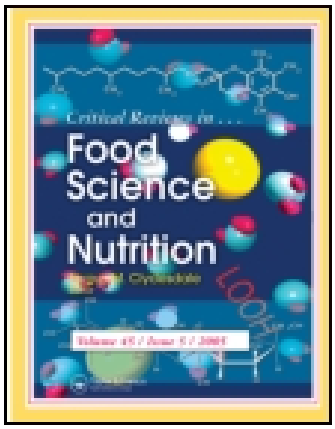

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Polyphenols and the Modulation of Gene Expression Pathways: Can We Eat Our Way Out of the Danger of Chronic Disease?

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Polyphenols and the Modulation of Gene Expression Pathways: Can We Eat Our Way Out of the Danger of Chronic Disease?

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Plant-derived dietary polyphenols may improve some disease states and promote health. Experimental evidence suggests that this is partially attributable to changes in gene expression. The rational use of bioactive food components may therefore present an opportunity to activate or repress selected gene expression pathways and, consequently, to manage or prevent disease. It remains to be determined whether this use of bioactive food components can be done safely. This article reviews the associated controversies and limitations of polyphenol therapy. There is a paucity of clinical data on the rational use of polyphenols, including a lack of knowledge on effective dosage, actual chemical formulations, bioavailability, distribution in tissues, the effect of genetic variations, differences in gut microflora, the synergistic (or antagonistic) effects observed in extracts, and the possible interaction between polyphenols and lipid domains of cell membranes that may alter the function of relevant receptors. The seminal question of why plants make substances that benefit humans remains unanswered, and there is still much to learn in terms of correlative versus causal effects of human exposure to various nutrients. The available data strongly suggest significant effects at the molecular level that represent interactions with the epigenome. The advent of relatively simple technologies is helping the field of epigenetics progress and facilitating the acquisition of multiple types of data that were previously difficult to obtain. In this review, we summarize the molecular basis of the epigenetic regulation of gene expression and the epigenetic changes associated with the consumption of polyphenols that illustrate how modifications in human nutrition may become relevant to health and disease.

Keywords Chromatin, DNA methylation, epigenetics, food, histone modification, miRNA, nutrients, nutrition, plants

INTRODUCTION

Observational studies have long suggested an association between the so-called Mediterranean diet, a collection of dietary characteristics in humans who eat moderately and typically have olive oil as their main source of fat, and a reduced risk for coronary heart disease (CHD). This reduced risk of CHD was thought to be an independent effect of the dietary ratio of monounsaturated to saturated fatty acids (Keys et al., 1986). However,

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despite considerable research, the major mechanisms of the fat ratio's influence on the pathogenesis of atherosclerosis have not been fully discerned (Masana et al., 1991). Interest was then directed toward other dietary factors, particularly the health effects provided by antioxidant vitamins. The effects were plausible and were initially confirmed in a large observational study (Khaw et al., 2001) linking a high intake of antioxidant vitamins to reduced general mortality. However, randomized controlled trials (Heart Protection Study Collaborative Group, 2002) completely overturned these results, leading to controversy, confusion, and disappointment.

Despite the confounding and biasing factors, adherence to the Mediterranean diet repeatedly demonstrates beneficial effects associated with a reduced incidence of CHD, cancer, Parkinson's disease, and Alzheimer's disease, along with a consequent reduction in overall mortality (Trichopoulou et al., 2003). Whether this differential response is caused by dietary peculiarities or by other differences in lifestyle remains unknown, but most results seem to indicate that the presence of bioactive compounds in specific foods may be responsible for changes in health status. Although these findings should be interpreted cautiously, plant-derived polyphenols have some of the greatest potential among the current potential sources of these beneficial compounds. Polyphenol mechanisms are not well understood, but diet-gene interactions are likely involved. Virgin olive oil, for instance, demonstrates many in vivo nutrigenomic effects, including the down-regulation of numerous pro-atherogenic genes (Konstantinidou et al., 2010). Crude phenolic extracts from extra virgin olive oil have been added to a growing list of dietary components that have relevant effects on cancer cells and possess an epigenetic mechanism of action (Oliveras-Ferraros et al., 2011). However, similar effects have been observed with oleic acid alone, indicating that it is the combined action of multiple components in a certain food or nutritional composition that provides the health benefits (Menendez and Lupu, 2006; Menendez et al., 2013). These and other findings provide a new perspective from which to examine the Mediterranean diet and other dietary modifications that will likely develop into exciting new directions in the future.

NOT ALL POLYPHENOLS ARE CREATED EQUAL: THE IMPORTANCE OF FULL CHARACTERIZATION AND OTHER ASSOCIATED CONTROVERSIES AND LIMITATIONS

The Relative Concentration of Polyphenols in Foodstuffs

Polyphenols are present in plants as mixtures rather than as isolated compounds, a fact that it is frequently ignored in the search for patentability or in performing experimental studies. Several thousand of these phytochemicals have already been identified. According to the nature of their backbone structures, different families or groups have been defined: phenolic acids, flavonoids, and the less common stilbenes and lignans. Flavonoids may themselves be further classified as flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols (catechins and proanthocyanidins). It is currently accepted that polyphenols, mainly phenolic acids, are secondary metabolites of plants that are mainly synthesized in response to a major stress, such as draught, ultraviolet radiation or pathogenic infection. Therefore, in the fruits and vegetables that are cultivated and eaten in Western societies, in which stress and pathogens are kept to a minimum to enhance production, a low or very low amount of polyphenols is present (possible exceptions are onions, garlic, and cruciferous vegetables). It does not seem feasible to eat enough fruits and vegetables to ingest enough polyphenols to influence health, even assuming that these compounds are extremely active and readily available. If polyphenols are associated with a range of health benefits in humans and consumption should be increased, then the currently advocated dietary changes are not sufficient to achieve these benefits.

To increase the ingestion of polyphenols, a complementary strategy would be to change certain agricultural practices and to produce concentrated dietary supplements. However, qualitative factors as well as quantitative factors should be considered. Certain polyphenols are widely distributed, whereas others are specific to particular foods. In addition, polyphenols often exist in poorly characterized mixtures. Moreover, knowledge of their composition is limited to a few varieties for which there are acceptable degrees of availability, price, and acceptance. Many exotic and tropical types of plant-derived products have yet to be analyzed despite the fact that they may represent a major potential source of polyphenols (Beltrán-Debón et al., 2010; Beltrán-Debón et al., 2011). Moreover, the manufacture of supplements is challenged by variations in the polyphenol content of plants, which is partially derived from ripeness at the time of harvest, processing and storage (Burda et al., 1990; Spanos and Wrolstad, 1992; Parr and Bolwell, 2000; van der Sluis et al., 2001; Asami et al., 2003). Environmental factors and methods of culinary preparation are also important, including exposure to light, organic culture (the higher the stress, the higher the polyphenol content), rainfall, soil type, fruit yield per tree, boiling, peeling, frying, and the use of a microwave (Scalbert et al., 2005). Industrial food processing also affects polyphenol content (Vinson and Hontz, 1995; Macheix and Fleuriet, 1998). In some instances, this effect is commercially unavoidable, as in the production of fruit juice in which several steps are specifically aimed at removing certain polyphenols that are responsible for discoloration and haze formation. Therefore, both the chemical characterization of the final product and information on the effects of further manipulation should be taken into account in the assessment of nutritional advice.

