

# WINE AND HEALTH: scientific evidences and mechanisms

Conference organized by Comitato Grandi Cru d'Italia  
in collaboration with the Scientific Committee for the Wine  
Pavilion of the Ministry of Agricultural, Food and Forestry Policies

Convivium Room  
"VINO - A Taste of Italy" Pavilion  
Expo Milano 2015



Tuesday, October 27<sup>th</sup> 2015

# INTRODUCTION

The body of evidences about the beneficial effects of wine on our health is substantial and continuously growing. The most compelling evidences regard the protection from cardiovascular diseases and neurodegenerative diseases, which by the way constitute the leading cause of premature death in the Western world. Further studies are needed to determine the role of wine in protecting the metabolic diseases and certain types of cancer, but there are indications that even there the effects may be important. In this workshop, organized with the support of Comitato Grandi Cru d'Italia, four distinguished scientists who devoted much of their time to the study of the biological effects of wine, will outline the state of the scientific evidence in favor of the valuable role of wine in the Mediterranean diet and explain the mechanisms of action of this activity.

I hope that EXPO 2015 will give a chance to increase the popularization of what wine really represents for human health and to spread worldwide the Italian wine culture. This culture looks to the wine not as a simple nice drink, but as a real food, an essential constituent of the Mediterranean diet and probably the most important factor of its benefits. If this culture will spread in countries that represent emerging markets this will further benefit our economic balance.

*Curated by **Prof. Enzo Grossi** - Scientific Advisor Italian Pavilion EXPO 2015*

Enzo Grossi, born 1951, is a medical doctor specialized in Gastrointestinal Diseases, with long lasting experience in Clinical Research and Pharmaceutical Medicine, applied mathematics and informatics.

The experience has been gained in Hospital, University and Pharmaceutical Company settings. Author of more than 150 full papers indexed on PubMed. H index = 34.0; i10-index= 108; Editor of 20 books or special issues of Scientific Journals. Member of a variety of Scientific Societies and Scientific Boards.

Presently E. Grossi acts as Scientific Advisor at Bracco Foundation in Milano and as Scientific Advisor to Italian Pavillon EXPO 2015. Prof. Grossi teaches at IULM University in Milano and Bologna University a new discipline: "Culture and Health".



# WINE AND HEALTH: SCIENTIFIC EVIDENCES AND MECHANISMS

## Program

11.00am - *Introduction*

**Prof. Enzo Grossi**

Scientific Advisor Italian Pavilion EXPO 2015

11.10am - *Wine, cardiovascular protection and longevity*

*Wine and health: affairs of the heart*

**Prof. Giovanni de Gaetano**

Head of the Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo Neuromed in Pozzilli

11.35am - *Wine and neuroprotection*

*Wine, Mediterranean diet and neurodegenerative disorders*

**Prof. Ramon Estruch**

Member of the European Foundation for Alcohol Research Advisory Board; Associate Professor in the School of Medicine at the Barcelona University

12.00am - *Antioxidant effect*

*What is good and what is bad for you: the advantage of ambiguity. The case of alcohol and wine*

**Prof. Fulvio Ursini**

Full Professor of Biochemistry & Human Nutrition, School of Medicine, University of Padova

12.25am - *Gut microbiota*

*Modulating the human gut microbiome for improved health: is there a role for wine?*

**Dr. Kieran Tuohy**

Group Leader for Nutrition and Nutrigenomics at the Centre for Research and Innovation, Istituto Agrario di San Michele all'Adige, Fondazione Edmund Mach

