REVIEW

In vitro Metabolomic Approaches to Investigating the Potential Biological Effects of Phenolic Compounds: An Update

Úrsula Catalán 1,a, Laura Barrubes 1,b, Rosa Maria Valls 1,c, Rosa Solà 1,d*, Laura Rubió 1,e,2

1 Functional Nutrition, Oxidation and Cardiovascular Diseases Group (NFOC-Salut), Technological Center of Nutrition and Health (CTNS), Institut d’Investigació Sanitària Pere Virgili (IISPV), Faculty of Medicine and Health Sciences, Universitat Rovira i Virgili, Reus 43201, Spain
2 Food Technology Department, Universitat de Lleida-AGROTECNIO Center, Lleida 25198, Spain

Received 23 March 2016; revised 15 December 2016; accepted 22 December 2016
Available online 24 May 2017
Handled by William C.S. Cho

KEYWORDS
Cell-based; Metabolomics; Phenolic compounds; Mechanism of action; Disease prevention

Abstract Dietary phenolic compounds (PCs) have been receiving interest for their presumed roles in disease prevention. However, there is a lack of studies on the underlying molecular mechanisms. In this regard, in vitro metabolomic approaches are suitable for the investigation of the molecular changes in response to PC exposure. Up to date, the biological effects of PCs have only been examined for PCs from rosemary (Rosmarinus officinalis), olive oil, and resveratrol using cell-based metabolomic approach, although transcriptomic and/or proteomic studies have also been conducted in the same in vitro cell experiment in some cases. Our integral analysis of the reviewed studies suggest that PCs may be involved not only in basic cellular processes or macro- and micro-nutrient metabolism, but also in specific metabolic pathways that have been thoroughly investigated. These modulated pathways could have a clinical impact on neurodegenerative diseases, type 2 diabetes, cancer, and cardiovascular diseases. In conclusion, the in vitro metabolomic approaches provide additional information of the molecular mechanisms involved in disease risk reduction of dietary PCs. In order to elucidate the mechanisms of action of PCs, more metabolomic cell-based studies are needed and testing the physiological conjugated forms of PCs in these cell systems could be of special interest.

* Corresponding author.
E-mail: rosa.sola@urv.cat (Solà R).
a ORCID: 0000-0001-8884-9823.
b ORCID: 0000-0001-7736-7044.
c ORCID: 0000-0002-3351-0942.
d ORCID: 0000-0002-8359-235X.
e ORCID: 0000-0001-8973-2942.

Peer review under responsibility of Beijing Institute of Genomics, Chinese Academy of Sciences and Genetics Society of China.
Introduction

Phenolic compounds (PCs) are characterized by a chemical structure of hydroxylated aromatic ring(s). They are ubiquitously present in plants as secondary metabolites [1] and represent the most quantitative phytochemicals supplied by the diet [2]. So far, ~8000 PCs have been identified, which can be classified into different subclasses according to the number of aromatic rings in their structure, the elements that bind the rings with each other, and the substituents linked to the rings. Accordingly, four main families can be identified, namely phenolic acids, flavonoids, stilbenes, and lignans [3].

PC consumption is estimated at about 1564.56 mg of gallic acid equivalent/person/day [4]. The most important nutritional sources of PCs are fruits and vegetables, green and black tea, red wine, coffee, cocoa, and extra virgin olive oil [5]. Likewise, herbs, spices, nuts, and algae are potentially important sources of PCs as well, depending on culinary habits [6]. During the absorption and metabolism process, PCs are also subjected to changes and their bioactivity can consequently be modified [7].

PCs have been widely examined in humans, animals, and in vitro studies [1]. Currently, there is an increasing interest in exploring the practical applications of PCs focusing on their health-promoting and disease-preventing properties against type 2 diabetes mellitus (T2DM) [8], cardiovascular diseases (CVDs) [9], neurodegenerative diseases [10], or cancer [11]. However, mechanistic studies are still lacking.

In this context, metabolomics, transcriptomics, and proteomics may contribute to elucidating the molecular targets of PCs [12]. Each omics technology, alone or all together, is offering the researchers the possibility of linking food with health and diseases. The comprehensive vision to improve consumer’s well-being and knowledge using and integrating advanced omics platforms is called ‘foodomics approach’ [13]. Therefore, foodomics might provide a huge quantity of data about the pathways which PCs could be involved in and the information extracted could be translated to prevent, improve the time course, or even reverse the disease progress [13].

In particular, the metabolomic approach is becoming one of the mostly-used tools currently for investigating changes in the metabolome of biological systems, providing information on the small molecules in cells or tissues and defining the metabolic signature, thus leading to enhanced understanding of the disease mechanisms [14,15]. Metabolomics assesses the final downstream products of gene transcription and is a good reflection of the biological system operation, namely its metabolic expression data are

standing of the mechanisms of action [18]. However, in vitro metabolomics can focus on a small number of components, providing practical global knowledge about the metabolic pathways that PCs are involved in [19].

