

# Tea Expert Newsletter

Issue nine

## **Flavonoids and cardiovascular benefits:**

clinical evidence and  
mechanistic insights on  
the benefits of red wine,  
tea, and cranberries:

**Proceedings of the  
Unilever co-sponsored  
symposium at the VI  
International  
Conference on  
Polyphenols and  
Health**



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# FLAVONOIDS AND CARDIOVASCULAR BENEFITS: CLINICAL EVIDENCE AND MECHANISTIC INSIGHTS ON THE BENEFITS OF RED WINE, TEA, AND CRANBERRIES

**PROCEEDINGS OF THE UNILEVER CO-SPONSORED SYMPOSIUM AT THE  
VI INTERNATIONAL CONFERENCE ON POLYPHENOLS AND HEALTH**  
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## “From the editor”

The series of biennial International Conference on Polyphenols and Health (ICPH) conferences began in 2003, with the aim of raising awareness of polyphenols and their effect on health. Polyphenols are widely recognised as functional components of foods, beverages and plants, with a potential role in the protection of human health from chronic diseases. The conference aims to bring together researchers from around the world engaged in this field, including medicine, biology, chemistry, nutrition, pharmacology, toxicology, plant and crop science.

We previously reported on the 2011 ICPH conference where Unilever held a sponsored session entitled, “Wake Up to Flavonoids”, in issue 4 of our expert newsletter series. At the

latest ICPH meeting (October 2013), Unilever held a co-sponsored session together with PepsiCo and Ocean Spray entitled, “Flavonoids and cardiovascular benefits: clinical evidence and mechanistic insights on the benefits of red wine, tea, and cranberries”. The aim of the session was to focus on the mechanistic insights of the protective effects of polyphenols, and clinical evidence on the consumption of flavonoid-rich foods including cranberries, tea, red wine, and grape juice. This newsletter provides a summary of this sponsored session as well as of selected sessions covering the science behind cardiovascular benefits, and the key messages shared by the scientists around the path to dietary recommendations.

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# 1. INTRODUCTION

The VI International Conference on Polyphenols and Health (ICPH) recently took place in Buenos Aires, Argentina (October 16-19 2013).<sup>1</sup> This is a biennial world conference that gathers the most prominent scientists in the field of polyphenols and health, to share and debate their latest research. The conference attracts scientists from all over the world. This is the sixth conference of its kind, with previous meetings held in Vichy, France (2003), Davis, USA (2005), Kyoto, Japan (2007), Harrogate, UK (2009) and Barcelona, Spain (2011). The next meeting will be held in Tour, France in 2015.

This time, the conference was organized by Dr. Cesar Fraga and his local team at the School of Pharmacy and Biochemistry in Buenos Aires, supported by an international advisory board of well recognized experts in different aspects of polyphenols and health. The meeting included 3 plenary lectures,<sup>14</sup> oral sessions, and more than 100 posters.

Dr Helmut Sies (Heinrich-Heine, University Dusseldorf, Dusseldorf, Germany) gave the opening lecture, which was dedicated to Dr. Federico Leighton. Dr Leighton was a professor at the Catholic University, Chile (died in 2012), who pioneered the study of wine polyphenols and promoted the benefits of the Mediterranean diet, making great contributions to the advancement of the research in this area. Dr Sies gave an overview of how the science of polyphenols has evolved, from the early hypothesis of polyphenols acting as classical antioxidants (now dismissed)

to the current status of the science and future challenges. The conference extensively covered the research on metabolism, metabolomics, molecular aspects of polyphenol actions, cardiovascular benefits, cancer prevention, and polyphenol-gut interactions. There were sessions on neurocognition, long-term degenerative diseases, and epigenomics, Dr Augustin Scalbert (International Agency for Research on Cancer, Lyon, France) gave a plenary lecture on his work on metabolomics and the progress on the expansion of the Phenol Explorer database, and Dr Andrew Waterhouse (UC-Davis, Davis, USA) gave a plenary lecture on wine polyphenols, starting with the history of wine, the early observation of the 'French Paradox', and the current knowledge on wine consumption patterns and benefits. One highlight of the conference was the incorporation of a session dedicated to the discussion around dietary recommendations for flavonoids.

