NUTRINSIGHT

Proceedings of the symposium

# Do we need dietary polyphenols for health? State-of-the-art and perspectives



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#### EDITORIAL

#### **Dr Margaret Ashwell OBE**

NUTRITION CONSULTANT, ASHWELL ASSOCIATES, UK.

Kraft Foods Europe R&D organised a symposium at the 11th European Nutrition Conference organised by the Federation of European Nutrition Societies (FENS)[http://www.fensmadrid2011. com]. The purpose was to share evidence about the potential health benefits of polyphenols including polyphenols from fruits, as well as from other food sources such as cocoa, coffee, and cereals.

The main dietary sources of polyphenols in the European diet appear to be beverages (coffee, tea, wine), fruits, cocoa products, and, to a lesser extent vegetables, legumes and cereals. Polyphenols are a large group of compounds which protect plants against a variety of stresses (Chapter 1). When consumed in our diet, they might be beneficial for health and wellbeing in adulthood and in the elderly population. Evidence for their protective effect is based on many epidemiological, clinical, animal, cellular *in vitro* and mechanistic studies.



Polyphenols exhibit a range of *in vitro* biological activities that are potentially in keeping with them protecting against agerelated diseases such as cardiovascular disease (CVD), diabetes and cancer (Chapter 2). More importantly, there have been many observational and clinical studies on human subjects using polyphenol rich foods showing that biomarkers of cardiovascular risk, energy utilisation, digestion, inflammation, lipid metabolism and diabetes are often significantly improved. Many mechanisms of action have been proposed and it is quite clear that their role as antioxidant does not explain all the effects of polyphenols (Chapter 3).

This booklet is a summary of the symposium presentations by Prof F A. Tomás-Barberán (Research professor, CEBAS-CSIC, Murcia, Spain), Dr Paul Kroon (Research Leader - Polyphenols and Health Group, Institute of Food Research, Norwich, UK) and Dr Francesco Visioli (IMDEA-Food, Madrid, Spain).

Professor Tomás-Barberán set the scene by covering types, sources, consumption and bioavailability of dietary polyphenols (Chapter 1). Dr Kroon then gave an overview of the evidence of potential health benefits of polyphenols from epidemiological studies and intervention trials (Chapter 2). Finally, Dr Visioli discussed possible mechanisms by which these benefits could occur (Chapter 3).

The timing was particularly opportune since this FENS symposium followed very shortly after the 2011 International Conference of Polyphenols & Health held in Sitges, Barcelona [http://www. icph2011barcelona.com]. All three speakers had attended this comprehensive conference and this ensured that the information presented at this symposium was fully up to date. The symposium was very well attended and lively discussions followed each paper, which reflects the interest of the nutrition community for polyphenols and their potential for health.

# **1 TYPES, FOOD SOURCES, CONSUMPTION AND BIOAVAILABILITY OF DIETARY POLYPHENOLS**

by Prof Francisco A. Tomás-Barberán

This chapter will describe what polyphenols are, where they are found in our diet and how much we eat. It will deal also with the level of bioavailability of polyphenols and their metabolites pointing out potential effectiveness on the body.

### **1.1** Types and food sources

### Polyphenols, a complex group of phytochemicals

Polyphenols include a chemically complex and large family of phytochemicals. They are, by far, the main secondary metabolites in plants, and therefore are present in all foods of plant origin. The common structural feature of all polyphenols is the presence of phenolic hydroxyl group(s). Simple monomeric phenolics, such as benzoic acid derivatives and hydroxycinnamic acid derivatives, usually co-exist in plants with oligomeric and polymeric derivatives (tannins and lignans etc). **Figure 1** shows some of the most common groups of polyphenols (phenolic acids, lignans, flavonoids and stilbenes) with some molecules of interest and examples of their main food sources.

Flavonoids, a well-studied class, form a large polyphenol subgroup with a carbon skeleton built of 2 phenyl rings (C6) bridged by a chain of 3 carbon atoms (C3) forming a heterocyclic 6-membered ring with oxygen and 2 carbon atoms from an adjacent phenyl ring. These include flavones and flavanones (found in citrus fruits); flavonols (found in tea, onions, apples) and flavan-3-ols (catechins and epi-catechins and proanthocyanidins) which are found in tea, red wine, cocoa/chocolate, apples. Other anthocyanins are found in fruits, vegetables and nuts including coloured berries and aubergine. Isoflavones (found in soy) are another important class of flavonoids.

There is also much interest in stilbenes such as resveratrol (in red wine) and other phenolics such as the hydroxycinnamates - in coffee (chlorogenic acids), in whole grain (ferulic acids). Minor phenolics such as hydroxytyrosol, found in olives, should not be overlooked. Currently, olive oil polyphenols characterised by their content of hydroxytyrosol and its derivatives are the only polyphenols so far to have achieved a positive opinion for a health claim in Europe [*EFSA*, 2011]. The health claim approved by EFSA states that consumption of olive oil polyphenols contributes to the protection of blood lipids.



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Source: Adapted from D'Archivio et al., 2007; Cheynier, 2005

### The content of polyphenols in foods

**Figure 2** shows the total polyphenol content of common food sources expressed as gallic acid equivalents measured by the Folin-Ciocalteu method (gallic acid is one of the basic hydroxybenzoic acid structures, and is used as a reference for total phenolics quantification). This method evaluates the reducing ability of all phenol groups. Because of the extraction process, some reducing sugars can react as well, leading to an overestimation of total polyphenol content.

Cocoa powder and chocolate are rich in polyphenols (5953 mg/100g and 2160 mg/100g, respectively) – mainly catechins and proanthocyanidins – and dark berries such as blueberry are high too (471 mg/100g) – anthocyanins. The polyphenols content of some other foods can be lower (coffee, tea) but their high consumption may result in an important contribution to total polyphenols intake.

The content and chemical nature of these phytochemicals differ largely from one food to another and some foods contain a wide mixture of polyphenols. The Folin-Ciocalteu method does not give the nature of individual phenolic compounds in each food.

However, there are some specific analytical methods to assess content of individual phenolic compounds. These methods are very diverse and can vary from one lab to another leading to a disparity of results for a same molecule analysed.





Source: 'Kraft Foods internal data; <sup>2</sup>Phenol-Explorer Database, http://www.phenol-explorer.eu/, consulted in August 2011

# Importance of extraction process for accurate analysis of the polyphenols content in foods

The different analytic methods often underestimate the polyphenols content in certain foods that contains some non-extractable phenolics.

Non-extractable phenolics have been generally overlooked in food composition analysis and databases. Apples and berries contain mainly extractable polyphenols, but in other fruits, such as pears, redcurrants and kiwi fruits, up to half their polyphenols are non-extractable by standard methods. Bananas are an extreme example and virtually all their polyphenols are non-extractable [Tarascou et al., 2010]. This means that the values in databases are underestimated and therefore polyphenol consumption is probably higher than estimates.