Taking Pills or Enriching Foods? The Challenge of Integrating Clinical Information

The idea that isolating individual compounds from plants with health benefits would be commercially sound is widely

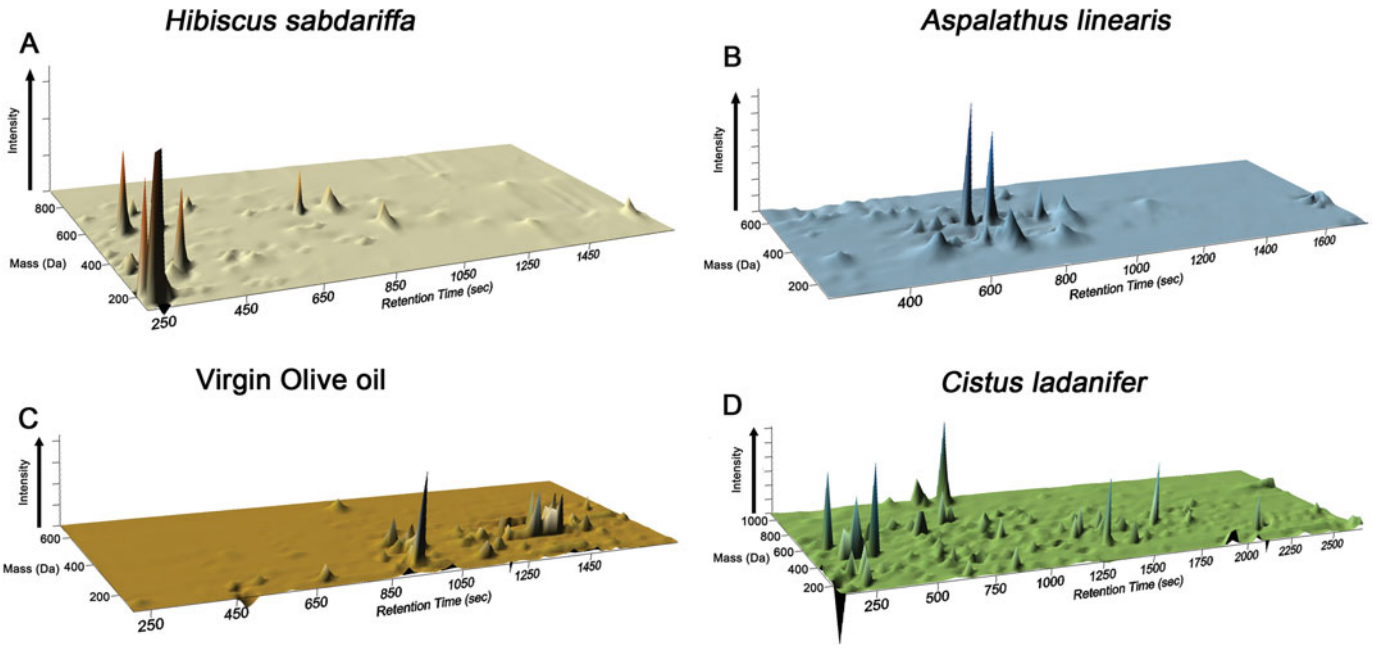

Figure 1 The identification of phenolic compounds in plants is a technically resolved issue. As shown in three-dimensional peak chromatograms of different plant extracts from relatively unknown or tropical plants grown under considerable stress (A, B), this stress may result in increased levels of valuable complementary and active polyphenols that are components (C, D) of diets adopted in Western societies. (Color figure available online).

accepted but apparently unsubstantiated by scientific data. There is a wide range of potentially bioactive components in supposedly medicinal plants, and current techniques provide relatively simple, rapid, and inexpensive methods of providing information on the composition of polyphenols in plants (Fig. 1). As depicted in Fig. 2, relevant polyphenols may be obtained from different parts of a plant, each providing a diverse chemical composition, which is further illustrated in the supplementary tables. Whether individual chemicals or the naturally present combinations of polyphenols should be tested for their benefits to humans is currently uncertain. However, the fact that plant bioactive components may act on several molecular targets simultaneously should be taken into account. Though each individual polyphenol may provide a certain effect, it is likely that the synergistic effects of the components are greater than the individual effects. This is also true for all the components of a given diet; it is extremely unlikely that protective or beneficial effects rely on a single food item. Moreover, a recent study has shown that in clinical trials, inter-individual variability is high and that the design of an intervention represents a major challenge (Egner et al., 2011). In this study, the authors compared the bioavailability of glucoraphanin and putatively active biotransformed sulforaphane from cruciferous vegetables resulting from the action of gut bacteria. The addition of another dietary component from *Raphanus sativus* positively modified this transformation (Egner et al., 2011). Moreover, dietary patterns, genetic variation, and the modulation of biotransformation are clearly interconnected, as exemplified by variations in cytochrome P450 CYP1A2. This cytochrome activates several procarcinogens and is induced and inhibited by cruciferous and apiaceous vegetable intake, respectively (Peterson et al., 2009). The bacterial metabolism of soy isoflavones varies among individuals, producing metabolites with different bioactive properties (Lampe, 2009). In addition, plant polyphenols are usually combined with fiber, polysaccharides, and oligosaccharides of unknown activity in a proportion of 40–60% of the total weight of the soluble material. Moreover, if the nonpolyphenolic part of the extract is removed, an intense bitterness limits its use in some applications and suggests that a pill formulation would be more appropriate. This is important because in food processing, saccharides may be either conserved or eliminated in the production of polyphenolic extracts (Segura-Carretero et al., 2008; Fernández-Arroyo et al., 2011). Whether these nonpolyphenolic components remain active has yet to be elucidated, but they likely contribute to a prebiotic effect and other health-related effects (Broeckaert et al., 2011). Prebiotics stimulate the growth of a limited number of bacteria in the colon, usually a beneficial relative increase in Bifidobacterium and/or *Lactobacillus* species (Gibson et al., 2004; MacFarlane et al., 2006; Wong et al., 2006). Among other effects, the fermentation of prebiotics by colonic bacteria gives rise to the production of short-chain fatty acids and butyrate, which appears to be of great interest because the fermentation process may inhibit the growth of colonic carcinoma cells (Scheppach et al., 1995). This putative mechanism may explain the observed cancer-suppressing properties of dietary fiber.

