

## **SHORT TERM SCIENTIFIC MISSION (STSM) REPORT COST Action FA 1403**

**Topic:** “Interindividual variation in response to consumption of plant food bioactives and determinants involved – Analysis of individual datasets”

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**Host:** Dr. Eileen Gibney UCD Institute of Food and Health (Dublin Ireland)

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### **1. Aim**

Plant foods are rich sources of a large range of bioactive compounds which have a potential beneficial effect on cardio-metabolic biomarkers. Due to heterogeneity in individual responsiveness, it is necessary to identify the groups of the population among which the bioactive would have distinct effect and the factors driving this association. Therefore, the Main Tasks within COST Positive WG2 are to assess inter-individual variation in selected clinical and molecular biomarkers of cardio-metabolic risk in response to plant food bioactives consumption and determine factors of inter-individual variation. This current report refers to the progress of the pilot study involving the analysis of individual datasets to study the Interindividual variation in response to consumption of plant foods bioactives and factors associated with it.

The primary objectives were defined:

- A. Liaise with COST partners to assess the availability of the datasets
- B. Identify the variables of the interest in the available datasets
- C. Finalize the collaboration and data sharing agreement
- D. Identify the merging strategy and propose statistical analysis plan

Apart from the task of the analysis of individual datasets, secondary objective of this STSM was to contribute to current meta-analysis on the effect of phytosterols on cardio-metabolic biomarkers by continuing the data extraction.

### **2. Description of the work carried out during the STSM and main results obtained**

All COST Positive partners were contacted inquiring regarding the studies they have conducted at their institution, what is the bioactive and outcomes they studied and whether they will be willing to share raw dataset. The criteria for immediate exclusion were:

- Laboratory studies
- Non-clinical trials
- Non-CVD related outcomes
- Non-published data
- Informed consent didn't include the agreement to share the data for secondary analysis

Among 38 studies identified, 18 studies were excluded: animal models studies (N=3), non-clinical trials (N=2), non-CVD related outcome (N=6), non-published data (N=3), Informed consent didn't include the agreement to share the data for secondary analysis (N=1), bioactives is not relevant (n=3). The rest of the studies were examined regarding the bioactive studied. Description of the main results obtained are presented below. The datasets for further analysis are still under discussion, as the response from one more Partner is pending. The bioactive studied by the majority of studies and giving the bigger sample size after merging will be selected.

The collaboration and data sharing agreement has been finalized, the database construction and proposed statistical analysis section has been added. The agreement document was approved by promoters of the Project and prepared for final approval by the Scientific Head.

During the period of my STSM I have continued to extract the data for "The effect of phytosterols and phytostanols on cardio-metabolic biomarkers: systematic literature review and meta-analysis". Though the extraction hasn't been finished as planned, I have significantly moved forward and presented the progress of the work during the 5<sup>th</sup> COST Action meeting which has taken place in Poland.

### **3. Follow up work**

- a. Obtain the ethical approval to perform secondary analysis
- b. Obtain selected datasets, perform database construction
- c. Perform the statistical analysis to study inter-individual variation
- d. Present the results in the next WG2 meeting
- e. Prepare the manuscript

### **4. Future collaboration with the Host Institution and foreseen publications / articles resulted from this STSM**

This STSM has strengthened the collaboration between UCD Institute of Food and Health and Spanish National Cardiovascular Research Centre (CNIC) within the COST Action POSITIVE to progress with the individual data analysis to study inter-individual variation in biomarkers of cardio-metabolic risk in response to plant food bioactives consumption. The analyses carried out will be supervised by Dr. Eileen Gibney from the University College Dublin (host institution). Foreseen publications resulting from the STSM will be discussed in the next COST meeting.