FOOD	% EXTRACTABLE	% NON-EXTRACTABLE
Apple and berries	90-100	0-10
Grape	50	50
Pear	50	50
Cranberry	50	50
Red currant	50	50
Kiwi fruit	20	80
Banana	0	100

Table 1: Distribution of polyphenols between extractable and non-extractable compounds in some fruits

Source : Adapted from Tarascou et al., 2010

### Polyphenols food composition database

The measures of polyphenols content in foods have allowed building food composition databases on polyphenol content, either global or focussed on specific subclasses.

A USDA database has been available since 2004 [www.ars.usda.gov] to estimate proanthocyanidin contents of foods; databases for isoflavones and flavonoids have been available since 2008 and 2011. These have all been based on a compilation of literature sources.

A very exciting recent development is the Phenol-Explorer web based database [www.phenol-explorer.eu] which has been collated from published papers by Dr Augustin Scalbert and colleagues from the Institut National de la Recherche Agronomique in France (INRA). This database covers 502 polyphenols in 452 foods. It includes not only flavonoids, but also phenolic acids, lignans, and stilbenes, with invidual glycosides and esters. The database provides information about the type of polyphenols, their food source content, their metabolites, and their pharmacokinetics.

The EuroFIR BASIS is also an on-line database developed within the EuroFIR NoE (European Food Information Ressource Network of Excellence). It gathers composition and biological activity data for plants and plant foods, compiled from critically evaluated published data [http://ebasis.eurofir.org/Default.asp].

However, the problems of non-extractable polyphenols and non-homogeneity of analysis methods still exists; even the most comprehensive database will only be as good as the analytical data that has been published in the literature. Good quality polyphenol databases are key for accurate estimations of polyphenol intake of foods in populations. We urgently need standardisation of the analysis methods, especially for non-extractable polyphenols, to better characterise the polyphenol profile in foods in our diet.

### **1.2 Consumption of dietary polyphenols**

### Estimation of daily diet intake of total polyphenols

The mean daily total polyphenol intake could reach more than one gram [*Pérez-Jiménez et al., 2011*]. This French study has given us recent information on total polyphenol intake based on the SUVIMAX French cohort (1995-1996). The SUVIMAX cohort consisted of 4942 middle-aged participants who consumed a total of 337 polyphenols with at least half of the population consuming 258 polyphenols [*Pérez-Jiménez et al., 2011*].

Intake was estimated by using the recent Phenol-Explorer database. They found that 98 polyphenols were consumed at levels of more than 1 mg/day and the mean total intake was 1193 mg/day. The maximum intake was 1.8 g/day.

Previous studies in other countries reported daily polyphenol intake of  $863 \pm 415 \text{ mg/d}$  in Finland [Ovaskainen et al., 2008] and  $853 \pm 512 \text{ mg/d}$  from beverages in Japan [Fukushima et al., 2009].

Different cultural habits and food preferences could explain population differences and the great variability observed in polyphenol intake.

### Estimation of daily intake of specific subclasses of polyphenols

Earlier estimations of intakes focussed on subclasses of polyphenols and were fairly low at 23 mg/day of flavonols and 200-300 mg/day of flavonoids [Hollman & Katan, 1999]. The Zamora-Ros study provides a more recent estimation of flavonoid intake of 313 mg/d from the EPIC-Spain cohort [Zamora-Ros et al., 2010]. Some of the most recent data on subclasses come from the French study [Pérez-Jiménez et al., 2011], where average flavonoid intake was 512 mg/day per person and hydroxycinnamates intake reached 599 mg/day per person. These two classes were the major polyphenols consumed.

The difference in estimates observed above can come from underestimation of some compounds (polymeric, non-extractable, condensed compounds) by usual methods and the heterogeneity in the analytical methods used.

### Main food contributors to intake of polyphenols

In the SUVIMAX French cohort, coffee and fruits are the main polyphenol providers with respective contributions of 520 mg/d and 206 mg/d. Tea, alcoholic beverages, cocoa products, and vegetables provide around 100 mg/d each; cereals provides 50 mg/d, and seeds, oils and seasonings contribute to a much lesser degree **(Figure 3)**.

Considering the polyphenols subclasses, fruits are the main sources of flavonoids intake in the diet (35%), whereas nonalcoholic beverages (mainly coffee and tea) were the main sources of phenolic acids (nearly 80%).



#### Figure 3 : Total dietary polyphenols intake in France (mg/day)

Source: Adapted from Pérez-Jiménez et al., 2011.

# **1.3 Bioavailability and metabolism**

Although the daily intake of phenolics can be quite high, the absorption of these phytochemicals can range widely according to their structure. Whatever their bioavailability, these compounds can already have a direct effect on digestive tract. Moreover, their metabolism can lead to active metabolites that can be bioavailable and active in the body.

### **Biological effects of polyphenols in the gastro-intestinal (GI) tract**

Before being absorbed into the bloodstream and metabolized, the polyphenols go through the GI tract where they can already have some useful effects. These include anti-inflammatory effects [Larrosa et al., 2010], prebiotic effects on the microbiota [Selma et al., 2009; Tzounis et al., 2011; Larrosa et al., 2010], interaction with other nutrients in the gut (such as lipid peroxidation) [Ligumsky et al., 2008; Kanner et al., 2011] and interaction with enzymes such as alpha-glucosidases, alpha-amylases and pancreatic lipases [Frei et al., 2011]. There is also evidence of *in vitro* effects with gut cell lines which could indicate anti-tumoral properties [González-Sarrías et al., 2009].

### **Pharmacokinetics**

The pharmacokinetics of polyphenols can give clues to where they, and their metabolites, are absorbed, their distribution in tissues and also about bioavailability. Animal model studies and analysis of human biopsies and tissues after surgery show the metabolites and concentrations that reach the tissues. These are usually in the nM range [González-Sarrías et al., 2010; Azorín-Ortuño et al., 2011].

Stalmach and colleagues [Stalmach et al., 2009] have analysed the circulating hydroxycinnamates compounds and their metabolites after ingestion of coffee polyphenols. They found that some compounds, like caffeic acid, are absorbed fairly quickly and the peak plasma concentrations can be reached within 1 hour. On the other hand, other compounds or metabolites reach their highest concentrations in plasma in 4-5 hours indicating that the absorption of these polyphenols take place in the colon and probably need to be metabolized prior to be absorbed.

