Part A. PERSONAL INFORMATION

CV date	19/01/2023

First name	Juan Carlos		
Family name	Espín de Gea		
Gender (*)	Male	Birth date	26/11/1968
ID number	34785457G		
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ORCID (*): 0000-0002-1068-8692			

(*) Mandatory

A.1. Current position

Position	Research Professor		
Initial date	27/3/2010		
Institution	Agencia Estatal Consejo Superior de Investigaciones Científicas (CSIC)		
Department/Center	Lab. Food & Health (Group on Quality, Safety, and Bioactivity of Plant Foods); Dept. Food Sci. & Technol. (CEBAS-CSIC)		
Country	Spain	Telephone:	+34-968396200, Ext: 445344
Keywords	Polyphenols and health; clinical trials; cardiometabolic; gut microbiota; cancer; bioavailability; animal models; inter-individual variability; metabotypes; personalized nutrition		

A.2. Previous positions (research activity interruptions, art. 14.2.b)

Period (last 20 years)	Position/Institution/Country/Interruption cause
16/11/2001-30/5/2002	Postdoctoral Ramón & Cajal Program (CEBAS-CSIC)/Spain
31/5/2002-12/6/2006	Tenured Scientist (CEBAS-CSIC)/Spain
13/6/2006-26/3/2010	Senior Research Scientist (CEBAS-CSIC)/Spain

A.3. Education

Ph.D., Licensed, Graduate	University/Country	Year
Biological Sciences Ph.D. (*Extraordinary Award*)	Murcia	1997
Biological Sciences Ms.C. (*Sobresaliente*)	Murcia	1997
Biological Sciences Bs.C. (*Sobresaliente*)	Murcia	1991

Part B. CV SUMMARY *(max. 5000 characters, including spaces)* (count: 4,979)

I am a Research Professor at CSIC (promoted at age 40). I have been an uninterruptedly Principal Investigator of national and international public and private projects on dietary (poly)phenols and health, covering scientific production and transfer of knowledge (dissemination, patents, and contracts). ***As PI, I have obtained 1,222,600€ in research projects + 252,000€ in private contracts in the last 10 years.***

Indicators of scientific production and impact (Scopus and WOS metrics). SCOPUS Author ID: 7003487173; WoS Researcher ID: G-6231-2011: (on January/19th/2023):
H-index=84; >21,700 cites (>16,500 last 10 years); 221 JCR articles (125, last 10 years; 97% Q1). *Highly-cited researcher* (Clarivate) from 2018 to 2022 (consecutively). I have 165 papers with above-average impact ("FWCI", weighted by field, SCOPUS), 1 "*hot paper*", and 23 *highly cited papers* (top 1% of the corresponding area): 17 in Agricultural Sciences, 3 in Clinical Medicine, and 3 in Pharmacology & Toxicology (WOS). ***I have been the first and(or) corresponding and(or) last author in 94% of my publications***, which have been cited in the 93rd percentile.

Research lines: (Poly)phenols and health, integrating clinical trials, animal and cell models, and multi-omics approaches. My research focuses on i) the in vivo traceability of (poly)phenols to understand the drivers of (poly)phenol effects and ii) the high interindividual variability in the metabolism and activity observed after (poly)phenols consumption, emphasizing the gut microbiota. My approach suggests considering the human health effects individually within the context of "personalized nutrition".

1. Traceability of dietary (poly)phenols. This line refers to how (poly)phenols and derived metabolites are absorbed, metabolized, excreted, and biodistributed in tissues. My approach, "*first in vivo, then in vitro*," tries to counteract wrong conclusions from the vast number of in vitro studies on (poly)phenols far from physiological conditions. Our studies on the distribution of (poly)phenol-derived metabolites in the prostate, breast, and colorectal cancer patients' tumor tissues are relevant to identifying the molecular forms and concentrations that reach cancer tissues (to explore mechanisms in vitro by testing

those physiological conditions). We have also described for the first time the role of human exosomes in the biodistribution of (poly)phenol-derived metabolites and how these vesicles can target certain tissues (ongoing project: PID2019-103914RB-I00).