**TABLE 1: FLAVANONES**

Institution / Contact	Sample size	Sex, age	Design	Bioactive/ bioactive subgroup	Bioactive/ matrix	Outcome studied
INRA Christine MORAND	24	M 50-65y	RCT, cross over, 4 weeks periods	<b>Flavanones</b>  <b>Hesperidin + narirutin</b>	500 ml orange juice (292 mg hesperidin and 47.5 mg of narirutin), 500 ml control drink + hesperidin (292 mg) or 500ml drink + placebo  matrix: <b>ORANGE JUICE</b>	SBP, DBP, Pulse pressure, glucose, insulin, TG, TCHOL, LDL-c, HDL-c, CRP, IL-6, vWF, sICAM-1, sVCAM-1, NOx, FRAP, uric acid
INRA Christine MORAND	48	F 50-65y	RCT, cross over, 6 months with 2 months wash out	<b>Flavanones</b>  <b>Naringenin</b>	340 mL grapefruit juice (210 mg naringenin glycosides) or control drink without bioactive  matrix: <b>GRAPEFRUIT JUICE</b>	SBP, DBP, Pulse pressure, glucose, insulin, HOMA IR, CRP, IL-6, vWF, sICAM-1, sVCAM-1, FRAP, ORAC, TG, TCHOL, LDL-c, HDL-c, creatinine, FMD dilation, brachial diameter, PAT ratio, NO, Endothelin 1.
UEA / Aedin Cassidy, P Curtis	16	M 51-69y	RCT, cross over, 5 hours post intake	<b>Flavanones</b>  <b>Narirutin and hesperidin</b>	767 mL orange juice (320mg hesperidin and 48mg of narirutin) or hesperidin supplement drink (320mg hesperidin and 16 narirutin) or control  matrix: <b>ORANGE JUICE</b>	SBP, DBP, glucose, TG, TCHOL, LDL-c, HDL-c, heart rate, RPH-PAT, Cardiac RBS, cfPWV, cAlx@HR75, serum soluble gp91, P selectin expression (unstimulated platelets, ADP activated platelets, collagen related peptide activated platelets), Fibrinogen receptor expression.

**Total sample size: 128**

**TABLE 2: FLAVAN – 3 – OLS**

Institution / Contact	Sample size	Sex age	Design	Bioactive / Bioactive subgroup	Details of administration	Outcome available
Wageningen University / Peter Hollman	37	M+F 40-80y	RCT crossover	Flavan-3-ols  <b>Epicatechin</b>	(-)-epicatechin (100 mg/d), quercetin-3-glucoside (160 mg/d), or placebo capsules  Matrix: <b>CAPSULES</b>	SBP, DBP, MAP, FMD, aix75, ENDO, INSULINE, GLUCOSE, HOMA, CRP, NO
UEA / Aedin Cassidy, P Curtis	118	F 51-74y	RCT parallel design 1 year	Flavan-3-ols and isoflavones  <b>Epicatechin and isoflavones</b>	27 g chocolate (90 mg epicatechin (850 mg total flavan-3-ols)) and 100 mg isoflavones.  Matrix: <b>CHOCOLATE</b>	GLUCOSE, TCHOL, HDL-c, TG, HbA1c, LDL-c, anthropometric measures, insulin, CCA-IMT, SBP, DBP, MAP, PP, AI and aortic SBP, aortic DBP, aortic MAP, and aortic PP, carotid to femoral PWV, NO, ET1.
University of Barcelona/ Cristina Andres-Lacueva	42	M+F Average 67y	RCT crossover 28 days	Flavan-3-ols  <b>Epicatechin, catechin and proanthocyanidins</b>	500 mL of skimmed milk OR 40g cocoa powder mixed with 250ml of skimmed milk  Matrix: <b>COCOA POWDER</b>	GLUCOSE, TCHOL, TG, HDL-c, LDL-c, CRP, ICAM-1, VCAM-1, E-selectin, P-selectin, MCP-1, IL-6, SBP, DBP, heart rate, anthropometry
Institute of Food Research, Norwich Research Park/ Paul Kroon	14	M+F 45-70y	RCT crossover 24 hours	Flavan-3-ols  <b>Epicatechin</b>	300 g apple puree (70 mg epicatechin) OR 300 g water w/apple extract (70 mg epicatechin) OR 300 g water w/apple extract (140 mg epicatechin) OR 300 g water  Matrix: <b>APPLE PURE, WATER W/EXTRACT</b>	NO metabolites
See above	25	M+F 31-53y	RCT crossover (2, 6 and 24 h), and after 14 d of treatment	Flavan-3-ols  <b>Epicatechin</b>	230 g apple puree (100 mg epicatechin) OR 230 g apple puree (25 mg epicatechin) OR aspirin  Matrix: <b>APPLE PURE</b>	CRP, lipids, NO metabolites, ET-1

**Total sample size: 289**

**TABLE 3: ISOFLAVONES**

Institution / Contact	Sample size	Sex age	Design	Bioactive / Bioactive subgroup	Details of administration	Outcome available
UEA / Aedin Cassidy, P Curtis	28	M 50-75 y	RCT, crossover, 3 days	Isoflavones  <b>Daidzein</b>	Daidzein-rich soy protein bar providing ~160 mg soy isoflavones (aglycone equivalents), containing ~64 mg daidzein  Matrix: <b>SOY PROTEIN BAR</b>	cfPWV, blood pressure, endothelial function, and NO, BMI, lipids (LDL, TG). Augmentation index; cardiac output; equol producer; reactive hyperemia index, carboxy-methyl cellulose