### Factors affecting the bioavailability of polyphenols

Understanding the bioavailability, metabolism and tissue distribution is essential to evaluate the health effects of the polyphenols. Bioavailability of polyphenols is affected by three main factors (**Figure 4**):

- Food matrix and other constituents of the diet exerting their effects in the intestinal lumen,
- Genetic aspects of individuals affecting uptake into gut cells and into the bloodstream via a system of enzymes and transporters,
- Microbiota metabolism affecting the formation of metabolites in the colon and their subsequent uptake into the bloodstream.



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#### Figure 4: Polyphenols transit and absorption in the GI tract

Polyphenol interactions with some other food constituents, gut microbiota and intestinal cells. Sources of interindividual variability in polyphenol absorption and metabolism. Abbr. LPH (Lactose-phloridzin hydrolase), UGT (Glucuronyl transferases), SULT (Sulpho transferases), MRP (Multidrug resistance related protein). Source: From F A. Tomás-Barberán.

#### • Food matrix and other constituents of the diet

The solubility of the polyphenols in the food matrix they occur, impact their bioavailabity, with the more soluble, e.g. orange flavanones, being the most bioavailable [Vallejo et al., 2010]. Presence of pectins and fibres in the food matrix could increase bioavailability [Richling et al., 2011], as would sugar and oils [Martinez-Huelamo et al., 2011]. Protein, on the other hand, would decrease bioavailability.

As an example, in a study of epicatechin pharmacokinetics in cocoa, Neilson et al [*Neilson et al., 2010*] showed that in solid chocolate, sugar tended to increase polyphenols bioavailability whereas milk protein appeared to decrease it. On the other hand, in chocolate beverages, bioavailability of polyphenols was higher compared to solid chocolate and nutrients (especially sugars) impact less their bioavailability. This indicates that the physical state of the product as consumed appeared to be the principal factor governing bioavailability.

#### • Genetic susceptibility of individuals

**Figure 4** shows that several transporters and enzymes are needed for the uptake of polyphenols across the cells of the small and large intestine. Single nucleotide polymorphisms (SNP's) have been detected for several of these such as Phase II enzymes (SULT, UGT) [Ginsberg et al., 2010], Phase I enzymes (CY P450) [Chen et al., 2011] and membrane transporters (MRP etc.). It is therefore possible that bioavailability of polyphenols will be different in different individuals according to their genetic make-up.

#### • Microbiota metabolism

Recent research has shown that colon microbiota metabolism of large hydrophylic polyphenol molecules leads to smaller, more lipophilic metabolites [Selma et al., 2009] that are generally better absorbed than the original compounds. This allows them to reach the bloodstream and tissues where they can exert relevant biological effects. The metabolic processes involved include flavonoid ring fission, glycoside de-conjugation, de-acylation, de-hydroxylation, de-carboxylation, de-methylation and methylation. Different phenolics can lead to similar metabolites, which can be considered biomarkers of colonic metabolism if they are subsequently absorbed [Selma et al., 2009].

The gut microbiota of different individuals can be very dissimilar and therefore the intestinal metabolism of specific food phenolics can differ from one subject to another. Subjects can be divided into producers or non-producers of certain metabolites and this might explain why they can be responders or non-responders to the effects of polyphenols [*Braune et al., 2011*]. Thus, the potential health effects of polyphenols can be diverse depending on the gut microbiota composition and activity of the individuals.

The newly discovered existence of human enterotypes (*i.e.* distinct and robust clusters) could explain the large variability seen in diet intervention studies and could explain why some people respond to the beneficial effects of nutrients, including polyphenols, and some do not. There are three main enterotypes and they can be considered analogous to blood groups. These three enterotypes are based on three genus gut bacteria: Bacteroides, Ruminococcus and Prevotella; and on their relative importance in the gut [*Arumugam et al., 2011*]. Fecal metagenomes of human gut microbiomes have been examined from 39 people in six countries with previously published data sets and have confirmed that the enterotypes are not nation or continent specific [*Arumugam et al., 2011*]. The enterotypes are mostly driven by species composition, but abundant molecular functions are not necessarily provided by abundant species, highlighting the importance of a functional analysis to understand microbial communities.

So the existence of a limited number of well-balanced host-microbial symbiotic states, which might respond differently to diet and drug intake, could be another major factor influencing the bioavailability of polyphenols at individual level.





Key Points

- Cocoa, tea, coffee, fruit and cereals are sources of phenolic compounds. The content and chemical nature of these phytochemicals differs largely from one food to another. Cocoa is particularly rich in polyphenols, mainly flavan-3-ols catechin and epicatechin.
- The development of exhaustive databases and standardization of the analytical methods will be a key support for further polyphenols investigation.
- Daily intake of total polyphenols can reach more than one gram. Coffee and fruits are the main polyphenols providers (60%) in the French diet (SUVIMAX cohort).
- Although bioavailability of dietary polyphenols is limited, they already have important effects in the GI tract before being absorbed.
- Most of polyphenols are transformed in the colon by the intestinal microbiota.
  This conversion is often essential for absorption and modulates the biological activities of these compounds.
- The transformation of the native phenolics into their metabolites depends on the individuals and their difference in gut microbiota composition. This interindividual variability in gut microbiota could lead to varied health effects of each phenolic compound between different individuals.

# **2** DIETARY POLYPHENOLS AND DISEASE PREVENTION: A REVIEW OF THE EVIDENCE FROM EPIDEMIOLOGICAL AND INTERVENTION STUDIES

### by Dr Paul Kroon

This chapter will give an overview of the evidence relating dietary polyphenols to several diseases. It will look at the evidence for the effect of polyphenols on cardiovascular disease (CVD), diabetes, cancer and bone health. Numerous cohort and case-control studies have been reported describing associations between consumption of polyphenols/polyphenol-rich foods and disease risk, but these studies cannot prove any cause and effect relationship. In contrast to these epidemiological studies, randomised controlled trials can give some indication of cause and effect. In the case of CVD, there is enough evidence to consider both.

# 2.1 Polyphenols and cardiovascular disease

### **Epidemiological evidence**

Many factors influence the initiation and progression of cardiovascular disease and only some of those are of dietary origin [*Ashwell et al., 2000*]. Polyphenols have only recently been acknowledged to be a group of compounds within the diet which might play a role in prevention of CVD. One of the major factors that prevented completion of high quality epidemiological studies was the lack of a comprehensive and accurate database of polyphenol composition and content of foods. Today, such data sources are available (cf 1.1). Epidemiological studies, particularly prospective studies as opposed to cross-sectional studies, can show which sub-classes of polyphenols may be important (by their effects on mortality) but high-quality trials can confirm an effect and can often indicate the mechanisms of action of polyphenols.

