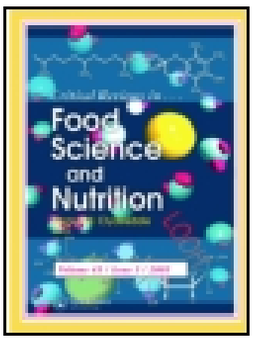

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Dietary polyphenols against metabolic disorders: How far have we progressed in the understanding of the molecular mechanisms of action of these compounds?

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ABSTRACT

The aim of this review was to critically assess the evidence supporting the metabolic and anti-inflammatory effects attributed to polyphenols and the potential mechanisms of action underlying these effects. The metabolic and anti-inflammatory properties of polyphenols and polyphenol-rich products have been shown mostly in rodents. These compounds appear to share multiple mechanisms of action at different body sites (gastrointestinal tract, microbiota, host organs) and the responsible molecules may be the original plant compounds, the microbial metabolites and (or) the host derived conjugates. Polyphenols may modify digestion and absorption of nutrients, microbiota composition and metabolism, and host tissue metabolic pathways but none of these mechanisms have been fully demonstrated *in vivo* and thus, more and better designed studies are needed. Furthermore, human clinical trials show inconsistent evidence of the metabolic and inflammation regulatory properties of polyphenols. Some of the principal limitations of these studies as well as recommendations to further progress in the understanding of the metabolic effects and mechanisms of action of polyphenols are discussed.

KEYWORDS

Intestine; microbiota; metabolites; hormones; cytokines; human clinical trials

Abbreviations: AMPK: 5′-AMP-activated protein kinase; ApoE: Apolipoprotein E; ApoB48: Apolipoprotein B 48; Apo100: Apolipoprotein 100; Asp: Aspartic acid; BBMV: Brush border membrane vesicles; BDNF: Brain derived neurotrophic factor; BP: Blood pressure; b.w.: Body weight; C: Cytosine; CAD: Coronary artery disease; CCK: Cholecystokinin; CEBPα/β: CCAAT-enhancer binding protein alpha/beta; COX-2: Prostaglandin G/H synthase 2; CRP: C-reactive protein; DBP: Diastolic blood pressure; DSS: Dodecyl sodium sulfate; ECG: Epicatechin gallate; EGC: Epigallocatechin; EGCG: Epigallocatechin gallate; G: Guanine; GAE: Gallic acid equivalent; GE: Grape extract; GLP-1: Glucagon-like peptide 1; Glu: Glutamic acid; GLUT2: Solute carrier family 2, facilitated glucose transporter member 2; GPE: Grape pomace extract; GSE: Grape seed extract; HBA1c: Glycosylated hemoglobin; HDL: High density lipoprotein; HF: High fat; ICAM-1: Intercellular adhesion molecule 1; IFN-γ: Interferon gamma; IGF-1: Insulin-like growth factor I; IL-1α: Interleukin 1 alpha; IL-1β: Interleukin 1 beta; IL-2: Interleukin 2; IL-4: Interleukin 4; IL-6: Interleukin 6; IL-8: Interleukin 8; IL-10: Interleukin 10; IL-12: Interleukin 12; IL-17A: Interleukin 17A; LDL: Low density lipoprotein; LPS: Lipopolysaccharides; MCP-1: Monocyte chemoattractant protein 1; MetS: Metabolic syndrome; MIP1α: Macrophage Inflammatory Protein 1α; Mir-155: MicroRNA 155; NAFLD: Non-alcoholic fatty liver disease; NFκB: Nuclear factor NF-kappa-B; eNOS: Endogenous nitric oxide synthase; iNOS: Inducible nitric oxide synthase; NO: Nitric oxide; NPC1L1: Niemann-Pick C1-like 1 cholesterol transporter; NPY: Pro-neuropeptide Y; oxLDL: oxidized low density lipoprotein; PAI-1: Plasminogen activator inhibitor 1; PBMCs: Peripheral blood mononuclear cells; PGE2: Prostaglandin E2; PMA: Phorbol 12-myristate 13-acetate; PPARs: Peroxisome proliferator-activated receptors; PPARGC1A: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SBP: Systolic blood pressure; SCFA: Short chain fatty acids; SGLT1: Sodium/glucose cotransporter 1; SIRT1: Sirtuin 1; SNPs: Single nucleotides polymorphisms; T2D: Type 2 diabetes; TGs: Triglycerides; TNF-α: Tumor necrosis factor alpha; Uro-A: Urolithin A; Uro-B: Urolithin B; VCAM1: Vascular cell adhesion molecule 1

