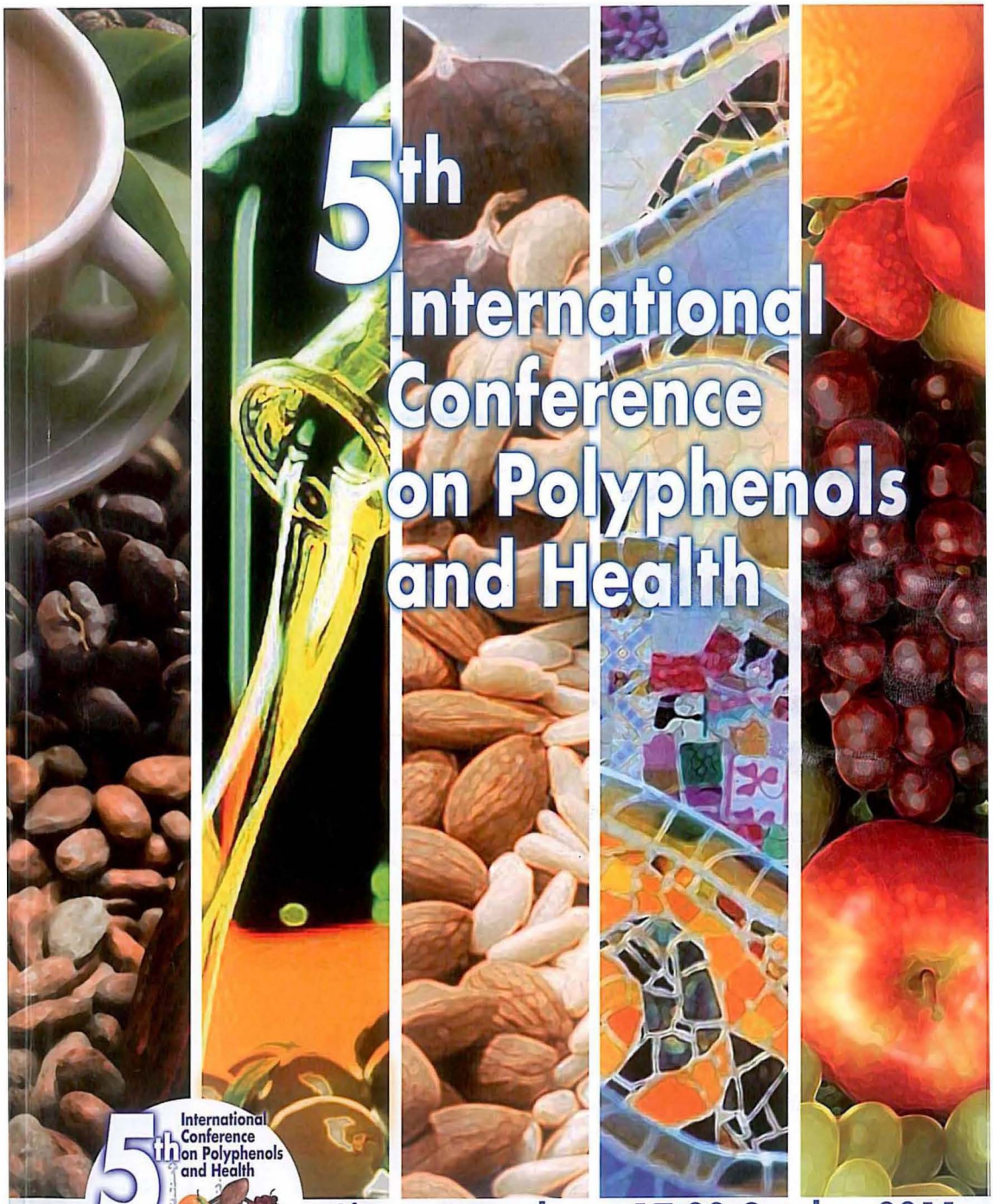

5th International Conference on Polyphenols and Health

5th International Conference on Polyphenols and Health
Sitges Barcelona 2011

Sitges, Barcelona, 17-20 October 2011

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STRUCTURAL MOTIVES OF 2,3-DEHYDROSILYBIN RESPONSIBLE FOR MODULATION OF MITOCHONDRIAL PRODUCTION OF REACTIVE OXYGEN SPECIES

