Dear Editor,

a recent paper by Margina et al. has shown that quercetin and epigallocatechin gallate induced a dose-dependent increase of membrane anisotropy and polarization in U937 monocytes and Jurkat T lymphoblasts, suggesting that anisotropy increase was correlated with the reduction of lipid peroxidation (Margina et al. 2012). This property has been reported also for erythrocytes.

In mice, the treatment with the bioflavonoids quercetin and diquertin on the physical work capacity, oxidant and antioxidant status of organism, and hemorheological parameters and deformability of erythrocytes have been studied under conditions of chronic physical overstrain provoked by sequential extraordinary running load. Both bioflavonoids significantly increased the physical work capacity of animals and prevent from the development of physical overstrain syndrome (Tipikin et al. 2011). Phenolic extracts from two monofloral Cuban honeys, rich in lipophilic compounds, were shown to possess the ability to inhibit 2,20-azobis(2-methylpropionamide)dihydrochloride (AAPH)-induced oxidative damage (hemolysis, lipid peroxidation and cytosolic depletion of reduced glutathione and decrease of superoxide dismutase activity) in erythrocytes (Alvarez-Suarez et al. 2012). Polyphenolic components showed an important total antioxidant capacity measured by trolox-equivalent antioxidant capacity assay (TEAC) and oxygen radical absorbance capacity assay (ORAC) assays, as well as a relevant radical scavenging activity performed by electron paramagnetic resonance (EPR) spectroscopy. In this study, about a dozen of phenolic compounds were identified using HPLC-LC/MS with quercetin as the most abundant flavonoid (Alvarez-Suarez et al. 2012). A possible target in this mechanism might be phosphatidylinositol-3-kinase (PI3K). Some recently reported evidence has shown that 4-hydroxy-2-nonenal (4-HNE) is a major lipid peroxidation product in the retina and the retinal pigment epithelium. When cultured ARPE-19 cells were treated with different concentrations of 4-HNE and a PI3K inhibitor, LY294002, the transcriptional activity of NF-E2-related factor 2 (Nrf2) and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-dependent manner (Chen et al. 2009). The modulatory subunit of GCL was up-regulated and GSH increased in a dose-de...
peroxidation may be considered also a possible cause in the eradication of microbial infection. For example, oral quercetin administration in guinea pigs decreases *H. pylori* infection in the gastric mucosa and reduces both the inflammatory response and lipid peroxidation. In the antrum of infected quercetin-treated animals, a significant diminution of neutrophil leukocyte infiltration was observed compared with the infected non quercetin-treated animals; furthermore, the lipid hydroperoxide concentration in the antrum was significantly decreased in infected animals treated with quercetin, whereas in the corpus no significant differences were observed (Gonzalez-Segovia et al. 2008). This aspect is very intriguing and encourages further research on flavonoids as anti-microbial substances. In the next future, biochemical and genetic studies on cellular and animal models on the mechanism(s) of action of phytochemicals provide a functional explanation of how and why a diet rich in fruits and vegetables is considered healthy. It is not unusual to find molecules that protect against diseases, which greatly differ from a physio-pathological point of view, such as oxidative stress-mediated disorders. Quercetin falls into this category and possesses a broad range of biological properties. Uptake, metabolism and circulating concentrations of quercetin and its metabolites suggest that a regular diet provides amounts of quercetin (<1 μM) not compatible with its chemopreventive and/or cardioprotective effects. However, it appears relatively easy to increase total quercetin concentrations in plasma (>10 μM) by supplementation with quercetin-enriched foods or supplements. Multiple lines of experimental evidence suggest a positive association between quercetin intake and improved outcomes of inflammatory cardiovascular risk. Quercetin can be considered the prototype of a naturally-occurring chemopreventive agent, especially for endothelium, because of its key roles in eliciting an anti-oxidative response, although several critical points must be taken into account when considering the potential therapeutic use of this molecule. The design of specific clinical trials is extremely warranted to depict possible applications of quercetin in oxidative stress and lipid peroxidation.

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Reply from D. Margina and M. Ilie

A great deal of scientific research has been focused lately on the role of food stuff in promoting health. There is an increased interest from both the consumers and researchers regarding the active role of food on the health state and on longevity. For example, the Mediterranean diet, flavonoid-rich, is considered to decrease the incidence of atherosclerotic based cardio-vascular disease and also to improve health in patients with hyperglycemia, obesity and insulin resistance – impairments with high incidence in modern societies. Quercetin and epigallocatechin gallate (EGCG) are among the most studied polyphenols in the frame of health-promoting food supplements (a search on PubMed with these terms returned as much as 1043 articles in 2011).