Introduction

Metabolic disorders

In normal physiology, energy intake, usage, and storage are generally balanced with the body needs. Deregulation of this "metabolic homeostasis" generally associated with high caloric intake and sedentary habits as well as variations in gut microbiota composition and host genetic make-up has led to the current epidemic of metabolic disorders and increased risk of cardiovascular diseases (Moran and Shanahan, 2014). Metabolic syndrome (MetS) is a disorder characterized by at least three of the following features: central adiposity (adipocyte and adipose tissue dysfunction), elevated fasting blood glucose and reduced insulin sensitivity, high levels of circulating triglycerides (TGs) and low levels of high density lipoprotein (HDL)-cholesterol and elevated blood pressure. MetS is also associated with chronic low-grade inflammation. The world prevalence of MetS is currently situated between 20% and 30% (Padwal,

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2014). The prevalence of obesity is increasing dramatically and it is estimated that by 2015, 700 million adults will be obese and more than two billion adults will become overweight (WHO, 2000).

The main organs and tissues implicated in the regulation of energy homeostasis are: the gut (both, intestinal tissue and microbiota), pancreas, liver, adipose tissue, muscle and brain. These organs constitute a complex network orchestrated by multiple signaling molecules and metabolites, hormones and neural activity (Yamada et al., 2008; Ito and Adachi-Akahane, 2013; Xie et al., 2013). MetS is a very complex disorder that may be characterized by: (i) deregulation in the hypothalamus of the appetite–satiety control processes through altered levels of neurotrophins such as the brain-derived neurotrophic factor (BDNF) which promotes changes in the food intake and absorption of nutrients (calories) (Chaldakov, 2011; Rios, 2013), (ii) these changes can have an important impact on gut microbiota causing alteration of the groups and proportions of commensal microorganisms residing in the lumen (Annalisa et al., 2014), (iii) hyperactivity in the pancreas leading to the increased production of insulin (hyperinsulinaemia) and eventually insulin resistance, (iv) as insulin increases, receptors and signaling pathways are downregulated in the liver, muscle, and adipose tissue leading to altered uptake and metabolism of the major energetic nutrients (glucose, fatty acids), (v) increased adipose mass with abnormal production of adipokines (e.g., higher levels of leptin and lower levels of adiponectin) and altered levels of inflammatory cytokines (e.g., tumor necrosis factor alpha (TNF-α), and interleukin 1 beta (IL-1β)), (vi) alteration of the hormones and circulating molecules leads to the deregulation of the communication with the central nervous system (Esser et al., 2014).

Caloric restriction and lifestyle changes (increased physical activity) are generally considered the initial approach against MetS with, however, variable efficiency (Onat, 2011; Prasad et al., 2012; Lovshin and Drucker, 2013). Specific drugs have also been developed and commercialized for the treatment against the particular features of MetS (Hainer and Hainerová, 2012). Orlistat is a well-known pancreatic lipase inhibitor which increases up to 30% TGs excretion in stools. At doses of 15 mg/day for a year can reduce body weight between 3% and 5% of initial weight. The proportion of patients achieving clinically meaningful weight loss ranges from 35% to 73% (Yanovski and Yanovski, 2014). Orlistat consumption is also associated with a reduction of serum TGs, increases in adiponectin (Rodina and Severin, 2013) and to a clinically significant reduction (37%) in diabetes type-2 (Baretić, 2013). Another metabolic drug currently in use is acarbose which inhibits enzymes needed to digest carbohydrates, specifically, α-glucosidase and pancreatic α-amylase. Intervention studies show a 6% reduction in diabetes risk over 3 years. It also reduces blood glucose levels, glycosylated hemoglobin (HbA1c), insulin resistance, inflammatory markers (TNF-α, interleukin 6 (IL-6)) and improves the lipid profile (Derosa and Maffioli, 2012). In the long term, drugs can have reduced effectiveness and secondary adverse effects (Derosa and Maffioli, 2012; Yanovski and Yanovski, 2014).

