Polifenoli nella riduzione dei fattori di rischio delle malattie croniche. Mito o realtà?

Maria Daglia
Department of Drug Sciences
University of Pavia
maria.daglia@unipv.it
polyphenols AND... health/disease
1) Distribution in foods and dietary intake

2) Bioaccessibility and bioavailability *in vitro* and *in vivo*

3) Protective activities against oxidative stress

4) Mechanism of action hypothesis
POLIFENOLI NEGLI ALIMENTI

• FLAVANOLI MONOMERI
• ACIDO CLOROGENICO
• ALTRI ACIDI IDROSSICINNAMICI
• GLICOSIDI DELLA QUERCETINA
• ANTOCIANINE
how much polyphenols do we take with the diet?

10 countries
521000 people

Total intake
1 to 1.2 g/day

POLYPHENOLS

1) Distribution in foods and dietary intake

2) Bioaccessibility and bioavailability *in vitro* and *in vivo*

3) Protective activities against oxidative stress

4) Mechanism of action - the epigenetic hypothesis
**BIOAVAILABILITY**

The fraction of administered dose that reaches immodified the systemic circulation

**POLYPHENOLS**

- **Oral cavity**
- **Blood Stream DISTRIBUTION**
- **PORTAL VEIN**
- **BILE**
- **Excretion**
- **URINE FAECES**

**Phase I**
- CYP 450

**Phase II**
- Conjugates
The route of absorption

Polyphenols

- Stomach
  - if absorbed
  - Small intestine
    - chemical modification by conjugation reactions in the liver
  - Colon
    - chemical modification by the colonic microbiota
  - Blood
  - Urine
  - Bile
  - Feces

- if not absorbed
Dietary polyphenols

If not absorbed

100 trillion microbes - 1000 species: bacterial phyla are:

• Firmicutes,
• Bacteroidetes
• Actinobacteria
Effects of ellagitannin-rich berries on blood lipids, gut microbiota, and urolithin production in human subjects with symptoms of metabolic syndrome

Riitta Puupponen-Pimiä¹, Tuulikki Seppänen-Laakso¹, Matti Kankainen², Johanna Maukonen¹, Riitta Törrönen³, Marjukka Kolehmainen³, Tiina Leppänen⁴, Eeva Moilanen⁴, Liisa Nohynek¹, Anna-Marja Aura¹, Kaisa Poutanen¹,³, Francisco A. Tómas-Barberán⁵, Juan C. Espín⁵ and Kirsi-Marja Oksman-Caldentey¹
RANDOMIZED CONTROLLED TRIAL
subjects with metabolic syndrome

Outcomes: body composition, blood pressure measurements, serum lipids, plasma glucose and insulin, plasma fatty acids, plasma antioxidant capacity, oxidative stress, inflammatory markers, adipokines, gut microbiota, ellagitannin metabolites.

consumed daily 300 g fresh berries:
100 g of strawberry puree,
100 g of frozen raspberries,
100 g of frozen cloudbberries.

20 treated patients

16-wk intervention trial:
  4-wk baseline period
  8 wk treatment
  4-wk recovery period,

The results
The results indicate that bioavailability of ellagitannins appears to be dependent on the composition of gut microbiota.

RESULTS

In the berry group, leptin concentration constantly increased throughout the 8-wk substitution period, while no such trend was seen in the control group.

In the berry group, systolic blood pressure decreased throughout the 8-wk substitution period.

significant difference in leptin concentrations

significant difference in systolic blood pressure

GUT MICROBIOTA COMPOSITION

The results indicate that bioavailability of ellagitannins appears to be dependent on the composition of gut microbiota.
Metabolism of Anthocyanins by Human Gut Microflora and Their Influence on Gut Bacterial Growth

Maria Hidalgo,† M. Jose Oruna-Concha,‡ Sofia Kolda,‡ Gemma E. Walton,§ Stamatina Kallithraka,§ Jeremy P. E. Spencer,‡ Glenn R. Gibson,‡ and Sonia de Pascual-Teresa*†

Inhibition of the growth of potentially harmful gut bacteria of the *Clostridium histolyticum* group.

Significantly enhanced the growth of total bacterial count and also the number of *Atopobium* spp. bacteria, which have been shown to have a potential positive effect on gut health.

Individual’s microbiota composition affects bioavailability of phenolics.
Dietary polyphenols

If absorbed

SERUM BIOAVAILABILITY OF POLYPHENOLS IS LOW

e.g. ANTHOCYANINS only reach up to $\mu$M levels
For instance...

Caffeoylquinic acid → hydrolysis → Caffeic acid → absorption → Small intestinal epithelium → caffeic acid-3-O-sulfate, ferulic acid-4-O-sulfate

Tmax 3h
For instance...