12.50am - *General Discussion and closing remarks*

## Prof. Giovanni DE GAETANO

Giovanni de Gaetano was born on the Gargano Promontory during the Second World War, few weeks after the Fascism fall and before the Armistice. During his secondary studies he was fascinated by the Greek and Latin culture and this passion for humanities paradoxically convinced him to choose medicine for his university studies. MD degree, Haematology specialist, PhD degree at Leuven University, Belgium, he was appointed Director of the Laboratory for Haemostasis and Thrombosis Reserch, at Mario Negri Institute, Milan, while being still a post-doc fellow. At the end of the Eighties, de Gaetano, Donati and a group of young Pilgrim Investigators moved to the Abruzzo region, to found a new research institute, the “Mario Negri Sud”. He was then Director of the Research Laboratories at the “John Paul II” Centre for High Technology Research and Education in Biomedical Sciences of the Catholic University, Campobasso, and is presently Head of the Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli (Isernia). He also holds two honorary doctorates from the University of Debrecen (Hungary) and Bialystok (Poland), and is an Italian Republic Knight. Author of about 500 peer-reviewed publications, with a H-index of 65, his major scientific contributions are related to the “discovery” of low-dose aspirin as an antiplatelet and antithrombotic drug and to the characterization of low-dose wine and beer consumption (in the context of a Mediterranean Diet) as associated with reduced cardiovascular outcomes.



## WINE AND HEALTH: AFFAIRS OF THE HEART

Cardiovascular diseases and cancer are responsible for over two-thirds of deaths in the Western world. Our societies run the risk of being unable to cope with the health costs of this pandemic, without considering the price to be paid in terms of quality of life of people. So far the prevailing approach has been the pharmacologic one. The research has produced remarkable results in this area; however, drug therapies have not always proved to be up to the expectations, especially with regard to primary prevention. That's why science has begun to explore new paths, finding answers in what simply has always been under our observation. Starting with the Mediterranean diet, a secular heritage that culturally binds all the countries of the Mediterranean basin. The Mediterranean diet is characterized by widespread consumption of plant foods, fresh fish, olive oil and a moderate consumption of wine at meals. Meat, dairy products and eggs are instead consumed less frequently. During the last decade, data of the epidemiological study cohort "Moli-sani" has clearly shown that the Mediterranean diet and especially wine consumed in moderation reduces the risk of cardiovascular events, cerebrovascular and neurodegenerative diseases, and significantly decreases total mortality. Great benefits have been demonstrated not only in the field of primary prevention, but also in patients already affected by a previous clinical event or at high cardiovascular risk. In type 2 diabetes, for example, the wine consumed in moderation as part of Mediterranean-type diet was effective in reducing both the risk of death and the incidence of new cardiac events. The path is not without difficulties, because prevention means changing the lifestyle of large populations and waiting a long time to get concrete results. But the improvement in lifestyle, especially of wine consumed regularly during meals, must remain the first soil in which to germinate a successful prevention strategy.

## Prof. Ramon ESTRUCH

Professor Ramon Estruch is Senior Consultant at the Internal Medicine Department of the Hospital Clinic (Barcelona) since 2002. He is also Associate Professor in the School of Medicine at the Barcelona University since 1996, Member of the Board of Directors of the CIBER Obesity and Nutrition, Institute of Health “Carlos III”, Government of Spain, since 2006 and Member of the Advisory Board of the ERAB (European Foundation for Alcohol Research) from European Union since 2010.

The main research lines developed are the following: 1) Cardiovascular effects of Mediterranean diet; 2) Mechanisms of the effects of moderate wine and beer intake: Effects on the expression and function of cellular and endothelial adhesion molecules related to development of atherosclerosis; 3) Effects of chronic alcohol consumption on heart, liver and brain; 4) Effects of different alcoholic beverages on immune system; 5) Effects of olive oil, nuts and cocoa in lipid profile and inflammatory biomarkers related to atherosclerosis.

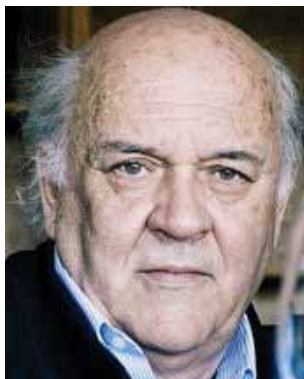
He has published more than 320 manuscripts in peer-review journals such as N Engl J Med, JAMA, Ann Intern Med, Circulation, Arch Intern Med, Am J Clin Nutr, J Nutr, Diabetes Care and PloS One, among others.