Plant polyphenols to combat MetS

For decades now, plant foods, plant extracts, and plant derived bioactive compounds such as fatty acids and polyphenols have been investigated as a potential alternative to synthetic drugs against metabolic diseases. Some of these products or compounds appear to act as anti-obesity agents (Trigueros et al., 2013), modulate adipose tissue inflammation (Siriwardhana et al., 2013), ameliorate insulin resistance (Munir et al., 2013) and prevent cardiovascular diseases (Kishimoto et al., 2013). The metabolic effects of plant products rich in polyphenols and of some of their main polyphenolic constituents have been extensively reviewed. Despite differences in experimental design, products tested, doses, etc., an important number of studies using rodent models of obesity and (or) diabetes (either diet-induced or genetic models) have reported that pomegranate and some of its main polyphenolic compounds ellagitannins, ellagic acid, gallic acid (Larrosa et al., 2010; Al-muammar and Khan, 2012; Banihani et al., 2013; Medjakovic and Jungbauer, 2013), grape extracts, resveratrol and procyanidins, tea extracts and flavan-3-ols (Bladé et al., 2010; Chuang and McIntosh, 2011; Tomé-Carneiro et al., 2013a, 2013b; Wang et al., 2014), and citrus extracts and flavanones (Assini et al., 2013) have all some beneficial metabolic effects, i.e., reduction of body weight gain and of circulating levels of lipids and glucose, improvement of insulin sensitivity and decrease of blood pressure and of chronic inflammation. In general, it appears that the regular intake of these products and compounds may contribute to reduce or prevent some of the MetS individualities. However, and despite all the animal studies as well as an increasing number of human trials, some fundamental questions remain to be answered: how much and by which mechanisms can plant bioactive polyphenols combat metabolic disorders? Which precise molecules are responsible for these effects? And, are they any safer and more efficient than drugs?

An important topic to clarify in order to answer these questions is the absorption, metabolism, and tissue distribution of dietary polyphenols. Numerous bioavailability studies have now contributed to estimate the concentrations and body sites where these compounds and (or) their derived metabolites can be detected. Although exact values of the daily average intake of polyphenols have not been definitively established, it has been estimated that after the consumption of a meal rich in plant foods (fruits, cereals, vegetables) and plant derived beverages (juice, coffee, tea) the intake of polyphenols may reach up to g quantities per day (Landete, 2012) and that the total concentration of polyphenols and metabolites is likely to reach high μM to mM levels in the gut and thus, the gastrointestinal tract and its microbiota represent important targets for effects of these compounds on metabolism (Williamson, 2013). The gut lumen may accumulate some plant original compounds (glycosides), their aglycones and also some transformed and (or) metabolized molecules, both host and microbial metabolites. Circulating individual concentrations of host and microbial metabolites (mostly phase I and phase II conjugates) are currently estimated to be in the range of nM to low μM. Tissue levels may be more in the nM range (Lewandowska et al., 2013). There is therefore opportunity for these compounds and metabolites to act at different sites and through different

mechanisms. Given the heterogeneity of products and compounds and the similarities between reported metabolic regulatory effects, it is plausible that some of these products and compounds may share common mechanisms of action.