Peak	Compound	Molecular Formula	RT (min)	[M-H]$^-$
	Hibiscus sabdariffa			
1	Hydroxycitric acid	$C_6H_8O_8$	3.20	207.0140
2	Hibiscicus acid	$C_6H_6O_7$	3.42	189.0035
3	Chlorogenic acid (isomer I)	$C_{16}H_{18}O_9$	5.20	353.0891
4	Chlorogenic acid	$C_{16}H_{18}O_9$	7.10	353.0872
5	Chlorogenic acid (isomer II)	$C_{16}H_{18}O_9$	7.60	353.0871
6	Myricetin-3-arabinogalactose	$C_{26}H_{28}O_{17}$	10.00	611.1271
7	Quercetin-3-sambubioside	$C_{26}H_{28}O_{16}$	12.60	595.1309
8	5-O-Caffeoylshikimic acid	$C_{16}H_{16}O_8$	13.40	335.0768
9	Quercetin-3-rutinoside	$C_{27}H_{30}O_{16}$	14.50	609.1462
10	Quercetin-3-glucoside	$C_{21}H_{20}O_{12}$	16.00	463.0873
11	Kaempferol-3-O-rutinoside	$C_{27}H_{30}O_{15}$	17.50	593.1512
12	N-Feruloyltyramine	$C_{18}H_{20}NO_4$	26.70	312.1234
13	Kaempferol-3-(*p*-coumarylglucoside)	$C_{30}H_{26}O_{13}$	27.60	593.1312
14	Quercetin	$C15H_{10}O_7$	28.40	301.0339
15	Delphinidin-3-sambubioside	$C_{26}H_{30}O_{16}$	4.40	595.1446
16	Cyanidin-3-sambubioside	$C_{26}H_{30}O_{15}$	5.70	579.1493
	Aspalathus linearis			
1	Patuletin 7-glucoside	$C_{22}H_{21}O_{13}$	4.60	493.0990
2	Esculin	$C_{15}H_{15}O_9$	4.77	339.0717
3	Safflomin A	$C_{27}H_{31}O_{16}$	5.19	611.1620
4	Quercetin-3-*O*-robinobioside	$C_{27}H_{29}O_{16}$	6.32	609.1506
5	Carlinoside*	$C_{26}H_{27}O_{15}$	7.98	579.1336
6	Vicenin-2	$C_{27}H_{29}O_{15}$	8.23	593.1482
7	Carlinoside or isocarlinoside or neocarlinoside 2″-*O*-*b*-arabinopyranosylorientin	$C_{26}H_{27}O_{15}$	8.61	579.1334
8	Carlinoside or isocarlinoside or neocarlinoside or 2″-*O*-*b*-arabinopyranosylorientin	$C_{26}H_{27}O_{15}$	8.83	579.1355
9	(*S*)-eriodictyol-6-*C*-*β*-D-glucopyranoside	$C_{21}H_{21}O_{11}$	8.97	449.1087
10	Carlinoside or isocarlinoside or neocarlinoside or 2″-*O*-*b*-arabinopyranosylorientin	$C_{26}H_{27}O_{15}$	9.40	579.1335
11	(*R*)-eriodictyol-6-*C*-*β*-D-glucopyranoside	$C_{21}H_{21}O_{11}$	9.68	449.1082
12	Isoorientin	$C_{21}H_{19}O_{11}$	11.21	447.0935
13	(*S*)-eriodictyol-8-*C*-*β*-D-glucopyranoside	$C_{21}H_{21}O_{11}$	11.34	449.1020
14	(*R*)-eriodictyol-8-*C*-*β*-D-glucopyranoside	$C_{21}H_{21}O_{11}$	11.62	449.1084
15	Orientin	$C_{21}H_{19}O_{11}$	12.26	447.0930
16	Aspalathin	$C_{21}H_{23}O_{11}$	13.26	451.1253
17	Aspalalinin	$C_{21}H_{21}O_{11}$	13.53	449.1082
18	Rutin	$C_{27}H_{29}O_{16}$	14.32	609.1452
19	Isovitexin	$C_{21}H_{19}O_{10}$	14.58	431.0991
20	Quercetin-3-*O*-glucoside/galactoside	$C_{21}H_{19}O_{12}$	15.57	463.0880
21	Luteolin-7-*O*-glucoside	$C_{21}H_{19}O_{11}$	15.89	447.0932
22	Nothofagin	$C_{21}H_{23}O_{10}$	17.76	435.1309
23	Secoisolariciresinol	$C_{20}H_{25}O_6$	22.01	361.1644
24	Luteolin	$C_{15}H_9O_6$	28.20	285.0348
25	Quercetin	$C_{15}H_9O_7$	28.41	301.0292
A	5,7,dihydroxy-6-*C*-glucosyl-chromone	$C_{15}H_{15}O_9$	4.94	339.0705
B	Eriodictyol 5,3′di-*O*-glucoside	$C_{27}H_{31}O_{16}$	5.05	611.1600
C	Quercetin-3-*O*-arabinoglucoside	$C_{26}H_{27}O_{16}$	5.50	595.1285
D	Isoquercitrin	$C_{21}H_{19}O_{12}$	15.97	463.0891
E	Scoparin	$C_{22}H_{21}O_{11}$	20.40	461.1070
	Virgin olive oil			
1	Hydroxytyrosol	$C_8H_{10}O_3$	8.00	153.0557
2	Tyrosol	$C_8H_{10}O_2$	9.90	137.0608
3	Vanillin	$C_8H_8O_3$	11.70	151.0401
4	*p*-coumaric acid	$C_9H_8O_3$	13.50	163.0401
5	Hydroxytyrosol acetate	$C_{10}H_{12}O_4$	14.00	195.0663
6	Elenolic acid	$C_{11}H_{14}O_6$	15.00	241.0718
7	Hydroxy elenolic acid	$C_{11}H_{14}O_7$	15.40	257.0667
8	Decarboxymethyl oleuropein aglycon	$C_{17}H_{20}O_6$	16.30	319.1187
9	Hydroxy D-oleuropein aglycon	$C_{17}H_{20}O_7$	16.60	335.1136
10	Syringaresinol	$C_{22}H_{26}O_8$	18.20	417.1555
11	Pinoresinol	$C_{20}H_{22}O_6$	18.80	357.1344
12	Decarboxymethyl ligstroside aglycon	$C_{17}H_{20}O_5$	19.20	303.1229
13	Acetoxy pinoresinol	$C_{22}H_{24}O_8$	19.30	415.1398
14	Hydroxy D-ligstroside aglycon	$C_{17}H_{20}O_6$	19.90	319.1187
15	10-Hydroxy oleuropein aglycon	$C_{19}H_{22}O_9$	23.00	393.1191
16	Oleuropein aglycon	$C_{19}H_{22}O_8$	23.20	377.1242
17	Luteolin	$C_{15}H_{10}O_6$	23.70	285.0405
18	Hydroxypinoresinol	$C_{20}H_{22}O_7$	24.60	373.1293
19	Methyl D-oleuropein aglycon	$C_{18}H_{22}O_6$	25.40	333.1344
20	Ligstroside aglycon	$C_{19}H_{22}O_7$	25.60	361.1293
21	Apigenin	$C_{15}H_{10}O_5$	25.80	269.0451
22	Methyl oleuropein aglycon	$C_{20}H_{24}O_8$	26.20	391.1398
	Cistus ladanifer			
1	Quinic acid	$C_7H_{11}O_6$	2.40	191.0556
2	Shikimic acid	$C_7H_9O_5$	2.90	173.0455
3	Hexahydroxydiphenoyl-D-glucose (isomer)	$C_{20}H_{17}O_{14}$	4.10	481.0624
4	Hexahydroxydiphenoyl-D-glucose (isomer)	$C_{20}H_{17}O_{14}$	4.70	481.0625
5	Hexahydroxydiphenoyl-D-glucose (isomer)	$C_{20}H_{17}O_{14}$	6.00	481.0625
6	Gallic acid	$C_7H_5O_5$	7.60	169.0144
7	Glucogallin (isomer)	$C_{13}H_{15}O_{10}$	7.80	331.0677
8	Punicalin	$C_{34}H_{21}O_{22}$	9.20	781.0531
9	Gentisoil glucoside	$C_{13}H_{15}O_9$	9.80	315.0722
10	Glucogallin (isomer)	$C_{13}H_{15}O_{10}$	10.40	331.0665
11	Digaloil-*β*-D-glucopiranose	$C_{20}H_{19}O_{14}$	10.80	483.0779
12	Pedunculagin	$C_{34}H_{23}O_{22}$	11.10	783.0680
13	Epigallocatechin	$C_{15}H_{13}O_7$	11.40	305.0659
14	Uralenneoside	$C_{12}H_{13}O_8$	12.60	285.0617
15	Punicalagin (isomer)	$C_{48}H_{27}O_{30}$	13.20	1083.0593
16	Strictinin	$C_{27}H_{21}O_{18}$	13.90	633.0758
17	Punicalagin (isomer)	$C_{48}H_{27}O_{30}$	15.10	1083.0595
18	Cornusiin B	$C_{48}H_{29}O_{30}$	15.60	1085.0745
19	Mirciaphenone B	$C_{21}H_{21}O_{13}$	17.40	481.0947
20	3,4′-Dihydroxypropiophenone-3-*β*-D-glucoside	$C_{15}H_{19}O_8$	17.80	327.1071
21	Quercetin diglycoside	$C_{27}H_{29}O_{17}$	19.40	625.1414
22	Phenethyl-*β*-primeveroside	$C_{19}H_{27}O_{10}$	19.70	415.1609
23	Kaempferol diglucoside	$C_{27}H_{29}O_{16}$	20.00	609.1458

