RESEARCH PROTOCOL

Evaluation of the effect of consuming yogurts fortified with dietary sources of vitamin E and omega-3 on classical biomarkers of cardiovascular disease and blood levels of vitamin E.

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GENERAL INFORMATION

Title: Evaluation of the effect of consuming yogurts fortified with dietary sources of vitamin E and omega-3 on classical biomarkers of cardiovascular disease and blood levels of vitamin E.
Estimated start date: 01-03-2022
Estimated execution end date: 30-08-2023
Type of research: Applied research
This activity involves research on vertebrate animals: No
This activity involves the participation of employees or patients of a hospital institution: No
This activity has international collaboration and/or funding: No
Do you consider that this activity or the results that will be obtained from it are confidential: Si
Socio-economic objective: Health
Keywords: cardiovascular disease; tocotrienol; alpha linolenic acid; fermented milk drink; lipid profile; vitamin E
Big area: Medical and Health Sciences
Area: Health Sciences
Discipline: Nutrition and Dietetics
Activities to be undertaken involve the collection of wild species: No

SUMMARY: BACKGROUND, STATE OF THE ART AND PROBLEM FORMULATION

The food profile of western culture is characterized by a high energy density, due mainly to the high sugar intake, and the low consumption of fruits, vegetables and foods source of mono and polyunsaturated fatty acids. This food landscape has been linked as a risk factor for the development of cardiovascular disease (CVD), which, as indicated by the World Health Organization, is the leading cause of death in the world.

In the preliminary results of the National Nutritional Situation Survey (ENSIN) 2015, it was reported that overweight in the adult population has increased by 5.2% from 2010 to 2015, which is a risk factor for the manifestation of CVD (WHO/OPS Group of Experts, 2011). This confirms the need to impact on the healthy lifestyles of the population by promoting a balanced, adequate and safe diet, as the diet is one of the modifiable risk factors for preventing the development of CVD.

In Colombia, according to the 2005 and 2010 ENSIN surveys, the majority of the population consumes oil-fried foods, has a low consumption of fruits, vegetables, fish and high consumption of processed and ultra-processed products. This diet profile is characteristic of western culture, with low intake of food sources of essential fatty acids (EFA), fat-soluble vitamins, fiber and phytonutrients. A good alternative to increasing the consumption of EFA, and preventing the development of CVD with food, is to add or enrich mass consumir products such as dairy derivatives, as these foods are considered by the majority

According to data in the ENSIN of 2015, dairy products are frequently consumed by Colombians, where the estimated milk intake for the population is 94.2% in a regular month and 94.2% for dairy derivatives such as cheese, yogurt and kumis (Ministerio de salud, 2015). Comparing these data with the one from the ENSIN of 2010, we can observe an increase in the consumption of milk and dairy derivatives since it went from 85.5% to 93.4% respectively (Minesterio de Protección Social, 2010). Similarly, the Fondo

Nacional del Ganado FNG (Fedegan) reported that between 2010 and 2014, milk consumption increased by 3.6 litres, from 139.4 litres per person to 143 litres a year; and of the 1.715 million litres of milk produced, about 26% of the total production, are devoted to the production of regional cheeses. Additionally, fermented beverages such as yogurt, move around $470 million and is expected to bill $602 million by 2023. Its main leaders are Alpina, Yogo Yogo and Bonyurt, with shared of 18.1%, 17.8% and 14.4% respectively. These are followed by Regeneris and Algarra (Euromonitor, 2019).

Food sources of omega 3 are mainly vegetable oils and marine foods such as fish, fish oils, and algae. While the sources of vitamin E in the form of tocotrienol are mainly palm oil and achiote. Usually in the western culture, these foods are not regularly consumed, which causes the industry to look for alternatives to transport these compounds into mass consumption foods, such as milk and dairy products.

Milk and dairy products have an adequate nutritional profile, thanks to their content of protein, calcium, riboflavin, among other nutrients (Alvídrez-Morales, A, González-Martínez, B.E., Jiménez-Salas, 2002; Santillan Urquiza, Mendez Rojas, & Vélez Ruiz, 2014). Strategies such as reducing sodium chloride (NaCl) in cheeses and decreasing the fat content in milk and derivatives have been implemented to combat some diseases such as hypertension and dyslipidemia (Millone, Olagnero, & Santana, 2011).