The main aim of this review is to highlight the current understanding of the metabolic benefits of some major groups of polyphenols and the progress in establishing the underlying mechanisms of action. In the following sections, we shall review the potential mechanisms of action of these compounds and metabolites at various body sites and evaluate the current evidences of polyphenols as regulators of energy metabolism and inflammatory status that may contribute to explain the metabolic benefits of these compounds.

Potential mechanisms of action of polyphenols

Inhibition of gut enzyme digestion

Polyphenols can interact with proteins through hydrogen bonds or hydrophobic attraction forming small soluble and large insoluble protein–polyphenol aggregates. This binding can alter the protein three-dimensional structure and affect its biological activity (Bandyopadhyay et al., 2012). Within the gut, interactions of polyphenols with digestive enzymes altering their catalytic activity are possible and may represent an under-reported mechanism for delivering some of the metabolic benefits attributed to these compounds. Table 1 shows a list of recent reports looking at the inhibitory activity of polyphenol-rich products and of some representative polyphenols against α-amylase, pancreatic lipase, and glucosidases activity. Although these studies have been done *in vitro* and using animal (porcine) enzymes, the results suggest that there is a potential for these molecules to inhibit digestive enzymes *in vivo*. Despite metabolic transformation and absorption, the milieu of the small intestine lumen may retain a mixture of all those tested compounds which may interact with digestive enzymes and interfere with lipids and carbohydrates digestion. A regular intake of abundant dietary polyphenols may maintain a reduced action of these digestive enzymes. Even if this is only about 1% inhibition, it has a comparable potential to reduce diabetes and obesity risk to some of the current digestion inhibitory drugs (e.g., orlistat, acarbose)

Table 1. Polyphenol-rich extracts and polyphenols as modulators of gut digestive enzyme activity, gastrointestinal motility and glucose/lipids transport/absorption in the intestine.

Compound/Product	Effect and or IC_{50}	Enzyme activity	Reference
Modulation of gut digestive enzyme activity			
Procyanidin B3	~3914 μM	Trypsin	Goncalves et al. (2011)
EGCG; Caffeoyl-quinic acids	~2.0 μM; ~12–300 μM	Pancreatic Lipase	Cha et al. (2012)
Bark oligomeric proanthocyanidins	~38–500 μg/L, 80 μg/L ~20–90% inhibition	α-Amylase, Pancreatic Lipase	Kusano et al. (2011)
Oligomeric proanthocyanidins from *Salacia reticulate*	15–1250 ppm	Pancreatic Lipase	Koga et al. (2013)
Oligomeric procyanidins from apple extract	Inhibitory effect	Pancreatic Lipase	Sugiyama et al. (2007)
Ellagitannins with β-galloyl groups at glucose C-1	Strong inhibitory effect	α-Amylase	Xiao et al. (2013)
Pomegranate flower, pomegranate extract, pomegranate leaf extract	Inhibitory effect	Intestinal and salivary α-Glucosidase Pancreatic lipase activity	Medjakovik and Jungbauer, (2013) Al-Muammar and Khan, (2012)
Oligomeric proanthocyanidins and ellagitannins from grape and pomegranate	Inhibit activity 3–55%	α-Amylase, Gluco-amylase	Barret et al. (2013)
Anthocyanin-rich honeysuckle berry extract	Increases activity	Small intestine lactase microbial α- and β-glucosidase	Jurgoński et al. (2013)
Naringenin	Inhibitory effect	α-Glucosidase	Priscilla et al. (2014)
Neohesperidin dihydrochalcone	Activates	Porcine pancreatic α-amylase	Kashani-Amin et al. (2013)
Mulberry extract rich in phenolics and flavonoids	Inhibits activity, 0.6, 0.9, >5 mg/mL	Intestinal maltase, sucrase, pancreatic α-amylase	Adisakwattana et al. (2012)
Proanthocyanidin-rich berries	Inhibit activity 50 and 100 μg of GAE/mL	Pancreatic α-amylase	Grussu et al. (2011)
Resveratrol	Inhibits activity, expression and secretion 50–100 μM	Pancreatic bile salt-dependent lipase	Sbarra et al. (2005)
Resveratrol and resveratrol containing extracts	Inhibits activity	α-Amylase, α-glucosidase, β-galactosidase	Hetta et al. (2014)
Grape extract GE with resveratrol-3-glucoside	Inhibits activity, 1.35 mg/mL	α-Amylase	Miao et al. (2014)
Grape seed and tea extracts and catechin 3-gallates	Inhibits activity	α-Amylase, α-Glucosidase	Yilmazer-Musa et al. (2012)
Gallic acid and polyphenol-rich aqueous extract from *Limonium* spp.	Inhibits activity	α-Amylase, α-Glucosidase, Pancreatic lipase	Foddai et al. (2014)
EGCG	Inhibits activity 34%, 20 μM	Pancreatic amylase	Forester et al. (2012)
Phenolics extracted from *Citrus maxima*	Inhibit activity	α-Amylase, α-Glucosidase	Oboh and Ademosun, (2011)