Beyond the common biofluids analyzed in metabolomics (plasma, urine, and fecal extracts), cell cultures offer the possibility for studying food ingredients or bioactive compounds (as well as new drugs or xenobiotics) in human biological materials more economically. In vitro studies can also offer benefits in terms of ethical considerations and can result in faster development [14].

Despite that, very few comprehensive studies have been performed that focus on the research of the molecular changes in response to PC exposure. Thus, in the present update, we aimed to integrate all the available bibliographic information related to the changes in the endogenous metabolite profile induced by the external stimuli of PCs based on an in vitro metabolomic approach. To our knowledge, this is the first time that underlying mechanisms of PCs in the disease risk reduction resulting from in vitro metabolic expression data are discussed.

Search strategy for the bibliographic review

The bibliographic review was carried out in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Scopus (http://www.sciencedirect.com). The following terms were used for the search: ‘polyphenols’, ‘phenolic compounds’, ‘cells’, ‘mechanism of action’, and ‘metabolomics’.

The search strategy flowchart is shown in Figure 1. Using the first search strategy, we found 29 publications, including 9 in PubMed and 20 in Scopus, of which four were excluded from PubMed search for being reviews, for not being a cell culture experiment, or for evaluating metabolomics of the tested food compounds. Nineteen publications were excluded from Scopus search for matching publications found in the PubMed search, for being reviews, or for evaluating metabolomics in human or hamster biofluids, or plants.

Using the second search strategy, we found 28 publications (24 in PubMed and 4 in Scopus), of which 24 were excluded from PubMed search for matching publications found in the first search strategy, for being editorials or reviews, or for evaluating metabolomics on plants, mice, rats, or human samples. Four publications were excluded from Scopus search for matching those found using the first strategy and by PubMed search using the second strategy, for being a review and for conducting metabolomics in human biofluids.

Using the third search strategy, we found 23 publications (4 in PubMed and 19 in Scopus), of which three were excluded from PubMed search for evaluating metabolomics on plants. Nineteen publications from Scopus search were excluded for matching publications found using the first two strategies and by PubMed search using the third strategy, for corresponding to reviews, for being a book chapter, or for evaluating metabolomics on plants and fungus.

Using the fourth search strategy, we found 8 publications (8 in PubMed and 0 in Scopus), of which eight were excluded from PubMed search for being the same publications found using the first three strategies, for being a review, or for evaluating metabolomics on plants, mice, or pigs. No publications were found in Scopus. Finally, seven in vitro metabolomic
studies based on the effects of several PCs were selected [20–26]. Table 1 shows the main characteristics of the selected publications. Among these, five publications provided information regarding rosemary phenolic extract on human colon cancer cells HT-29 [20,21,23,24] and human erythroleukemia cell lines K-562 [22]. Valdés et al. [20] tested the contribution of carnosic acid, the major PC in rosemary, individually instead of using the whole phenolic extract. The other two studies examined the effect of a phenolic extract from virgin olive oil containing secoiridoids, phenolic alcohols, and lignans on colon cancer cells SW-480 and HT-29 [26], and the effect of resveratrol on human hepatocellular carcinoma cells HepG2 [25].

PC modulation of metabolic pathways and their association with common diseases

Information regarding the metabolic pathways supporting the biological role of PCs has been obtained from the metabolomic evaluation after the in vitro experiments with rosemary and olive oil phenolics and resveratrol [20–26]. The chemical structure and food sources of the main PCs analyzed in the present update are represented in Figure 2. Based on the reviewed studies, we concluded that the principal functions modified by these PCs can be classified into (1) basic cellular processes, (2) macro- and micro-nutrient metabolism, and (3) specific metabolic pathways. The cellular processes and pathways that were found to be modulated are listed and classified in Figure 3.

The basic cellular processes modulated by PCs of the present review include: organismal systems, cell proliferation and viability, cellular development, cellular growth, cell death, cell-cycle metabolism, cell adhesion, cell migration, cellular movement, cell-to-cell interaction, cellular function and maintenance, transport of molecules, environmental and genetic information processing, as well as energy metabolism. The macro- and micro-nutrient metabolism modulated by PCs is related to protein, amino acid, lipid, glycan, nucleotide, carbohydrate, cofactors, and vitamins. Only the rosemary phenolic extract but not olive oil phenolic extract and resveratrol can modify macro- and micro-nutrient metabolism and specific metabolic pathways (Figure 3). The specific metabolic pathways modulated are explained in greater detail below.