#### • Dietary flavonols and CVD death risk

The first epidemiological study on flavonoids was conducted using the relatively small Zutphen elderly cohort in the Netherlands (806 men), and arguably this study was responsible for a rapid increase in flavonoid and health research [*Arts et al., 2001a*]. A meta-analysis [*Huxley & Neil., 2003*] of seven prospective cohort studies included papers from 1993-2001 with a total of 105,000 subjects concluded that high flavonol intakes may be associated with decreased risk from coronary heart disease (CHD) mortality. For the highest intakes, most flavonols came from tea whereas for the lowest intakes the major sources were fruits and vegetables. The average daily intake ranges between 2 mg and more than 34 mg. There were 2087 fatal CHD events and the combined risk ratio was 0.80 (95% CI 0.69-0.93) after adjustment for known CHD risk factors and other dietary components between the highest tertile and the lowest tertile of flavonol consumption. In other words, those consuming the most flavonols exhibited a reduced overall risk across all these studies of about 20%.

#### • Dietary flavanols and CVD death risk

There are only a few prospective studies looking at flavan-3-ols. The Zutphen Elderly Study [*Arts et al., 2001a*] showed that catechins, whether from tea or other sources, may reduce the risk of ischemic heart disease mortality (p<0.02), but not of stroke.

On the other hand, in a prospective study on 34,492 postmenopausal women from lowa [*Arts et al., 2001b*], there was a strong inverse association between the intake of (+)-catechin and (-)-epicatechin and coronary heart disease death (risk ratios from lowest (median intake 3.7 mg/day) to highest quintile (median intake 52.7 mg/day): 1.00, 0.95, 0.97, 0.77, 0.76).

This inverse association was most pronounced in women at low risk of coronary heart disease (non-smokers, free of diabetes mellitus and cardiovascular diseases). However, a high intake of «gallates» (more than 29.2 mg/day), catechins typical of tea, was not associated with coronary heart disease death. Of the major catechin sources, apples and wine were inversely associated with coronary heart disease death. This data suggests that preventive effects might be limited to certain types of catechins, or that these are indicators of other dietary components or a healthy lifestyle in general.

#### • Flavonoids and CVD death risk

Another prospective study [Mink et al., 2007] looked at 34,489 postmenopausal women from the lowa Women's Health Study; this was the first published report that used USDA databases to estimate cardiovascular disease, coronary heart disease, stroke and total mortality risks associated with consumption of all flavonoid classes. The authors compared quintiles of intake and concluded that dietary intakes of flavanones, anthocyanidins, and certain foods rich in flavonoids were associated with a 22% reduction in CHD between the highest (median = 93.7 mg/day) and the lowest (median = 7.6 mg/day) quintile of intake. Anthocyanidins also lead to 12% reduction in CHD mortality risk when they are consumed versus when they are not present in the diet.

#### • Flavonoid subclasses and hypertension

In a very recent study, a pooled analysis was performed on 87,242 women from Nurses Health Study II, 46,672 women from the Nurses Health Study I, and 23,043 men from the Health Professionals Follow-Up Study. Updated USDA databases were used to quantify the consumption of the different flavonoid classes. The association between the quintiles of all flavonoid classes and the incident risk of hypertension (HT) was investigated [*Cassidy et al., 2011*]. In 14 years, there were 29,018 and 5629 cases of HT in women and men, respectively.

For anthocyanins, there was a 8% decrease in HT risk between the highest (mean consumptions range between 16.2 mg/d and 21.9 mg/d depending on the cohorts) and the lowest (mean consumptions range between 5.7 mg/d and 6.8 mg/d depending on the cohorts) quintiles of consumption (**Figure 5**). Apigenin was correlated to a 5% reduction in HT risk when comparing the highest to the lowest quintiles of consumption. Catechin intake was also associated with a decrease of 6% in HT risk in participants of age lower than 60 years. These authors concluded that anthocyanins and some flavone (apigenin) and flavan-3-ol compounds may contribute to the prevention of HT. These vasodilatory properties may result from specific structural similarities (including the B-ring hydroxylation and methyoxylation pattern). The dose-response curves from the three different cohorts and for the combined data clearly indicated that there was a clear trend for reduced risk of incident hypertension with higher anthocyanin intakes.





### **Intervention studies**

Many trials have looked at the effect of polyphenols on endothelial dysfunction, a prognostically relevant key event in atherosclerosis. Endothelial dysfunction is characterized by a decreased bioactivity of nitric oxide (NO) and impaired flow mediated dilatation (FMD), which is a measure of the compliance of the forearm artery in response to sheer stress (caused by blood flow). FMD evaluates the ability of the arteries to dilate in response to an increase in the demand for blood, oxygen and nutrients and is reduced if endothelial function is impaired in any way. Several intervention studies have therefore tested the effect of polyphenols on FMD. There are also a large number of studies that have measured changes in blood pressure, and plasma lipid profiles (particularly the levels of low density lipoproteins (LDL) and high density lipoproteins (HDL) and triglycerides) in response to a flavonoid-rich food or diet.

Several hundred human intervention trials have been conducted with polyphenols – a few with isolated polyphenols but more with polyphenol-rich foods. Although the former can pinpoint the beneficial effect of a sub class of polyphenols, the latter represents the real life situation and can be considered more relevant, even if less informative.

#### • Flavanols and isoflavone and CVD

Several trials have been done to evaluate the effect of flavanols on CVD endpoints. However the duration of the trials has usually been fairly short and the maximum duration is 18 weeks. To determine longer term effects, Curtis et al *[Curtis et al., 2012]* have recently reported a one year combined flavan-3-ol and isoflavone intervention in 118 postmenopausal women (93 completed the study) with type 2 diabetes who were on lipid lowering medication. They consumed two portions of 13.5 g chocolate which contained 850 mg flavan-3-ols (including 90 mg epicatechin) and 100 mg isoflavones as aglycone equivalents per day. They were able to demonstrate improved lipoprotein profiles in patients, even though they were already on lipid lowering therapy (including statins). LDL-cholesterol decreased in flavonoid enriched-chocolate group by 5% whereas it slightly increased in the placebo group **(Figure 6)**.





Source: Adapted from Curtis et al., 2012

Taking into account the different parameters measured during this trial, they found that the estimated 10-year total coronary heart disease risk (derived from UK Prospective Diabetes Study algorithm) was slightly lowered in the flavonoid group (-1.04 % in flavonoid versus placebo group).

#### • Flavonoid-rich foods and cardiometabolic risk factors

A meta-analysis of 133 RCTs published up until June 2007 (some acute and some chronic) was performed to review the effectiveness of flavonoids and flavonoids-rich foods on cardiovascular disease risk [Hooper et al., 2008]. Of these trials most of them assessed the effect of flavanols. Interventions have shown that cocoa/chocolate (8 studies) significantly improved endothelial function measured as FMD and reduced blood pressure, and that cocoa/chocolate, soy/soy protein isolates (39 studies) and green tea (4 studies) decreased plasma LDL (a beneficial effect on lipid profile). However, in some cases it was not clear that the beneficial effects could be ascribed to the polyphenols contained in these foods or extracts. For many of the other flavonoids, there was insufficient evidence to draw conclusions about efficacy and dose necessary to reach a significant effect. The optimal dose of specific flavonoids for cardiovascular protection needs further research.