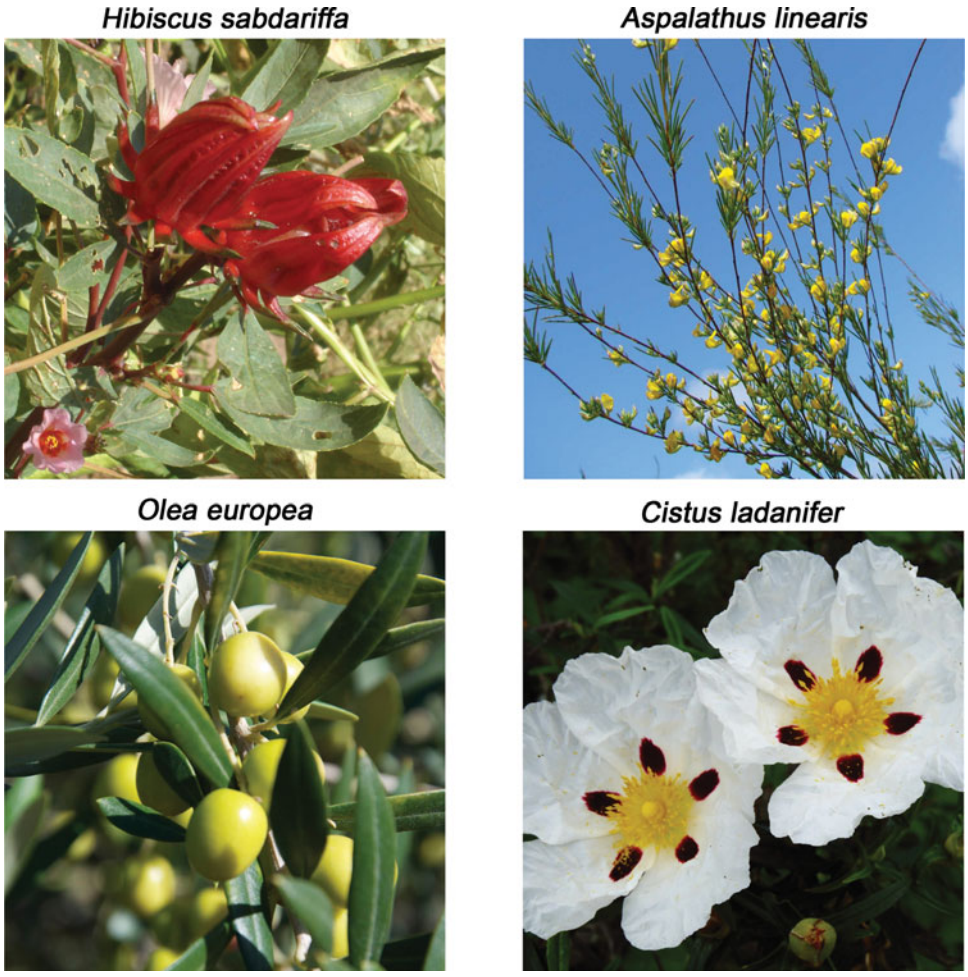

Figure 2 Photographs of plants depicted in Figure 1 also show that the source of polyphenols is not limited to an individual part of the plant and may be obtained from the calyx (*Hibiscus sabdariffa*), leaves (*Aspalathus linearis*), fruits (*Olea europaea*) or petals (*Cistus ladanifer*). (Color figure available online).

Eating a significant amount of polyphenols is challenging because most are found in food at a volume of mg/kg fresh weight. At least three strategies are currently being explored to surmount this difficulty: (1) the preparation of dietary supplements (the so-called nutraceuticals) from standardized extracts, (2) the consumption of so-called functional foods with added bioactive compounds, and (3) the development of engineered plants with increased polyphenol content. The addition of compounds as popular food derivatives is resulting in a trend to view many foods as both sustenance and medicine. The boundary between nutraceuticals and functional foods is not always clear, and regulations differ. Nutraceuticals are sold as pills, extracts, tablets, and in other familiar forms, and their main characteristic is that they provide polyphenols in amounts that exceed those that can be found in foods (Zeisel, 1999). The validity of these strategies has already been reviewed (Espín et al., 2007). Methodological problems have apparently been overcome in the production of engineered plants with increased polyphenol content (Niggeweg et al., 2004). A vector that encodes interacting transcription factors that induce anthocyanin biosynthesis in snapdragon flowers (*Antirrhinum majus*) has been expressed in transgenic tomatoes (Butelli et al., 2008). The resulting product contains at least 3 g/kg wet weight of anthocyanins. The commercial future of this product is uncertain because the color produced by the anthocyanins may prove challenging in marketing the tomatoes, but these tomatoes would nonetheless provide high amounts of the bioactive compound.

Further Unresolved Issues

A paucity of data prevents the successful integration of clinical information with variables indicating the health effects of polyphenols at the organ level. For instance, a substantial endorsement has recently been obtained for olive polyphenols (European Food Safety Authority, 2011), but the data required to clinically recommend a higher intake of such polyphenols and a method to acquire this data are not yet available. Data on excretion, metabolism by the microbiota, hepatic metabolism and accumulation in tissues, circulating metabolites, cellular uptake and albumin binding are insufficient. Moreover, data on actual bioavailability are scarce, and it is plausible that cellular

metabolites may differ from those found in plasma. The kinetics of penetration and the elimination of polyphenol in tissues are completely unknown. Whether polyphenols accumulate in specific organs remains to be ascertained, and the presence of cellular-specific mechanisms to incorporate polyphenols is controversial (Lapidot et al., 1998; Suganuma et al., 1998; Schramm et al., 1999; Chang et al., 2000; Youdim et al., 2000; Datla et al., 2001). The currently accepted data may add additional uncertainty. For instance, interesting patterns may be revealed in differences in the rates of consumption of flavanols in the populations of different nations based on the ingestion of a few sources of polyphenols (apples, pears, red wine, tea, and chocolate). In addition, inter-individual variability in polyphenol intake is extremely high (Radtke et al., 1998; Arts et al., 2000; Santos-Buelga and Scalbert, 2000; Scalbert and Williamson, 2000), and plasma concentration depends on the nature of the polyphenol and the food source (King and Bursill, 1998; Miyazawa et al., 1999; Rein et al., 2000; Erlund et al., 2001). An obvious conclusion is that because of the wide range of existing polyphenols and the considerable number of factors that can modify their concentrations, the available information on the quantities of polyphenols consumed daily throughout the world as well as the reference food-composition tables is useless. Despite this pessimistic perspective, we acknowledge the substantial effort put forth by the scientific community in the field of bioavailability and efficacy (Scalbert and Williamson, 2000; Manach et al., 2005). Although technical drawbacks are outside the scope of this review, it seems apparent that the documented bioavailability of polyphenols is low, and their concentrations in plasma rarely exceed 1 μM, even with an estimated dietary intake of up to 1 g/day. No data are available on the actual activities or effects of predicted metabolites. To produce beneficial effects on tissues other than the gastrointestinal tract itself, polyphenols must be absorbed and carried to target tissues and organs. Similar to well-characterized drugs, polyphenols will be subjected to the same protective xenobiotic-metabolizing and efflux mechanisms that result not only in major changes in biological activity but also in increased rates of excretion from the body (Scheepens et al., 2010; Vauzour et al., 2010; Visioli et al., 2011). Polyphenols undergo conjugation reactions that are mainly catalyzed by uridine diphosphoglucuronosyl transferases, sulfotransferases, and glutathione-S-transferases. These mechanisms are very efficient, and detection of aglycones is difficult with current methods. This is relevant because in some studies, most metabolites exhibited reduced biological activity, but in others, they demonstrated greater activity than the parental polyphenols (Lambert et al., 2007; Landis-Piwowar and Dou, 2008). The detection of 445 cellular-specific mechanisms that incorporate polyphenols is controversial mainly as a result of technical issues (Chang et al., 2000). We have recently used nano-liquid chromatography-electrospray ionization time-of-flight mass spectrometry (nanoLC-ESI-TOF MS) in an in vitro and in vivo model (Fernández-Arroyo et al., 2012), and the results may be important for designing strategies, other than increasing ingestion, that improve bioavailability. Natural products may modulate intestinal microflora and the action of efflux transporters and inhibit glucuronidation (Lambert et al., 2004; Selma et al., 2009). Following positive results previously obtained in a chemoprevention study (Nair et al., 2010), we are also currently developing biocompatible, biodegradable, and non-toxic nano-size liposomal formulations to further increase the bioavailability of polyphenols for the prevention of metabolic diseases.

In contrast, the identification of phenolic compounds in plants, a first and necessary step, seems to be a technically resolved issue. Liquid chromatography coupled with mass spectrometry (MS) using electrospray ionization (ESI) as an interface provides an efficient resolution of a wide range of polar compounds. Furthermore, time-of-flight-MS or ion-trap-MS provide the necessary measurements to selectively characterize compounds in complex matrices (Fu et al., 2009; Arráez-Román et al., 2010; Rodríguez-Medina et al., 2009). However, the sensitivity of these techniques is limited and barely reproducible when used in biological samples (Kawai et al., 2008). In conclusion, new research tools are needed to clarify the above-mentioned questions, and novel approaches to the application of knowledge about bioactive compounds to human nutrition are required.