Methylglyoxal degradation

Methylglyoxal (MGO) is a highly reactive dicarbonyl compound produced as a by-product of glycolysis and represents the main precursor of advanced glycation end-products that are related to several diseases. Normally, cells are protected against MGO by the glyoxalase system, the main detoxification pathway of MGO [27]. Increased levels of MGO and glyoxalase system dysfunction have been related to several age-related diseases, such as diabetes, CVD, cancer, and neurological disorders [28]. There is evidence supporting that ferulic acid and related PCs can decrease MGO induced-cytotoxicity in reduced glutathione (GSH)-depleted rat hepatocytes by exerting a radical scavenging protective mechanism [29]. These findings are consistent with the reported up-regulation of the gene encoding aldo–keto reductase family 1 member C1 (AKR1C1) in the HT-29 colon cancer cell line after the incubation with the phenolic diterpene carnosic acid [20]. AKRs are known as the major enzymes implicated in...
| Cell types | PCs and tested concentration | Type of omics analysis | Method | Databases used for metabolite identification | Expression changes | Biological functions and pathways | Ref. |
|------------|-----------------------------|------------------------|--------|---------------------------------------------|--------------------|-------------------------------------|------|
| Human colon cancer cells: HT29 | Rosemary phenolic extract (carnosic acid: 256.0 µg/mg; 9.9 µg/ml) | Transcriptomics | Microarray; RT-qPCR | — | 281 DEGs out of 341 identified genes | Methylglyoxal degradation; dopamine, tryptophan, melatonin, noradrenaline, and serotonin degradation; ethanol degradation; bile acid and retinoid A biosynthesis; LPS/IL-1-mediated inhibition of RXR function; transport of molecules; metabolism of terpenoid; metabolism of ROS; polyamine metabolism | [20] |
| | Metabolomics (nontargeted) | CE-MS and HILIC/ UPLC-MS | HMD, METLIN, and KEGG | 21 DEMs | Glutathione metabolism; polyamine metabolism | | |
| | Rosemary phenolic extract (carnosol: 226.4 µg/mg; carnosic acid: 151.5 µg/mg; 10 µM (total rosemary phenols)) | Transcriptomics | Microarray; RT-qPCR | — | 1308 DEGs | Cellular development; cell death; cellular growth and proliferation; cell cycle; glutamate and glutathione metabolism | [21] |
| | Metabolomics (nontargeted) | CE-MS, RP/UPLC-MS, and HILIC/UPLC-MS | HMD, METLIN, KEGG compound, and PubChem | 65 DEMs | Glutathione metabolism; urea cycle and metabolism of amino groups; polyamines homeostasis; cell proliferation and viability | | |
| | Rosemary phenolic extract; 10 µM | Metabolomics (nontargeted) | CE-ESI-TOF MS | | 44 metabolites identified | Glycan biosynthesis and metabolism; organismal systems; excretory system; neuroactive ligand-receptor interaction; amino, carbohydrate, lipid, nucleotide, energy, cofactor, and vitamin metabolism; environmental and genetic information processing | [24] |
| Human colon cancer cells: SW480 and HT29 | Extra virgin olive oil extract (decarboxymethyl oleuropein aglycone: 238.4 mg/kg); 0.01%–0.1% | Metabolomics (nontargeted) | nanoLC-ESI-TOF-MS | — | 20 metabolites were identified in cells and culture medium | Uptake and metabolism of polyphenols; cell-cycle metabolism | [26] |
| Human hepatocellular liver carcinoma cells: HepG2 | Resveratrol; 40 µM | Metabolomics (nontargeted) | 1H NMR spectroscopy | — | 9 DEMs out of 34 identified metabolites | Energy metabolism: Krebs cycle | [25] |
| Human erythroleukemia cells: K562 and K562/R | Rosemary phenolic extract (carnosol: 226.4 µg/mg; carnosic acid: 151.5 µg/mg; 5, 10 µM) | Transcriptomics | Microarray; RT-qPCR | — | 289 DEGs in K562; 387 DEGs in K562/R | Cellular movement; cell-to-cell signaling and interaction; free radical scavenging; cell death; NRF2-mediated oxidative stress response; LPS/IL-1-mediated inhibition of RXR function; aryl hydrocarbon receptor signaling; protein synthesis; antigen presentation; cellular function and maintenance | [22] |
| | Metabolomics (nontargeted) | CE-MS and UPLC-MS | | 121 DEMs in K562; 105 DEMs in K562/R | Aminoacyl-tRNA biosynthesis; glutathione metabolism; arginine and proline metabolism; nitrogen metabolism; glutamate metabolism; urea cycle and metabolism of amino groups | | |

Note: LPS, lipopolysaccharide; IL-1, interleukin-1; RXR, retinoid X receptor; CE-MS, capillary electrophoresis–mass spectrometry; HILIC/UPLC-MS, hydrophilic-interaction ultra-performance liquid chromatography coupled to mass spectrometry; HMD, human metabolome database; ROS, reactive oxygen species; MALDI-TOF/TOF-MS, matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry; RP, reverse phase; ESI, electrospray ionization; NMR, nuclear magnetic resonance; NRF2, nuclear factor-like. DEG, differentially-expressed gene; DEP, differentially-expressed protein; DEM, differentially-expressed metabolite.
in the reduction of carbonyl substrates that are involved in the synthesis of endogenous compounds as well as xenobiotic detoxification, providing a protection against cellular damage [30].

**Polyamine metabolism**

Polyamines such as putrescine, spermidine, and spermine can interact with proteins, DNA, and RNA, and play various roles in cell growth and proliferation. Variations in polyamine levels have been related with certain diseases such as stroke, cancer, renal failure, inflammation, or diabetes [31]. Thus, polyamine function and metabolism is an attractive target for therapeutic intervention, especially for antiproliferative usages [32].