# WINE, MEDITERRANEAN DIET AND NEURODEGENERATIVE DISORDERS

Cognitive decline and dementia are major public health concerns in modern societies since an increased lifespan has resulted in an increasing frequency of these age-related diseases. Since there is no specific treatment for these disorders, preventive measures should be used to delay their onset. Healthy lifestyle habits have been considered crucial in reducing the risk of these diseases. Mediterranean diet and its main food components, including red wine, have been extensively studied in relation with occurrence of cognitive decline and Alzheimer disease. Data from large observational studies have suggested that increasing adherence to Mediterranean-type diets relates to better cognitive function and a reduced risk of dementia. In addition, randomized feeding trials, such as the PREDIMED trial (PREvención con Dieta MEDiterránea) have demonstrated with the highest level of scientific evidence that an increased adherence to traditional Mediterranean diet is associated with improved cognitive function. When the role of the different foods included in the Mediterranean diet was analyzed, we observed that the participants with better cognitive function were those with higher consumption of wine, extravirgin olive oil, coffee and walnuts, all foods very rich in polyphenols. Red wine is a food very rich in polyphenols, but it also contains alcohol (ethanol). Alcohol by itself has also been postulated to act as neuroprotective factor though with different mechanisms. In this context, several case-control and cohort studies have analyzed the effects of different alcoholic beverages on cognitive function and incidence of Alzheimer disease and concluded that moderate alcohol consumption is associated with a reduced risk of developing cognitive decline and dementia. However, several other studies have observed that moderate wine consumption (an average of 1.5 glasses a day) can be more effective in slowing down age-related cognitive decline. This higher effect of red wine compared to other alcoholic beverages has been attributed to its high polyphenol content. Part of protective effects of polyphenols contained in red wine has been attributed to an scavenging activity as well as an activation of SIRT-1, among others.

Fulvio Ursini MD, born 1951, serves as professor of biochemistry at the School of Medicine of Padova and as Director of the Post Graduate School on human nutrition. The leitmotif of its studies has been the mechanisms of antioxidant effect. He studied the chemistry of the interaction between enzymatic systems-reducing hydroperoxides and chain breaking antioxidants. This interplay contributed to bridging the long lasting gaps between chemistry, biochemistry and cell biology of free radical oxidations in biology. He discovered the selenoperoxidase GPx4 and clarified the role of selenium catalysis in male fertility. In the frame of studies on redox reactions he described the post-prandial oxidative stress and its link to the protective role of foods containing nucleophiles, namely wine. The pathophysiological outcome of these studies led to the description of an innovative modification of LDL, where a misfolding of a specific loop of ApoB, leads to amyloid-like aggregates compatible with an atherogenetic effect. He first proposed the adaptive mechanism of parahormesis to explain the paradoxical effect of antioxidant activating the nucleophilic tone. He was the founder and co-organized of the series of Congresses on Wine & Health (Italy, France, USA, Chile, South Africa, Australia). H-index (from Google Scholar) 63.





# WHAT IS GOOD AND WHAT IS BAD FOR YOU: THE ADVANTAGE OF AMBIGUITY THE CASE OF ALCOHOL AND WINE

The intake of organic and inorganic compounds (nutrients) satisfies our need of energy and essential substrates and cofactors for specific biochemical reactions. Besides nutrients, foods provide a plethora of chemicals (xenobiotics) absent in the metabolic pathways and not supporting any known indispensable function. Xenobiotics have been described as poisons, drugs or health protecting factors. The dose defines the threshold between these effects. More specifically, the notion of hormesis underscores the fact that a compound toxic at high doses can be health protecting below a threshold, eventually leading to the apparent paradox that a low dose of a toxic compounds is more healthy than abstention. A paradigmatic case is that of alcohol, the moderate assumption of which is more protective than abstention in respect of the risk of cardiovascular diseases, neurodegenerations, inflammatory diseases and total mortality. Among alcoholic beverages, wine is a food that most largely contributes to human health by providing also a series of phytochemicals extending the hormetic effect of alcohol. In other words, wine is by far more protective than alcohol and the reversion point from protection to a harmful effect is shifted at higher doses. Mechanistically, these concepts are framed in the modern view of diseases where damage evolves from an excess of response to injury. Here several phytochemicals present in wine (as in some fruits and vegetables) contribute to maintenance of an optimized inflammatory/anti-inflammatory balance. Pathways of inflammation usually adopt electrophiles (oxidants) as signal transducers, while the counteracting feedback responses are primed by nucleophiles (anti-oxidants). As usual in biology, the primary events activate the feedback, i.e. electrophiles are competent for the activation of the nucleophilic response. Fruit, vegetables, and mainly wine, provide a major source of nutritional anti-oxidants (nucleophiles) but kinetic and metabolic constraints do not permit the direct antioxidant effect in vivo, unsuccessfully searched in the last decades. These compound, instead, give rise by autoxidation to minute amounts of electrophiles (oxidants) in turn competent for the activation of the nucleophilic (antioxidant) anti-inflammatory response. We named this mechanism para-hormesis since the increased defense is primed by a fake damage. In conclusion the "black swan" case of the health protective effect of alcohol is untangled on the light of hormesis, while the evidence that wine does it much better is a para-hormetic effect, where components of wine switch-on the nucleophilic defense mechanisms just by mimicking the signal of oxidants. The prohibitionist recommendation, therefore, to abstain from any intake of alcohol and wine, besides non supported by epidemiology, is also rejected by basic science evidence as it prevents a useful boost of the capacity of optimally dealing with stress. A little or, better, a fake harm trains you to become stronger.