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Objectives: Flavonolignans silybin and 2,3-dehydrosilybin isolated from the seeds of milk thistle (Silybum marianum) possess pleiotropic biological activities including anticancer and cytoprotective effects. Due to their antioxidant activity, we tested these compounds and large series of their semisynthetic derivatives on their inhibitory effects on mitochondrial reactive oxygen species (ROS) production. The aim of this study was to determine structural features of these compounds responsible for their function as uncouplers of oxidative phosphorylation.
Methods and materials: Isolated intact rat heart mitochondria were used for detection of respiration, membrane potential and ROS production using the Oroboros Oxygraph.
Results: Titration (0.01 – 20 μM) of silybin and its derivatives resulted in only a mild decrease in the mitochondrial ROS production, whereas 2,3-dehydrosilybin and some of its methyl-derivatives having free 7-OH group exerted more profound effect. Introduction of more acidic carboxylic function into the structure of 2,3-dehydrosilybin led to even higher decrease of ROS production as a consequence of their ability to uncouple mitochondria.
Conclusions: Present SAR-study enabled to define structural motives responsible for uncoupling activity and decrease of mitochondrial ROS production: 3-OH connected to 2-phenylchromen-4-one moiety and free 7-OH group. Moreover, the effect of these compounds on ROS production seems to be indirect, as compounds with blocked antioxidant functions were still potent uncouplers.
Grants: P301/11/0662 P207/10/0288 OC09045 LD11051 AV0Z502005

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ANTI-INFLAMMATORY EFFECTS OF PLANT POLYPHENOLS IN HUMAN KERATINOCYTES EXPOSED TO VARIOUS INFLAMMATORY STIMULI

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Anti-inflammatory effects of plant polyphenols in human keratinocytes exposed to various inflammatory stimuli Patapovich Ala; Kastsiuk Uladzimir; Lulli Daniela; Pastore Saveria; De Luca Chiara; Korkina Liudmila Exposure of normal human epidermal keratinocytes (NHEK) to inflammatory stimuli such as solar UV irradiation and lipopolysaccharide (LPS) was exploited to study acute inflammatory responses in the skin and possible protection by plant polyphenols (PPs). UV irradiation (1.0 J/cm2, 90% UVA + 10% UVB) was produced by Solar Simulator. Gene expression was analyzed by Q RT-PCR, aryl hydrocarbon receptor (AhR) and p65 NF-kappaB was investigated in the nuclear fraction by Western Blot. Exposure of NHEK to solar UV irradiation resulted in a significant increase in mRNA expression of inflammatory markers. Proinflammatory effects of UV irradiation were dose dependent. However, if expression of TNFá, IL-8, and ICAM1 mRNA was positively correlated with the dose of irradiation, the greater impact on the expression of COX2 mRNA was made by lower doses of UV. Studying effects of PPs on UV-induced stress response of NHEK revealed their positive influence on inflammatory signaling. The most effective was quercetin and verbascoside. Pretreatment of keratinocytes with these compounds markedly prevented over expression of proinflammatory genes. Quercetin and verbascoside also suppressed NF-kappaB activation and AhR-mediated signaling, while rutin, polydatin and resveratrol further activated NF-kappaB and AhR machineries in UV-exposed NHEK. The PPs also remarkably inhibited LPS-induced inflammatory response. However, significant differences in the effects of plant polyphenols on expression of inflammation-related genes, on NF-kappaB activation and on AhR-mediated signaling were found between NHEK treaded with solar UV and LPS. Thus, the beneficial effect of plant polyphenols may be a result of modulation of signal transduction pathways at the level of NF-kappaB and AhR transcriptional activity.