Protective effects against cancer of PCs have been described in HT-29 cells treated with carnosic acid, which are potentially related to polyamine metabolism modulation. This metabolic change is explained by an up-regulation of the gene encoding monoamine oxidase type B (MAO-B) that is involved in the enzymatic transformation of N-acetylputrescine to 4-acetamidobutanal, thus resulting in the reduced level of N-acetylputrescine with carnosic acid treatment [20]. Similarly, Caco-2 cells exposed to a procyanidin-enriched extract showed a significant reduction in two key enzymes of polyamine biosynthesis (ornithine decarboxylase and S-adenosylmethionine decarboxylase), leading to a decrease in intracellular polyamines [33]. These results suggest that polyamine pathway could be an important target for PCs as antiproliferative agents.

**Dopamine, noradrenaline, and serotonin degradation**

Dopamine, noradrenaline, and serotonin are neurotransmitters, and their reduction contributes to the occurrence of cognitive decline and neurodegeneration [34]. Specifically, the dopaminergic system as well as abnormal serotonin neurotransmission may be related with the occurrence of Alzheimer’s disease (AD) [35] and Parkinson’s disease (PD) [36]. A foodomic approach has revealed that carnosic acid induces transcriptional regulation of several genes implicated in the degradation of dopamine, noradrenaline, and serotonin, providing new evidence for potential signaling pathways modulated by PCs [20]. In line with these observations, a potential effect of epigallocatechin-3-gallate has been shown against lipopolysaccharide-induced neurotoxicity through reducing inflammatory mediators' tumor necrosis factor-alpha and nitric oxide and maintaining dopamine levels in midbrain [37].

Another canonical pathway implicated in neurotransmitter metabolism and revealed to be regulated by rosemary phenolics in this update is the tryptophan depletion [20], which has been shown to take part in the development of AD, PD, and Huntington’s disease (HD) [38]. Recent findings have also shown that PCs can inhibit tryptophan breakdown in peripheral blood mononuclear cells [39].

**Melatonin degradation**

A relationship has been established between melatonin and aging, neurodegeneration [40], T2DM [41], autism [42], as well
as bone status [43]. This pineal hormone has atheroprotective effects [44] and is able to behave as a ‘smart killer’ by modulating apoptosis processes in cancer cells and promoting survival in non-tumor cells [45]. This update shows for first time the association between polyphenols and melatonin degradation pathway at the gene level, after the in vitro exposure of cells to rosemary phenolics [20].

**Ethanol degradation**

It has been reported that heavy or binge alcohol intake increases the risk of all-cause mortality, whereas moderate consumption, especially of wine and beer, might have cardioprotective effects [46]. A foodomic study has revealed that, enzymes related to ethanol degradation pathway were positively modulated in HT-29 cells after treatment with carnosic acid. In particular, the up-regulation of the gene encoding aldehyde dehydrogenases 3A1 (ALDH3A1) could also counteract the formation of aldehydes produced by monoamine oxidases [20]. In line with this study, catechins from black tea partially prevent alterations of oxidative parameters induced by ethanol in old rats [47]. These findings suggest a beneficial effect of PCs on the ethanol degradation pathway.

**Terpenoid metabolism**

Terpenoids (also called isoprenoids) and particularly retinoic acid, have been shown to down-regulate proliferation markers and to inhibit tumor growth, angiogenesis, and metastasis [48]. Additionally, direct actions of retinoids have been reported in insulin secretion through pancreatic β-cell function [49], and the maintenance of immunity, reproduction, and embryonic development [50]. Early work has also shown that the level of long-chain isoprenoid dolichol is decreased, whereas the level of dolichyl phosphate and ubiquinone is increased in brains of AD patients [51]. Moreover, as the important regulators of macrophages [52], retinoid X receptors (RXR) might inhibit the initial inflammatory process preceding the atherogenesis [53]. Pathway analysis indicates that the metabolism of terpenoid pathway could be significantly repressed in HT-29 cells treated with carnosic acid by the reduced expression of genes encoding alcohol dehydrogenase 1C (ADH1C), endothelin 1 (EDN1), nuclear receptor subfamily 4 group A member 1 (NR4A1), and prolactin receptor (PRLR) [20], suggesting an anticancer protective effect of carnosic acid. Along the same line, a cancer prevention effect has been reported after a long term consumption of a green tea phenolic extract in rats with induced colon carcinoma, due to the increased levels of RXRα [54].

**GSH metabolism**

GSH is considered to be one of the most important scavengers of reactive oxygen species (ROS), which has been involved in the progression of a number of aging diseases, such as cancer, CVD, and neurodegenerative diseases [55]. GSH depletion has
been described as a common process of apoptotic cell death initiated by various stimuli [56]. Thus, GSH modulation has been thoroughly investigated for potential anticancer treatments.

