IV CONGRESO IBEROAMERICANO DE INGENIERÍA DE LOS ALIMENTOS

# DIETARY PHENOLIC COMPOUNDS (PC): MIND THE GAP BETWEEN IN VITRO AND IN VIVO STUDIES.

## THE IMPACT OF GUT MICROBIOTA ON PC BIOAVAILABILITY

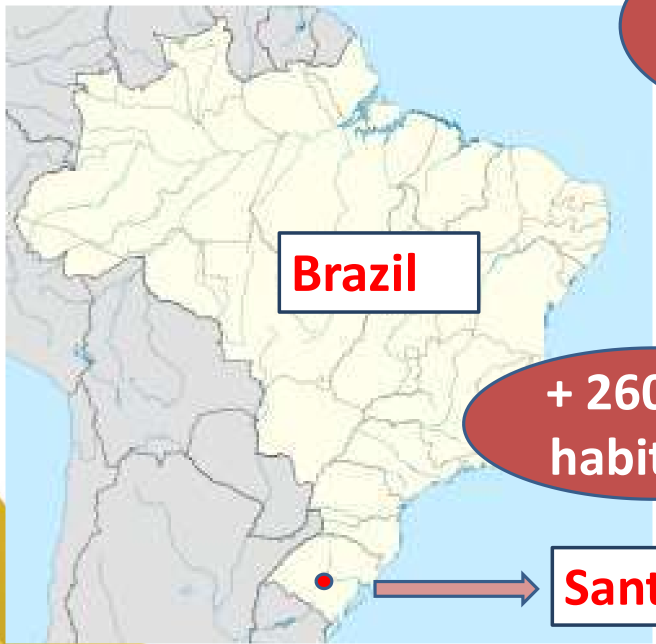
TATIANA EMANUELLI
UNIVERSIDADE FEDERAL DE SANTA MARIA
BRASIL

Organiza: AIALU

# UNIVERSIDADE FEDERAL DE SANTA MARIA

+ 26,000 Students





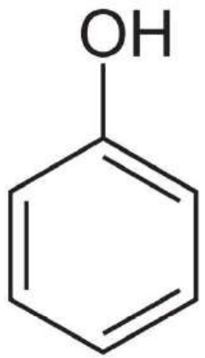

+ 260,000 habitants

Santa Maria

# DIETARY PHENOLIC COMPOUNDS

## PLANT SECONDARY METABOLYTES

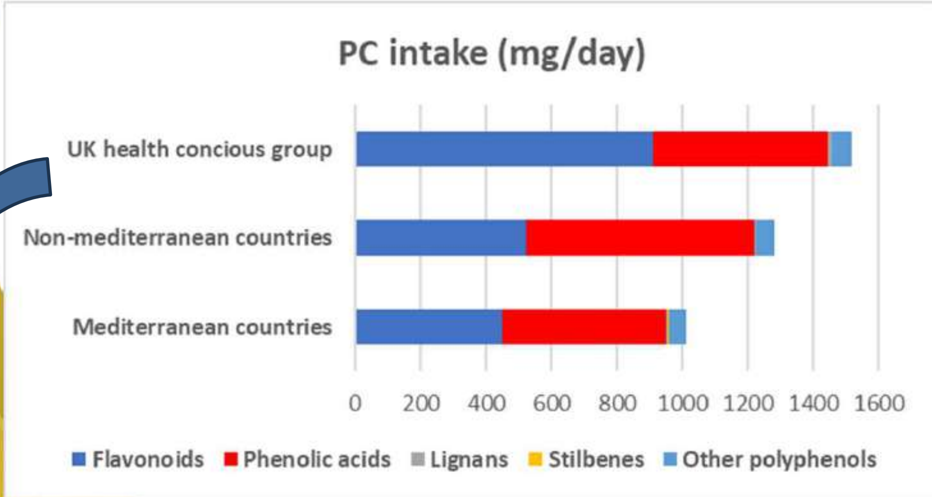
**Biological activities**



- Antioxidant
- Anti-inflammatory
- Immunomodulatory
- Anticancer
- Neuroprotective
- Cardioprotective

# DIETARY PHENOLIC COMPOUNDS VS. DISEASE RISK

EPIC STUDY: 36,037 PARTICIPANTS




1.0 a 1.5 g of polyphenols/day

*Eur J Nutr. 2016 June ; 55(4): 1359–1375. doi:10.1007/s00394-015-0950-x.*

*Systematic review with meta-analysis*

**Flavonoid intake and risk of CVD: a systematic review and meta-analysis of prospective cohort studies**

*British Journal of Nutrition* (2014), **111**, 1–11

Effect of cocoa flavanol supplementation for the prevention of cardiovascular disease events: the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) randomized clinical trial

*Am J Clin Nutr* 2022:115:1490–1500

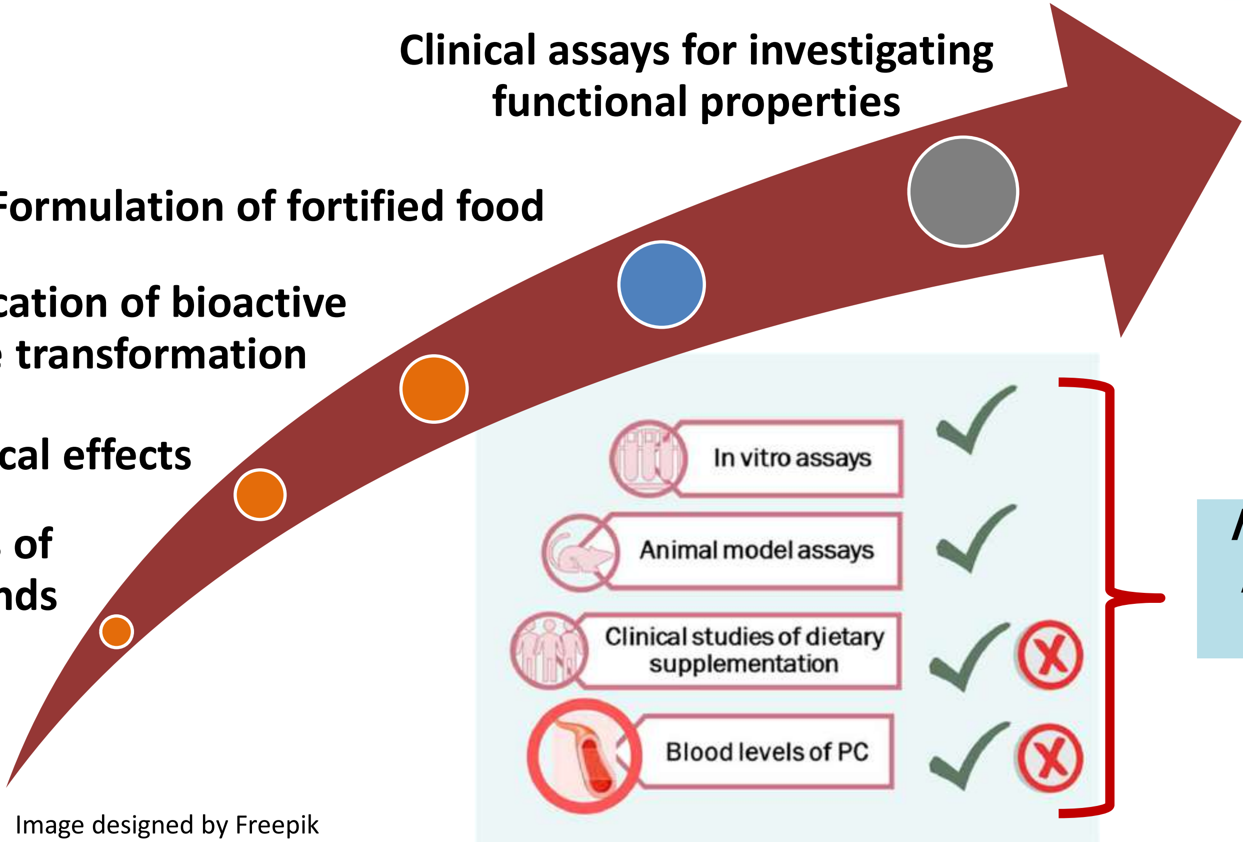
**Higher dietary anthocyanin and flavonol intakes are associated with anti-inflammatory effects in a population of US adults**[1]