(*Continued on next page*)

Table 1. (Continued)

Compound/Product	Model	Effect on motility	Reference
Reported effects on gastrointestinal motility			
Polyphenol rich extract catechin, caffeic acid, quercetin	Guinea-pig ileum, dose dependant	Increases smooth muscle contractility, stimulant gastrointestinal motility	Bencsik et al. (2013)
Citrus flavone, nobiletin	Isolated rat jejunal segments	Stimulates and inhibits contractility	Xiong et al. (2014)
Naringin, naringenin	Whole-cell patch clamp methods	Transient increase in intracellular levels of Ca and activation of ghrelin receptors: potential pro-kinetic effect on intestinal motility	Jang et al. (2013a)
Naringin	Rats gastrointestinal motility	Activation of ghrelin receptor and strong pro-kinetic activity	Jang et al. (2013b)
Isoflavone genistin	Isolated rat jejunal segments Rats gastrointestinal motility	Inhibits contractility in a dose dependent manner	Xiong et al. (2013)
Daidzein	Isolated jejunal smooth muscle fragment	Inhibitory effects on intestinal motility	Chen et al. (2012)
Isoliquiritigenin	Isolated rat stomach fundus, isolated rabbit jejunum, guinea pig ileums	Dual role: spasmogenic muscarinic receptors and spasmolytic effects Ca channels	Chen et al. (2009)
Caffeic acid phenethyl ester	Isolated rat jejunal segments	Inhibits spontaneous ileal contractions through Ca channels	Aviello et al. (2010)
Flavonoid-rich extract catechin, epicatechin, quercetin kaempferol	Mice, phenol red marker	Reduce gastric emptying and intestinal transit	Baggio et al. (2009)
Flavonoids apigenin, flavone, kaempferol, morin, myricetin, naringin, rutin, naringenin, silibilin, silymarin, taxifolin	Mice	Reduce intestinal transit mediated through adrenergic receptors and Ca	Di Carlo et al. (1993)