In the following sections, this newsletter will give a summary of selected sessions covering the science behind cardiovascular benefits, and the key messages shared by the scientists around the path to dietary recommendations. Much progress has been made on the understanding of polyphenols and health, and it is clear that human intervention trials are very consistent on cardiovascular health benefits of flavonoids. However, there are still gaps that need to be addressed in order to be in a position to make dietary recommendations.



## 2. FLAVONOIDS AND CARDIOVASCULAR BENEFITS

### CLINICAL EVIDENCE AND EPIDEMIOLOGICAL CONSIDERATIONS

This session on polyphenols and cardiovascular health was co-chaired by Dr. Carl Keen (University of California-Davis) and Dr. Kevin Croft (University of Western Australia). The session was sponsored by MARS Inc. and FLAVIOLA. The following talks were presented at this session.

#### POLYPHENOLS, ENDOTHELIAL FUNCTION AND CARDIOVASCULAR DISEASE

Thomas Lüscher. University Heart Center, University Hospital Zurich and Cardiovascular Research, Institute of Physiology, University of Zurich, Switzerland

#### THE EFFECT OF DIETARY POLYPHENOLS ON VASCULAR FUNCTION AND BLOOD PRESSURE

Kevin Croft. School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia

#### CARDIOVASCULAR BENEFITS OF COCOA FLAVANOLS IN THE HEALTHY GENERAL POPULATION: RELEVANCE TO DIETARY RECOMMENDATIONS

Christian Heiss. Division of Cardiology, Pulmonology, and Vascular Medicine, Medical Faculty, University Dusseldorf, 40225, Dusseldorf, Germany

#### FLAVANOLS AND HEALTH: EPIDEMIOLOGICAL CONSIDERATIONS

Gunther Kuhnle Department of Food & Nutritional Sciences, University of Reading; Department of Public Health and Primary Care, University of Cambridge, UK

#### SUMMARY

The session gave an overview on the clinical evidence on flavonoids and cardiovascular health benefits (with emphasis on the effect of flavanols) and epidemiological considerations.

Human intervention trials consistently show a protective effect of cocoa intake.<sup>2</sup> First evidence of a protective effect of cocoa was obtained in Kuna Indians, a native population living on islands off the coast of Panama, who are protected against the age-dependent increase in blood pressure, and whose mortality from cardiovascular events is remarkably low. The factors related to this protection are clearly environmental rather than genetic because the protection is lost to migration to urban Panama City. One distinctive aspect of Kunas' lifestyle is the enormous amounts of cocoa that they consume daily.

The beneficial effects of cocoa on cardiovascular health may be the consequence of a direct effect on the endothelium [through (-)-epicatechin metabolites] or through modulation of risk factors (such as LDL-cholesterol or insulin sensitivity). In terms of dietary recommendations, Dr. Lüscher highlighted the difference between cocoa and chocolate. It is now known that the processing of cocoa may decrease the amount of (-)-epicatechin (which is believed to

be the main active in cocoa), therefore, the health benefits of the original cocoa may be decreased in the final product. Additionally, chocolate contains sugar, fat, and milk, all of which significantly change the nutritional profile and add calories, and may even counteract the beneficial properties of cocoa.

Dr. Croft showed that both flavonoid-containing foods and isolated flavonoids exert beneficial effects on surrogate markers of cardiovascular health. For isolated flavonoids, evidence shows that (-)-epicatechin and quercetin can augment nitric oxide (NO) status and reduce endothelin-1 concentrations, and may thereby improve endothelial function in humans.<sup>3</sup> On the other hand, flavonoid-rich apples and nitrate-rich spinach can also augment NO status, enhance endothelial function, and lower blood pressure acutely, all outcomes that may benefit cardiovascular health.<sup>4</sup>

A recent study also shows that black tea consumption resulted in lower rates of systolic and diastolic blood pressure variation during night time.<sup>5</sup> These effects, which were immediate at day 1 and sustained over 6 months, were independent of the level of blood pressure and heart rate. This study showed that black tea solids, other than caffeine,

can influence the rate of blood pressure variation during night time. Thus, small dietary changes have the potential to significantly influence the rate of blood pressure variation.