Dairy products can be vehicles of bioactive compounds, adding, replacing and/or reducing the most variable component, the lipid fraction. Therefore, some vegetable sources with adequate EFA profiles and vitamin content with antioxidant effect such as vitamin E, are of interest in the development of functional foods (FF), as they can be used as ingredients to improve the fat profile of milk-derived foods.

In Colombia, Sacha Inchi and Palma crops are an alternative to the replacement of illegal crops, as the processing of their fruits represents an economic opportunity for the sustainable development of vulnerable communities, in the context of the post-conflict- Sacha Inchi (Plukenetia volubilis L.) is a plant with great economic potential thanks to the transformation of its fruit (seeds) into products of high added value, mainly the oil containing 50% ALA (18:3ω-3), 36.8% AL (18:2ω-6) for an omega 3: omega 6 ratio of 0.76 and a total tocols content of 211.8 mg/100g (Wang, Zhu, & Kakuda, 2018). The ω-3:ω-6 ratio is desirable to reduce the risk of developing several chronic diseases of high prevalence, such as cardiovascular diseases, cancer, and inflammatory and immune diseases (Vanegas-Azuero & Gutiérrez, 2018), and that is why this oil is of great interest to the human health. For its part, *Elaeis guineensis x Elaeis oleífera-OxG* [HPO] crossing palm oil hybrid is attractive for its high content of carotene (1036.9mg/100g), tocotrienols (26.4mg/100g) and monounsaturated fatty acids (MUFA) (55.8%) (Mozzon, Pacetti, Giuseppe, & Paolo, 2015; Mozzon, Pacetti, Lucci, Balzano, & Frega, 2013). However, these cultivars are not very well known to consumers, and therefore their nutritional benefits are not massively exploited.

Since actual consumers are now more worried about their diet, and expect to have more than just satisfaction, which means, some health benefit, is why FF are still a trend (Bimbo et al., 2017; Ganesan, Brothersen, & McMahon, 2014; Markey et al., 2017). FF are a healthy alternative for consumers as they provide beneficial health effects. Dairy matrices have been the most versatile, being classified as products with an adequate nutritional profile. Therefore, they can be reformulated to enhance their functional potential. For example, they can serve as a vehicle for dietary sources of tocotrienol (vitamin E) and alpha-linolenic acid (ALA). To date, the inclusion of Colombian Sacha Inchi oil (SIO) in yogurt has not been

investigated, nor has it been examined whether, when used as a vehicle due to its high ALA content, it exerts a beneficial effect on the cardiovascular health of consumers. On the other hand, the inclusion of Colombian hybrid palm oil has not been studied. However, it has been reported that consumption of up to 20 ml, due to its high content of gamma-tocotrienol, is a potent inhibitor of endogenous cholesterol production (Ojeda et al., 2017, 2016). To date, there are no studies investigating the effect of consuming yogurts supplemented with these Colombian oils on the cardiovascular health of consumers.

In this context of promoting healthy eating and based on the characterization of the western diet, which does not meet the daily requirements for essential fatty acids (EFAs) and fat soluble vitamins such as vitamin E, the present research project aims to describe the effect of daily consumption of two fermented dairy beverages supplemented with dietary sources high in tocotrienols and ALA on classical biological markers of cardiovascular disease (CVD) and vitamin E, over a period of three months, in individuals with cardiovascular risk. The products are currently being developed as part of a doctoral thesis in the Food Science and Technology program at the Universidad Nacional de Colombia, Bogotá campus, Faculty of Agricultural Sciences. If satisfactory results are obtained, new dairy products could be developed for the Colombian market, promoting the cultivation of Sacha INchi and Palm by diversifying the use of their fruits as sources of bioactive compounds. The present research proposal aims to answer the following question: what is the effect of consuming yogurts fortified with dietary sources of omega-3 and vitamin E on cardiovascular disease biomarkers and vitamin E in healthy adults?

OBJECTIVES

General: Evaluate the effect of consumption of two fermented dairy beverages fortified with SIO and HPO, on the lipid profile and vitamin E, in individuals at risk of CVD.

Specifics:

1. Describe the health, nutritional status and intake of the individuals before and after the intervention.
2. Establish the changes over time in the lipid profile, Apo A, Apo B and vitamin E in the blood after the intervention.

MATERIALS AND METHODS

The study will be presented to the research and ethics committee of the Faculty of Sciences of the Pontificia Universidad Javeriana. The effect of consumption of fermented dairy beverages fortified with SIO and HPO will be evaluated on the response variables: plasma lipid profile (HDL-C, LDL-C, Triglycerides, TC), Apolipoprotein A, Apolipoprotein B and vitamin E level in blood.

