SCIENTIFIC REPORT - SHORT TERM SCIENTIFIC MISSION (STSM)

(COST Action FA1403, POSITIVe)

STSM topic: Meta-analysis training and its application in evaluating polyphenols' effects on cardio-metabolic health.

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Aim and background

Epidemiological studies suggest that higher polyphenol intake from fruits and vegetables is associated with decreased risk of cardiovascular disease. However, these bioactives promote individual physiological responses and that way clinical trial data lack of homogeneity and precise interpretation of those health implications. Polyphenols have also shown to have anti-thrombotic properties, which is another asset which describes them as promoters of cardiovascular health.

However, the data regarding platelet activity varies substantially from trial to trial, and depend on the applied methodology, used agonists, and their concentrations as well. Therefore, data reported from randomized clinical trials are very heterogeneous, and their systematization and categorization so as to perform meta analysis and satisfy all the exclusion and inclusion criteria is very challenging.

Prior to this STSM, the WG2 group has performed an extensive search via PubMed and Web of Science databases, with a specific criteria that referred to the polyphenol compounds, their source and platelet activity. The inclusion criteria for the trials were the following ones: randomized, controlled trials, platelet outcomes. Exclusion criteria were as it follows: not controlled, in vitro, co-intervention, no extractable data, language apart from English, non human study, not flavonols.

Part of the WG2 team has already done and published a meta-analysis on different cardio-metabolic risk factors and their relationship with flavonols. This STSM should be the extension on their previous work, so as to explore the inter-variability in platelet response to ingestion of those compounds, specifically from tea, apple and cocoa.

Working plan

This STSM is defined according to two main objectives:

a) The first one is reviewing and double checking of the trials that were included in the extraction process, and rearranging their data into comprehensive table to be used for meta analysis;
b) The second one is acquiring knowledge of meta analysis software as well as applying it on the data of interest.

The work is being performed at the University of Glasgow (host institution) under the supervision of dr. Emilie Combet Aspray. The steps of the first objective that were to be carried out during this STSM were defined as it follows:

1. Review all the trials included in the extraction, so as to ensure that all inclusion criteria were met;
2. Rearrange database table and subsetting it according to the outcomes of interest (platelets activity), and include relevant factors, cohort descriptives and study quality determinants;
3. Stratify the subset based on the applied methodology, acute/chronic studies, markers of platelet activity, then on their varying concentrations of agonists (if added), and locating the number of available papers for the specific outcomes;
4. In case of insufficient number of trials included, add the studies done on anthocyanins and ellagitannins and merge them together. Our plan was to try to extent the groups of polyphenols, and locate as many papers as possible according to the initial search;
5. Merge all the data, and summarize it into one table which outlines the number of studies done on a specific parameter with a specific method, and describe it as well.

After the first 11 days of STSM the first objective was accomplished, together with an additional evaluation of two papers regarding flavanols' impact on platelet function (provided by the other members of WG2 team). Apart from that, 4 other trials that were firstly excluded as they investigated grape seed polyphenols were reviewed and evaluated. However, after reviewing this 6 papers, none of them were included in further analysis due to: the presence of acute studies which could not be merged with the chronic ones, the lack of possibility for data extraction, or the presence of co-intervention. The outcome of the first 5 defined steps are presented in the table bellow which summarizes the data from total of 16 papers included, according to the parameter, the applied methodology and the number of available papers:

Parameter	Method	No of papers
ADP (1/2.5/5/10)	LTA	1
ADP (4/8)	LTA	1 acute+1 chronic
ADP (2)	LTA	2 chronic + 1 acute
ADP (0.1/0.3/1/3/10/30)	Plate reader	1
ADP (8)	Impedance aggregometry	1
Collagen (2)	LTA	2 chronic + 1 acute
Collagen (0.2/0.6/4/8)	LTA	1
Collagen (0.1/0.3/1/3/10/30)	Plate reader	1
Collagen (2)	Impedance aggregometry	1
P selectin	ELISA	5 chronic
P selectin	PFA	1
TBX2	RIA	1
TBX2	EIA	1acute+1chronic
PFA (epinephrine collagen)	PFA	2
PFA (ADP collagen)	PFA	2 acute + 2 chronic
Platelet adhesion	Microscope	1 acute + a mixed

After discussing with dr. Emilie Combet, we made a decision to perform meta-analysis on p-selectin as it was the parameter described with the largest number of studies, and that way defined the steps of the second objective:

1. Data entry into the Comprehensive Meta-Analysis software V3 in a pre-post fashion, where the focus will be on the following measures: sample mean and SD (pre and post) for both the control and treatment group, together with their sample size, and the p value for the pre/post correlations;
2. Run the analysis and interpret the results.

Outcomes

After this second evaluation, I was trained in conducting the meta-analysis on flavonols, anthocyainins and ellagitannins and their impact on only one selected outcome - p-selectin. All other parameters were excluded mostly because the intervention periods were mixed – both acute and chronic studies were merged together, which is impossible to analyse and interpret together.

After running the analysis, the results confirmed a significant mean effect size of polyphenol intervention on decreasing the level of p-selectin in the treatment group. That is, people who were consuming polyphenols had an overall of 0.194 ng/ml lower levels of p-selectin compared with the ones that were not. Furthermore, inspection of the forest plot and the heterogeneity statistics confirmed that there there wasn't any between-study variation that is due to the effect size differences from one study to the other. However, when interpreting these results we must be cautious, because of the different polyphenol sources, different polyphenols classes, intervention durations and dose variability. However, this conclusion navigated us to define our future goals and steps of research.

Future research and colaboration

At the end of this STSM, dr. Emilie and I concluded and defined future objectives of our co-operation on the same research question as it follows:

1)Expand the inclusion criteria for the polyphenols' group with flavonons, and review and evaluate the data from the existing data search and extraction process (which had been already performed by the member of WG2 team);

2)Try to modify the search criteria so as to increase the number of studies and the rationale for meta-analysis;

3)Present the outcomes of this STSM on the next COST meeting which is going to be held in Thessaloniki this September, and see if there are any other groups working on data extraction regarding polyphenols (other than those which were already evaluated);

4)Finally, after these 3 steps, conclude whether the paper will be written in the form of a systematic review of meta-analysis, or combined.

This STSM has strengthened the collaboration between CENM (University of Belgrade) and University of Glasgow within the COST Action POSITIVe to progress with the data analysis, and to complete the on-going investigation of polyphenols' impact on platelet activity as a cardio-metabolic risk factor. All the future work that will be performed at CENM will be supported by dr. Emilie Combet Aspray from the University of Glasgow.