The next speaker, Dr. Heiss, gave an overview on Project FLAVIOLA.<sup>6</sup> This is a collaborative research project that studies the function and delivery of flavanols, to provide the foundations for the development of innovative and natural food products that have a far-reaching impact on European public health and well-being. The project consists of 6 work packages that investigate not only bioavailability of flavanols, metabolic profiles after intake, and vascular effects, but also different aspects that potentially affect the intake of flavanol-containing foods -such as age and gender.

Human intervention trials using a standardized test material of cocoa flavanols show beneficial effects of flavanol intake on a variety of surrogate markers of cardiovascular health (such as blood pressure, flow-mediated dilation or arterial

stiffness). Importantly, the effect of flavanol consumption is consistent across different segments of the population (young and elderly; men and women) indicating cocoa flavanol benefits are manifested in all populations. For correct evaluation of the effects of flavanols, timeframe of consumption (whether the study is acute, chronic, or acute-on-chronic), food matrices, and dose should all be taken into consideration.

Despite the fact that most human intervention trials have seen a beneficial effect of cocoa flavanol intake, observational studies are not so consistent on the association of dietary flavanols with cardiovascular benefits. How can this discrepancy be explained? The accurate estimation of daily intake, the proper characterization of flavanol-rich foods, the timeframe after consumption, and the particular endpoints of analysis may, at least in part, account for the discrepancies.

## 3. FLAVONOIDS AND CARDIOVASCULAR BENEFITS

### CLINICAL EVIDENCE AND MECHANISTIC INSIGHTS ON THE BENEFITS OF RED WINE, TEA, AND CRANBERRIES

This session was co-chaired by Dr. Valerie Schini-Kerth (University of Strasbourg) and by Dr. Olga Pechanova (Slovak Academy of Sciences). The session focused on mechanistic insights of the protective effects of polyphenols, and clinical evidence on the consumption of flavonoid-rich foods including cranberries, tea, red wine, and grape juice. This session was co-sponsored by Unilever, PepsiCo and Ocean Spray.

#### NATURAL PRODUCT-DERIVED POLYPHENOLS ENHANCE THE CARDIOVASCULAR PROTECTIVE ENDOTHELIAL FUNCTION IN HEALTH AND DISEASES BY TARGETING ENOS, OXIDATIVE STRESS AND THE ANGIOTENSIN SYSTEM

Valerie Schini-Kerth, University of Strasbourg, Illkirch, France

#### CRANBERRIES, FLAVONOIDS, AND HEART DISEASE

Johanna Dwyer, Schools of Medicine and Nutrition Science and Policy, and Jean Mayer USDA Human Nutrition Research Center at Tufts University Boston USA

#### THE LINK BETWEEN TEA AND TEA FLAVONOIDS AND CARDIOVASCULAR HEALTH, WITH FOCUS ON VASCULAR FUNCTION

Douglas Balentine. Unilever, Englewood Cliffs, NJ, USA

#### MOLECULAR BASIS OF THE EFFECTS OF RED WINE POLYPHENOL ON CARDIOVASCULAR DISEASES ASSOCIATED WITH ALTERATIONS OF ANGIOGENESIS

Ramarason Andriantsitohaina INSERM U1063, Institut de Biologie en Santé, Angers, France



### SUMMARY

Moderate consumption of wine is associated with cardiovascular protection most likely by increasing the endothelial formation of nitric oxide (NO). Red wine polyphenols cause endothelium-dependent relaxation of coronary arteries, which are critically dependent on a redox-sensitive mechanism.<sup>7</sup>