PLANT POLYPHENOLS ARE NOT SYNTHESIZED BY MAMMALS BUT MAY INTERACT WITH KEY REGULATORS TO PROVIDE HEALTH BENEFITS: A COUNTERINTUITIVE EFFECT IN STRESS-RESPONSE PATHWAYS

Xenohormesis

Plants obviously produce substances that are of benefit to human health, and although humans are fully aware of this fact, we are largely indifferent. Despite 60% of the world population relying on plants for the treatment of diseases and ailments, a myriad of plant-derived medicines wallow in obscurity. A potentially negative factor restraining major research efforts is that plant active molecules interact with numerous endogenous molecular targets in humans. However, these molecules are surprisingly safe even at high doses (Corson and Crews, 2007). To illustrate this point, resveratrol directly modulates over 30 enzymes and receptors without any known toxicity, with salutary effects being obtained by inhibiting enzymes and activating others (Baur and Sinclair, 2006). Similarly, tea polyphenols and curcumin provide numerous health benefits and affect dozens of molecular targets (Chen and Dou, 2008; Goel et al., 2008).

The most relevant questions remain unanswered are: why do plants make substances of benefit to human health, and what are the mechanisms that permit active functions in a xenobiotic environment? Current hypotheses are unsatisfactory but are better than having no explanatory possibilities. It is possible that before the separation of the plant and animal kingdoms, biosynthetic pathways evolved that created signaling chemicals with similar structures. It is also possible that the multifaceted action of these molecules is the result of their interaction with regulatory DNA

sequences that control transcription, facilitating a gene that can respond to indirect inputs (Kushiro et al., 2003). Xenohormesis has recently been suggested as a potential mechanism (hypothesis) to partially explain the effect of plants on animals (Howitz and Sinclair, 2008). Previously, hormesis was defined as the process by which a mild stress can have health benefits, preparing the organism for a better use of defensive mechanisms against presumably more severe dangers. The term xenohormesis was coined to indicate such interactions among species. An environmental stress to a plant leaves a chemical in the form of the plant's polyphenol content, which then provides resistance to stress in humans who eat the plant. This suggests the existence of mechanisms that detect this stress-induced polyphenol content. Thus, the stress occurs in the plant, and the beneficiaries are the animals that sense the chemical cues upon ingestion. If xenohormesis is the actual mechanism of the effects of polyphenols, this would indicate that, contrary to what it is generally believed, most benefits from polyphenols do not result from their intrinsic antioxidant properties but from the evolutionarily adaptive modulation of molecules involved in stress-response pathways. Some of the effects of polyphenols represent relatively simple chemical mechanisms (e.g., antioxidants), but some resemble those produced by signaling molecules or chemical messengers (Taylor and Grotewold, 2005; Oliveras-Ferraros et al., 2011). Stressed plants would constitute an extensive source of safe xenohormetic molecules that may artificially modulate a variety of enzymes involved in the regulation of the stress response and survival. An unexpected interest in this topic has emerged based on findings indicating that low calorie intake (calorie restriction, CR), as an example of a mild stress, increases survival in numerous experimental models. These effects are similar to those described for polyphenols via the activation of sirtuins (Howitz et al., 2003; Cohen et al., 2004). More recently, glucose restriction experiments have provided an elegant and plausible connection between critical metabolic regulators, indicating that polyphenols should be viewed as signaling molecules (Fulco et al., 2008). Glucose restriction triggers AMPK activity, and this activates the gene encoding the NAD synthetic enzyme, Nampt, which is necessary for the activation of the sirtuin SIRT1. This is even more encouraging after considering that only ATP and NAD provide an indication of energy status as sensed by AMP-kinase (the AMP/ATP ratio) and the sirtuins (which require NAD to deacetylate substrates). Many polyphenols are modifiers of transcription (Shay and Banz, 2005). Although the mechanisms are difficult to ascertain as a result of the pleiotropic actions of polyphenols, the suppression of NF-kB activity suggests that polyphenols have relevant roles in the modulation of insulin resistance and inflammation (Paur et al., 2008). This is particularly important because these effects overlap with known risk factors for chronic diseases. The facts that animals and plants share a high degree of sequence homology between the extracellular signal-regulated kinase (ERK) pathways, that many polyphenols can modulate kinase pathways, including AMPK, and that polyphenols may simultaneously modulate redox signaling and inhibit mitochondrial function, are all potential mechanisms at play (Zang et al., 2006; Nunn et al., 2009). Therefore, a reduction in stress signaling with an increase in mitochondrial free radicals and a subsequent reduction in ATP production may be predictable outcomes of polyphenol ingestion, suggesting important implications for chronic diseases and, ultimately, for aging.

Calorie restriction (CR) is, therefore, a pro-longevity strategy for humans, (Colman et al., 2009), but the adoption of such a revolutionary change in lifestyle is unlikely. Instead, the search for CR-mimetic molecules promises to be a research area of great interest and with potential commercial yields. The goal would be to identify compounds that target metabolic and stress response pathways without actually restricting caloric intake. We have recently proposed this for metformin (Menendez et al., 2011) and polyphenols other than resveratrol (Beltrán-Debón et al., 2011).

Chronic Diseases and Aging: A Road Paved with Oxidation and Inflammation

Conceivably, increasing longevity should prevent diseases that cause higher mortality, and in this way, the prevention of the chronic inflammation associated with aging is a potential mechanism for the action of polyphenols. Chronic inflammation is currently accepted as the major cause of at least 6 of the top 10 causes of death, including atherosclerosis and cancer, diseases that largely determine human life expectancy (McGeer and McGeer, 2004). If polyphenols have a major impact on aging, it is likely a consequence of beneficial effects related to these diseases, probably by acting on metabolic and inflammatory pathways (Rull et al., 2010). Such pathways are extremely complex and provide numerous candidate molecular targets (Figure 3). This complexity helps explain the repeated failures of numerous strategies to assess an exact and simple mechanism of the action of polyphenols on these pathways.

An acute inflammatory response is usually considered to be beneficial and is terminated within days. Chronic inflammation, however, lasts for weeks, months or years and results in severe cellular damage, mostly caused by macrophages differentiated by the action of chemokines. Among the chemokines, monocyte chemoattractant protein-1 (MCP-1) is the most actively involved, and it plays a major role in the regulation of both metabolism and inflammation (Rull et al., 2010). Consequently, MCP-1 has recently been considered an attractive therapeutic target. Interestingly, the production and secretion of MCP-1 may be safely modulated in humans by certain polyphenols (Beltrán-Debón et al., 2010). As described above, this action is probably independent of the antioxidant effects but should be included in the equation. This is because the sustained generation of reactive oxygen and nitrogen species (e.g., $OH^{\bullet}$, $NO^{\bullet}$, $O2^{\bullet}$, $OONO^{\bullet}$) contributes to the pathological consequences of chronic inflammation, inflicting oxidative and nitrosative damage on critical genes and proteins (Cerutti 1985; Hofseth et al., 2003; Nair et al., 2006). It is particularly important to highlight $NO^{\bullet}$, which