2. Inter-individual variability in the metabolism and effects of dietary (poly)phenols: towards personalized nutrition. The human inter-individual variability makes it challenging to identify (poly)phenol effects in the general population. The so-called metabotypes are metabolic phenotypes with specific gut microbiome-derived metabolites that characterize some polyphenols' metabolism. We identified three metabotypes according to the individuals' ability to produce the gut microbial-derived urolithins from the polyphenol ellagic acid, determining the so-called metabotype 0 (urolithin non-producers), metabotype-A (urolithin A producers), and metabotype-B (Uro-A, B, and IsoA producers). We pioneered the impact of metabotypes on health, and the specific bioactivity of some metabolites, including urolithins. In our previous project (AGL2015-64124-R), we identified the implication of genotype, aging, gender, physiological status, and gut microbiota in the variability of the effects exerted by polyphenols. We characterized the gut microbiota (composition and functionality) of these metabotypes, suggesting them as possible microbiota biomarkers for identifying gut dysbiosis and susceptibility to chronic-degenerative processes. We also described the key contribution of medication to interindividual variability (affecting the gut microbiota and, thus, (poly)phenol effects). We also isolated crucial gut bacteria involved in the human urolithin metabotypes. In the ongoing project PID2019-103914RB-I00, we have isolated a third bacterium and demonstrated the use of this consortium to customize the individuals' metabotypes and the beneficial effects using animal models (patent-pending). Recently, we have described the most detailed metabolism of resveratrol by the human gut microbiota, identifying a new microbial metabolite (4-hydroxydibenzyl) and two novel gut microbiota metabotypes associated with resveratrol metabolism (lunularin producers and non-producers). This finding could help with the controversy over resveratrol's health effects. In a large cohort, we also observed the associations between the known human metabotypes (equol, urolithins, and lunularin). Identifying human metabotypes and their causative association with health effects is an attractive initiative with excellent international projection. This research was partially included in 12 Thesis+1 ongoing, with an average of 8 publications derived directly from each Thesis.

Part C. RELEVANT MERITS

C.1. Publications *(*corresponding author)*. Ten relevant papers:

1 Iglesias-Aguirre CE; Vallejo F; Beltrán D; Berná J; Puigcerver J; Alajarín M; **Espín JC*** (2022). Lunularin Producers vs. Non-Producers: Novel Human Metabotypes Associated with the Metabolism of Resveratrol by the Gut Microbiota. *J. Agric. Food Chem.* 70:10521. Q1. Open access (OA). 8 cites.

2 García-Villalba R; Giménez-Bastida JA; Cortés-Martín A; (3 authors); **Espín JC***; González-Sarrías A (2022). Urolithins: a comprehensive update on their metabolism, bioactivity, and associated gut microbiota. *Mol. Nutr. Food Res.* e2101019. (Q1, Highly-cited in Agricultural Sciences; Hot paper-top 0.1% of papers-Agricultural Sciences). OA. 55 cites.

3 Iglesias-Aguirre CE; Cortés-Martín A; Ávila-Gálvez MA; (3 authors); **Espín JC*** (2021). Main drivers of (poly)phenols effects on human health: metabolites production or gut microbiota-associated metabotypes? *Food Funct.* 12:10324. (Q1, FWCI). OA. 43 cites.

4 Cortés-Martín A; Selma MV; Tomás-Barberán FA; González-Sarrías A; **Espín JC*** (2020). Where to Look into the Puzzle of Polyphenols and Health? The Postbiotics and Gut Microbiota Associated with Human Metabotypes. *Mol Nutr Food Res*, 64:e1900952. (Q1, Highly-cited in Agricultural Sciences). 135 cites.

5 Ávila-Gálvez MÁ, García-Villalba R; Martínez-Díaz F; (4 authors); **Espín JC*** (2019). Metabolic Profiling of Dietary Polyphenols and Methylxanthines in Normal and Malignant Mammary Tissues from Breast Cancer Patients. *Mol Nutr Food Res*, 63:e1801239. (Q1, FWCI). 62 cites.