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THE ELLAGITANNIN METABOLITES, UROLITHINS, AND THEIR GLUCURONIDE CONJUGATES IMPROVE TNF-alpha INDUCED INFLAMMATION AND ASSOCIATED MOLECULAR MARKERS IN HUMAN AORTIC CELLS

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Objectives: Consumption of fruits like pomegranate, berries and walnuts has been associated with cardiovascular health benefits. These products contain relevant amounts of the polyphenol antioxidants ellagitannins (ETs). Numerous in vitro as well as some in vivo studies indicate that ETs show relevant antiatherogenic, antithrombotic, anti-inflammatory and antiangiogenic activity which supports a potential preventive effect against cardiovascular diseases. However, ETs exhibit low bioavailability and are transformed in the gut to ellagic acid (EA) and its microbiota metabolites urolithins. Urolithin-A (Uro-A) and urolithin-B (Uro-B) are found in the plasma, mostly as glucuronide or sulphate conjugates, at concentrations in the nM to low μM range. The aim of the current work is to investigate whether the ET metabolites, urolithins and their glucuronide derivatives, exhibit vascular protective effects.
Materials and methods: Human aortic endothelial cells (HAECs) were treated with the inflammatory cytokine TNF-á and each of the tested compounds, urolithins and their glucuronide conjugates (15 μM), for 4 h and 12 h to determine monocytes adhesion and endothelial cells migration, respectively. The expression levels of related adhesion cytokines and growth molecular markers were also measured.
Results: Uro-A and, more noticeably, Uro-A glucuronide inhibited monocytes adhesion and endothelial cells migration in TNF-á treated cells without impairing their viability. The observed effects were associated to a regulation of several associated molecular markers.
Conclusions: Our results indicate that the gut microbiota ET-derived metabolite, Uro-A, and its glucuronide conjugate, ameliorate the inflammatory response in human aortic endothelial cells by moderately reducing the adhesion of monocytes and the migration of endothelial cells and regulating the levels of associated molecular markers. Our results suggest that these metabolites may be, at least in part, involved in the beneficial effects against cardiovascular diseases attributed to the consumption of ET-containing foods.

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ANTIOXIDANT ACTIVITY OF THYMUS CITRIODORUS

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Background and aims: Thymus citriodorus, or lemon thyme, is used as a medicinal plant in the treatment of asthma and other respiratory diseases, although the mechanism of its beneficial properties is poorly understood. The aim of the present study was to determine the antioxidant ability of the polyphenols present in this plant.
Methods: An ethanolic extract was prepared and its antioxidant activity was determined by in vitro measurement of its 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) scavenging potential, reducing power, and protective effects against the generation of reactive oxygen species (ROS) induced by potassium dichromate (5 and 25 lM) in hepatoblastoma HepG2 cells. The non-toxic range of extract concentrations was determined by MTT test, after exposure of HepG2 cells to the extract (1–200 μg/mL) for 72 h. ROS generation was measured by flow cytometry using dichlorofluorescein diacetate after 48 h of incubation with the extract.
Results and discussion: Concentrations of extract able to decrease to 50% (EC50) DPPH absorbance and reducing power were 0.32±0.05 mg/mL and 0.77±0.15 mg/mL, respectively. These findings indicate that the components of the extract have a relevant radical scavenging ability towards nitrogen free radicals and high reducing capacity. As revealed the MTT test, maximal non-toxic concentration of the extract was 50 μg/mL. This concentration was further used to treat HepG2 cells resulting in a decreased rate of ROS production, both under basal conditions or when oxidative stress was induced by potassium dichromate. Antioxidant protection was approximately 60%.
Conclusion: Our results suggest that, since luteolin-7-O-glucoside, apigenin-7-O-glucuronide and rosmarinic acid are major components of Thymus citriodorus ethanolic extract [1], these phenolic constituents may be involved in its antioxidant properties. Accordingly, further investigations to elucidate the actual contribution of each compound to the overall protective effect are needed.
References: [1] Pereira, O. R. et al. Food Chem. submitted for publication