Aedin Cassidy, Gail Rogers, Julia J Peterson, Johanna T Dwyer, Honghuang Lin, Paul F Jacques

*The American Journal of Clinical Nutrition*, Volume 102, Issue 1, July 2015,

## SUSTAINABLE DEVELOPMENT

# From agro-food wastes to functional foods





***No specific dietary recommendations approved for PCs***

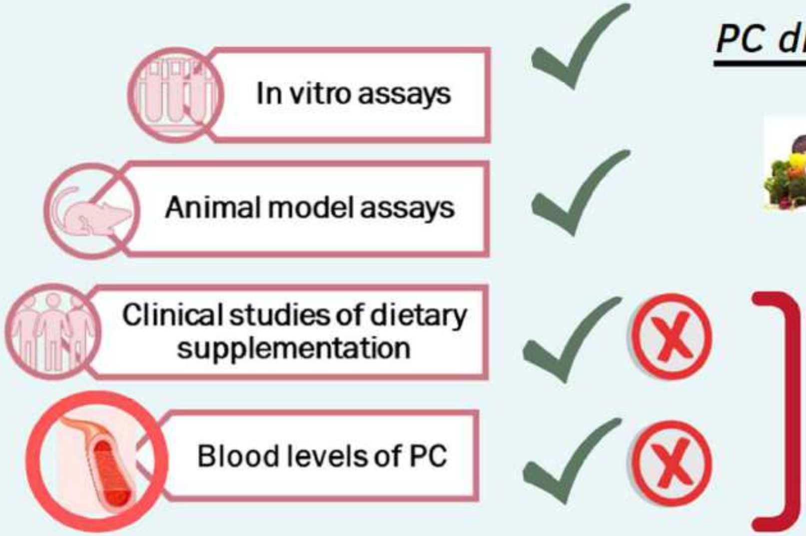
Image designed by Freepik

# OBJECTIVE

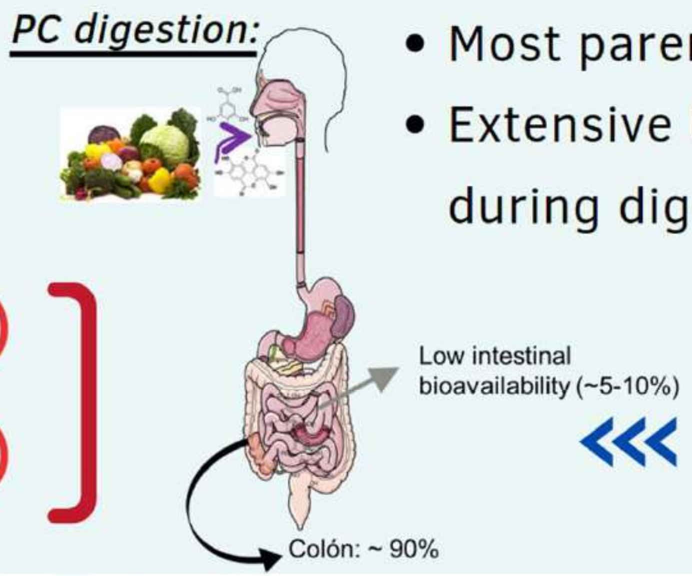
- ✓ Why there is a gap between the in vitro and in vivo/clinical studies on the biological properties of PC?
- ✓ What happens with PC during food digestion?
- ✓ Which is the role of gut microbiota on the biological effects of PC?
- ✓ Case studies: How can we overlap/reduce this gap between in vitro and in vivo studies?

# Why there is a gap between in vitro and in vivo studies/clinical trials for PC?

- Diversity of compounds
- Most parent PC scarcely absorbed
- Extensive biotransformation of PC during digestion:



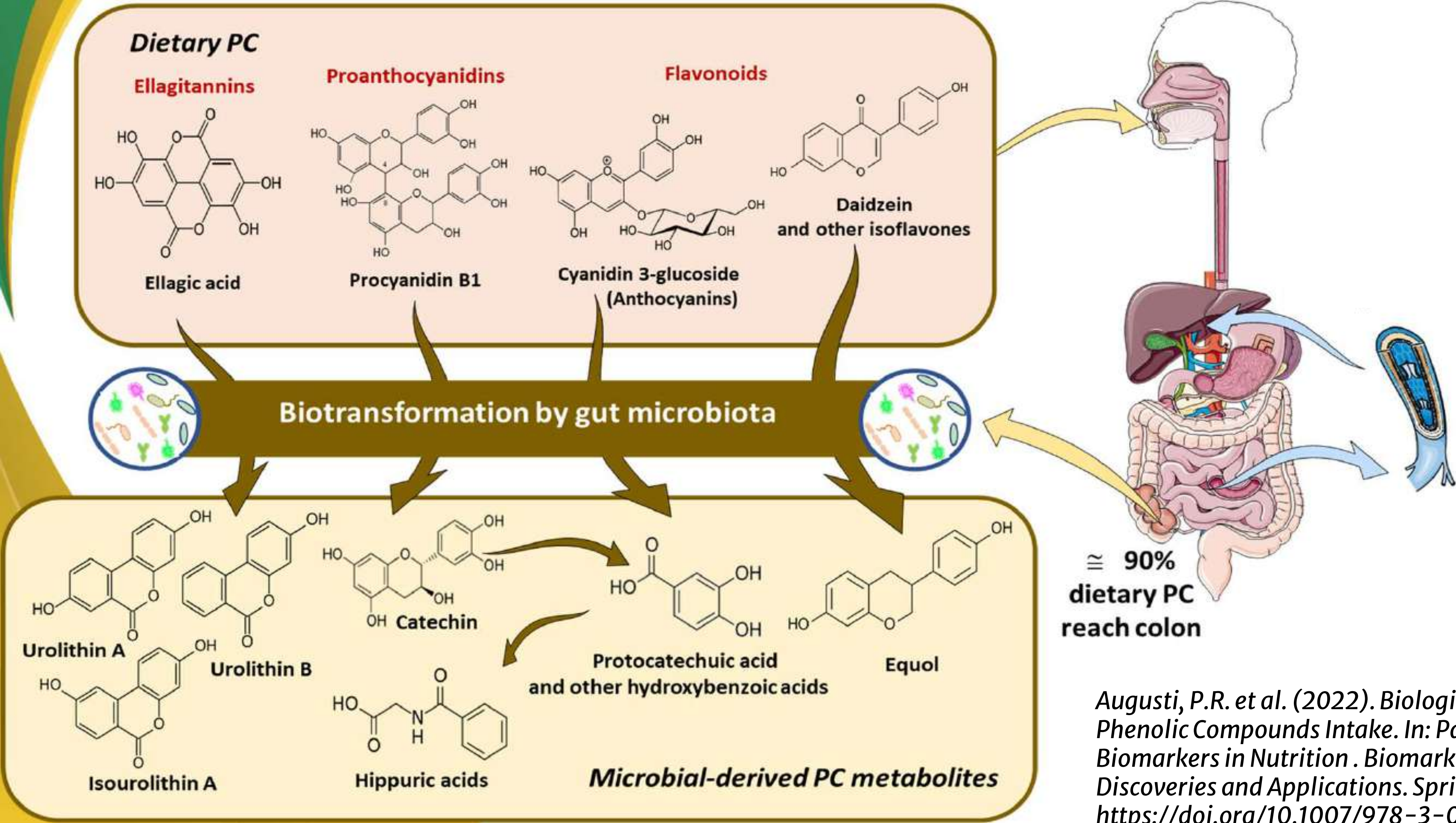

*Nutrients 2019, 11: 1355.*




- **Chemical degradation**
- **Intestinal and phase I and II enzymes**
- **Gut microbiota**