#### • Flavanol-rich cocoa and CVD

The ingestion of flavanol-rich cocoa beverage containing 917 mg of total flavanols in healthy male adults was associated with acute elevations in levels of circulating NO species, an enhanced FMD response of conduit arteries, and an augmented microcirculation [Schroeter et al., 2006]. In addition, the concentrations and the chemical profiles of circulating flavanol metabolites were determined, and multivariate regression analyses identified (-)-epicatechin and its metabolite, epicatechin-7-O-glucuronide, as independent predictors of the vascular effects after flavanol-rich cocoa ingestion (Figure 7).



#### Figure 7: Changes in FMD and NO metabolites following high flavanol cocoa drink

Ingestion of a high flavanol cocoa drink (hFCD, 917mg of total flavanols) exerted significant increases in FMD **(A)**, plasma NO metabolites (RXNO) **(B)**, and circulating flavanols **(C)** compared with a low-flavanol control drink (lFCD, 37 mg). \*, P < 0.05 vs. baseline at o h of respective day; #, P < 0.05 vs. respective time point on control day. Source: Schroeter et al., 2006

In another study [Heiss et al., 2007], 306 mg total flavanols were consumed thrice daily. A day-on-day increase in brachial artery FMD was shown which is important because of the transient nature of the FMD effect.

#### • Orange flavanones and CVD

In a randomised, double-blind placebo-controlled crossover trial lasting 4 weeks, Morand et al showed that the flavanone, hesperidin, contributes to the vascular protective effects of orange juice [Morand et al., 2011]. In this study, 24 healthy, overweight men (age 50-65 y) were given either 500 mL orange juice (OJ) naturally containing 341.9 mg of flavonoids in which 292 mg was hesperidin, 500 mL control drink plus 2 capsules containing each 146 mg of hesperidin (CDH), and 500 mL control drink plus 2 capsules of placebo (CDP) each day. In the fasted state, OJ and CDH reduced diastolic blood pressure compared to CDP (p < 0.02). Microvascular endothelial activity, measured by combined laser Doppler flowmetry and iontophoresis, was not affected after chronic intake of OJ and CDH during 4 weeks. On the other hand, acute intake of OJ and CDH improved postprandial microvascular endothelial activity. It is interesting to note that hesperidin supplementation didn't differ in term of effects compared to orange juice with naturally-occurring hesperidin.

#### • Black tea and FMD and blood pressure

There are numerous studies that have investigated the effects of consuming tea on FMD and blood pressure (BP). A dose response relationship was demonstrated between black tea and FMD [*Grassi et al.*, 2009]. Black tea intake decreased systolic (-2.6 mmHg, P = 0.0007) and diastolic (-2.2 mmHg, P = 0.006) BP as well as stiffness index (P = 0.0159). But in fact, it has also been shown that green tea is as effective at improving FMD responses as black tea [*Jochmann et al.*, 2008]. This is somewhat surprising because the nature of the polyphenols in black tea are completely different to those in green tea; green tea largely contains monomeric catechins such as epigallocatechin gallate (EGCG) whereas black tea contains only minor quantities of monomers and instead is rich in higher molecular weight products of catechin oxidation including theaflavins, thearubigens and theatannins. This should be allowed thanks to the metabolisation of these phenolic compounds by the gut microbiota [*Lee et al.*, 2006].

### **Conclusion on polyphenols and CVD**

Epidemiological data tends to show a positive association between polyphenols especially flavonoids and CVD and CHD (flavonols, flavanols and flavanones reduce the risk of CHD mortality by around 20%).

Data from intervention trials are less consistent. However, they provide information related to the way polyphenols may have positive effects on CVD and CHD, including improvements in endothelial function and lipoprotein profiles. The positive effect on endothelial function could also be linked to the improvement observed in blood pressure and reduced risk of hypertension.

A precise characterization of food composition in term of polyphenol profile, along with a better understanding of interactions with the food matrix, should help identify the bioactive compounds and allow determining the required dose for expected effect.

There is also a need for well-controlled intervention studies taking into account the inter-individual variability related to polyphenol bioavailability and metabolism.



# 2.2 Effect of polyphenols on diabetes

### Coffee and diabetes: epidemiological evidence

Van Dam *[van Dam, 2008]* has considered the relationship between coffee and diabetes by reviewing 17 studies (from diverse populations across the US, Europe and Japan) published since 2002. Fourteen of them showed an inverse relationship. A dose-response relationship was shown with 4 cups/day or more being associated with substantially lower risk of type 2 diabetes, whereas results were more variable for lower levels of consumption. High coffee consumption was associated with lower post-prandial glucose in non-diabetics (several cross-sectional studies) and decreased incidence of impaired glucose tolerance (two prospective studies). Coffee is a rich source of phenolics, particularly chlorogenic acid, but contains caffeine which is also bioactive. Furthermore, all of the five published studies reporting increased consumption of decaffeinated coffee also showed reduced risk of diabetes which should tend to show that the polyphenols play a protective role in the development of diabetes.

### Flavanols, isoflavones and diabetes: an intervention study

The one year intervention trial reported by Curtis et al. *[Curtis et al., 2012]* in 116 postmenopausal women with type 2 diabetes (see page 15) also showed that insulin sensitivity was improved with flavanols and isoflavones in chocolate. In this intervention, the consumption of 2 portions of 27 g flavonoid-enriched chocolate containing 850 mg flavan-3-ols during 1 year lead to an improvement in insulin sensitivity (net difference in insulin secretion between the test and the control groups was -1.36 mU/L; p=0.02) and a decrease of insulin resistance measured as HOMA-IR (net difference in HOMA-IR index was -0.78 between the intervention and the control group; p=0.004) (Figure 8).



Figure 8: The improvement in insulin sensitivity by flavonoids intake Source: Adapted from Curtis et al., 2012

### Conclusion on polyphenols and diabetes development

Epidemiological studies tend to show a positive effect of polyphenols, particularly flavonoids, on the prevention of diabetes. This effect should be induced by a reduced insulin resistance and an improvement in insulin sensitivity. Additional studies are also needed to better understand the mechanism of actions and the dose required to have an effect.