Several metabolomic studies in leukemia and colon cancer cell lines have demonstrated that rosemary phenolics increase GSH levels with a rise of the GSH/glutathione disulfide (GSSG) ratio [20,22]. Combined with the transcriptomic data, functional analysis underscored an activation of ROS metabolism and expression modification of several genes related to oxidative degradation pathways in both cell lines. These results suggested that rosemary phenolics could enhance the detoxifying cellular capabilities, which is necessary for cancer growth inhibition. It has also been suggested that PCs modify intracellular GSH concentrations through modulating detoxification processes and protein glutathionylation, as well as adjusting the redox switching of protein functions [57].

**Aminoacyl-tRNA biosynthesis**

Aminoacyl-tRNA synthetases (ARSs) are essential for the first step in protein synthesis. It has been reported that defects in ARS functions may contribute to several diseases such as cancer [58]. A metabolomic approach for leukemia cells treated with rosemary PCs showed an increased expression of the gene encoding valyl-tRNA synthetase (V.ARS), which is related to aminoacyl-tRNA biosynthesis pathway. In addition, the authors also detected changes in the amount of related metabolites, in particular some amino acids such as Met, Leu, Glu, Tyr, Lys, and Phe [22]. Along the same line, an increase in aminoacyl-tRNA content in osteoblastic MC3T3-E1 cells was observed due to the action of the isoflavone genistein [59]. These results seem that the PCs could have an essential role mainly in the cellular functions and pathways, evidence is not strong enough concerning bioavailability and metabolism of PCs. Therefore, future metabolomic cell-based studies should be performed to test the conjugated forms of PCs found in plasma with the concentration range of 0.1–10 µM, the maximum plasma concentrations detected after normal consumption of PC-rich foods [73]. Thus, human data concerning bioavailability and metabolism of PCs are of great value for future studies focusing on defining biological activities of PCs.

The metabolic data available up till now offer promising knowledge about the role of dietary PCs in preventing and/or protecting against various diseases through the modifica-

**Translational perspective of PCs in disease prevention**

After in-depth examination of the pathways modulated by the PCs studied, the next step is to analyze the illnesses and disorders involving these pathways. Based on the integrated data, it seems that the PCs could have an essential role mainly in the prevention of neurodegenerative disorders, T2DM, cancer, and CVD (Table 2). In particular, carnosic acid and carnosol, the main PCs present in rosemary, appear to be implicated in most of the metabolic pathways analyzed in Table 2.

Resveratrol is mainly involved in energy metabolism regulated by a peroxisome proliferator-activated receptor [67,68], and this pathway has been related to the nervous system, cancer, diabetes, and neurodegenerative disorders, such as AD [69,70]. Extra virgin olive oil phenolic extract is mostly associated with cell-cycle metabolism. Dysregulation of this process has been related with the etiology of major chronic pathologies such as cancer, atherosclerosis, inflammation, and neurodegenerative disorders such as AD, HD, and PD [71].

**Bile acid biosynthesis**

Beside the well-established role of bile acids in cholesterol homeostasis and lipid absorption, Kuipers et al. have also demonstrated glucose-lowering actions of bile acids in insulin-resistant states and T2DM [64]. Additionally, high concentrations of deoxycholic acid have been shown to induce cell proliferation, causing hyperproliferation in the colorectal mucosa, which is an early stage in colorectal cancer [65]. Administration of 0.5% apple phenolic extract in rats leads to an up-regulation of the expression of farnesoid X receptor that takes part in the bile acid biosynthesis and consequently improved blood cholesterol levels [66]. Investigation on colon cancer HT-29 cells treated with carnosic acid has revealed that the phenolic carnosic acid from rosemary can modulate the biological process of bile acid biosynthesis [20].

**Future developments**

The metabolic data available up till now offer promising knowledge about the role of dietary PCs in preventing and/or protecting against various diseases through the modifica-
tion of several metabolic pathways. Thus, metabolomic profiling techniques used in cell-based studies provide unprecedented opportunities to evaluate the mechanisms-of-action for PCs, with complementary data of human studies. Metabolomic data also provide a more realistic understanding of the role of PCs in disease recognition/prevention. According to Lee [74], the in vitro metabolomic model can be employed to fully elucidate whether the in vivo observations actually have molecular basis.

In conclusion, assessing the biological effects of specific PCs by in vitro metabolomic approaches has contributed to better definition of a metabolomic signature and enhanced understanding of disease mechanisms in response to PCs exposure. Moreover, the reviewed metabolomic data have provided the possible clinical impact of PCs on common diseases, concluding that PCs are mainly implicated in neurodegenerative diseases, T2DM, cancer, and CVDs. Despite its analytical capacity, the utilization of metabolomic approach in the study of disease prevention by PCs is still in its infancy. Therefore, new and more refined metabolomic approaches testing other types of PCs are needed to finally elucidate the underlying mechanisms of specific PCs in human physiological and pathological processes.

Competing interests

The authors have declared no competing interests.