*J. Nutr. Biochem. 2021, 97: 108787.*

# BIOTRANSFORMATION OF DIETARY PC BY THE COLONIC GUT MICROBIOTA

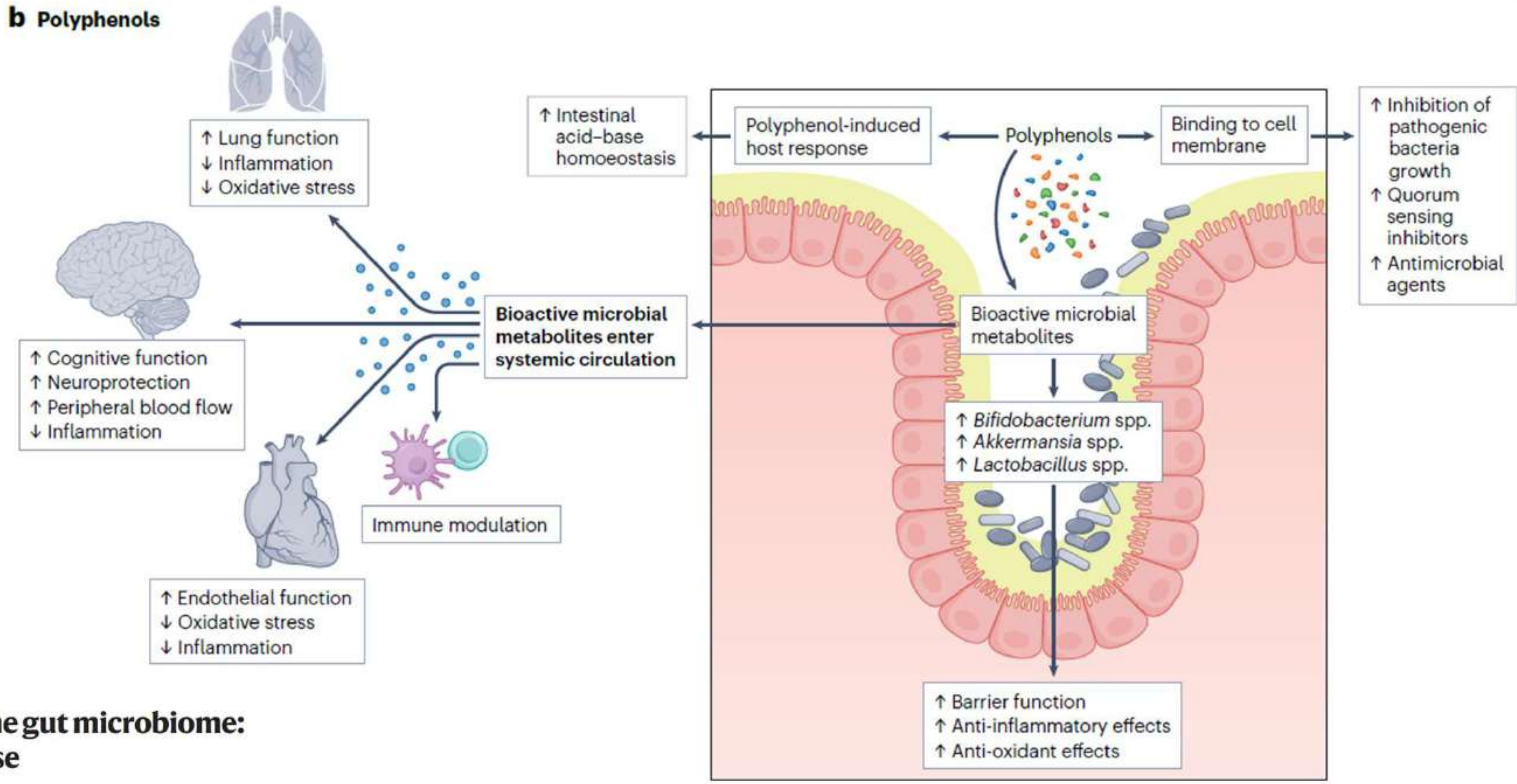



**Low bioavailability of intact dietary PC** (5-10% in the small intestine)

*Augusti, P.R. et al. (2022). Biological Markers of Plant Phenolic Compounds Intake. In: Patel, V.B., Preedy, V.R. (eds) Biomarkers in Nutrition . Biomarkers in Disease: Methods, Discoveries and Applications. Springer, Cham. https://doi.org/10.1007/978-3-030-81304-8_60-1*

# TWO-WAY INTERACTION BETWEEN PC AND GUT MICROBIOTA

## Bioavailability and bioactivity

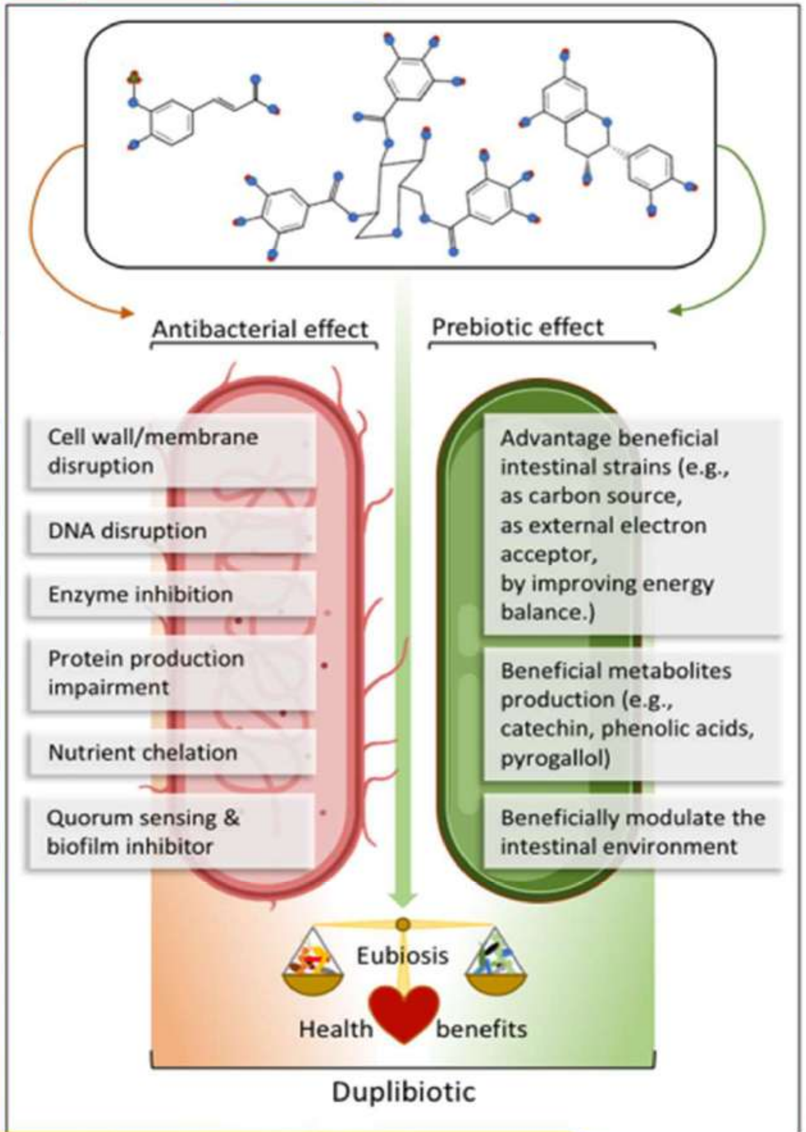



Review Article | Published: 15 July 2024

**The interplay between diet and the gut microbiome: implications for health and disease**

Fiona C. Ross, Dhrati Patangia, Ghjuvan Grimaud, Aonghus Lavelle, Eugene M. Dempsey, R. Paul Ross & Catherine Stanton