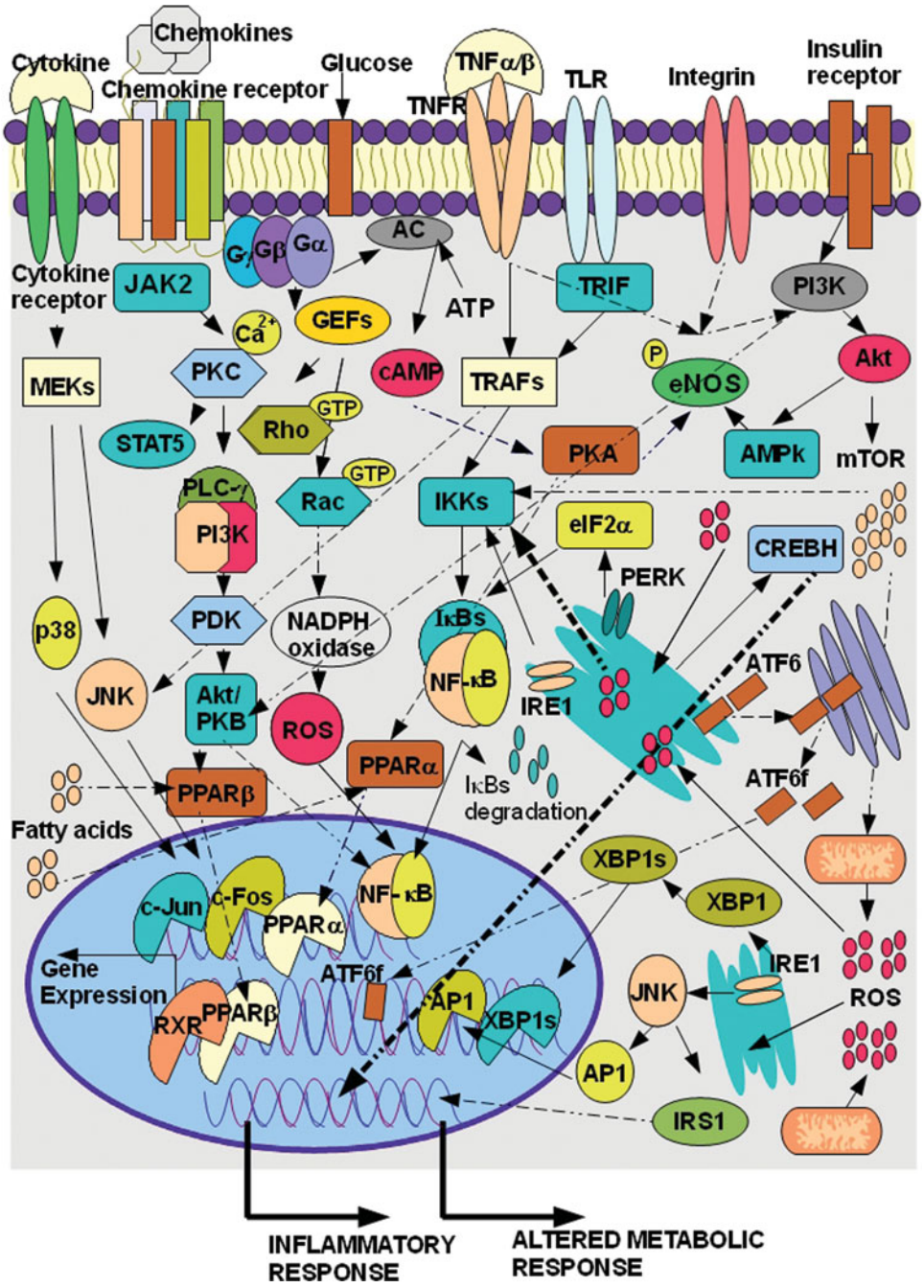

Figure 3 Putative molecular targets for polyphenols showing their influence on the cellular inflammatory and metabolic responses, which may be interpreted as an integration of multiple pathways in response to cellular stress. These pathways are extremely complex even when factors being repressed are not depicted to prevent oscillatory or chaotic patterns. Multiple targets, multiple signals, and different dimensions (space-time) hamper the recognition of simple patterns and probably represent an example of a self-organizing, self-repairing reaction-diffusion system originally proposed in Turing's classic 1952 paper "The chemical basis of morphogenesis." AC (adenylate cyclase); Akt (v-Akt murine thymoma viral oncogene); AP1 (activator protein 1); ATF6 (activating transcription factor 6); cAMP (cyclic adenosine monophosphate); CREBH (cyclic-AMP responsive element-binding protein); eIF2α (α-subunit of eukaryotic factor 2α); IKK (IκB kinase); IRE1α (phosphorylated inositol-requiring 1α); JAK (Janus kinases); JNK (JUN N-terminal kinase); NF-κB (transcription factor nuclear factor-κB); PDK-1 (phospholipid-dependent kinase-1); PERK (double-stranded RNA-dependent protein kinase (PKR)-like ER kinase); PI3K (phosphatidylinositol-3 kinase); PKB (protein kinase-B); PPARs (peroxisome proliferator-activated receptors); STAT (signal transducers and activators of transcription Factors); TRAF2 (tumor-necrosis factor-α (TNF-α)- receptor-associated factor 2); XBP1 (X-box-binding protein 1). (Color figure available online).

is relevant in the pathogenesis of both atherosclerosis and cancer by acting as a key signaling molecule (Marletta, 1994; Espey et al., 2000). $NO^{\bullet}$ interacts with p53, a key molecular node in the inflammatory stress response pathway, regulating the expression of a specific set of genes (Ambs et al., 1998; Hofseth et al., 2003). Other key regulators of inflammation can either stimulate or inhibit the development of atherosclerosis or cancer (Dranoff 2004; Coll et al., 2007; Lue et al., 2011). Most of these regulators lead to the activation of NF-kB (Figure 3) and the consequent activation of transcription factors relevant for proliferation, differentiation, survival, angiogenesis, cell cycle, and senescence. Current evidence suggests that dietary polyphenols may counteract such activation, but the exact mechanisms remain unknown. In this context, studies from our group have previously highlighted the importance of the interaction between polyphenols and the lipid domains of cell membranes that may contribute to understanding the beneficial effects of polyphenols at the cellular level. In particular, we have shown that stilbenes (Garcia-Garcia et al., 1999), galloylated catechins (Caturla et al., 2003), seco-iridoids (Caturla et al., 2005), phenylpropanoids (Funes et al., 2010), diterpenes (Perez-Fons et al., 2010), and norlignans (Laporta el al., 2007) all may change the physical properties of phospholipid bilayers (viscosity, lipid packing, phase transition temperature, lateral segregation, and surface charge) that influence the control of cell metabolism. More specifically, these effects contribute to their antioxidant capacity and combine with their electron donor ability to protect lipid membranes against oxidative damage. Polyphenols may also target cell surface receptors and proteins that are localized in the so-called lipid rafts. These structures participate in cellular signal transduction, endocytosis, and the transmembrane translocation of different components (Tarahovsky et al., 2008) and may be important in mediating the antibacterial or anticancer effects of some polyphenols (Adachi et al., 2007; Cushnie et al., 2008). Finally, quercetin, luteolin, and anthocyanins also modulate cell surface receptors that are important in the regulation of their anti-inflammatory activity by altering membrane lipid rafts (Xia et al., 2007; Kaneko et al., 2008).

EPIGENETIC CONTROL AS A MAJOR MECHANISM OF GENE REGULATION: THE ROLE OF NUTRIENTS AND POLYPHENOLS

A relatively recent line of thinking suggests that the pleiotropic and redundant effects of polyphenols are probably the consequences of actions on the epigenome. Moreover, polyphenols are well-documented modulators of innate and adaptive immune responsiveness, affecting the expression of numerous inflammation-related genes (Magrone and Jirillo, 2010). The idea that the modulation of inflammation is mediated by epigenetic mechanisms is both challenging and plausible because the complexity of the immune system requires layers of well-coordinated actions to control its initiation and termination (Taganov et al., 2007; Jones et al., 2010). Two obvious and related questions arise: does either inflammation and/or oxidation trigger epigenetic phenomena? If so, do such inflammation-associated mechanisms regulate the expression of genes involved in the inflammatory response? The data are still inconclusive. If answers are affirmative, research in this field may lead to a rapid identification of novel links between inflammation and chronic diseases to guide therapeutic actions.

Epigenetics and Nutrition: A Rising Star

The importance of the epigenome in the development of chronic diseases is being increasingly appreciated. With the completion of the human genome sequence, there has been an increasing focus on understanding the functional roles of gene products and the mechanisms regulating the expression of such genes. Epigenetics, currently defined as genomic information superimposed on the actual DNA sequence, is responsible for the preservation of patterns of gene expression for each cell type and acts as a regulatory factor to modulate gene function. The epigenome code defines when and whether a gene will be active or silent. It is immediately apparent that the move from a purely genetic to an epigenetic model is crucial for developing prevention strategies for some diseases because intervention in the epigenome is theoretically possible. Altering epigenetic pathways is a strategy that is currently being tested with the aim of arresting changes while they are still reversible. Dietary factors, mainly polyphenols, are able to modify such epigenetic pathways (Jaenisch and Bird, 2003; Egger et al., 2004; Bird, 2007; Goldberg et al., 2007; Turner, 2007).