Epicatechin → absorption
Small intestinal

Sulfation
Methylation
Glucuronidation

Tmax for conjugates of 2 h
POLYPHENOLS

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Experimental animals

Clinical trials
Protective activities against chronic pathologies

**OXIDATIVE STRESS**

- ✓ antioxidant
- ✓ antiapoptotic,
- ✓ cardioprotective,
- ✓ neuroprotective,
- ✓ nephroprotective,
- ✓ anticancer

**ACTIVITIES**

**ABITUDINI ALIMENTARI:**

prevenzione e terapia tra evidenze scientifiche e comunicazione

20/21
SETTEMBRE 2018
Scuola Superiore di Polizia
Conclusions: We found no evidence that acute intake of black tea significantly altered endothelium-dependent vasodilation of forearm resistance arteries in healthy middle-aged subjects. Interventions with a longer duration of tea ingestion are required to further explore the (long-term) impact of tea flavonoids on blood pressure regulatory mechanisms. This trial was registered at clinicaltrials.gov as NCT02328339.
CLINICAL TRIAL

Single-blind randomized placebo-controlled crossover intervention study

20 men aged 18–34 years within the normal range for BMI not hypertensive.

Abstract We investigated whether a test drink enriched in pomegranate polyphenols, consumed with a high-fat meal, can reduce postprandial lipaemia and improve vascular function and blood pressure compared to placebo. Nineteen young, healthy men completed a randomized, controlled crossover trial. The active drink (containing a pomegranate extract) was consumed during a high-fat meal (ET-DUR) or 15 min before (ET-PRE), and the placebo drink (no pomegranate extract) was consumed during the high-fat meal (CONTROL). Postprandial lipaemia was assessed by venous plasma TAG 0–2 h, and capillary plasma TAG 0–4 h. Blood pressure and digital volume pulse, to measure reflection index (DVP-RI) and stiffness index (DVP-SI), were monitored at baseline, 2 and 4 h. There was no inhibition of postprandial lipaemia by the active drink compared to CONTROL. ET-PRE caused a greater increase in the venous plasma TAG at 2 h compared to CONTROL and ET-DUR (treatment effect P=0.001). The incremental area under the curve 0–4 h for capillary plasma TAG was not significantly different between treatments. Systolic blood pressure (SBP) increased in the ET-PRE and ET-DUR groups to a lesser extent than the CONTROL group (treatment effect P=0.041). There were no treatment effects for DVP-RI, DVP-SI or diastolic blood pressure. In conclusion, the consumption of a single drink containing ET-rich pomegranate extract did not decrease postprandial plasma TAG concentrations, but suppressed the postprandial increase in SBP following the high-fat meal.
As a matter of fact polyphenols

1) are widely distributed in plant foods and commonly consumed with the diet

2) Some polyphenols resulted to be bioaccessible and bioavailable in humans

3) are able to modify gut microbiota decreasing pathogenic bacteria and increasing beneficial microbiota

4) Long term studies show that they exert beneficial effects **WHILE** the acute intake of foods rich in them does not produce significant effects

Epigenetic mechanisms

Modulation of gene expression
Epigenetic changes

1. DNA methylation
2. histone post-translational modifications
3. miRNA-mediated post-transcriptional alterations

Endogenous
- Noncoding
- Single-stranded RNAs
- 22 nucleotides

Complementarity between the miRNA and its target:

- miRNAs that bind to the 3’ UTR of mRNA with imperfect complementarity **block** protein translation
- miRNAs that bind to mRNA with perfect complementarity **induce targeted** mRNA cleavage
Modulation of human miR-17–3p expression by methyl 3-O-methyl gallate as explanation of its in vivo protective activities

Valeria Curti¹,², Enrica Capelli², Federica Boschi¹, Seyed Fazel Nabavi³,⁴, Andria I. Bongiorno⁵, Solomon Habtemariam⁶, Seyed Mohammad Nabavi³,⁴ and Maria Daglia¹

Methyl-3-O-methyl gallate

miR-17–3p → regulation of cellular redox status

It interferes with transcription of the mRNAs responsible for the synthesis of antioxidant enzymes.
Peripheral blood mononuclear cells
Vascular endothelia cells (EVC-304)

1.25, 12.5, 25, 50, 100 ng/ml

**miR-17–3p decrease**
The expression levels of miR-17–3p decrease increase in the levels of mRNA coding for the ANTIOXIDANT ENZYMES.
Enantioselective Modulatory Effects of Naringenin Enantiomers on the Expression Levels of miR-17-3p Involved in Endogenous Antioxidant Defenses

Valeria Curti 1,2, Arianna Di Lorenzo 1,2, Daniela Rossi 1, Emanuela Martino 3, Enrica Capelli 3, Simona Collina 1 and Maria Daglia 1,4
MiR-17-3p behavior was in agreement with the increased levels of target mRNAs coding for two antioxidant enzymes, MnSOD and GPX2.
Defining the role of polyphenols in the maintenance of health and prevention of diseases requires to know:

1) Bioavailability
2) Metabolism
3) Physiological effects
4) Mechanisms of action

Different mechanisms depending on the site of action

- Direct antioxidant activity in the gastro intestinal system
- Indirect antioxidant activity at systemic level
- Gut microbiota modification
Interaction with cell signaling pathways

Gene Regulators

- Similarities between polyphenol(s) regarding expression of miRNAs.
  - Relationship between the chemical structure of polyphenols and their impact on miRNAs?

Modulation of expression of genes
THE ROAD AHEAD
Phenolic compound research...
Still a lot to be done...

DOSAGE

PHYSIOLOGICAL EFFECTS

INTERACTIONS

SUPPLEMENTATION WAYS

SIDE EFFECTS
Thank you for the attention!

Maria Daglia
maria.daglia@unipv.it