*Nature Reviews Microbiology* (2024) | Cite this article




# PC vs. GUT MICROBIOME INTERACTION

Modulation of microbiota composition


frontiers in Nutrition

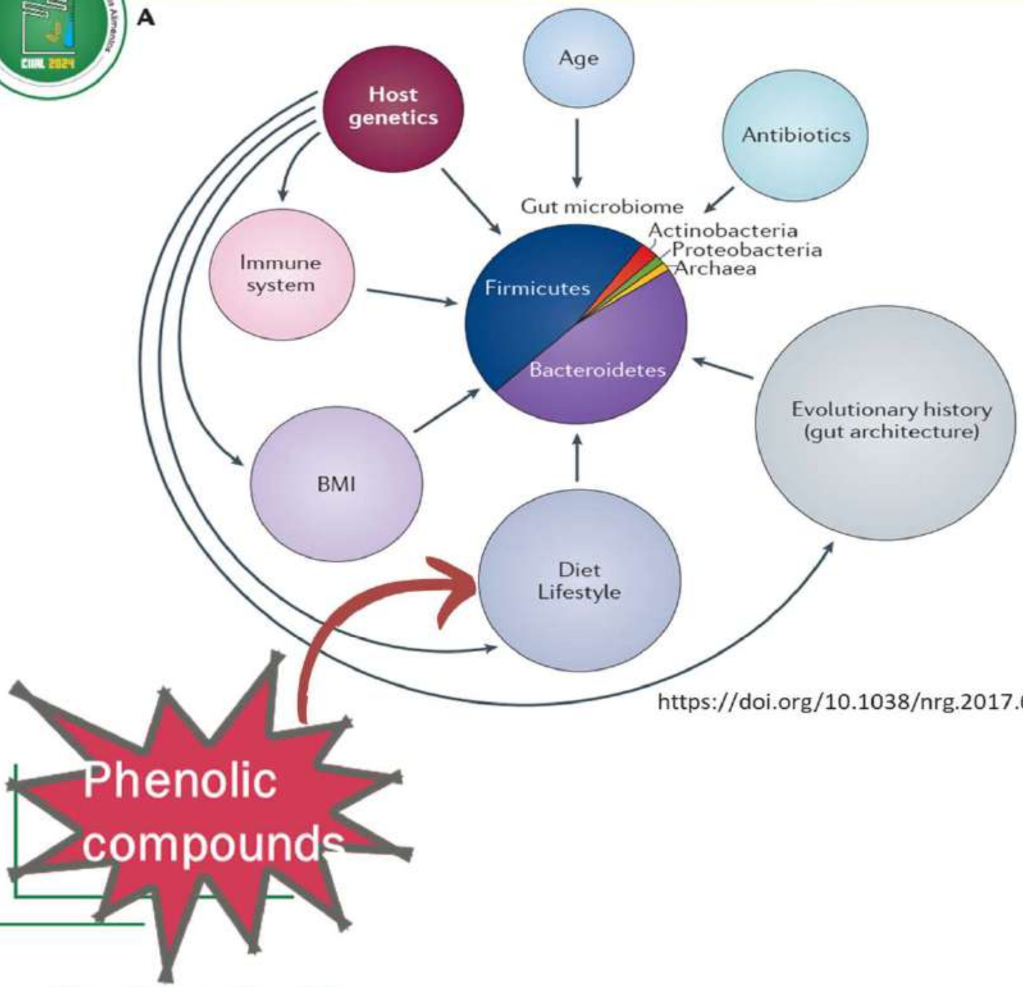
REVIEW
published: 28 June 2021
doi: 10.3389/fnut.2021.689456


## Polyphenol-Mediated Gut Microbiota Modulation: Toward Prebiotics and Further


Maria Carolina Rodríguez-Daza[1,2†], Elena C. Pulido-Mateos[1,2†], Joseph Lupien-Meilleur[1,2†], Denis Guyonnet[3], Yves Desjardins[1,4] and Denis Roy[1,2*]


*https://isappscience.org/do-polyphenols-qualify-as-prebiotics-the-latest-scientific-perspectives/*

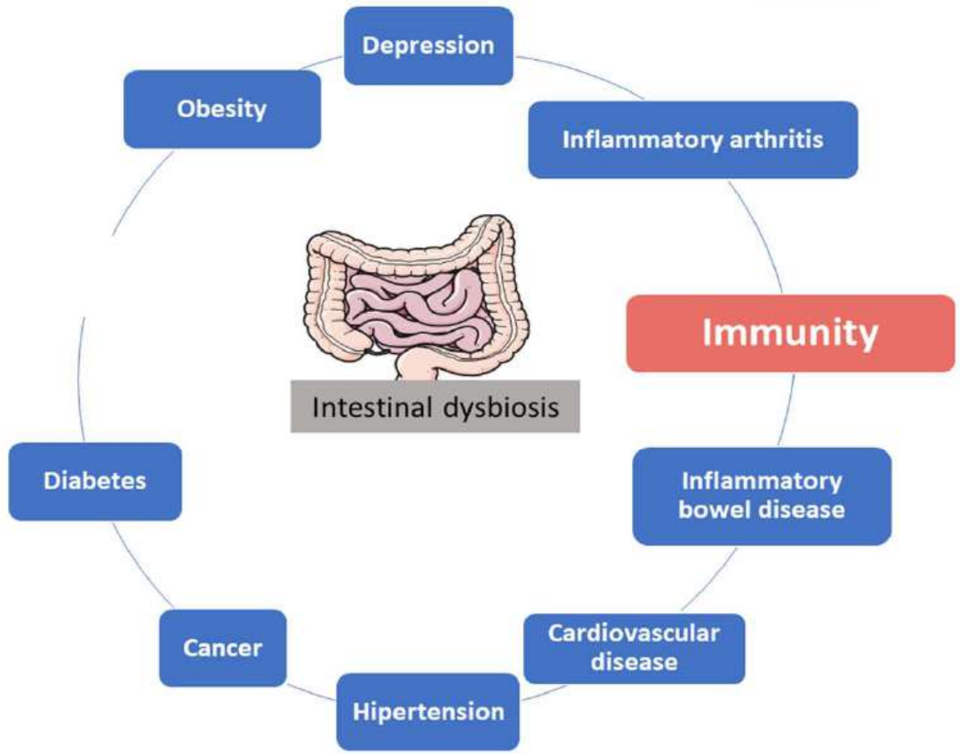
## Determinants of gut microbiome:




https://doi.org/10.1038/nrg.2017.63

# RELATED DISEASES

## Eubiosis vs. disbiosis



# PC vs. GUT MICROBIOME INTERACTION

## Bioactivity

Details | Related | Refe

**Gut Microbiota Metabolism of Anthocyanin Promotes Reverse Cholesterol Transport in Mice Via Repressing miRNA-10b**

Dongliang Wang, Min Xia, Xiao Yan, Dan Li, Lei Wang, Yuxuan Xu, Tianru Jin, and Wenhua Ling

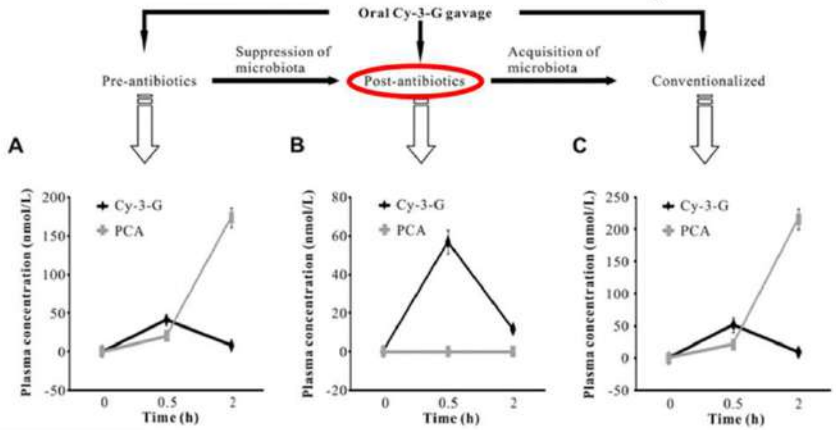
**Originally published** 19 Jul 2012 | https://doi.org/10.1161/CIRCRESAHA.112.266502 | Circulation Research. 2012;111:967–981

