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Editorial

Dietary Polyphenols and Their Effects on Cell Biochemistry and Pathophysiology

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Polyphenols, occurring in fruit and vegetables, wine, tea, extra virgin olive oil, chocolate, and other cocoa products, have been demonstrated to exert beneficial effects in a large array of disease states, including cancer, cardiovascular disease, and neurodegenerative disorders. Many of the biological effects of polyphenols have been attributed to their antioxidant properties, either through their reducing capacities per se or through their possible influences on intracellular redox status. As such, polyphenols may protect cell constituents against oxidative damage and have been reported to limit the risk of various degenerative diseases associated with oxidative stress, including cardiovascular diseases, type 2 diabetes, and cancer. However, accumulating evidence suggests that the classical hydrogen-donating antioxidant activity is unlikely to be the sole explanation for their cellular effects *in vivo*. Indeed, it has recently become clear that, in complex biological systems, polyphenols are able to exhibit several additional properties which are yet poorly understood. It is evident that polyphenols are potent bioactive molecules and a clear understanding of their precise mechanisms of action as either antioxidants or modulators of cell signaling is crucial to the evaluation of their potential as chemopreventive or anticancer agents and inhibitors of neurodegeneration.

This special issue comprises 14 original research articles that further expand our understanding of the biological functions of polyphenols from different sources and 9 review articles that summarize the current knowledge on the beneficial effects of polyphenols on health.

Potential Effect of Polyphenols in Cancer. Although epidemiological studies have not yet provided conclusive results on the chemopreventive and anticancer effect of tea polyphenols, there is an increasing trend to employ these substances as conservative management for patients diagnosed with less advanced prostate cancer. Two groups (S. Cimino et al. and P. Davalli et al.) review the most recent observations related to tea polyphenols and human prostate cancer risk, in an attempt to better outline their potential employment for preventing prostate cancer.

The original paper by C. Oleaga et al. shows that polyphenolic extracts from coffee, as well as the single constituent caffeic acid, decrease cyclin D1 in HT29 colon cells, thus suggesting chemopreventive properties for both substances. P. Baumeister et al. presented data regarding antimutagenic effects of curcumin and epigallocatechin-3-gallate in human oropharyngeal mucosa cultures exposed to cigarette smoke condensate indicating that dietary polyphenols are capable of preventing tobacco-related genotoxicity in the mucosa of the upper aerodigestive tract.

Regarding other cancer types, two groups (D. Zhang et al. and C. Widén et al.) report the antioxidant and growth inhibiting effects of flavonoid extracts on erythrocyte and an erythroleukemia cell line, respectively.

Caffeic, syringic, and protocatechuic acids are phenolic acids deriving directly from food intake or generated following gut metabolism of polyphenols. L. Zambonin et al. explore the antioxidant activity of these compounds in membrane models and in a leukaemia cell line, HEL.

These compounds showed a chain-breaking antioxidant in membrane models and were able to contrast the intracellular ROS increase due to exogenous oxidative stress in both leukaemia and normal cells. These data further support the antioxidant ROS-depleting approach as a valuable strategy in cancer therapy.

Potential Effect of Polyphenols in Cardiovascular Diseases. Quercetin, a naturally occurring flavonoid, has been shown to down regulate inflammatory responses and to exert cardioprotection. C. Angeloni and S. Hrelia present a study on the protective effect of quercetin on rat cardiac dysfunction during sepsis and demonstrate that this flavonoid is involved in the inhibition of cell growth as well as the induction of apoptosis. These results suggest that quercetin might serve as a valuable protective agent in cardiovascular inflammatory diseases.

Vascular protective effects and antiatherogenic properties of anthocyanins have now been recognized. M. Akhlaghi and B. Bandy compared the protective effect elicited by different flavonoids using rat embryonic ventricular H9c2 cells subjected to simulated ischemia-reperfusion and to tert-butyl hydroperoxide. They also tried to distinguish between indirect (preconditioning) effects versus direct effects. The results supported the possibility that catechins have the capacity to act as preconditioning agents while in acute situations of oxidative stress quercetin and epigallocatechin gallate are the most potent antioxidants amongst the flavonoids tested.

The study by J. Paixão et al. expands our knowledge about the molecular mechanisms underlying the vascular protection afforded by anthocyanins in the context of prevention of endothelial dysfunction and atherosclerosis. Data reported that malvidin-3-glucoside decreases the formation of reactive species after cell aggression and inhibits mitochondrial apoptotic signaling pathways induced by peroxynitrite.