Type of study

An experimental study will be carried out consisting of a controlled clinical trial with three arms, each of which will be determined by the administration of two oils and a control. The oils will be transported into a fermented milk drink. Participants will be selected using a criterion of convenience through a call at the

Pontificia Universidad Javeriana. As a result, it is expected to select 66 individuals, 50% men and 50% women, who meet the inclusion criteria. Individuals will be stratified by sex and will be randomized in equal numbers to each of the three treatment groups, such that each treatment group will have 33 people in which the sexes will be equally distributed.

The sample size was determined taking into account the literature in which the same biomarkers have been evaluated (Brenna, Plourde, Stark, Jones, & Lin, 2018; Gonzales & Gonzales, 2014; Nayebifar, Ghasemi, & Karimipour, 2020; Qureshi, Sami, Salser, & Khan, 2001, 2002). It is important to highlight that to date there are no studies that contemplate the two oils carried in a fermented drink; even though there are studies with hybrid palm oil, alone and in other foods, there are none with Sacha Inchi oil, for the postulated response variables. Upon encountering this panorama, this study will provide a parameter to determine the sample size in subsequent studies. Finally, the postulate of the Food and Drug Administration (FDA) was taken into account, which states that the total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80 subjects (FDA, 2019), so it is considered that it can also be applied as a criterion for foods since the guidelines for drug testing are rigorous.

Following these criteria, it was determined to take 54 subjects in total with an oversample of 20% (66 individuals in total) to compensate for possible dropouts during the follow-up stage. Compliance with the proposed number of participants and the collection of their blood samples will be subject to the evolution of the Covid-19 pandemic and government preventive isolation guidelines.

Target population

Inclusion criteria: adult men <50 years old and women <40 years old, healthy, with TC levels ≥200mg/dl, with regular consumption of fermented milk beverages at least three times/week, with a maximum level of moderate physical activity and who sign the informed consent.

Exclusion criteria: TG >700mg/dl, hyperlipidemia undergoing pharmacological treatment, drug or alcohol addiction, smokers, history of allergy to red palm olein and/or milk and its derivatives, consumption of nutritional supplements, being pregnant or breastfeeding, having menopause, presence of chronic disease (HTN, Diabetes Mellitus, among others) and a BMI >29.9

The sample will be selected using a convenience criterion through a call at the Pontificia Universidad Javeriana. Individuals will be stratified by sex and randomized using the method called “unrestricted randomization” to the three groups. The size was determined considering the literature in which the same biomarkers have been evaluated (Brenna, Plourde, Stark, Jones, & Lin, 2018; Gonzales & Gonzales, 2014; Nayebifar, Ghasemi, & Karimipour, 2020; Qureshi, Sami, Salser, & Khan, 2001, 2002). The FDA postulate was considered, which states that the total number of subjects included in Phase 1 studies varies with the drug but is generally in the range of 20 to 80 subjects (FDA, 2019). Following these criteria, it was determined to take 54 subjects in total with an oversample of 20% (66 individuals in total), each group with 21 subjects to compensate for possible dropouts and guarantee 18 per group. Each participant must sign an informed consent.

Development

The differential nutritional characteristics of the fermented milk drinks to be used in the study are presented below. It is important to clarify that all drinks will comply with current regulations for fermented drinks. (Ministerio de salud, 1986).

Table 1. Lipids and vitamin E in 200g of yoguts.

Characteristics (200g/yogurt)	Control yogurt	SIO yogurt	HPO yogurt
Total, lipids (%)	3	3	3
SFA (%)	2	7	35
MUFA (%)	0.8	10	56
PUFA (%)	0.1	85	12
Vitamin E (mg/100g)	0.06	6.09	2.88

SFA: saturated fatty acids, MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids,

The analyzes of TC, c-HDL, LDL and triglycerides will be determined by the enzymatic colorimetric method; Apo A and Apo B by immunoturbidimetry and vitamin E by HPLC, in the clinical laboratory of the San Ignacio University Hospital. Each phase of the study includes supervision and support actions for participants to promote and generate adherence (Ministerio de Salud y Protección Social & Colciencias, 2014)). The intervention phase follows the recommendations of the European Food Safety Authority for claims related to cardiovascular health (Turck et al., 2018). Diagram 1 shows the study design, which consists of three phases.