is companion of

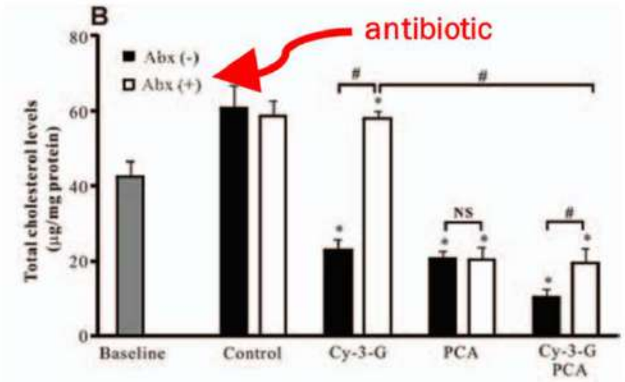
Other version(s) of this article


September 28, 2012
Vol 111, Issue 8

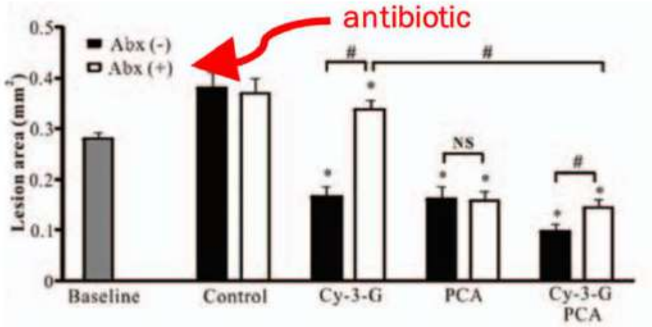
**PCA Is a Gut Microbiota Metabolite of Cy-3-G**




Effect of Cy-3-G on cholesterolemia depends on the gut microbiota




Effect of Cy-3-G on atherosclerotic lesion depends on gut microbiota



# PC vs. GUT MICROBIOME INTERACTION

## Bioactivity

**Common Phenolic Metabolites of Flavonoids, but Not Their Unmetabolized Precursors, Reduce the Secretion of Vascular Cellular Adhesion Molecules by Human Endothelial Cells**

Emily F Warner, Qingzhi Zhang, K Saki Raheem, David O'Hagan, Maria A O'Connell, Colin D Kay

*The Journal of Nutrition*, Volume 146, Issue 3, March 2016, Pages 465–473, https://doi.org/10.3945/jn.115.217943

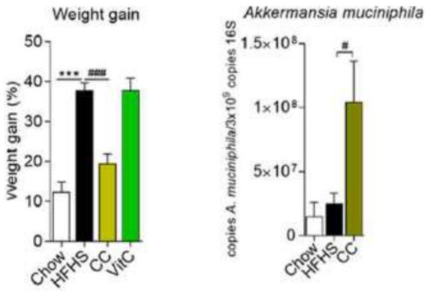
Gut. 2018 Jul 31. pii: gutjnl-2017-315565. doi: 10.1136/gutjnl-2017-315565. [Epub ahead of print]

**Treatment with camu camu (*Myrciaria dubia*) prevents obesity by altering the gut microbiota and increasing energy expenditure in diet-induced obese mice.**

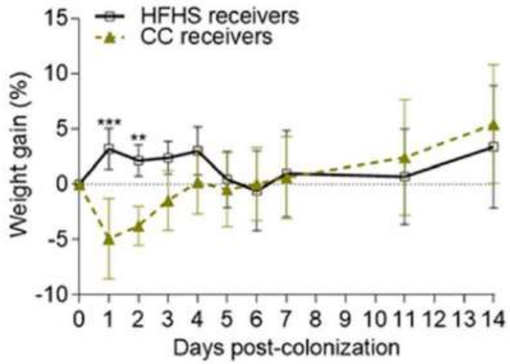
Anhê FF[1,2], Nachbar RT[1], Varin TV[2], Trottier J[3,4], Dudonné S[2], Le Barz M[1,2], Feutry P[2], Pilon G[1,2], Barbier O[3,4], Desjardins Y[2], Roy D[2], Marette A[1,2].

Camu camu fruit

CC prevents obesity and modulates gut microbiota




Reconstitioon of germ-free mice with fecal microbiota of animals treated with CC reduxes weight gain



# USE OF IN VITRO MODELS OF STATIC DIGESTION TO OBTAIN RELEVANT PC SAMPLE FOR IN VITRO STUDIES OF BIOACTIVITY

## Case study I

Objective

Static digestion associated with a colonic fermentation assay with human feces to elucidate the catabolism and bioaccessibility of an anthocyanin-rich fruit

Journal of Functional Foods 65 (2020) 103714

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

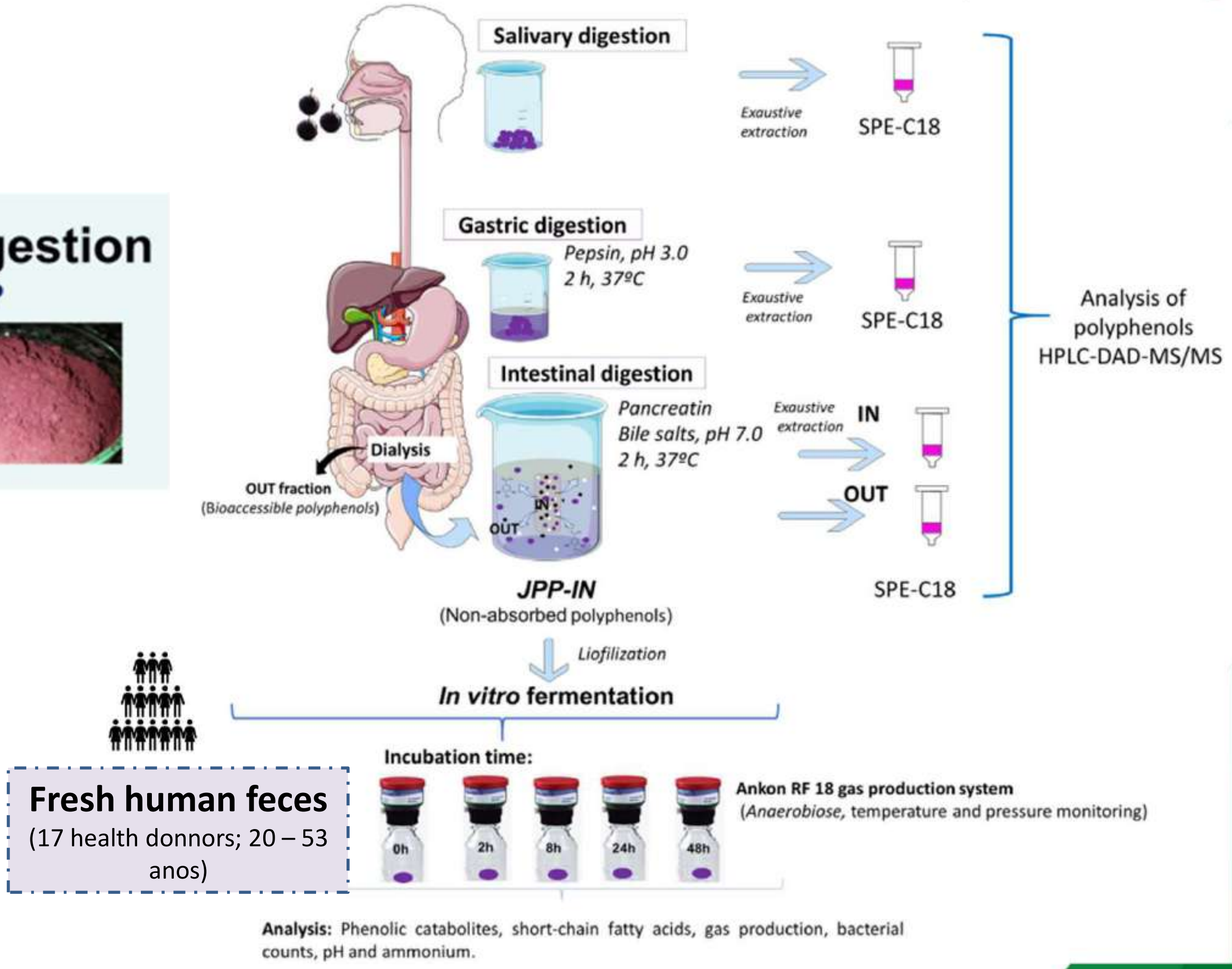
Bioaccessibility and catabolism of phenolic compounds from jaboticaba (*Myrciaria trunciflora*) fruit peel during *in vitro* gastrointestinal digestion and colonic fermentation