# 2.3 Polyphenols and cancer

There are also numerous reports of associations between polyphenol intake and various types of cancer. Although the data from such studies are overall equivocal, with some studies showing no effect, there is a definite tendency towards a protective effect of increased polyphenol consumption. The best indications arise from meta-analyses where the data from several studies investigating the same cancer sites are combined and reanalysed. As an example, a meta-analysis for flavonoids and lung cancer reported data from twelve studies, located in Finland (3), the US (4), Uruguay, Spain, and the Netherlands (3) [Tang et al., 2009]. There were 5073 cases and 237,981 non-cases. There was a relative risk of 0.76 (Cl 0.63-0.92). An increase in 20 mg flavonoids per day was associated with a 10% reduction in risk. This will obviously be an exciting area of future research.

However, there are almost no reports of high quality dietary intervention studies demonstrating the effects of polyphenol consumption on cancer risk or disease progression. This is largely because of the lack of easily measurable and validated biomarkers for cancer, and the variability in the aetiology of cancers within the same and between different tissues.

# 2.4 Polyphenols and bone health

A study conducted with 3000 women undergoing osteoporosis screening in Scotland [Hardcastle et al., 2011] demonstrated a significant positive association between energy-adjusted total flavonoid intakes and bone mineral density (BMD) at the femoral-neck and lumbar spine sites ( $p \le 0.05$ ). It was also reported that the annual percentage change in BMD was associated with intakes of procyanidins and catechins ( $p \le 0.05$ ), and that flavanone consumption was negatively associated with bone-resorption markers ( $p \le 0.001$ ).

Previous research has shown that hesperidin (an orange flavanone) prevented bone loss in ovariectomised rodents [Horcajada et al., 2008; Habauzit et al., 2009]. However, when the effect of two years dietary hesperidin supplementation was investigated on bone metabolism in post-menopausal women, no effect on bone mineral density (BMD) was found at any site [Habauzit et al., 2011]. But, in this parallel, placebo-controlled double-blind trial in which 110 women were randomised to take either 500 mg hesperidin or placebo, a significant group x time effect on bone turnover index was shown. There is also a report showing that supplementation of rat diets with quercetin inhibited the rate of bone loss in a rodent model of osteopenia (a pre-osteoporosis condition) [Liang et al., 2011].

- Flavonoids are the polyphenols that have been the most studied for their health benefits.
- The strongest evidence supports the effect of polyphenols and especially of flavonoid classes on the risk of CVD and CHD. Cocoa polyphenols could potentially have an effect on CVD via several putative mechanisms: increased vascular reactivity, reduced blood pressure, improved blood lipid profile.
- There is also relevant evidence for their beneficial effect on diabetes development, osteoporosis and some cancers. But it is currently not possible to determine the specific role of polyphenols.
- Evidence for the benefits of polyphenol-rich foods is increasing. There is a need to focus future research on long-term intervention studies specifically designed to estimate the separate effects of polyphenols from the other compounds of the foods.

# MECHANISMS OF ACTION OF POLYPHENOLS: NEWLY EMERGING EVIDENCE

### by Dr Francesco Visioli

The antioxidant activity of polyphenols potentially explains all the results from epidemiology and trials described in Chapter 2 and, for many years, this has been assumed to be their major mechanism of action. However, although there are many studies showing *in vitro* antioxidant effects of polyphenols often at high and not physiological concentrations (>10  $\mu$ M), solid scientific evidence of their *in vivo* antioxidant activities is scant and the biological relevance of direct antioxidant of polyphenols is being questioned [*Visioli et al., 2011; Hollman et al., 2011*].

So, how do polyphenols improve cardiovascular prognosis? This chapter will explain that the mechanisms of action of polyphenols are manifold and include anti-inflammatory, and detoxifying activities and that the antioxidant activities may be more indirect than previously thought **(Figure 9)**.



#### Figure 9: Some of the manifold activities of polyphenols

The activities of polyphenols are complex: from antioxidant effect already well-studied to prebiotic effects on the gut flora Source: From F. Visioli

# 3.1 Antioxidant activities of polyphenols

### **Direct antioxidant activities?**

The antioxidant hypothesis is the term used to describe the oxidative damage to important molecules such as proteins, lipids, and DNA which accumulates with ageing. This can lead to the pathogenesis of many age-related diseases such as CVD [Hollman et al., 2011]. The moieties producing the damage range from the highly reactive hydroxyl radical (OH) with a short half-life to the less reactive oxygen and nitrogen species with longer half-lives which are able to diffuse from their initial site of origin. These oxidants are counterbalanced by a range of antioxidant systems, mainly consisting of enzymes but with some low molecular weight antioxidants. Some enzymes interact directly with oxidants such as catalase, glutathione peroxidase/reductase, and superoxide dismutase and some contribute indirectly to counteract oxidation at target sites e.g. quinone reductases. There is also a support system of ancillary antioxidant enzymes such as transport systems, metabolizing and conjugating enzymes (Phase I and Phase II).

A direct antioxidant effect for polyphenols in vivo is now thought to be unlikely. Why?

- As discussed in Chapter 1, polyphenols have a limited bioavailability and only very low concentrations (nM) are present in the blood stream and tissues after ingestion of polyphenols compared with other endogenous and exogenous antioxidants. In contrast, most of the *in vitro* studies have used polyphenols at non physiological doses ( $\mu$ mol/L to mmol/L),

- Further, the extensive metabolism of polyphenols during absorption and distribution in the body modifies the structure of the polyphenols which highly impact their bioavailability and their biological activity *[Visioli et al., 2011]*.

Now considering the present evidence on physiological effects of polyphenols, it appears that a direct effect of polyphenols is questionable due to the very low concentrations in plasma. However, presently, no evidence allow to attribute the beneficial physiological effects to a direct antioxidant effects rather than other mechanisms of action [Visioli et al., 2011; Hollman et al., 2011].

### Indirect antioxidant activities of polyphenols

Some phytochemicals, including polyphenols, are processed by the body as xenobiotics. They stimulate stress-related cell signalling pathways that result in increased expression of genes encoding cytoprotective genes. One example of a transcription factor is Nrf2 (nuclear factor erythroid-2-related factor). It binds to the Antioxidant Response Element (ARE) in cells and thus regulates enzymes involved in antioxidant functions or detoxification (e.g. thioredoxin reductase-1 and glutathione peroxidases).

Polyphenols might increase gene transcription of Nrf2 mediated by such response elements [*Yang et al*, 2011; *Scapagnini et al*, 2011] (Figure 10). This provides grounds for the theory of hormesis, *i.e.* when mild stress triggers defence mechanisms. In the case of polyphenols it indicates how they could have an indirect antioxidant action [*Visioli et al.*, 2011].