Phase I

1. Screening in the anthropometry laboratory of the Faculty of Sciences of the PUJ, which consists of the following activities:
    a. Characterization of individuals to know their sociodemographic data (age, sex, educational level, economic status).
    b. Application of a morbidity survey, to know their diseases, clinical history, biochemical parameters, cardiovascular risk (using the Framingham risk scale)
    c. Evaluation of body composition by dual X-ray absorptiometry - DEXA (lean mass, fat mass, bone mass, mineral density), estimation of BMI and measurement of abdominal circumference.
    d. Exploration of eating habits (consumption frequency questionnaire and 24-hour recall).
2. Training
    a. Record consumer diaries three days a week (two weekdays and one weekend day) and will be informed that they will receive a weekly, unannounced phone call for a 24-hour reminder and survey. about the level of physical activity.
    b. Preparation for taking blood samples in accordance with the protocol of the San Ignacio University Hospital.

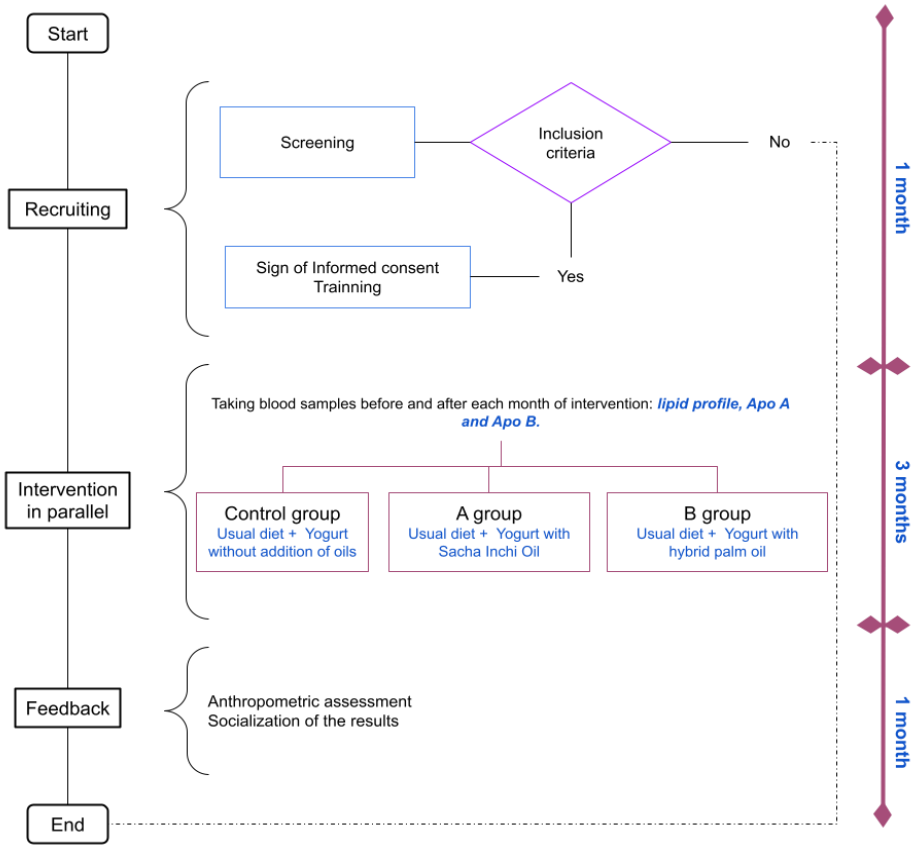

Figure 1. Study design.

Phase II

The subjects will continue with their usual diet with a modification in their pattern of consumption of milk and dairy products, since fermented milk drinks will be supplied at a rate of 250g/day for one month. These will be prepared following good food handling practices (Ministerio de Salud y Protección Social, 2013), in the pilot research plant in milk and dairy products processes, of the National University of Colombia, Bogotá headquarters. All raw materials are safe for human consumption (GRAS). Through unrestricted random sampling, subjects will be assigned into three branches:

1. Control: corresponds to the subjects who will be given a fermented milk drink
2. Treatment 1 corresponds to the subjects who will be supplied with the fermented milk drink with total replacement of milk fat matter with SIO.
3. Treatment 2 corresponds to the subjects who will be supplied with the fermented milk drink with total replacement of milk fat matter with HPO.