Andréia Quatrin[a], Cristine Rampelotto[a], Roberson Pauletto[a], Luana Haselein Maurer[b], Sabrina Marafiga Nichelle[a], Bruna Klein[a], Renata Fritzsche Rodrigues[a], Mário Roberto Maróstica Junior[c], Bruna de Souza Fonseca[a], Cristiano Ragagnin de Menezes[a], Renius de Oliveira Mello[a], Eliseu Rodrigues[d], Vivian Caetano Bochi[e], Tatiana Emanuelli[a,*]

# Case study I

## *In vitro* gastrintestinal digestion


| | Amount (mean ± SD) |
|---|---|
| *Proximate composition* | |
| Moisture (%) | 17.1 ± 0.2 |
| Ash (%) | 3.3 ± 1.0 |
| Protein (%) | 5.6 ± 0.0 |
| Lipids (%) | 1.3 ± 0.2 |
| Total dietary fiber (%) | 24.4 ± 1.0 |
| Soluble dietary fiber (%) | 9.3 ± 0.9 |
| Insoluble dietary fiber (%) | 15.1 ± 0.1 |
| Non-fibrous carbohydrates (%) | 48.3 ± 0.4 |
| *Phytochemicals* | |
| Soluble polyphenols (g gallic acid equivalents/100 g JPP) | 9.67 ± 0.42 |
| Insoluble polyphenols (g condensed tannins/100 g JPP) | 0.73 ± 0.15 |

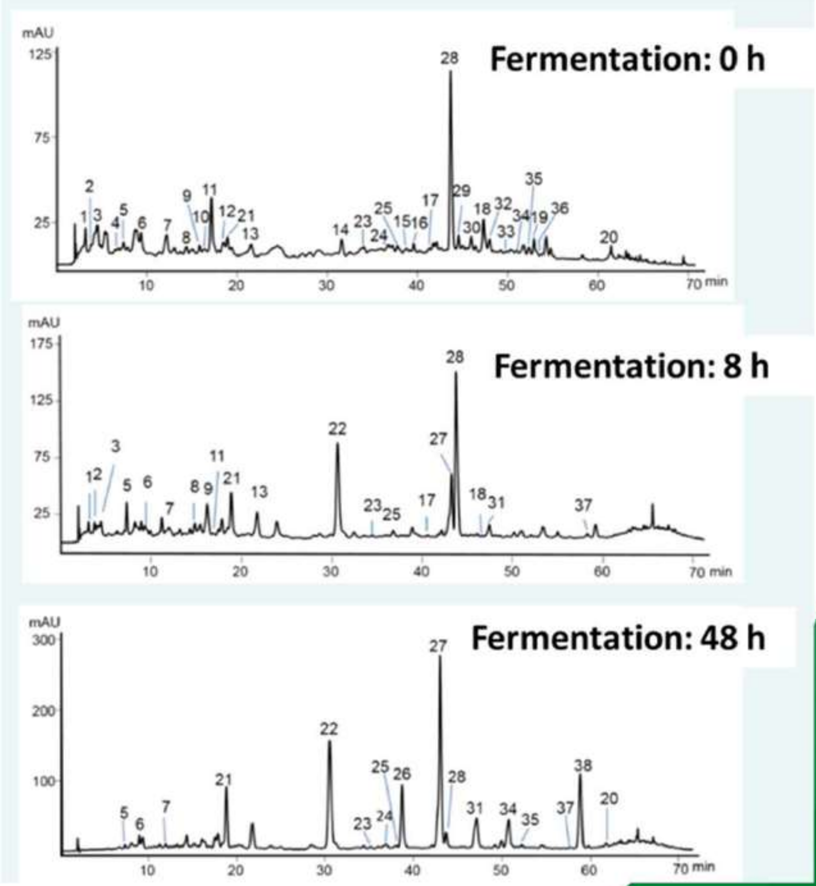


# Case study I

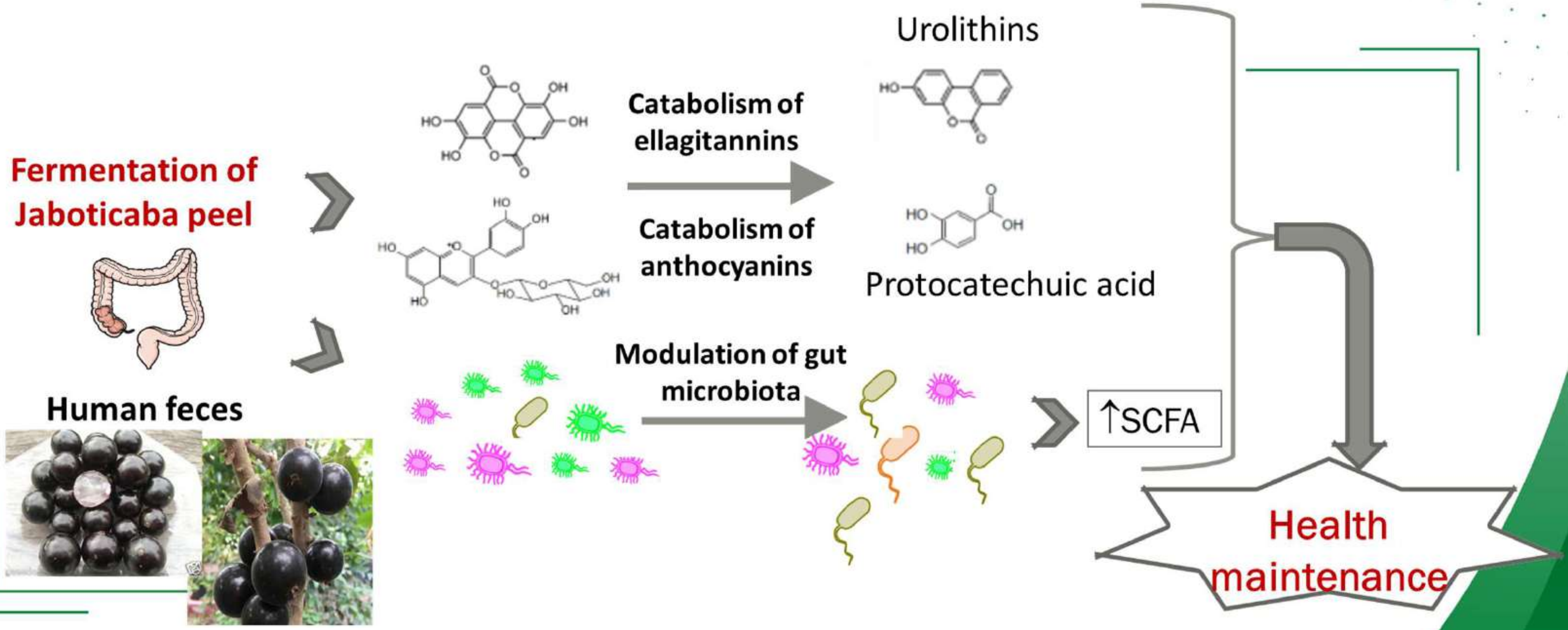
## Profile of PC from JPP-IN (LC-$MS^n$)