Acknowledgments

This work was partially supported by grants (Grant Nos. AGL2009-13517-C03-03 and AGL2012-40144-C03-02) from the Spanish Ministry of Education and Science (Ministerio de Educación y Ciencia, Spain), a Sara Borrell post-doctoral grant (CD14/00275; Spain), a Pla estratègic de recerca i innovació en salut (PERIS) post-doctoral grant (SLT002/16/00239; Catalunya, Spain). We also thank the support of Institut d’Investigació Sanitària Pere Virgili (IISPV) and Centre Tecnològic de Nutrició i Salut (CTNS), Reus, Spain. NFOC-Salut group is a consolidated research group of Generalitat de Catalunya, Spain (2014 SGR 873).

References

[1] Boudet AM. Evolution and current status of research in phenolic compounds. Phytochemistry 2007;68:2722-35.
[2] Liu RH. Potential synergy of phytochemicals in cancer prevention: mechanism of action. J Nutr 2004;134:347S-85S.
[3] Manach C, Scalbert A, Morand C, Remésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr 2004;79:727-47.
[4] Pedret A, Valls RM, Hernández-Castillejo S, Catalán Ú, Romeu M, Giralt M, et al. Polyphenol-rich foods exhibit DNA antioxidant properties and protect the glutathione system in healthy subjects. Mol Nutr Food Res 2012;56:1025-33.
[5] D’Archivio M, Filesi C, Vari R, Scaccuzchio B, Masella R. Bioavailability of the polyphenols: status and controversies. Int J Mol Sci 2010;11:3211-22.
[6] Visioli F, De La Lastra CA, Andres-Lacueva C, Aviram M, Calhau C, Cassano A, et al. Polyphenols and human health: a prospectus. Crit Rev Food Sci Nutr 2011;51:524-46.
[7] Velderrain-Rodriguez GR, Palafos-Carlos H, Wall-Medrano A, Ayala-Zavala JF, Chen CY, Robles-Sánchez M, et al. Phenolic compounds: their journey after intake. Food Funct 2014;5:189–97.

[8] Bahadoran Z, Mirmiran P, Azizi F. Dietary polyphenols as potential nutraceuticals in management of diabetes: a review. J Diabetes Metab Disord 2013;12:43.

[9] Khurana S, Venkataraman K, Hollingsworth A, Peche M, Tai TC. Polyphenols: benefits to the cardiovascular system in health and in aging. Nutrients 2015;3:5779–82.

[10] Bhullar KS, Rupasinghe HP. Polyphenols: multipotent therapeutic agents in neurodegenerative diseases. Oxid Med Cell Longev 2013;2013:891748.

[11] Ding Y, Yao H, Yao Y, Fai LY, Zhang Z. Protection of dietary polyphenols against oral cancer. Nutrients 2013;5:2173–91.

[12] Ramirez T, Daneshian M, Kamp H, Bois FY, Clench MR, Coen M, et al. Metabolomics in toxicology and preclinical research. ALTEX 2013;30:209–25.

[13] Capozzi F, Bordoni A. Foodomics: a new comprehensive approach to food and nutrition. Genes Nutr 2013;8:1–4.

[14] Mishur RJ, Rea SL. Applications of mass spectrometry to metabolomics and metabolomic identification of biomarkers of aging and of age-related diseases. Mass Spectrom Rev 2012;31:70–95.

[15] Theodoridis GA, Gika HG, Want EJ, Wilson ID. Liquid chromatography-mass spectrometry based global metabolite profiling: a review. Anal Chim Acta 2012;711:7–16.

[16] Griffin JL, Bollard ME. Metabonomics: its potential as a tool for toxicology and safety assessment and data integration. Curr Drug Metab 2004;5:389–98.

[17] Clarke CJ, Haselden JN. Emerging risk biomarkers in cardiovascular diseases and disorders. J Lipids 2015;2015:971453.

[18] Ibáñez C, Simó C, García-Cañas V, Cifuentes A, Castro-Puyana M. Metabolomics, epiphenolics and proteomics applications of capillary electrophoresis-mass spectrometry in Foodomics: a review. Anal Chim Acta 2013;802:1–13.

[19] Valdés A, García-Cañas V, Simó C, Ibáñez C, Micó V, Ferragut JA, et al. Comprehensive foodomics study on the mechanisms operating at various molecular levels in cancer cells in response to individual rosemary polyphenols. Anal Chem 2014;86:9807–15.

[20] Ibáñez C, Valdés A, García-Cañas V, Simó C, Celebier M, Rocamora-Reverte L, et al. Global foodomics strategy to investigate the health benefits of dietary constituents. J Chromatogr A 2012;1248:139–53.

[21] Valdés A, Simó C, Ibáñez C, Rocamora-Reverte L, Ferragut JA, García-Cañas V, et al. Effect of dietary polyphenols on K562 leukemia cells: a foodomics approach. Electrophoresis 2012;33:2314–27.

[22] Ibáñez C, Simó C, García-Cañas V, Gomez-Martinez A, Ferragut JA, Cifuentes A. CE/LC-MS multiplex platform for broad metabolomic analysis of dietary polyphenols effect on colon cancer cells proliferation. Electrophoresis 2012;33:2328–36.