Understanding the relationship between nutrients and epigenetics is an extremely attractive goal. Some concepts have already found a clinical application. Although the benefits and risks of fortifying basic foodstuffs with added folic acid remain unresolved, it seems that periconceptional folic acid supplementation has a strong protective effect against neural tube defects (Lumley et al., 2011). In mice, this nutrient restores the functions of genes with altered DNA methylation patterns. Folic acid is active in a strain of mice that has a defect in a pigment gene called *agouti* (Duhl et al., 1994). Unlike most other *agouti* mutations, expression of the A^{wy} alleles is variable and subject to parental imprinting effects. Dams with extra folic acid alter the phenotype (a change in hair color) of their offspring via increased CpG methylation at the A^{wy} (Wolff et al., 1998; Cooney et al., 2002). Additionally, in mice with defects in the axin gene, folic acid supplements during pregnancy reduce kinking in the pups' tails by half. Interestingly, folic acid alters the methylation of each gene in a different way (Waterland et al., 2006). Other examples are also illustrative. In *Apis mellifera* (honey bees), depending on whether they are fed royal jelly or beebread, the larvae grow to be either queens or workers. This developmental change represents not only marked physiological, morphological, behavioral, and reproductive differences but also a dramatic difference in lifespan, as queens outlive workers by 10-fold (Corona et al., 2007; Kucharski et al., 2008).

The Impact of Nutrients on MicroRNA Expression

Epigenetic regulation is currently considered an important factor in the pathogenesis of atherosclerosis and cancer via molecular targets related to microRNA (miRNA) (Hussain and Harris, 2007; Wierda et al., 2010). MiRNAs constitute approximately 3% of the human genome, indicating that several thousand human genes may be regulated via this mechanism (Lewis et al., 2005). MiRNAs are small (approximately 22 nucleotides) gene-silencing RNAs that bind to their target mRNAs and lead to their cleavage and degradation. Precursor miRNAs that are produced in the nucleus undergo several rounds of processing in both the nucleus and cytoplasm before they are loaded onto the RNA-induced silencing complex to modify the target mRNAs (Bird 2007; Hussain and Harris 2007).

The influence of nutrients in miRNA-related effects has been scarcely studied in humans (Chen and Xu 2010). The effect of exogenous miRNA has not been closely examined despite the presence of miRNAs in most foodstuffs that are usually conserved across species (Xia et al., 2011). In addition, miRNAs appear to play regulatory roles in adipocyte differentiation, insulin action, fat metabolism, and the regulation of fat cell size and numbers (McGregor and Choi 2011). Additionally, more than 50 miRNAs are down- or up-regulated in the liver of diet-induced obese mice. The overexpression and knock-down of miR-107 caused the expression of a putative target, fatty acid synthase, to decrease and increase, respectively, further suggesting the correlation of miRNAs and their targets in diet-induced alterations (Park et al., 2011). More importantly, the incorporation of isomers of linoleic acid has proven useful in obesity by influencing the expression of some miRNAs, both in humans and in mice. In a cell model, nutrient exposure also seems to be related to miRNAs (Whigham et al., 2007; Parra et al., 2010; Teferedegne at al., 2010).

Interactions among the various components of the epigenetic machinery emphasize the integrated nature of the mechanisms involved in the maintenance of global gene expression and have important implications for the global relationship between epigenetics, nutrition, and chronic diseases (Saito and Jones 2006; Chellappan et al., 2010). Under normal conditions, miR-34a expression is inhibited, resulting in increased hepatic sirtuins. In contrast, under pathophysiological conditions, such as in the fatty livers of obese mice, the transcription of miR-34a is no longer inhibited, and hepatic sirtuins decrease (Lee and Kemper 2010). Evidence of the direct influence of polyphenols on miRNA expression is still limited. For instance, treatment with curcumin significantly changes the levels of 29 miRNAs in pancreatic cell lines, and it seems useful, in combination with gemcitabine, in pancreatic cancer management (Sun et al., 2008; Ahmad et al., 2010). Epigallocatechin gallate (EGCG), a major type of green tea polyphenol, modifies the expression of some of the miRNAs in human hepatocellular carcinoma HepG2 cells: in one study, 13 were up-regulated and 48 were down-regulated (Tsang and Kwok 2010). Similar results have been reported with soy polyphenols (mainly genistein) in several cancer cell models and involve miR-200 (a-c), let-7 (a-f), miR-27b, and miR-146a (Parker et al., 2009; Sun et al., 2009; Li et al., 2010). More recently, our data indicate that plant-derived polyphenols may be beneficial in the treatment of fatty liver disease via the regulation of expression of miRNA paralogs miR103/107 and miR-122 (Joven et al., 2012).

The Impact of Nutrients on DNA and Histone Methylation

Nucleosomes consist of approximately 146 base pairs of DNA wrapped twice around a histone octamer. Nucleosomes are the fundamental building blocks of *euchromatin,* which is transcriptionally active, and *heterochromatin*, which remains condensed throughout the cell cycle and is generally considered to be transcriptionally inactive. It has been well documented that chromatin is not a passive element for the storage of genetic information, but it can regulate transcriptional processes through the modification of both DNA and histones (Luger et al., 1997; Berger 2007). Both DNA and histone methylation are dependent on S-adenosyl-L-methionine (AdoMet, SAdoMet, SAM, or SAMe), an important enzymatic cofactor. The benefits and risks of AdoMet as a nutrient are unclear, but it is currently marketed as a food supplement. Three families of DNA methyltransferases (Dnmt1–3) and one regulatory factor (Dnmt3L) are found in mammals. Dnmt1 is considered to be the major maintenance methyltransferase, and Dnmt1$^{-/-}$ mice show embryonic lethality as a consequence of severe hypomethylation. The in vivo Dnmt2 function remains elusive. Dnmt3a and Dnmt3b, which share little homology with either Dnmt1 or Dnmt2, are the de novo methyltransferases. Dnmt3a$^{-/-}$ mice develop to term but die at 4 weeks of age, and Dnmt3b$^{-/-}$ embryos do not thrive and die from growth impairment and neural tube defects (Li et al., 1992; Xie et al., 1999; Ooi et al., 2009). Histone methylation can occur in lysine (K) or arginine (R) residues. Lysine methylation is regulated by complex mechanisms related to approximately 100 SET domains encoded in the human genome, collectively known as HKMTs (histone lysine methyltransferases) (Cheng et al., 2005; Cazzonelli et al., 2009). Protein arginine methylation is a common posttranslational modification in eukaryotes and is catalyzed by two major types of protein arginine methyltransferases (PRMTs) (Bedford and Richard, 2005).

The methylation process is reversible and modifiable by nutrients. In particular, diets containing low amounts of methyl donor nutrients (methionine, choline and folate) seem to facilitate carcinogenesis, and different combinations of diets may alter the expression of specific genes by modifying DNA methylation (Newberne and Rogers 1986; Wolff et al., 1998). Nutrients with this characteristic are mainly (1) B vitamins (folate, vitamins B12, and B6), as coenzymes of one-carbon metabolism; (2) methyl donors, such as methionine, choline, serine, and betaine; (3) micronutrients that can modify one-carbon metabolism (retinoic acid, zinc, selenium); and (4) polyphenols that modify the activity of DNA methyltransferases. It seems obvious that diminished availability of dietary methyl donors for