6 Cortés-Martín A; García-Villalba R; González-Sarrías A; (4 authors) Selma MV; **Espín JC*** (2018). The gut microbiota urolithin metabotypes revisited: the human metabolism of ellagic acid is mainly determined by aging. *Food Funct*, 9:4100. (Q1, FWCI). 96 cites.

7 González-Sarrías A; Romo-Vaquero M; García-Villalba R; Cortés-Martín A; Selma MV; **Espín JC*** (2018). The endotoxemia marker lipopolysaccharide-binding protein is reduced in overweight-obese subjects consuming pomegranate extract by reshaping the gut microbiota: a randomized clinical trial. *Mol Nutr Food Res*, e1800160. (Q1, FWCI). 85 cites.

8 González-Sarrías A; García-Villalba R; Romo-Vaquero M; (5 authors); **Espín JC*** (2017). Clustering according to urolithin metabotype explains the interindividual variability in the improvement of cardiovascular risk biomarkers in overweight-obese individuals consuming

pomegranate: A randomised clinical trial. *Mol Nutr Food Res*, 61:1600830. (Q1, Highly-cited paper in Agricultural Sciences, WOS). 143 cites.

9 Nuñez-Sánchez MA; García-Villalba R; Monedero T; (11 authors); **Espín JC*** (2014). Targeted metabolic profiling of pomegranate polyphenols and urolithins in plasma, urine, and colon tissues from colorectal cancer patients. *Mol Nutr Food Res*, 58:11991. (Q1, Highly-cited paper in Agricultural Sciences, WOS). 175 cites.

10 Larrosa M; González-Sarrías A; Yañéz-Gascón MJ; (5 authors); **Espín JC*** (2010). Anti-inflammatory properties of a pomegranate extract and its metabolite urolithin-A in a colitis rat model and the effect of colon inflammation on the phenolic metabolism. *J Nutr Biochem*, 21:717. (Q1, Highly-cited paper in Agricultural Sciences, WOS). 371 cites.

C.2. Congresses: 85 international (24 invited conferences, 44 oral, 41 posters), and 11 national oral communications, and 11 Master conferences. Relevant congresses:

1. **Espín JC.** *Polyphenols: Where are we now, and what's next?* XV World Congress on Polyphenol Applications. September/2022, Valencia. (Keynote Introduction). (Best Scientific Award).
2. **Espín JC**, (4 authors); Boya, P. *The autophagy activator urolithin A and its journey to the brain: insights from a mouse model of physiological aging.* 2nd International Meeting Neuroaging. Alcalá de Henares, May/2022. (Invited conference).
3. Ávila-Gálvez MA; (7 authors); **Espín JC.** *Metabolic profiling of dietary polyphenols and methylxanthines in normal and malignant mammary tissues from breast cancer patients.* (Invited conference). Natural Products in Cancer Prevention and Therapy (Phytochemical Society of Europe). Naples, September/2018.
4. **Espín JC** (8 authors). *Human gut microbiota metabolism of ellagic acid. Interindividual variability for urolithin production is correlated with health status: Cause or consequence?* 7th Int. Conference on Polyphenols and Health. Tours, France, October/2015. (Invited conference).
5. **Espín JC.** *Biological significance of the gut microbial ellagic acid-derived metabolites urolithins*. American Institute for Cancer Research (AICR). October/2010 (Washington DC). (Closing Plenary Session).

C.3. Research projects (49 competitive projects: 36 national; 13 international, 14 as PI). Relevant projects:

1 1R01CA252045-01A1. *Microbiota, metabolites, and colon neoplasia.* National Cancer Institute (NIH, USA). (01/05/2021-30/4/2026). ($3,552,110). **Consortium Principal Investigators (PIs):** Rosenberg DW (Univ. Connecticut, USA); Weinstock G (Jackson Labs, USA) and **Espín JC** (CEBAS-CSIC, Spain).