Dr Schini-Kerth indicated that the specific class of the polyphenols is important, not just the total amount. Different polyphenols (with different chemical structures) may have very different physiological functions. Fruits and berries are known to contain high levels of polyphenols, which cause endothelium-dependent relaxations in isolated arteries. The effect involves endothelium-derived NO, but it appears to be dependent on their polyphenolic composition rather than on the polyphenolic content.<sup>8</sup>

The vascular protective effect of grape-derived polyphenols has been attributable, in part, to their direct action on blood vessels by formation of NO. Concord grape juice regulates the expression of endothelial NO synthase (eNOS) leading to an increased formation of NO in endothelial cells. The stimulatory effect is a redox-sensitive event involving PI3-kinase/Akt, p38 MAPK and JNK pathways, and the inactivation of the FoxO transcription factors, FoxO1 and FoxO3a, thereby preventing their repression of the eNOS gene.<sup>9</sup> Interestingly, animal experiments showed that the protective effect of 2-week treatment with red wine polyphenols persists for 2 weeks after stopping intake of red wine polyphenols, and this effect seems to involve the normalization of the angiotensin system.<sup>10</sup>

Dr. Dwyer reviewed the evidence from epidemiological and human intervention studies on the association between cranberries, flavonoids and heart health. Cranberries are a particularly rich source of phenolic phytochemicals, such as flavonols, anthocyanidins, (-)-epicatechin and procyanidins, particularly dimers with A-type of chemical bond which are unique to cranberries (as opposed to B-type of bond, more common in other fruits and cocoa). Cranberry is rarely consumed fresh, due to its astringent taste; instead, it is popularly consumed in beverages (juices) or in dietary supplements. The manufacturing process will also determine the amount and quality of the bioactives from cranberries that will end up in the final product. Factors such as fruit variety and processing add complexity to the study of the health benefits of cranberries from an epidemiological point of view, because it is difficult to estimate the real intake and identification of the cranberry bioactives.

Anthocyanins from cranberry juice are bioavailable in humans following an acute dose.<sup>11</sup> Chronic cranberry juice consumption has positive cardiovascular benefits, such as

the reduction of carotid femoral pulse wave velocity - which is a clinically relevant measure of arterial stiffness.<sup>12</sup> The mixed outcomes from clinical studies with cranberry products could also result from interventions testing a variety of products, often uncharacterized in their composition of bioactives.<sup>13</sup>

Tea is an infusion prepared from the leaves of *Camellia sinensis* that has been enjoyed since ancient times. Today, tea is recognized as one of the main sources of flavonoids in the Western diet. Green tea is rich in monomeric flavanols (catechins); black tea also contains catechins and it is rich in catechin-derived molecules, such as theaflavins, which are unique to black tea. The full and complete identification of all the flavonoids in black tea is difficult, but significant progress has been made in the characterization of one of the most complex fractions of black tea, the thearubigins.

Dr. Balentine presented the evidence for the association of tea consumption with health benefits, in particular in the context of cardiovascular health. Flow-mediated vasodilation (FMD) represents the ability of the arteries to dilate, and it is predictive of future cardiovascular events. An improvement of 1% FMD reduces the risk of cardiovascular disease by 13-15%.<sup>14</sup> Human intervention trials with tea have consistently shown that tea improves the ability of the arteries to dilate. Two or three cups of tea a day (250-415mg flavonoids) are enough to improve FMD by 2.6%.<sup>15</sup> Human intervention trials have also shown a physiological meaningful reduction of systolic and diastolic blood pressure (2% and 1.5%, respectively).<sup>16</sup> Considering the massive consumption of this beverage at a global level, the impact of this beverage on public health may be highly significant.