one carbon-metabolism may affect DNA methylation, but actual evidence is scarce (Waterland 2006). In mice, folate and vitamin B12 present some association with DNA methylation, but the data are not particularly robust (Friso and Choi 2005). There are no reports indicating that vitamin B6 or vitamin B12 affects DNA methylation. In mice, dietary fat and cholesterol elicit a relative AdoMet deficiency with decreased hepatic concentrations of both methionine and downstream products (taurine and glutathione), indicating a defect in methylation as a major consequence of excess nutrients in the pathogenesis of liver inflammation (Rull et al., 2009; Vinaixa et al., 2010). Moreover, in rats, the hypomethylation of DNA was detected within a single week after initiation of the methyl-deficient diet, indicating that the mechanism is rapid and intense (Wainfan et al., 1989). Dietary deficiencies in other micronutrients may also decrease DNA methylation by altering the availability of methyl groups (retinoic acid), reducing the utilization of methyl groups enzymatically (zinc) or enhancing the trans-sulfonation pathways (selenium) (Dreosti 2001; El-Bayoumy 2001; Rowling et al., 2002). It is well documented that the hypermethylation-induced transcriptional silencing of tumor suppressor genes is a frequent epigenetic defect in many human cancers. The reversal of this situation, mainly by inhibiting Dnmt activity, is a plausible mechanism for current and future drugs, but available Dnmt inhibitors are toxic and nonspecific. A paradigmatic example is 2'-dioxy-5-azacytidine, a drug that, in addition to its demethylating properties, may induce cell sensitization to chemotherapy and is consequently currently under consideration for use in the treatment of certain malignancies (Schnekenburger et al., 2011). A broad clinical application of this drug, as well as of decitabine, another Dnmt inhibitor, is restricted by a number of undesired effects that include cytotoxicity, nonspecific targeting, and structural instability (Lim et al., 2011). However, dietary polyphenols have been shown to directly inhibit Dnmt without the associated toxicity to partially reverse hypermethylation status (Lee et al., 2005). EGCG concentration and the time-dependent reversal of the hypermethylation of tumor-suppressing genes have been documented in human cancer cells, but these results remain controversial. Other related polyphenols, such as catechins, epicatechin, epicatechin gallate, and epigallocatechin, share these actions (Stresemann et al., 2006; Fang et al., 2007; Kato et al., 2008; Tsao et al., 2009; Pandey et al., 2010). Similar effects and results may be found with soy isoflavones (mainly genistein, biochanin or daidzein), polyphenols from tomatoes, red fruits, and certain vegetables (mainly lycopene) and other catechol-containing polyphenols (mainly caffeic acid or chlorogenic acid) (Lee and Zhu 2006; Chalabi et al., 2007; Tang et al., 2008; Majid et al., 2010). The list of plant-derived components that diminish Dnmt activity or expression is continuously growing. Of particular note are the compounds obtained from cruciferous vegetables, such as sulforaphane and isothiocyanates, curcumin, rosmarinic acid, resveratrol, myrecetin, apigenin, and garcinol (Fang et al., 2007). Of particular interest, in the Mediterranean diet, proto-catechuic acid, obtained from olives, and quercetin, a usual component in fruits and vegetables, also have demonstrated effects against Dnmt activity (Lee et al., 2005; Paluszczak et al., 2010).

The Impact of Nutrients on Histone Acetylation

Silent chromatin is enriched in deacetylated histones, whereas active chromatin is hyperacetylated. Dietary polyphenols can regulate gene expression through changes in histone modifications (Nair et al., 2008). The deregulation of histone acetylation contributes to the pathogenesis of diseases in which inflammation plays a major causal role (Mariadason et al., 2000; Marcu et al., 2006). The removal of an acetyl group from histone tails is catalyzed by histone deacetylases (HDACs). HDAC members are classified into four groups depending on their homology with yeast proteins (Classes I-IV). All except class III enzymes are considered "classical" HDACs because they share sequence similarity and require zinc for their activity. However, class III HDACs, often called sirtuins (SIRT1–7), mediate their actions in an NAD^+-dependent manner. Histone deacetylation may antagonize the transcriptional activation of genes, and aberrant promoter deacetylation, as a consequence of HDAC mistargeting, also leads to the inappropriate inhibition of gene expression (Feng et al., 2007). Alterations in acetylation-related gene expression may also be associated with the activity of histone acetyl transferases (HATs) that add acetyl groups to histone tails. Histones are not exclusive targets for HATs, which also catalyze the acetylation of a number of transcription factors, corepressors, and coactivators. The relationship between HDACs and HATs is poorly understood, but current knowledge suggests that they may represent potent therapeutic targets for modulating deregulations of the pathways that lead to chronic disease (Zhao et al., 2005). Nutrients, particularly polyphenols, are known to possess potent HAT and HDAC inhibitory activities. Several dietary compounds, including butyrate (formed in the colon from the fermentation of dietary fiber), diallyl disulfide (present in garlic and other *Allium* vegetables), and sulforaphane (found in cruciferous vegetables), have the ability to inhibit class I and II HDAC enzymes, and all have been associated clinically with protective anticancer effects. These compounds have also been shown to inhibit cell proliferation and stimulate apoptosis in a manner analogous to other nondietary HDAC inhibitors, such as trichostatin A (Bernhard et al., 1999; Mariadason et al., 2000; Myzak and Dashwood 2006). Among the polyphenols, there is evidence from in vitro and in vivo models suggesting that curcumin may modify histones. Curcumin binds covalently to HAT enzymes and, at least in cancer cells, this is associated with the repression of HAT-dependent chromatin transcription (Marcu et al., 2006; Balasubramanyam et al., 2004). Curcumin may also prevent the hyperacetylation induced by HDAC inhibitors and may induce relevant changes in gene expression associated with inflammation (Marcu et al., 2006; Morimoto et al., 2008; Chiu et al., 2009). A compound extracted from cashew nuts, anacardic acid, is a specific HAT inhibitor, and its chemical formula has been used to develop synthetic HAT

inhibitors and activators (Balasubramanyam et al., 2003; Eliseeva et al., 2007). Tea polyphenols have been mainly studied in the context of DNA methylation but may also act as modifiers of HAT activity. The modulation of HDACs, sirtuins and HMTs is controversial, but tea polyphenols may increase histone methylation and reduce acetylation, leading to chromatin compaction and the transcriptional silencing of genes in cancer cells. Other tea polyphenols, such as polyphenon B and theophylline, are associated with the down-regulation of the inflammatory response through the modulation of HAT, HDAC activity, and NF-kB activation (Choi et al., 2009; Cosio et al., 2009; Murugan et al., 2009). Garcinol, a highly cytotoxic derivative from *Garcinia* fruit rinds, is a potent HAT inhibitor (Arif et al., 2009). Various allyl derivatives from garlic induce increased histone acetylation via the direct inhibition of HDAC active sites (Nair et al., 2008). There is also a growing list of compounds, such as isoflavones from soy, isothiocyanates, equol, sanguinarine, caffeic and chlorogenic acids, and dihydrocoumarin, that are responsible for histone modifications (Rajendran et al., 2011). In some cases, these plant-derived products are also known for their action on DNA methylation as mentioned above. Quercetin inhibits HAT activity on the promoter region of genes associated with the manifestation of inflammation, but it also activates sirtuins (Howitz et al., 2003; Wood et al., 2004; Ruiz et al., 2007). Resveratrol has become the referent among the sirtuin activators, and it is thought to be a mimetic factor of caloric restriction (Howitz et al., 2003; Wood et al., 2004; Howitz and Sinclair 2008). This drug also has salutary effects on cancer and metabolic disorders, probably by activating PGC-1 alpha, although the exact mechanism of action is currently controversial (Borra et al., 2005; Lagouge et al., 2006; Wang et al., 2008; Boily et al., 2009).

CONCLUDING REMARKS

Although there remains much to learn about the correlative versus causal effects of exposure to various nutrients, the effects of polyphenols are attributable to changes, among others, in gene expression in which epigenetic mechanisms seem to play a major role. These include changes in the DNA methylation pattern, regulation of histone modifications and changes in the expression of some miRNAs. These effects may help to provide the necessary tools for a rational use of polyphenols in the clinical setting. Current initiatives involve developing a substantial research effort to understand epigenetic mechanisms and their association with nutrients. The task is not easy because there are conceivably numerous and different epigenomic profiles that are probably cell or tissue specific, and each one directs a specific gene expression that influences the phenotype. However, characterizing the epigenome is extremely important in determining how diet impacts changes in gene expression both in healthy and disease states and to elucidate the impact of dietary manipulation and the potential for using nutritional interventions to restore health.

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