2 TED2021-130962B-C22. *Milk extracellular vesicles for enhancing the bioavailability and bioactivity of dietary (poly)phenols.* Transición Ecológica y Transición Digital-2021, MCIN. 01/12/2022-30/11/2024. (126,500€). **PIs:** González-Sarrías, A and **Espín, JC.**

3 PID2019-103914RB-I00. *Frontier strategies through fecal transplants: Human polyphenol gut microbiota metabotypes, cardiometabolic risk, and cognitive impairment (MetaboGut).* 01/06/2020-31/05/2023. (193,600€). **PIs**: **Espín JC** and Selma MV.

4 Grant agreement 951994. *Enhancing research and innovation capacity of Tubitak MRC Food Institute on dietary polyphenols and bioavailability/bioefficacy.* European Commission. (145,000€). 01/12/2020-30/11/2023. **PI-CSIC**: González-Sarrías, A.

5 NAG2103009. *Diets and foods for smart aging.* Interdisciplinar Plataform PTI+ NEUROAGING. MCIN. 01/04/2021-31/12/2022. (100,000€). **PIs-CEBAS: Espín JC** and Tomás-Barberán F.

6 PIE-CSIC 201770E081. *Dietary polyphenols against breast cancer: molecular and metabolic studies.* Intramural Especial Project. (60,000€). 1/12/2017-30/11/2019. **PI: Espín JC.**

7 AGL2015-94124-R. *Dietary ellagitannins as a tool to study the inter-individual variability of polyphenols metabolism.* (325,000€). 1/1/2016-31/12/2019. **PIs: Espín JC** and Selma MV.

8 FP7-KBBE-2012-2.2-01. *Beneficial effects of dietary peptides and polyphenols on cardiovascular health in humans (BACCHUS).* EU Commission. VII PM. (October/2012-September/2016). (CEBAS, 405,000€). **Coordinator**: P. Kroon (IFR, UK).

9 AGL2011-22447. *The role of pomegranate ellagitannins and their metabolites, urolithins, in colorectal cancer: Metabolic and molecular studies in animal models and patients.* (320,000€). 1/1/2012-31/12/2015. **PI: Espín JC.**

10 BFU2007-60576/BFI. *Dietary resveratrol as cardioprotector: Bioavailability, metabolism, gene expression modulation and cardiovascular function in humans and pigs.* (313,995€). 1/10/2007-30/9/2010. **PI: Espín JC.**

C.4. Contracts, technological, or transfer merits: 50 private contracts (20 as PI; 17 international)

1 *Scientific-technical advice and development of new nutraceuticals.* Company: Kern Pharma S.L. (Barcelona) (60,500€). 1/1/2022-31/12/2023. **PI: Espín, JC.**
2 *Prebiotic effects of phenolic-rich chokeberry and cranberry extracts in healthy volunteers: a targeted and non-targeted metabolomic analysis of urine and fecal samples.* Company: DIANA SAS (Canada). (46,000€). 1/12/2021-30/6/2022. **PI: Espín, JC**, co-IP: Vallejo, F.
3 *Effect of soluble prebiotic fiber (Nutriose) in healthy volunteers: a non-targeted metabolomic analysis of urine samples.* (01/10/2020-30/04/2021). (34,850€). Company: Roquette FRÈRES (France). **PI: Espín, JC**; co-IP, Vallejo, F.
4 *Pharmacokinetics and metabolism of bioactive phenolics from orange, lemon, and milk thistle extracts.* 01/10/2019-30/06/2020. (78,650€). Company: EUROMED (Barcelona). **PI: Espín, JC.**
5 *Effect of different technological and biotechnological processes on the bioavailability and efficacy of phenolic bioactives of specific foods and dietary supplements.* 26/04/2018-25/06/2021. (107,161 €). Company: NESTEC LTD (Switzerland). PI. F. Tomás-Barberán.
6 *Prebiotic effect of controlled-release pomegranate extract formulations.* Company: Lab. Admira. S.L. (Murcia, Spain); 2/1/2012-1/1/2015. 30,000€. **PI: Espín JC.**
7 *Research contract to characterize the biological effects of Nutracitrus' extracts.* 12/10//2007-11/10/2009. (73.080€). Company: NUTRACITRUS S.L. (Elche, Spain). **PI: Espín JC.**

Patents: 5 patents (I have led the second patent with more royalties for the CSIC to date: 1,250,00€).