[23] Celebier M, Ibáñez C, Simó C, Cifuentes A. A foodomics approach: CE-MS for comparative metabolomics of colon cancer cells treated with dietary polyphenols. Methods Mol Biol 2012;869:185–95.

[24] Massimi M, Tomassini A, Sciuoppa F, Sobolev AP, Desvillettes LC, Miccheli A. Effects of resveratrol on HepG2 cells as revealed by 1H-NMR based metabolomic profiling. Biochim Biophys Acta 2012;1820:1282–9.

[25] Fernández-Arroyo S, Gómez-Martinez A, Rocamora-Reverte L, Quirantes-Piné R, Segura-Carretero A, Fernández-Gutiérrez A, et al. Application of nanoLC-ESI-TOF-MS for the metabolomic analysis of phenolic compounds from extra-virgin olive oil in treated colon-cancer cells. J Pharm Biomed Anal 2012;63:128–34.

[26] Allaman I, Bélanger M, Magistretti PJ. Methylglyoxal, the dark side of glycolysis. Front Neurosci 2015;9:23.

[27] Maessen DEM, Stehouwer CDA, Schalkwijk CG. The role of methylglyoxal and the glyoxalase system in diabetes and other age-related diseases. Clin Sci (Lond) 2015;128:839–61.

[28] Maraf A Al, Lip H, Hong W, O’Brien PJ. Protective effects of ferulate acid and related polyphenols against glycoxal- or methylglyoxal-induced cytotoxicity and oxidative stress in isolated rat hepatocytes. Chem Biol Interact 2015:234:96–104.

[29] Singh M, Kapoor A, Bhatnagar A. Oxidative and reductive metabolism of lipid-peroxidation derived carbonyls. Chem Biol Interact 2015;234:261–73.

[30] Park MH, Igarashi K. Polymamines and their metabolites as diagnostic markers of human diseases. Biomol Ther (Seoul) 2013;21:1–9.

[31] Casero RA, Marton LJ. Targeting polyamine metabolism and function in cancer and other hyperproliferative diseases. Nat Rev Drug Discov 2007;6:373–90.

[32] Carnesecchi S, Schneider Y, Lazarus SA, Coelho D, Gossé F, Raul F. Flavanols and procyanidins of cocoa and chocolate inhibit growth and polyamine biosynthesis of human colon cancer cells. Cancer Lett 2002;175:147–55.

[33] Xu Y, Yan J, Zhou P, Li J, Gao H, Xia Y, et al. Neurotransmitter receptors and cognitive dysfunction in Alzheimer’s disease and Parkinson’s disease. Prog Neurobiol 2012;97:1–13.

[34] Martorana A, Koch G. Is dopamine involved in Alzheimer’s disease? Front Aging Neurosci 2014;6:252.

[35] Delaville C, Deurwaerdère P De, Benazzouz A. Noradrenaline and Parkinson’s disease. Front Syst Neurosci 2011;5:31.

[36] Al-Amri JS, Hagras MM, Mohamed IM. Effect of epigallocatechin-3-gallate on inflammatory mediators release in LPS-induced Parkinson’s disease in rats. Indian J Exp Biol 2013;51:357–62.

[37] Maddison DC, Giorgini F. The kynurenine pathway and neurodegenerative disease. Semin Cell Dev Biol 2015;40:134–41.

[38] Strasser B, Gostner JM, Fuchs D. Mood, food, and cognition: role of tryptophan and serotonin. Curr Opin Clin Nutr Metab Care 2016;19:55–61.

[39] Jenwineasuk A, Nopparat C, Mukda S, Wongchitrat P, Govitrapong P. Melatonin regulates aging and neurodegeneration through energy metabolism, epigenetics, autophagy and circadian rhythm pathways. Int J Mol Sci 2014;15:16848–84.

[40] Tuomi T, Nagorny CLF, Singh P, Bennet H, Yu Q, Alenkivist M, et al. Increased melatonin signaling is a risk factor for type 2 diabetes. Cell Metab 2016;23:1067–77.

[41] El-Ansary A, Al-Ghamdi M, Bhat RS, Al-Daihan S, Al-Ayadhia L. Potency of pre-post treatment of coenzyme Q10 and melatonin supplement in ameliorating the impaired fatty acid profile in rodent model of autism. Food Nutr Res 2016;60:28127.

[42] Zhang L, Su P, Xu C, Chen C, Liang A, Du K, et al. Melatonin inhibits adipogenesis and enhances osteogenesis of human mesenchymal stem cells by suppressing PPARγ expression and enhancing Runtx2 expression. J Pineal Res 2010;49:364–72.

[43] Favero G, Rodella LF, Reiter RJ, Rezzani R, Melatonin and its atheroprotective effects: a review. Mol Cell Endocrinol 2014;382:926–37.

[44] Lanoix D, Lacasse AA, Reiter RJ, Vaillancourt C. Melatonin: the smart killer: the human trophoblast as a model. Mol Cell Endocrinol 2012;348:1–11.