Phase III

In this phase, the results will be shared with the study participants and a final assessment.

Statistical analysis

A socio-economic-demographic characterization of the population will be carried out, by means and standard deviation and ranges. A database will be created in Excel and the intake will be analyzed using the Menus Plus 2018 software. To analyze data from blood samples, a repeated measures analysis of variance will be applied. Kolmogorov and Cramér-von Mises tests will be used to evaluate the Gaussian nature of the variables. Tukey-adjusted p values will be applied to examine differences between treatments. STATGRAPHICS CenturionXVIII software will be used.

POSSIBLE RESEARCH RESULTS

With this research, the characterization of the nutritional status, health status and quality of the diet of the target population will be obtained. Furthermore, after the intervention with fortified yogurts, it is expected to observe an improvement in the blood lipid profile parameters, Apo A, Apo B and vitamin E, of the participants compared to the initial values, which would minimize the risk of associated CVD associated to lipoproteins.

Expected products

Category	Product	Amount	Description
Other outreach products	Documentary Production	1	Submission of at least 1 scientific article in an indexed journal.
Presentation at scientific event	Presentation of paper or poster at international event	1	Participation in a conference related to the topic of clinical nutrition or food science and technology.
Project formulation and submission	Formulation and submission of other projects	1	Another project related to the characterization of the mechanism of the bioactive compound.

PARTICIPATING INSTITUTIONS

Participating entity/institution name	Temporal	Main financier	Other financier	Executor	Co-Executor	Assesment entity
UNIVERSIDAD NACIONAL DE COLOMBIA - BOGOTÁ	No	No	Yes	No	Yes	No
PONTIFICIA UNIVERSIDAD JAVERIANA (PUJ)	No	Yes	No	Yes	No	No

Pontificia Universidad JAVERIANA Colombia	**Research registration PUJ**	**Version:** 1
	Investigation project	

TEAM OF PONTIFICIA UNIVERSIDAD JAVERIANA

Responsible PUJ	Type of afiliation	Name	Rol	Dedication (weekly)	Departament	Faculty	Start date	Finish date
Yes	Professor	Lilia Yadira Cortes Sanabria	Main researcher	4	Nutrition and Biochemistry Department	Science	01-03-2022	30-08-2023
No	Professor	Ruby Alejandra Villamil Parra	Researcher	2	Nutrition and Biochemistry Department	Science	01-03-2022	30-08-2023
No	Professor	Diana Cristina Patino Cuervo	Researcher	4	Microbiology Departmen	Science	01-03-2022	30-08-2023

OTHER TEAM MEMBERS

Type of vinculation	Name	Entity to which it is afiliated
Extern	Luis Felipe Gutiérrez Álvarez	UNIVERSIDAD NACIONAL DE COLOMBIA -BOGOTÁ

RESEARCHER'S INFORMATION

Investigator's name: Lilia Yadira Cortes Sanabria	
Academic title: Doctor in Biological Sciences	
Highest academic degree: DOCTORATE	
Institution that awarded the highest academic title: PONTIFICIA UNIVERSIDAD JAVERIANA	**Year obtained:** 2012
Outstanding intellectual production (maximum 3):	Kovalskys, I., et al., (2018). Energy intake and food sources of eight Latin American countries: results from the Latin American Study of Nutrition and Health (ELANS). *Public health nutrition*, *21*(14), 2535–2547. https://doi.org/10.1017/S1368980018001222 Kovalskys, I., et al., (2015). Standardization of the Food Composition Database Used in the Latin American Nutrition and Health Study (ELANS). *Nutrients*, *7*(9), 7914–7924. https://doi.org/10.3390/nu7095373 Ferrari, G. L. M., (2020). Methodological design for the assessment of physical activity and sedentary time in eight Latin American countries - The ELANS study. *MethodsX*, *7*, 100843. https://doi.org/10.1016/j.mex.2020.100843
Group name: Food, nutrition and health, **Group category:** CATEGORY A1, **Researcher Category: [**associated**]**	
Investigator's name Ruby Alejandra Villamil Parra	
Academic title: MASTER IN FOOD SCIENCE AND TECHNOLOGY	
Highest academic title: MASTER	