1 *Enzymatic synthesis of hydroxytyrosol.* WO0216628. (14/5/2003). Main inventor: **Espín JC**. (Others: Soler-Rivas C; Wichers HJ; Tomás-Barberán F; García-Viguera C; Ferreres F. Licensed to Laboratorios ROVI (Madrid).
2 *Postharvest treatment of fruits and vegetables using UV irradiation*. WO02085137 (31/10/2002). Main inventor: **Espín JC** (others: Tomás-Barberán F, Cantos E). Exploited by Actafarma Lab.
3 *Compounds with anti-inflammatory activity.* **Espín JC**, Morales JC; Medina I. EP2514426A4 (17/4/2013). Licensed to PBL (Plant Biosystem Limited, UK).
4 *Microorganisms capable of converting ellagic acid and ellagitannins into urolithins and their use thereof.* PCT/ES2014/070207. WO2014147280 A1 (25/9/2014). Inventors: Tomás-Barberán FA; Selma MV; Beltrán D; García-Villalba R; **Espín JC.**
5 *Microbial consortia capable of reproducing the human urolithin metabotypes and use thereof.* EP22382999.5 (18/10/2022). Inventors: Selma MV, Tomás-Barberán FA, Beltrán D, García-Villalba R, **Espín JC.**

Knowledge transfer (dissemination): (last 10 years)

6 Research Projects Tutor for high school students (IDIES Program https://www.idies-murcia.es/): (**1**) MJ Alegría-Marcos, I López-Ruiz, AM Dólera Pertusa (2015). *Importance of the molecular structure in the anticancer action of bioavailable metabolites from pomegranate, urolithins, in a cell model of colorectal cancer*. Tutors: González-Sarrías, A, **Espín JC**. (**2**) M Oltra, M Ros, ME Martínez (2016). *Neuroprotective activity of polyphenol-derived metabolites in a cell model of neurodegeneration mediated by oxidative stress*. Tutors: González-Sarrías A, **Espín JC**. **(3)** M Caro, A Linnik, JC Espín-Aguilar. (2018). *Pomegranate extract to combat metabolic endotoxemia in obesity and colorectal cancer*. Tutors: González-Sarrías A, **Espín JC**. **(4)** L Bayona, A Clarke. (2019). *Two-way modulation between lovastatin and gut microbiota and their interaction with dietary polyphenols.*Tutors: García-Villalba R, Beltrán D, **Espín JC. (5)** NJ Farfán-Valdiviezo, E López-Martínez, S Megía-Vidal. (2020). *Senescence-mediated anticancer activity of phenolic metabolites detected in tumor tissues from breast cancer patients.* Tutors: Giménez-Bastida JA, **Espín JC,** González-Sarrías A. **(6)** R López, M Muñoz. *Evaluation of the effect of dietary polyphenols against angiogenesis in endothelial cells.* (2021). Tutors: Giménez-Bastida, JA, **Espín, JC,** González-Sarrías, A.

15 Scientific dissemination presentations at high school centers and universities (IES Alcantara, Alcantarilla; IES Valdivieso, Mazarrón; IES Pedro Guillén, Archena; Faculty of Biology (UMU), student-parent associations (Alcantarilla, Murcia), etc.

More than **30 appearances** disseminating our research in Press, radio, and TV: "The anti-inflammatory activity of resveratrol analogs" (TV7); "Pomegranate benefits: Our gut microbes rule", "Association between the gut microbiota and obesity in children", "Highly cited researchers in Murcia" (TV7, La Verdad, etc.); Onda Cero (program "+*conocimiento*"): "Obesity and lifestyle"; "We and our gut microbes"; "Plant foods and breast cancer"; "probiotics and prebiotics"; etc.