## Dr. Kieran TUOHY

Kieran Tuohy received his PhD from the University of Surrey (UK) in 2000. Between 2000 and 2006 he worked as a Post Doctoral Researcher in the Food Microbial Sciences Unit of Professor Glenn Gibson, University of Reading and in 2006, was appointed lecturer in the Department of Food Science and Nutrition, University of Reading. He now holds a tenured position at Fondazione Edmund Mach, Trento, Italy where he leads the Nutrition and Nutrigenomics Group. His research focuses on the health effects of diet: microbe interactions in the gut and the group has expertise in microbial ecology, fermentation technologies, nutrition, functional food design and testing, metabolomics and metagenomics. He has over 87 international, peer reviewed publications in the area of gut microbiology, a H index of 36 (Google scholar), and is co-editor of the book "Diet-Microbe Interactions in the Gut", Elsevier.



# MODULATING THE HUMAN GUT MICROBIOME FOR IMPROVED HEALTH: IS THERE A ROLE FOR WINE?

The human gut microbiota is now recognized as an important regulator of human health and comprises of thousands of different microbial species. These microorganisms interact closely with their human host through immune cross-talk and at the metabolic level. Indeed, small microbially derived metabolites like short chain fatty acids (SCFA) and small phenolic acids have recently been proven to play a regulatory role in diverse host physiological processes including energy intake and storage, immune homeostasis, gene expression and epigenetics and even brain development and cognitive function. These metabolites derive largely from the action of the gut microbiota on the foods we eat. In particular, microbial fermentation of non-digestible carbohydrates leads to the production of SCFA and the gut microbiota convert complex plant polyphenols into biological available and often biologically active derivatives. Similarly, the foods we eat, especially the amounts and types of carbohydrate and plant derived foods, appear to determine the community structure and diversity of the gut microbiota. Indeed, these two food constituents, fiber and plant polyphenols, can be considered the chemical cornerstones of the Mediterranean diet, a dietary pattern closely associated with both physical and mental health related quality of life. Astonishingly, recent dietary interventions in humans have shown that not only can red-wine impact on the flow of metabolites from the gut and the gut microbiota, but it can actually change the relative abundance of important groups of gut bacteria. In particular, Queipo-Ortuño et al., showed that moderate consumption of red wine or de-alcoholised red win, increased the relative abundance of potentially health promoting bacteria, including those involved in fiber degradation and the production of the beneficial SCFA butyrate, but also notably, bifidobacteria, organisms long associated with human health and often used as probiotics. In parallel, they also reported small but significant improvements in blood markers of inflammation and lipid metabolism, even in this small group of health subjects (n=10). They later showed that this increase in intestinal bifidobacteria was associated with reduced plasma lipopolysaccharide (LPS), a microbiota derived cell wall fragment, which causes systemic inflammation when is leaks from the gut and is associated with increased risk of metabolic syndrome and type 2 diabetes. Such studies highlight the potential of wine as a modulator of the human gut microbiota and their metabolic output, with potential to act on host physiology both within the gut and systemically.



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