Several studies support the antioxidant potential of certain phenolic phytochemicals (including quercetin and EGCG); other disease-preventative characteristics have been pointed out in several studies, including in the Letter to editor by Dr. Chirumbolo (Procházková et al. 2011).

However, the research concerning the effects of flavonoids is mostly based on animal and cell line models, human studies having a lower extent; some of the results attributed to polyphenols come from extremely old, even mythological observational studies (as cited by Larson et al. 2012). It is difficult to presume, from a relatively small number of well designed and controlled human trials, how polyphenols improve the cardio-vascular function or the glucose homeostasis (Ostertag et al. 2010; Alexandru et al. 2012). Clinical studies which investigate the potential role of polyphenols in health and disease are difficult to design, as long-term studies are interfered by the treatment and the evolution of the disease. Another limitation comes from the fact that flavonoids are intensely metabolized in the gastro-intestinal tract and in the liver, and the initial polyphenol concentration remaining bio-available is under debate. Moreover, there are recent reports showing that differences between human microflora are associated with qualitatively different patterns of metabolites in some flavonoids (Mladěnka et al. 2010). Also, there are interferences between different polyphenols at the level of metabolizing enzymes. For example, the methylation of green tea polyphenols in vivo may limit their direct effects. Quercetin acts as an inhibitor of catechol-O-methyltransferase (COMT) and is reported to increase the cellular absorption of EGCG and to decrease methylation rate; animal studies pointed out that quercetin induces a 2- to 3-fold increase of total and non-methylated EGCG in lung and kidney and an increasing trend in liver (Wang et al. 2012).

Another arguable point raises from the plasma polyphenol concentrations reached after normal dietary intake: some authors state that quercetin levels up to 10 μM may be achieved when using an enriched diet (Tribolo et al. 2008; Margina et al. 2012a,b), but others consider 2 μM as physiologically achievable and 10 μM as supraphysiological concentrations (Winterbone et al. 2009; Jin et al. 2010).

Cell line studies have also limitation in translating the results to in vivo research. Among them, one can cite the fact that studies performed on cells have to take into account not only the parent polyphenol but also the effect of the main metabolites generated in humans. Comparative results showed for quercetin that the main metabolites (quercetin 3'-sulfate, quercetin 3-glucuronide and 3'-methylquercetin 3-glucuronide) did not exhibit the anti-inflammatory effects that have been proved for quercetin on smooth muscle cells as well as on islet β-cells (Cho et al. 2012).

The mechanisms through which flavonoids modulate in vivo glucose homeostasis and influence the cardio-vascular function are not completed. Still, an analysis of 42 acute or short-term chronic clinical studies, that included 1297 participants, showed that flow-mediated dilatation and insulin resistance parameters was improved by chocolate or cocoa consumption, in association with a significant reductions in serum insulin (Hooper et al. 2012). Wedick et al. (2012) proved that a consumption of anthocyanin-rich foods, particularly blueberries and apples/pears was associated with a lower risk of type 2 diabetes in men and women. The anti-obesity effect of EGCG, is supported by in vivo data, which have shown that EGCG decreased food uptake, lipid absorption, blood lipids and leptin levels, also stimulating energy expenditure, fat oxidation, high density lipoprotein levels, and fecal lipid excretion (Moon et al. 2007). Green tea catechins have a protective effect on weight gain (Brown et al. 2011).

As stated by Dr. Chirimbolo, polyphenols improve outcomes of inflammatory cardiovascular risk; for example, quercetin inhibits the in vitro proliferation of autoimmune T-cells and the expression of the proinflammatory cytokine TNF-α in human mononuclear cells (Sternberg et al. 2008). Experimental studies report an antihypertensive effect of flavonoids registered for hypertensive animal models but not for healthy ones, without a positive effects on elevated blood pressure in humans (Mladěnka et al. 2010).

Still, even if authors state that additional larger, longer-duration and extensive trials are required to confirm the exact mechanism of cardiovascular benefits coming from polyphenols and their effects on glucose homeostasis and adipose tissue, incorporating plant foods that are rich in flavonoids in the diet of healthy individuals could help to reduce cardio-vascular risk (Ostertag et al. 2010; Alexandru et al. 2012).

In conclusion, the influence of polyphenols on health and disease is far from being completely understood, even if their role in diabetes, obesity and cardiovascular disease has been documented. Research approaches to clarify their chemical- molecular mechanisms of action, role in normal
and abnormal metabolic states as well as interaction with other agents (food, medicines, pollutants, etc.) are still needed, be they in silico, on fakes or other artificial models, in vitro and in vivo (in both animal and human). These could lead to a sound way of using polyphenol-rich diets in health and disease.

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