Red wine polyphenol compounds (RWPC) exert paradoxical effects on angiogenesis.<sup>17</sup> On the one hand, RWPC protect against deleterious ischemia whose correction requires pro-angiogenic properties to produce new blood vessels; on the other hand, numerous studies report that RWPC inhibit angiogenesis by acting on different vascular cells. Dr. Andriantsitohaina explained that the mechanism by which RWPC exert these paradoxical effects appears to be dependent on the dose used. Thus, low and high doses RWPC have respectively pro- and anti-angiogenic properties on post-ischemic neovascularization in vivo, offering important perspectives for the treatment and prevention of ischemic diseases (low dose) or cancer growth (high dose). Working with estrogen receptor (ER $\alpha$ )-deficient mice, Dr. Andriantsitohaina identified ER $\alpha$  as one of key targets/mediators of the vascular effects exerted by red wine polyphenols with respect to NO production, and may relate to mitochondrial function.<sup>18</sup>

# 4. THE ROAD TO EVIDENCE-BASED DIETARY RECOMMENDATIONS FOR FLAVONOIDS

## HOW DO WE GET THERE?

This session, sponsored by ILSI North America,<sup>19</sup> was chaired by Dr. Douglas Balentine (Unilever, Englewood Cliffs, NJ, USA) and Dr. John Erdman (University of Illinois, Urbana, IL, USA).

### HANDLE WITH CARE: FLAVONOIDS ARE DIFFERENT THAN ESSENTIAL NUTRIENTS

Douglas Balentine. Unilever, Englewood Cliffs, NJ, USA

### REPORTING REQUIREMENTS FOR FLAVONOID RESEARCH: A CRITICAL COMPONENT IN ENHANCING OUR UNDERSTANDING

Mario Ferruzzi, Purdue University, West Lafayette, IN, USA

### FLAVONOIDS: FROM DATA TO DATABASES TO ADEQUATE INTAKES

Jeffrey Blumberg, Jean Mayer USDA Human Nutrition Research Center on Aging and Friedman School of Nutrition Science and Aging, Tufts University, USA

### THE EVOLVING PATH TOWARDS DIETARY GUIDANCE FOR FLAVONOIDS: CHALLENGES, GAPS AND PRIORITIES MOVING FORWARD.

John Erdman Department of Food Science and Human Nutrition, University of Illinois, Urbana, IL 61801, USA

### FLAVONOIDS AND CARDIOVASCULAR HEALTH - WHAT PROGRESS HAS BEEN MADE TOWARDS PUBLIC HEALTH RECOMMENDATIONS FOR FLAVONOIDS?

Carl Keen Departments of Nutrition, and Internal Medicine, University of California, Davis, Davis, CA 95616, USA.

## SUMMARY

The ILSI (International Life Sciences Institute) is a global organization that aims to improve human health, environment, safety, and well being around the world. The North American branch of ILSI (ILSI North America)<sup>19</sup> is a public, non-profit scientific foundation that provides a neutral forum for government, academic, and industry scientists to discuss and resolve scientific issues of common concern for the well-being of the general public. ILSI North America (Bioactives committee) has been working on the critical evaluation of the science of flavonoids, and defining the framework for dietary recommendations.

Dr. Balentine opened the session with some of the questions the committee is trying to address, and gave an overview of critical aspects of the science of flavonoids that still need to gain more consistency. For instance, the high heterogeneity in study design, the diversity of biomarkers of exposure, and the poor characterization of the plant material used are some of the key points that were highlighted by different speakers. Dr. Balentine discussed that we usually look at

endpoints of disease risk reduction, but other biomarkers of health and wellness should also be considered. It was discussed that the type of intervention and clinical trials classically used for a drug-based approach are not appropriate for food compounds, or non-essential nutrients, as in the case of flavonoids.

Dr. Mario Ferruzzi gave details of the different areas that need to be strengthened, such as: the importance of a proper and full characterization of the material (which is not always well characterized by validated methods or reported); the development of databases to evaluate intake (to be able to judge the real exposure by dietary background, and this also includes the food matrix), the proper design of human studies (using proper guidelines for randomized clinical studies), and how we can design pre-clinical studies that help us understand the results obtained from clinical studies.