Figure 10: Indirect antioxidant activity of polyphenols. GSH: Reduced form of glutathione Source: From F. Visioli

One example is found in the paper by Visioli et al [Visioli et al., 2009] who reported a study in which 98 Chinese Malay subjects ingested an olive preparation which was high in phenolics. After 1h, no difference in plasma antioxidant capacity was observed but a significant increase in total plasma glutathione concentration was measured. The authors postulated that the observed effects of the olive phenols on glutathione levels might be governed by the antioxidant response element (ARE)-mediated increase in phase II enzyme expression.

# 3.2 Inflammation

Inflammation is involved in the onset and maintenance of several degenerative diseases and, while useful in the short-term to fight infections and promote wound healing, a longer term anti-inflammatory action represents an important target for selected food components. Several enzymes involved in inflammation depend on cellular "peroxide tone". Polyphenols have been shown to exert anti-inflammatory actions, via multiple mechanisms of actions that include interference with signal transduction and direct inhibition of pro-inflammatory enzymes.

E.g. a prospective study of premenopausal women has shown that whole grain cereal consumption is associated with decreased C-reactive protein and it is believed that the polyphenols in wholegrain may be responsible for this effect [Gaskins et al., 2010]. Recently, bioprocessed whole wheat bread with increased bioavailable polyphenols has shown an anti-inflammatory on *ex-vivo* LPS-challenged blood. In this trial, the ratios of pro-anti-inflammatory cytokines was improved after 3 days of consumption of the bioprocessed bread compared to control by healthy men [Mateo Anson et al., 2011].

In a mouse prostate cancer model, Siddiqui et al, have also demonstrated that tea polyphenols inhibit the NFκB signalling, which is a central control for inflammatory conditions [Siddiqui et al., 2008]. In the same way, cocoa polyphenols are able to reduce NFκB activation in different cell model [Vazquez-Agell et al., 2011].

# 3.3 Increasing nitric oxide bioavailability

There is now quite convincing evidence that flavanols (epicatechin) and probably other polyphenols also increase NO bioavailability [Schroeter et al., 2006] with increased plasma NO metabolites coinciding with improved FMD. So how do polyphenols improve NO bioavailability?

There are a number of possibilities and several have been shown to be plausible. These include (but are not limited to) inhibition of NADPH oxidase (NOX) [Steffen et al., 2008] and increase in levels of endothelial nitric oxide synthase (eNOS) or its activation [Schini-Kerth et al., 2010].

# **3.4 Prebiotic effects**

Increasing evidence also suggests that polyphenols can modulate the microbiota in the large intestine, potentially acting as prebiotics, thus influencing the immune response and modulating some aspects of lipid metabolism.

Recently, Tzounis et al *[Tzounis et al., 2011]* have shown the ability of cocoa polyphenols to modulate gut microbiota. In this trial, high-flavanol diet led to an increase in enteric Bifidobacteria, Enterococcus, and Lactobacilli whereas Clostridia were decreased. This kind of change in microbiota composition is thought to be beneficial for health *[Saulnier et al., 2009]*. Notably, bacterial changes was associated with a change in C-reactive protein concentration, a circulating marker of inflammation.

# 3.5 Metal chelation

Finally, one often overlooked mechanism of action of polyphenols, in particular of ortho-diphenols, is metal chelation [*Mladenka et al., 2010*]. Metals are normally circulated in blood and are also stored as part of other molecules. Examples are iron in hemoglobin and copper in ceruloplasmin. Unbound metals are toxic since they catalyse oxidative reactions, e.g. Fenton's formation of free radicals. Metal chelation by polyphenols, e.g. during food digestion when large amounts of peroxides are formed, lessens the risk of oxidative damage [Kanner & Lapidot, 2001].

Therefore, consumption of polyphenol-rich foods, e.g. extra virgin olive oil [*Visioli et al., 1995*] with meals might lessen oxidative damage independent of their mere antioxidant action.





- The potential mechanisms of action of polyphenols in improving cardiovascular prognosis are complex, manifold, probably interrelated and extended beyond their antioxidant properties.
- Their antioxidant properties appeared to be rather indirect due to their very low concentration in blood and tissues.
- Polyphenols have also been shown to exert anti-inflammatory actions (e.g. interference with signal transduction, direct inhibition of proinflammatory enzymes).
- They might also increase nitric oxide bioavailability leading to improved vascular reactivity.
- Increasing evidence also suggests that polyphenols can modulate the microbiota in the large intestine, potentially acting as prebiotics.
- Metal chelation by polyphenols, e.g. during food digestion when large amounts of peroxides are formed, may lessen the risk of oxidative damage.

### **Future perspectives**

Do we need dietary polyphenols for health? According to the current state-of-the-art on polyphenols science, it is clear that the biological functions of polyphenols in humans could play a role for health protection. But there are still areas to explore to better understand the potential of polyphenols in preventing non-communicable diseases.

There is a strong need to continue developing **appropriate nutrient database** using standardized methods to analyse polyphenols content in foods with special attempts on non-extractable polyphenols and metabolites. This will allow homogenized and precise characterization of foods in epidemiological studies and intervention trials.

Further research on **polyphenol bioavailabity** is required, with regards to the effects of food matrices on absorption, influence of age, gender, genotype and microbiota both on absorption and metabolism. These will help determine the physiological metabolic forms responsible for activity *in vivo* and biomarkers of polyphenols intake. The improvement of bioavailability and the development of polyphenols with enhanced biological activity protected in foods (e.g. by encapsulation) could be a future way to propose healthier foods in general or foods with specific health benefits.

On the other hand, **metabolomics** aimed at the investigation of the whole metabolome (combining food, microbial and endogenous metabolomes), has been proposed as a powerful tool to characterize both the intake and the effects of dietary components on the metabolism. It will help to identify and validate novel markers of polyphenol intake and these will allow much better estimates of the consumption of polyphenol-rich foods and correlations with health outcomes.

Finally, future research should focus on **long-term randomized, controlled dietary intervention trials** to conclude clearly on the unequivocal role that polyphenols play in preventing chronic disease. Attention should focus on the study design to allow the effects of polyphenols to be separated from the other components of the food/diet and on the appropriate selection of controls. Further markers for established risk factors are also essential in these trials to confirm the beneficial effects of these compounds and their mechanisms of actions. The use of Omics will also open up areas for this aim. The outcomes of well-designed studies (epidemiological and interventional) will be useful to develop **specific dietary recommendations on polyphenols**.

The science of polyphenols is already at an exciting stage in terms of potential health benefits and we are about to witness even greater advances in the future.