Institution that awarded the highest academic title: UNIVERSIDAD NACIONAL DE COLOMBIA	**Year obtained:** 2017
Outstanding intellectual production (maximum 3):	Villamil, R. A., et al., (2021). Cheese fortification through the incorporation of UFA-rich sources: A review of recent (2010-2020) evidence. Heliyon, 7(1), e05785. https://doi.org/10.1016/j.heliyon.2020.e05785 Villamil, R. A., Robelto, G. E., Mendoza, M. C., Guzmán, M. P., Cortés, L. Y., Méndez, C. A., & Giha, V. (2020b). Desarrollo de productos lácteos funcionales y sus implicaciones en la salud: Una revisión de literatura. Revista Chilena De NutriciÓN, 47(6), 1018–1028. https://doi.org/10.4067/s0717-75182020000601018
Group name: Food, nutrition and health, **Group category:** CATEGORY A1, **Researcher Category: [**Unclassified**]**	
Investigator's name: Diana Cristina Patino Cuervo	
Academic title: MAGISTER IN MICROBIOLOGY	
Highest academic title: MASTER	
Institution that awarded the highest academic title: PONTIFICIA UNIVERSIDAD JAVERIANA	**Year obtained:** 1999
Other intellectual production	Domínguez-Amorocho O & Patiño-Cuervo D. Proteína C reactiva ultrasensible (PCR-us) como marcador de riesgo de enfermedad cardiovascular. Medicina & Laboratorio. 2008;14(09-10):457-478. Fernández-Mora, T., & Patiño-Cuervo, D. (2007). La inflamación como factor causal emergentede la enfermedad cardiovascular. Universitas Scientiarum, 12(1), 15–34.
Group name: Clinical Laboratory Sciences-GCLC, **Group category:** CATEGORY C, **Researcher category:** member linked to a Master's degree	
Investigator's name: Luis Felipe Gutiérrez Álvarez	
Academic title: Doctor in Food Science and Technology	
Highest academic degree: Doctorate	
Institution that awarded the highest academic title: UNIVERSITE LAVAL	**Year obtained:** 2013
Other intellectual production	Torres Sánchez, E.G., Hernández-Ledesma, B., Gutiérrez, L.-F. (2021). Sacha Inchi Oil Press-cake: Physicochemical Characteristics, Food-related Applications and Biological Activity. Food Reviews International. DOI: 10.1080/87559129.2021.1900231 Sánchez-Camargo, A.P., Ballesteros-Vivas, D., Buelvas-Puello, L.M., Martinez-Correa, H.A., Parada-Alfonso, F., Cifuentes, A., Ferreira, S.R.S., Gutiérrez, L.-F. (2020). Microwave-assisted extraction of phenolic compounds with antioxidant and anti-proliferative activities from supercritical CO2 pre-extracted mango peel as valorization strategy. LWT, 137, 110414, https://doi.org/10.1016/j.lwt.2020.110414. Sanchez-Reinoso, Z., Mora-Adames, W.-I., Fuenmayor-Bobadilla, C.-A., Darghan-Contreras, A.-E., Gardana, C., Gutiérrez, L.-F. (2020). Microwave-assisted extraction of phenolic compounds from Sacha Inchi shell: Optimization, physicochemical properties and evaluation of their antioxidant activity. Chemical Engineering and Processing - Process Intensification, 153, 107922. https://doi.org/10.1016/j.cep.2020.107922

	Sánchez-Camargo, A.P., Gutiérrez, L.-F., Vargas, S.M., Martínez-Correa, H.A., Parada-Alfonso, F., Narváez-Cuenca, C.E. (2019) Valorisation of mango peel: Proximate composition, supercritical fluid extraction of carotenoids, and application as an antioxidant additive for an edible oil. The Journal of Supercritical Fluids, https://doi.org/10.1016/j.supflu.2019.104574
Research groups and their category: Food Biomolecules, category C, **Researcher Category:** [Senior]	

GROUPS AND LINES OF RESEARCH ASSOCIATED WITH THE ACTIVITY

Group of research	Lines of investigation
Food, nutrition and health	Food science and technology ; Human Nutrition
Clinical laboratory sciences-GCLC	Clinical Utility of Laboratory Tests

BUDGET

Items	Financier	Species counterpart	Cash counterpart	Total
Technical services	0	0	53.000.000	53.000.000
Materials and supplies	0	5.040.000	0	5.040.000
Personal PUJ	0	51.037.003,48	0	51.037.003,48
Use of equipment PUJ	0	8.064.059,32	0	8.064.059,32
Use of external equipment	0	20.000.000	0	20.000.000
External personal	0	14.848.464	0	14.848.464

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