# 4.



The aim of the databases is to provide the foundation for dietary intake. Dr. Jeffrey Blumberg discussed the importance of this information, in order to begin the process and carry it all forward to dietary recommendations or nutrient reference values. He highlighted the need to collect data appropriately, with information on the design, methods, nomenclature, and appropriate quality controls. The description of composition of plant-based food is not easy, as it may be affected by cultivar, environmental, geography, postharvest preparation, sample size, replication, etc. There are already a number of flavonoid databases in the public domain [USDA –ARS Database on Flavonoids, EUROFIR bioactive substances in Food plants information systems (BASIS), and the Phenol Explorer (INRA)]. How much information is enough to assess intake of flavonoids? All the databases will be constantly evolving, and more data will be always available to add.

Dr. John Erdman addressed the challenges, gaps and priorities going forward. The requirements for dietary recommendations of essential nutrients are clear; however, what level of evidence is required for non-essential nutrients? Are randomized clinical trials really needed, and if so, how many? Do we need systematic reviews? Dr. Erdman discussed that the amount of evidence needed must be in relation with the risk-benefit equation: for substances with small window of safety (high risk), it is clear that more evidence is needed to show that its intake is clearly beneficial

and surpasses the risk. For substances with low risk (such as lutein or flavonoids) less amount of evidence is expected to be required. However, regardless of the amount, the standards by which that evidence is gathered (proper design of clinical trials, identification of the material etc) for high or low risk substance should be the same.

Finally, Dr. Carl Keen shared his view on how close we are to a dietary recommendation. He presented an overview on how the science on flavonoids and cardiovascular benefits evolved over the years, and the significant progress that has been made. On endpoints, Dr. Keen discussed that perhaps we should bring all the measures together (platelet aggregation, flow-mediated dilation, arterial stiffness), as multiple biomarkers together should provide the best predictive value. There are a number of question still unanswered. For instance, how to assess adequate status for flavonoids, considering the short half life in plasma and the extensive metabolism? In the final conclusion Dr. Keen highlighted that the results obtained from numerous intervention trials support the conclusion that consumption of flavanol-rich foods can result in acute (1-30 days) improvement in vascular health parameters that are suggestive of decrease risk for selected chronic diseases. With respect to dietary recommendations for flavonoids, the emphasis should be on defined members of the class, rather than the entire class.

## 5. CONCLUDING REMARKS

### SOME KEY MESSAGES EMERGED FROM THE ICPH:

- 1) Significant progress has been made in the understanding of polyphenol bioavailability in humans. The main circulating forms (metabolites) present in circulation after intake have been identified, including conjugates of glucuronides, sulphates and methoxylated forms, and also gut-microflora derivatives (valerolactones and small molecule weight derivatives). Importantly, the timeframe (time after dosing) is highly important, considering that depending on the time point of observation, the profile of metabolites in plasma can be significantly different.
- 2) There is strong consensus that it is highly unlikely that polyphenols act as direct antioxidants, as it was early hypothesized. Polyphenols are highly metabolized and appeared in plasma at too low concentrations to justify a direct antioxidant action. The health benefits of dietary polyphenols may be explained by other non-antioxidant mechanisms, for instance, by positively affecting vascular function.
- 3) Clinical evidence from human intervention trials consistently indicates that flavonoid-rich foods have beneficial effects on cardiovascular health. Studies using cocoa flavanols or tea have shown a positive effect on surrogate markers, such as flow-mediated dilation or blood pressure.
- 4) In the path to dietary recommendations for flavonoids, much progress has been made to close the gaps in knowledge. There is general agreement among the scientific community that a framework is needed for establishing evidence-based dietary recommendations for non-essential nutrients, such as the flavonoids. There is also consensus that the recommendation should be on particular food components, such as flavan-3-ols, and not the food or general groups of compounds. Challenges still remain, and more evidence on specific flavonoids (not just the food) will be needed.

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## 7. AUTHOR



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During her postdoctoral work, Silvina's research interests have been centred around polyphenol-rich foods, redox biology and inflammation, with particular emphasis on cardiovascular health. Since she joined Unilever, Silvina's main research focus has been around green tea and health benefits, in particular energy metabolism. Along the years, Silvina has built a solid global scientific network which has facilitated fruitful collaborations between the industry and academic partners.

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