# **Appendix: Biographies of the speakers**



**Prof Francisco A. Tomás Barberán** Research Professor, CEBAS-CSIC, Murcia, Spain

fatomas@cebas.csic.es

PhD in Pharmacy, Valencia University, Research Professor of CSIC in Murcia (Spain). Co-author of more 250 publications in scientific journals of the areas of Phytochemistry, Agricultural Chemistry, and Food Science and Nutrition. These articles have been cited over 7000 times with an H index of 48. He has developed more than 80 research projects and contracts with industry. He is interested in the role of phenolic phytochemicals on food quality and health. His current research aims to the identification of those food constituents that provide health benefits, the mechanisms by which they act and the effect of genetic, agronomic and processing factors on these metabolites, their bioavailability and the efficacy in humans. He has supervised 20 PhD Thesis and has carried out research in laboratories from England (Reading), Switzerland (Lausanne), France (Lyon), and the USA (Davis). His research has also been oriented to the transfer to industry and he has registered 6 patents of which 3 have been licensed and derived products are actually in the market. He was awarded with the Rhone Poulenc Rorer Award by the Phytochemical Society of Europe in 1997, the Ramón Frial Award, on Food and Health Research in 2004 and the Danone Award to Nutrition and Health Research in 2006. He is Associate editor of the Journal of Agricultural and Food Chemistry of the American Chemical Society. He is a member of the Scientific Advisory Board of different Companies and of the European Joint Programming Initiative 'A Health Diet for a healthy Life'.



Dr Paul Kroon Research Leader, Plant Natural Products & Health Programme Institute of Food Research, Norwich, UK

paul.kroon@ifr.ac.uk

Paul Kroon completed an honours degree in botany at the University of Durham and a PhD in plant secondary metabolism at the University of Hull before joining the Institute of Food Research in Norwich as a biochemist. After a few years working on the enzymology of plant cell wall-degrading enzymes, Paul started to work on flavonoids and other dietary phenolics. He has led the Polyphenols and Health group at IFR since 2001.

His early work focussed on mechanisms of absorption from the gut, including work that established that lactase was essential for small intestinal absorption of dietary flavonoids. Subsequently, he has focussed his research on understanding how flavonoids are metabolised in humans including methods for measuring their appearance in blood, and exploiting this knowledge in two ways: firstly, by allowing the design of in vitro mechanistic studies that are physiologically relevant, and secondly by exploring what factors affect bioavailability and developing foods with improved bioavailability characteristics. He has published >100 peer-reviewed papers concerned with flavonoid absorption and metabolism in humans, the effects of metabolism on the properties of polyphenols, the effects of food processing and food matrix on polyphenol content, composition and bioavailability, and the efficacy and mechanisms by which polyphenols affect vascular function. Kroon's papers have been cited >3000 times and his H-index is 33. He has been awarded > £2.5 million to fund his research over the past 8 years. He chaired the composition group of the EuroFIR BASIS project which developed an online database of composition and bioactivity data for bioactive substances in foods, and has led IFR's contribution to various European research projects including FLAVO and two current projects (BaSeFood and ATHENA). Kroon is an Executive Editor for a leading food science journal, and an editor for the top-ranked food science/technology journal Molecular Nutrition & Food Science. He was Vice President of the International Society Groupe Polyphenols (2008-2010), and regularly presents his research at international scientific conferences.



Dr Francesco Visioli Madrid Institute for Advanced Studies-Food, Madrid, Spain

francesco.visioli@imdea.org

Francesco Visioli earned a degree in Pharmacy and Pharmaceutical Chemistry from the University of Milan and a PhD in Biotechnology from the University of Brescia. After being Full Professor of physiopathology at the UR4 of the Université Paris 6 "Pierre et Marie Curie", where he directed the "Micronutrients and cardiovascular disease" unit, he is now Senior Investigator at the Madrid Institute for Advanced Studies (IMDEA)-Food. He is also Assistant Professor at the College of Pharmacy, Oregon State University. After being involved in neurochemistry, Dr. Visioli's research currently concerns essential fatty acids, namely those of the omega 3, and series natural antioxidants, as related to atherosclerosis and cardiovascular disease. In particular, Dr. Visioli's group discovered the biological and pharmacological properties of olive oil phenolics, including hydroxytyrosol. In addition, Dr. Visioli is being studying bioactive components of plant foods, including lycopene from tomato and biophenols from wild greens. His research ranges from in vitro studies of bioactivity (test tubes, cell cultures) to *in vivo* tests, performed on laboratory animals and/or humans. Dr Visioli has a publication record of over 170 papers and book chapters, which have been cited over 4000 times. He gave invited lectures in over 60 meetings. As related to human health, Dr. Visioli created a method to evaluate the nutritional profile of foods (foodprofile.org), which was published in 2007 and field-tested in 2009. Dr. Visioli is member of the Board of Directors of the International Society for the Study of Fatty Acids and Lipids (ISSFAL), member of EFSA's expert database, and member of several learned societies, including the British Nutrition Society. Currently, Dr. Visioli is the Editor-in-Chief of Pharmacological Research, Associate Editor of Lipids and of Prostaglandins, Leukotrienes and Essential Fatty Acids, and First Editor of the British Journal of Nutrition, in addition to being a member of the Editorial Board of several other journals.

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#### **ABBREVIATIONS:**

ARE: Antioxidant Response Element CEBAS-CSIC: Centro de Edafología y Biología Aplicada del Segura – Consejo Superior de Investigaciones Científicas CHD: Coronary Heart Disease CI: Confidence Interval **CVD:** Cardiovascular Diseases **EFSA:** European Food Standard Agency EPIC: European Prospective Investigation of Cancer **EuroFIR:** European Food Information Resource FENS: Federation of European Nutrition Societies FMD: Flow Mediated Dilatation HDL: High Density Lipoprotein HOMA-IR: Homeostatic Model Estimated Insulin Resistance **HT:** Hypertension IMDEA: Madrid Institute for Advanced Studies **INRA:** Institut National de Recherche Agronomique LDL: Low Density Lipoprotein LPS: Lipopolysaccharide **NFKB**: Nuclear factor kappa B NO: Nitric Oxide Nrf2: Nuclear factor erythroid-2-related factor RCT: Randomized Controlled Trial SNP's: Single Nucleotide Polymorphisms SULT: Sulpho transferases SUVIMAX: SUpplémentation en VItamines et Minéraux Anti-oXydants **UGT:** Glucuronyl transferases **USDA:** United States Department of Agriculture

# NUTRINSIGHT



NUTRINSIGHT N°3 Do we need dietary polyphenols for health? State-of-the-art and perspectives

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Kraft Foods Europe - Biscuits R&D Un établissement secondaire de LU France\* 6 rue René Razel - 91400 Saclay - France

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Polyphenols; flavonoids; phenolic acids; bioavailability; metabolites; microbiota; cardiovascular disease; diabetes; antioxidant; inflammation; prebiotic.



For additional information, please contact:

Kraft Foods Europe - Biscuits R&D Nutrition Department 6 rue René Razel 91400 Saclay – France E-mail: elisabeth.riou@kraftfoods.com

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