| Tentative identification | RT | MS/MS |
|---|---|---|
| HHDP-galloylglucose and Monogalloyl glucose | 3.15 | **633.0761:** 301.0025, 275.0226, 249.0437 and **331.0701:** 169.0169 |
| Digalloylglucose and Gallic acid | 3.79 | **483.0806:** 169.0177 and 169.0174: 125.0263 |
| HHDP-galloylglucose and bis-HHDP-glucose | 4.49 | **633.0746:** 301.0021, 275.0225, 249.0433 and **783.0673:** 301.0030, 275.0236 |
| Digalloylglucose isomer | 6.79 | **483.0808:** 169.0177 |
| Protocatechuic acid | 7.35 | **153.0221:** 109.0315, 108.0233 |
| Bis-HHDP-glucose isomer | 9.24 | **783.0638:** 301.0011, 275.0214 |
| Castalin and HHDP-digalloylglucose | 12.09 | **631.0558:** 450.9974, and **785.0857:** 301.0010, 275.0214,249.0422, 169.0161 |
| Castalin isomer and (Epi)catechin | 14.82 | **631.0546:** 450.9974 and **289.0728:** |
| HHDP-galloylglucose | 16.20 | **633.0710:** 301.0021 |
| Digalloylglucose isomer | 17.05 | **483.0776:** 169.0151, 271.0464 |
| Trigalloylglucose | 18.35 | **635.0876:** 169.0162, 465.0676, |
| HHDP-digalloylglucose isomer and Dihydroxyphenyl-γ-valerolactone | 21.39 | **785.0807:** 300.9995, 275.0226 and **207.0646:** 163.0748 |
| Trigalloylglucose isomer | 31.49 | **635.0876:** 169.0162, 465.0676, |
| Castalin/Vescalagin | 38.61 | **466.0207(2):** |
| Trigalloylglucose isomer | 39.48 | **635.0857:** 169.0153 |
| Tetragalloylglucose | 41.62 | **787.0899:** 465.0679, 169.0159, 233.6043 |
| Tetragalloylglucose isomer | 47.24 | **787.0899:** 465.0679, 169.0159, 233.6043 |
| Pentagalloyl glucose | 52.84 | **469.0506 (2):** 169.0141 |
| Galloyl-castalagin | 61.43 | **542.0300(2):** |
| Ellagic acid hexoside | 35.03 | **463.0497:** 300.9993, 299.9928 |
| Ellagic acid pentoside | 37.75 | **433.0410:** 300.9986, 299.9922 |
| Ellagic acid pentoside and Ellagic acid | 43.59 | **433.0418:** 300.9998, 299.9920 and **300.9991:** |
| Myricetin-rhamnoside | 44.52 | **463.0835:** 316.0232, 317.0274 |
| Quercetin-hexoside | 45.87 | **463.0846:** 300.0260, 301.0315 |
| Quercetin-hexoside | 47.94 | **463.0844:** 300.0261, 301.0329 |
| Quercetin-pentoside | 49.72 | **433.0744:** 300.0264, 301.0322 |
| Quercetin-pentoside | 50.91 | **433.0736:** 300.0257, 301.0331 |
| Quercetin-pentoside | 52.21 | **433.0742:** 300.0254, 301.0334 |
| Quercetin-rhaminoside | 53.19 | **447.0931:** 300.0252,301.0337 |
| Delphinidin-3-glucoside | 11.31 | **465.0878:**303.0412 |
| Cyanidin-3-glucoside | 12.28 | **449.0950**:287.0470 |
| Peonidin-3-glucoside | 13.32 | **463.1073:** |

## Changes in PC profile during fermentation



# Case study I


Fermentation of Jaboticaba peel
Human feces
Catabolism of ellagitannins
Catabolism of anthocyanins
Modulation of gut microbiota
Urolithins
Protocatechuic acid
↑SCFA
Health maintenance

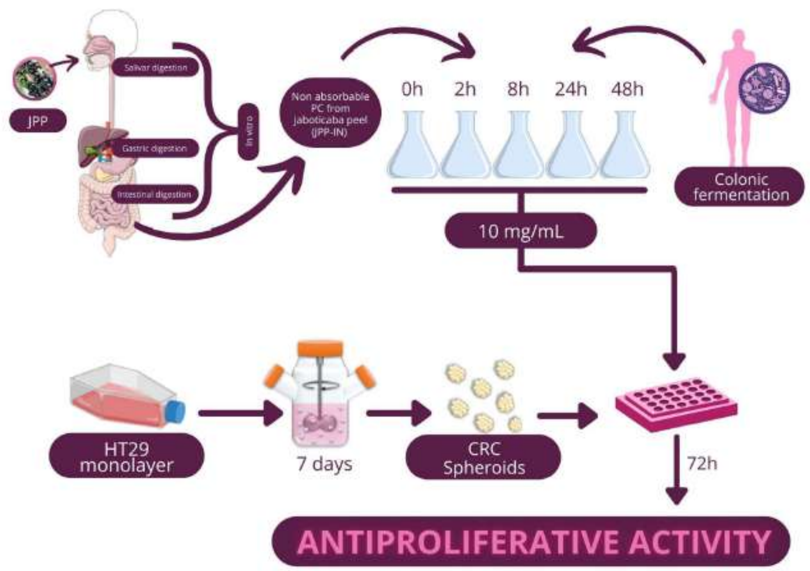
# Case study II

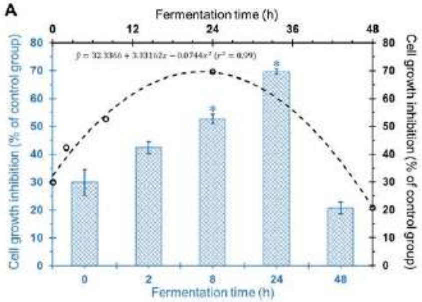
*molecules* MDPI

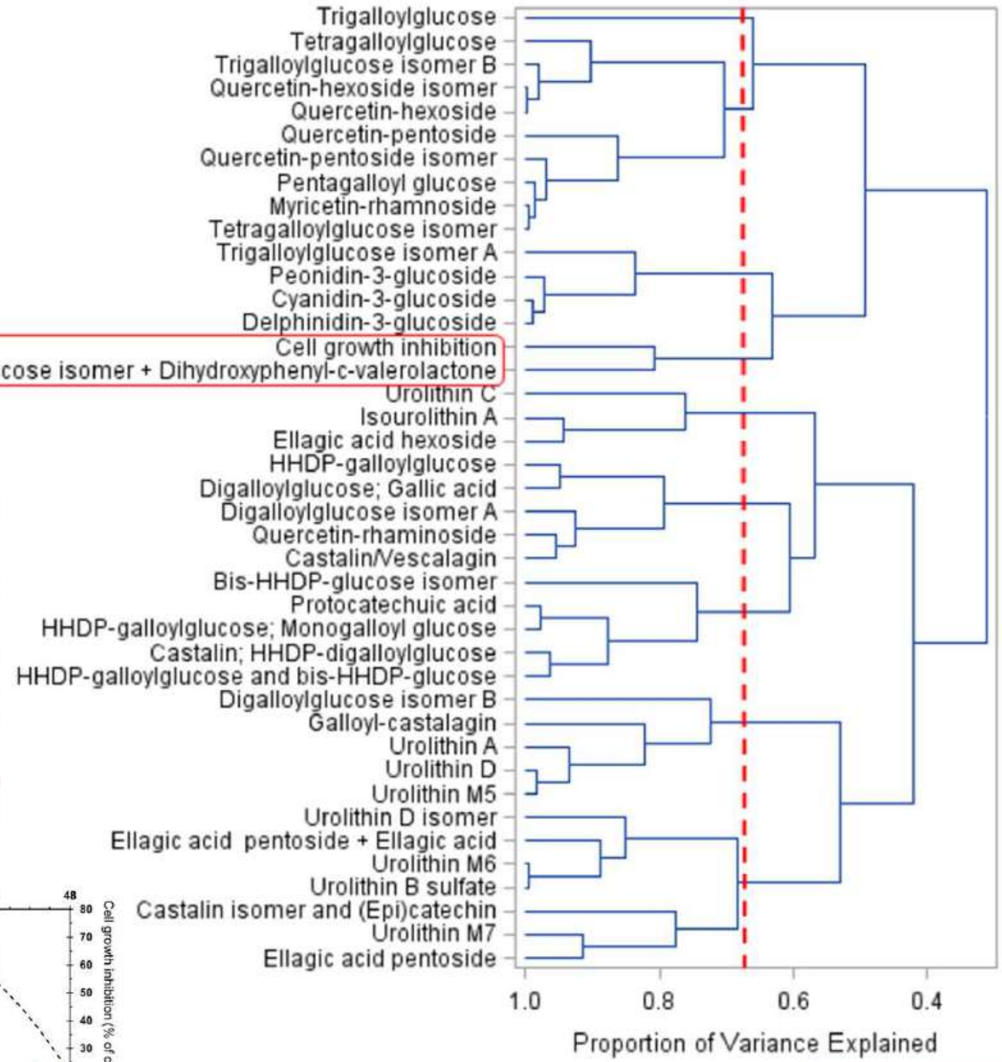
*Communication*

**Antiproliferative Effect of Colonic Fermented Phenolic Compounds from Jaboticaba (*Myrciaria trunciflora*) Fruit Peel in a 3D Cell Model of Colorectal Cancer**

