stress

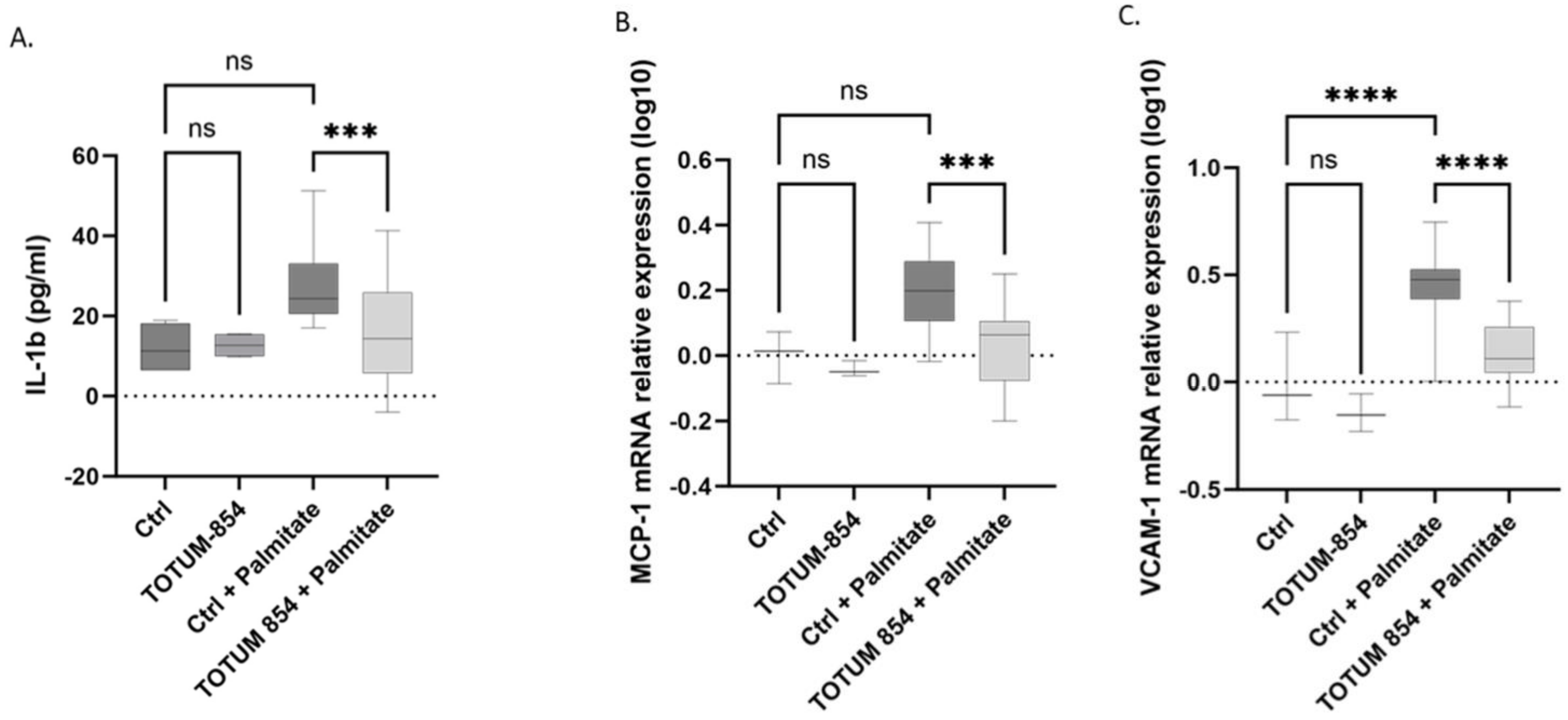




TOTUM-854 Metabolites Limit Oxidative Stress in a Lipotoxic Environment

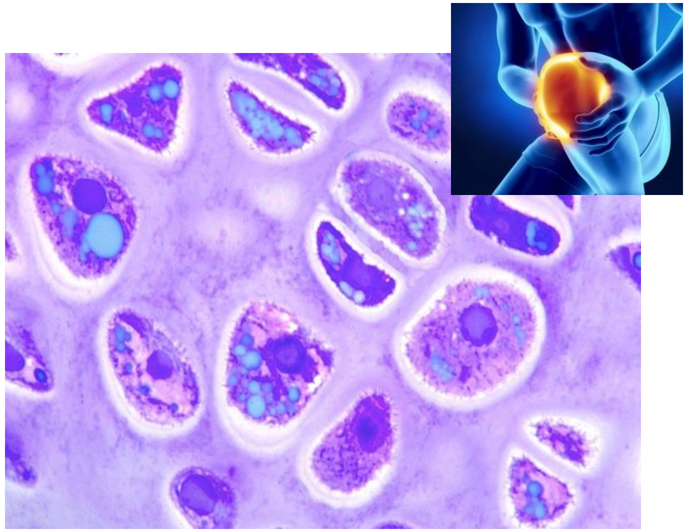


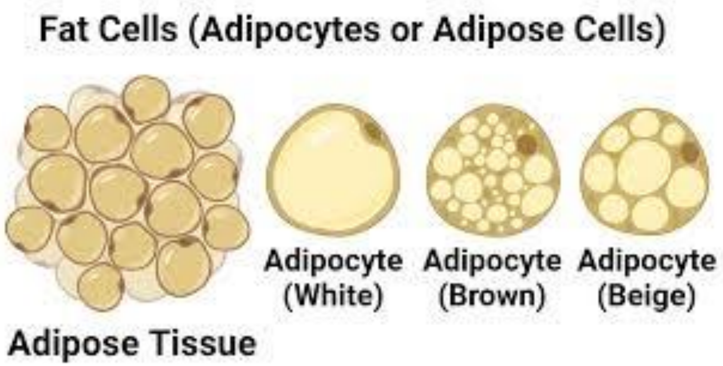
TOTUM-854 Metabolites Limit Oxidative Stress in a Lipotoxic Environment

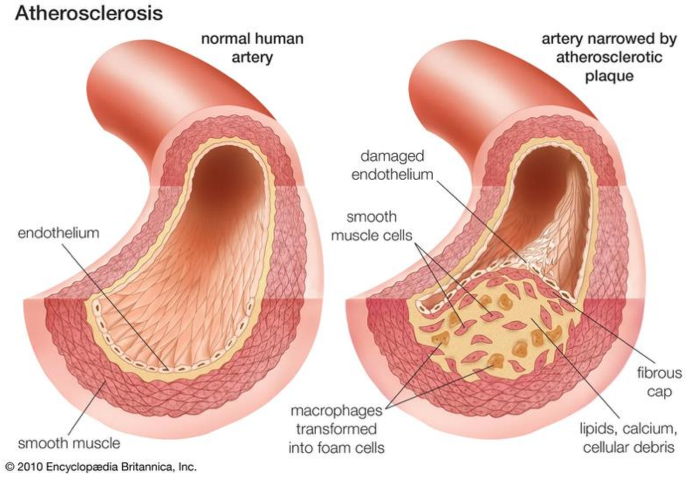


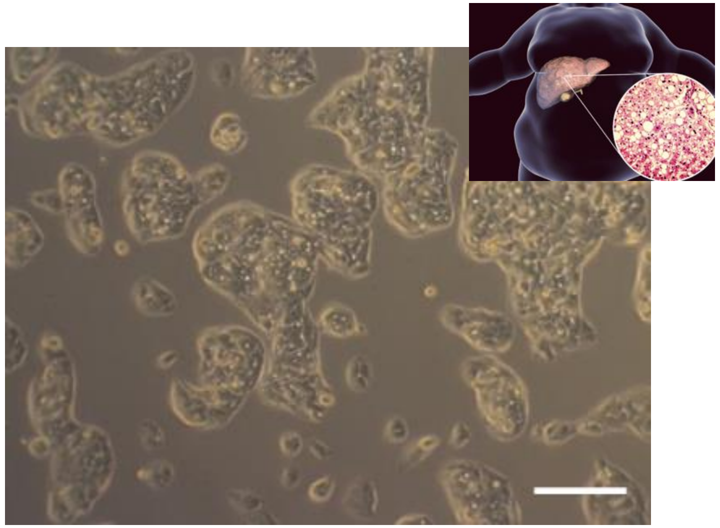
Improved endothelial cell functions

Conclusions









- ✓ Artichoke

- ✓ Bioavailable
- ✓ Metabolites

- ✓ Lipid metabolism
- ✓ Inflammation

- ✓ Health benefits
- ✓ Multiple targets
- ✓ Tissues

Blood

Cells

Clinic'n'Cell

Human data

WINNER NUTRA INGREDIENTS AWARDS 2022

Rapid Ex vivo clinical trials

linking metabolism to cellular biology

contact@clinicncell.com