**Total sample: 28**

**TABLE 4: ANTHOCYANINS**

Institution / Contact	Sample size	Sex age	Design	Bioactive / Bioactive subgroup	Details of administration	Outcome available
University of Belgrad Aleksandra Konic-Ristic	29	F 25-49y	Clinical trial	Anthocyanins	Chokeberry juice	Serological markers of oxidative stress and antioxidant defence, blood pressure, routine biochemical, and anthropometric parameters
University of Belgrad Aleksandra Konic-Ristic	20	F 45-65y	Clinical trial 4 weeks	Anthocyanins + glucomannan	Aronia juice-based supplement  100 mL of supplement per day as part of a regular diet, 2 g of stable glucomannan fibers	Anthropometric parameters, SBP, DBP, membrane fatty acid profile, and status of antioxidant enzymes in erythrocytes
University of Belgrad Aleksandra Konic-Ristic	23	F 33-67y	Clinical trial 4 weeks	Anthocyanins	Chokeberry juice, 200 mL of juice daily	Anthropometric parameters, SBP, DBP, membrane fatty acid profile, and status of antioxidant enzymes in erythrocytes
University of Belgrad Aleksandra Konic-Ristic	83	.m	RCT, three-arm, placebo controlled, double blind, cross-over	Anthocyanins	Aronia juice (1mg polyphenols GAE), aronia beverage (250 mg polyphenols GAE), and placebo	platelet activation (P-sel and GPIIB/IIIa expression, platelet-monocyte and platelet-neutrophil aggregation)

**Total sample size: 238**

**TABLE 5: FLAVONOIDS AND PHENOLIC ACIDS**

Institution / Contact	Sample size	Sex age	Design	Bioactive / Bioactive subgroup	Details of administration	Outcome available
University of Reading and Kings College Ana Rodriguez-Mateos, Jeremy Spencer	10	M 18-30y	Acute, randomized, placebo-controlled crossover trial	Anthocyanins, procyanidins, chlorogenic acid, phenolic acids and flavonols	<b>Blueberries (freeze-dried)</b>  319-1791 mg of blueberry polyphenols or control	Blood pressure: Systolic, Diastolic, pulse, FMD, PW
Kings College London Ana Rodriguez-Mateos	10	M 18-30y	Acute, randomized, placebo-controlled crossover trial	Procyanidins, anthocyanins, flavonols, phenolic acids	<b>Cranberry juice</b>  409-1910 mg of cranberry polyphenols or control	Blood pressure: Systolic, Diastolic, pulse, FMD, PWV
University of Belgrad  Aleksandra Konic-Ristic	40	.m	Acute parallel placebo controlled	Hexahydroxydiphenic acid ellagitannins anthocyanins, flavan-3 ols, flavonols	<b>Pomegranate juice</b>	Platelet function

**Total sample size: 60**

**TABLE 6: PHENOLIC ACIDS, FLAVONOIDS, NON-FLAVONOIDS**

Institution / Contact	Sample size	Sex age	Design	Bioactive / Bioactive subgroup	Details of administration	Outcome available
Rigas stradins university  Jelena Krasilnikova	.m	.m	.m	Tannins, flavonoids, lignans	Extracts from: alder, pine, willow	TG, LDL, HDL, TOTAL CHOL, antioxidants, SOD, GPx, TAS, enzymes
University of Belgrad  Aleksandra Konic-Ristic	80	.m	Acute parallel placebo controlled		Nettle, dill and Sideritis scardica water infusions	Platelet function

**TABLE 7: OTHER STUDIES:**

Institution / Contact	Sample size	Sex age	Design	Bioactive / Bioactive subgroup	Details of administration	Outcome available
Tufts University Jose Luis Penalvo	15	F	RCT, cross-over	Phenolic lipids  Alkylresorcinols	crisp bread  whole-grain wheat or whole-grain rye crisp bread (~100 g/d)	lipoproteins
University of Glasgow Emilie Combet	16	F + M	double blinded crossover RCT	Other polyphenols  Curcuminoids	.m	postprandial lipaemia, inflammatory markers, glycation markers, endotoxaemia