Paula Rossini Augusti [1,*], Andréia Quatrin [2], Renius Mello [2], Vivian Caetano Bochi [3], Eliseu Rodrigues [1], Inês D. Prazeres [4,5], Ana Catarina Macedo [4,5], Sheila Cristina Oliveira-Alves [4,5], Tatiana Emanuelli [2], Maria Rosário Bronze [4,5,6] and Ana Teresa Serra [4,5]



Food Research International 173 (2023) 113338

Contents lists available at ScienceDirect

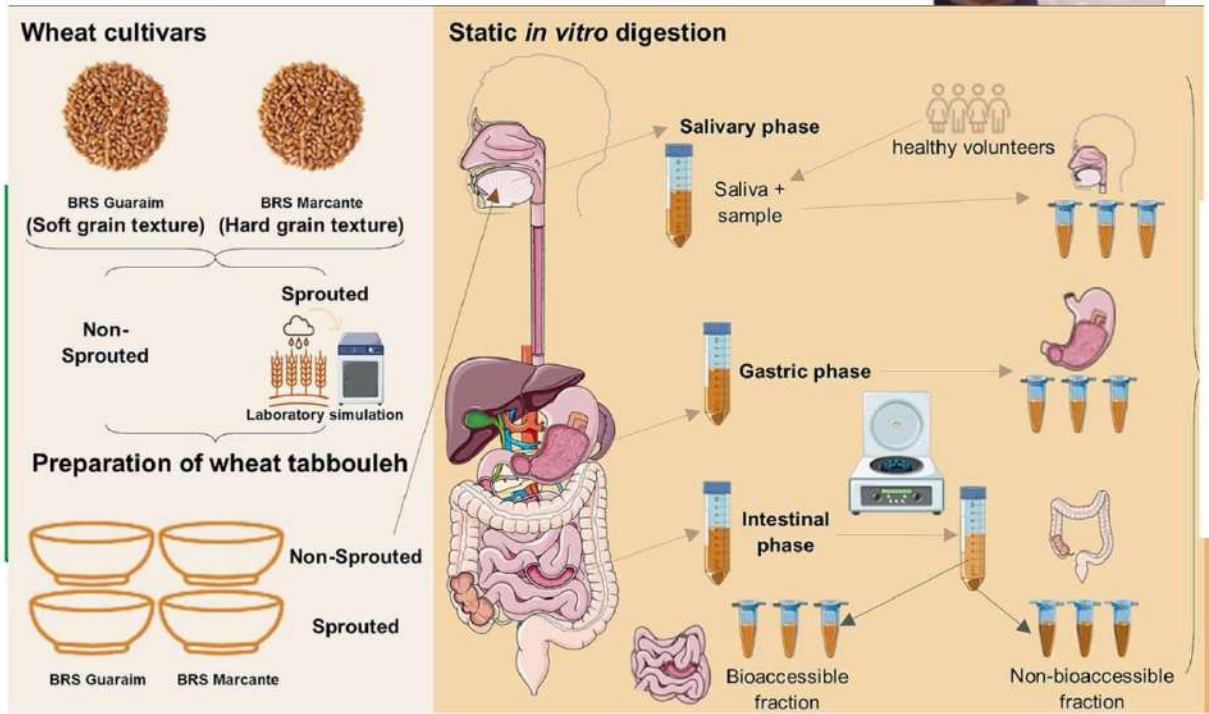
Food Research International

journal homepage: www.elsevier.com/locate/foodres


# Case study III

Influence of sprouting on the bioaccessibility and bioactivity of benzoxazinoids, phenolic acids, and flavonoids of soft and hard wheat cultivars

Julia Baranzelli[a], Sabrina Somacal[a], Camila Araujo Amorim Bonini[a], Franciele Aline Smaniotto[a], Camila Sant'Anna Monteiro[a], Dariane Trivisiol da Silva[b], Renius de Oliveira Mello[a], Jean Ramos Boldori[c], Cristiane Casagrande Denardin[c], Eliseu Rodrigues[d], Martha Zavariz de Miranda[e], Tatiana Emanuelli[a,b,*]



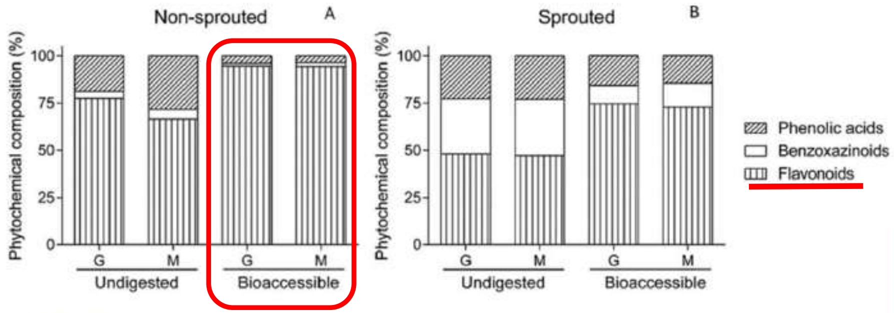




**Table 7**
*In vivo* antioxidant capacity ($IC_{50}$ values for the DCF assay in the *C. elega*… wheat cultivars.

| | BRS Guaraim | | Mean |
|---|---|---|---|
| | Non-sprouted | Sprouted | BRS Guaraim |
| Undigested | 142.7 ± 15.8 | 133.0 ± 19.9 | 137.8 ± 11.6[a#] |
| Bioaccessible | 4.46 ± 0.50 | 2.22 ± 0.59 | 3.34 ± 0.61[b#] |

# FINAL REMARKS

- Only a small fraction of dietary PC is available for absorption in the original form up to the small intestine.
- Most part of dietary PC reach the colon where they are metabolized by gut microbiota, generating low molecular weight compounds (microbial-derived PC metabolites), that can be absorbed and implicated in bioactivity.
- PC bioactivity depends on its biotransformation during digestion and after intestinal absorption.
- In vitro digestion assays can be coupled to in vitro bioactivity assays to overcome the gap between in vivo/clinical assays.

# RESEARCH GROUP

Grupo de pesquisa em
Compostos Bioativos

Camila Monteiro – Doutoranda PPGCTA – UFSM
Franciele Smaniotto – Doutoranda PPGCTA - UFSM
Juan Marcel Frighetto – Doutorando PPGCTA – UFSM
Dra. Sabrina Somacal – pós-doutoranda PPGCTA – UFSM
Profa. Milene T. Barcia – (UFSM)
Prof. Cristiano A. Ballus (UFSM)
Profa. Luana Haselein Maurer (UFSM)
Profa. Leila Picolli da Silva (UFSM)
Prof. Isaac Adedara (University of Ibadan/UFSM)
Scientific initiation students


**Partners:**

Profa. Vivian Caetano Bochi (UFCSPA)
Prof. Dr. Renius de Oliveira Mello (UFSM)
Prof. Dr Cristiano R. Menezes (UFSM)
Prof. Dr Eliseu Rodrigues (UFRGS)
Profa. Paula Rossini Augusti (UFRGS)
Profa. Greicy M. M. Conterato (UFSC)
Prof. Dr. Mário R. Maróstica Junior (UNICAMP)
Prof. Jesús Lozano Sánchez (Universiddade de Granada, Espanha)
Dra. Teresa Serra (IBET, Portugal)