[45] Chiva-Blanch G, Arranz S, Lamuela-Raventos RM, Estruch R. Effects of wine, alcohol and polyphenols on cardiovascular disease risk factors: evidences from human studies. Alcohol Alcohol 2013;48:270–7.

[46] Łuczaj W, Skrzydlewska E. Antioxidant properties of black tea in alcohol intoxication. Food Chem Toxicol 2004;42:2045–51.

[47] Fritz H, Kennedy D, Fergusson D, Fernandes R, Doucette S, Cooley K, et al. Vitamin A and retinoid derivatives for lung
cancer: a systematic review and meta analysis. PLoS One 2011;6:e21107.

Kane MA, Folias AE, Pingitore A, Perri M, Obrochta KM, Krois CR, et al. Identification of 9-cis-retinoic acid as a pancreas-specific autacoid that attenuates glucose-stimulated insulin secretion. Proc Natl Acad Sci U S A 2010;107:21884–9.

Gudas LJ. Emerging roles for retinoids in regeneration and differentiation in normal and disease states. Biochim Biophys Acta 2012;1821:21884–9.

Hooff GP, Wood WG, Mue¨ ller WE, Eckert GP. Isoprenoids, small GTPases and Alzheimer’s disease. Biochim Biophys Acta 2010;1801:896–905.

Perez E, Bourguet W, Gronemeyer H, de Lera AR. Modulation of RXR function through ligand design. Biochim Biophys Acta 2012;1821:57–69.

Sanz MJ, Albertos F, Otero E, Juez M, Morcillo EJ, Piqueras L. Retinoid X receptor agonists impair arterial mononuclear cell recruitment through peroxisome proliferator-activated receptor-γ activation. J Immunol 2012;189:411–24.

Yang CS, Li G, Yang Z, Guan F, Chen A, Ju J. Cancer prevention by tocopherols and tea polyphenols. Cancer Lett 2013;334:79–85.

Ballatori N, Krance SM, Notenboom S, Shi S, Tieu K, Hammond CL. Glutathione dysregulation and the etiology and progression of human diseases. Biol Chem 2009;390:191–214.

Ortega AL, Mena S, Estrela JM. Glutathione in cancer cell death. Cancers (Basel) 2011;3:1285–310.

Moskaug JO, Carlsten H, Myhrstad MCW, Blomhoff R. Polyphenols and glutathione synthesis regulation. Am J Clin Nutr 2005;81:277S–83S.

Kim S, You S, Hwang D. Aminoacyl-tRNA synthetases and tumorigenesis: more than housekeeping. Nat Rev Cancer 2011;11:708–18.

Yamaguchi M, Gao-Balch YH. Role of dietary soybean genistin in osteoporosis prevention. Int J Food Sci Nutr Diet 2013;27:27–34.

Zhao L, Ma J, Takeuchi M, Usui Y, Hatatori T, Okunuki Y, et al. Suppression of experimental autoimmune uveoretinitis by inducing differentiation of regulatory T cells via activation of aryl hydrocarbon receptor. Invest Ophthalmol Vis Sci 2010;51:2109–17.

Benson JM, Shepherd DM. Aryl hydrocarbon receptor activation by TCDD reduces inflammation associated with Crohn’s disease. Toxicol Sci 2011;120:68–78.

Gasiewicz TA, Henry EC, Collins LL. Expression and activity of aryl hydrocarbon receptors in development and cancer. Crit Rev Eukaryot Gene Expr 2008;18:279–321.

Amakura Y, Yoshimura M, Takaoka M, Toda H, Tsutsumi T, Matsuda R, et al. Characterization of natural aryl hydrocarbon receptor agonists from cassia seed and rosemary. Molecules 2014;19:4956–66.

Kuipers F, Bloks VW, Groen AK. Beyond intestinal soap–bile acids in metabolic control. Nat Rev Endocrinol 2014;10:488–98.

Cheng K, Raufman JP. Bile acid-induced proliferation of a human colon cancer cell line is mediated by transactivation of epidermal growth factor receptors. Biochem Pharmacol 2005;70:1035–47.

Osada K, Suzuki T, Kawakami Y, Senda M, Kasai A, Sani M, et al. Dose-dependent hypocholesterolemic actions of dietary apple polyphenol in rats fed cholesterol. Lipids 2006;41:133–9.

Wang YX. PPARs: diverse regulators in energy metabolism and metabolic diseases. Cell Res 2010;20:124–37.

Finck BN, Kelly DP. PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. J Clin Invest 2006;116:615–22.

Okoiana R, Serra-Calixto F, Serrano J, Goñi I. Intake and bioaccessibility of total polyphenols in a whole diet. Food Chem 2007;101:492–501.

Kroon PA, Clifford MN, Crozier A, Day AJ, Donovan JL, Manach C, et al. How should we assess the effects of exposure to dietary polyphenols in vitro? Am J Clin Nutr 2004;80:15–21.

Lee CY. Challenges in providing credible scientific evidence of health benefits of dietary polyphenols. J Funct Foods 2013;5:524–6.