Moreover, positive effects were also determined *in vivo* for the administration of red wine extracts on hypertensive rats, by A. Kondrashov et al.

Potential Effect of Polyphenols in Neurodegenerative Diseases. C. P. Dias et al. discuss in a review article some recent findings addressing the effects of different dietary polyphenols on hippocampal cell proliferation and differentiation, models of anxiety and depression. Dietary polyphenols appear to exert positive effects on anxiety and depression, possibly in part via the regulation of adult hippocampal neurogenesis (AHN). Studies on the effects of dietary polyphenols on behavior and AHN may play an important role in the approach to use diet as part of the therapeutic interventions for mental health related conditions.

Wine polyphenolic compounds are well known for the antioxidant properties such as their ability to scavenge free radicals and also regulate NO activity. Numerous neuroprotective mechanisms of action have been proposed, suggesting that polyphenols may exert their activities by inhibiting the production of reactive oxygen species, therefore reducing inflammation and modulating the activity of intracellular signal transduction molecules, as reported by A. Basli et al.

An extensive review by D. Vauzour reports recent evidence suggesting that polyphenols beneficial effects involve decreases in oxidative/inflammatory stress signaling, increases in protective signaling, and neurohormetic effects leading to the expression of genes that encode antioxidant enzymes, phase-2 enzymes, neurotrophic factors, and cytoprotective proteins. Specific examples of such pathways include the sirtuin-FoxO pathway, the NF-κB pathway, and the Nrf-2/ARE pathway. Together, these processes act to maintain brain homeostasis and play important roles in neuronal stress adaptation and, thus, polyphenols have the potential to prevent the progression of neurodegenerative pathologies.

In another review by S. Davinelli et al., the potential neuroprotective role of some polyphenols has been discussed. In particular, the authors have highlighted the correlations between the neuroprotective functions of the selected polyphenols and their potential therapeutic value in Alzheimer disease.

D. Hu et al. showed that schisandrin (SCH) significantly improved $A\beta_{1--42}$ induced short term and spatial reference memory impairments *in vivo*. Furthermore, in the cerebral cortex and hippocampus of mice, SOD and GSH-peroxidase activities, GSH level, and GSH/GSSG ratio were increased, and levels of malondialdehyde and GSSG were decreased by the treatment of SCH. These results suggest that SCH is a potential cognitive enhancer against Alzheimer's disease through antioxidative action.

In the study by J. Bournival et al., the effects of quercetin and sesamin on neuroinflammation induced by the parkinsonian toxin 1-methyl-4-phenylpyridinium (MPP+) in a glial-neuronal system have been investigated. These data demonstrate that quercetin and the lignan sesamin diminish MPP+-evoked microglial activation and suggest that both these molecules may be regarded as potent, natural, anti-inflammatory compounds.

Role of Polyphenols in Redox Modulation. M. Chohan et al. investigate the effect of cooking and digestion on the anti-inflammatory activity of the culinary herbs. This study shows that the culinary herbs, rosemary, sage, and thyme, in quantities used for cooking, possess significant anti-inflammatory activity that may be due to their polyphenol content.

Mate tea is obtained by the aqueous extraction of the leaves of *Ilex paraguariensis* and it is consumed every day by millions of individuals in South America. B. Scolaro et al. investigate the influence of acute and chronic intake of mate tea on the effects elicited by acute and chronic administration of ethanol. The results showed that acute and chronic mate tea administration prevented oxidative stress in the hippocampus and blood of rats, caused by the *in vivo* administration of ethanol. This suggests that mate tea may have a high antioxidant capacity, probably due to its bioactive components and that mate tea ingestion could prevent oxidative stress-related diseases.

J. Baran et al. address the relationship between apoptosis and delayed luminescence in human leukemia Jurkat T cells under oxidative stress and the protective effects of two flavonoids, quercetin and epigallocatechin gallate applied alone or in combination with menadione or H_2O_2. Menadione, epigallocatechin gallate, and H_2O_2, but not quercetin, interacted with flavine mononucleotide (FMN) and altered its electronic configuration, thus reducing delayed luminescence emission.

Relatively to review articles, I. Andújar et al. discuss the potential health benefits of cocoa polyphenols, P. Oyetakinwhite et al. survey the protective mechanisms of polyphenols from green tea with special emphasis of the effects on skin, and M. Ciz et al. summarized contemporary knowledge on the effects of various flavonoids on the respiratory burst of mammalian neutrophils.

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