Compound/Product	Model	Effect on glucose/lipids transport	Reference
Reported effects on glucose transport and lipids absorption			
Pomegranate extract	Brush border membrane vesicles (BBMV) from mouse small intestine Caco-2 cells	Inhibition IC_{50}= 424 μg/mL of Na dependent glucose uptake, reduces transporter expression in Caco-2	Kim et al. (2011)
Polyphenol rich herbal extract	Caco-2 cells	Inhibition of GLUT2 and SGLT1	Farrell et al. (2013)
Strawberry and apple extracts, quercetin-3-O-rhamnoside, phloridzin, 5-caffeoylquinic acid, pelargonidin-3-O-glucoside	Caco-2 cells	Inhibition of GLUT2 and SGLT1	Manzano and Williamson, (2010)
Flavonoids: myricetin, fisetin, quercetin, isoquercitrin,	GLUT2 expressed in *Xenopus* oocytes	Inhibition of glucose and fructose transport	Kwon et al. (2007)
Neohesperidin, phloridzin, phloretin, quercetin, apigenin, myricetin, catechin, epicatechin, EGCG, EGC, ECG	Caco-2 cells	Inhibition of glucose uptake through GLUT2 and or SGLT1	Johnston et al. (2005)
Tea extracts, catechins, ECG	Caco-2 cells, BBMV from rabbit small intestine	Inhibition of SGLT1 glucose transport	Shimizu et al. (2000) Kobayashi et al. (2000)
Tiliroside flavonoid glycoside	Male mice	Inhibition of GLUT2 and SGLT1	Goto et al. (2012)
Naringenin	BBMV from mouse small intestine	Inhibiton of Na-glucose cotransporter	Li et al. (2006)
Apple procyanidins	Caco-2 cells	Reduce the synthesis and secretion of ApoB48	Vidal et al. (2005)
Polyphenol-rich cinnamon extract	Freshly isolated intestinal enterocytes	Decreased the amount of ApoB48 secretion	Qin et al. (2012)
Resveratrol	Human kinetic study	Reduce the production of ApoB48 and Apo100	Dash et al. (2013)
Green tea, chokeberry and honeysuckle polyphenol extracts	Rat intestine perfusion	Reduce the absorption of cholesterol	Frejnagel and Wroblewska, (2010)
Flavonoids: hesperetin, apigenin, luteolin, quercetin and ECG	Caco-2 cells	Reduce cholesterol absorption by decreasing the levels of NPC1L1 transporter expressed in the intestine	Nekohashi et al. (2014)
Black tea polyphenols	Artificially prepared micelles	Reduce *in vitro* micellar cholesterol solubility	Ikeda et al. (2010)
Grape seed polyphenols: catechin, epicatechin and gallic acid	Artificially prepared micelles	Reduce the formation of cholesterol micelles	Ngamukote et al. (2011)

(Foddai et al., 2014). It is therefore plausible that a moderate but regular consumption of polyphenols may mimic a small and significant caloric restriction and contribute to moderate energy metabolism regulation.

Modulation of gastrointestinal motility

A few studies have investigated the effects of various polyphenols and of extracts rich in polyphenols on animal gut

contractility using isolated intestine segments and (or) color markers. The results are summarized in Table 1. It does appear that some of these products and compounds can affect muscle contractility in the intestine in both directions, stimulating or inhibiting (Aviello et al., 2010; Bencsik et al., 2013; Jang et al., 2013b; Xiong et al., 2013; Xiong et al., 2014) as well as reduce gastric emptying (Baggio et al., 2009) and therefore have the potential to further interfere with the digestion and absorption processes. Some of these effects appear to be associated with Ca cellular fluxes (Di Carlo et al., 1993; Aviello et al., 2010; Jang et al., 2013b) or interactions with specific receptors, such as adrenergic receptors (Di Carlo et al., 1993), muscarinic receptors (Baggio et al., 2009), or gut endocrine receptors such as ghrelin receptor (Jang et al., 2013a, 2013b). Changes in gastrointestinal motility caused by consumption of some polyphenols may further contribute to modulate the digestion and absorption of nutrients in the gut.

Direct effect on sugars and fats transport

Polyphenols have also the potential to reduce sugar absorption by affecting the main transporters of glucose present in the intestinal epithelial cells, solute carrier family 2 or facilitated glucose transporter member 2 (GLUT2) and sodium/glucose cotransporter 1 (SGLT1), (Williamson, 2013) (Table 1). Flavonoids such as quercetin, myricetin, or fisetin (Kwon et al., 2007; Johnston et al., 2005) and tea flavan-3-ols such as catechin, epicatechin, epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG, Kobayashi et al., 2000; Shimizu et al., 2000; Johnston et al., 2005) have all been reported to potently reduce glucose absorption through the inhibition of these transporters. Other flavonoids such as the flavanone naringenin (Li et al., 2006) and various polyphenol-rich extracts (Manzano and Williamson, 2010; Kim et al., 2011; Farrell et al., 2013) also interfere with glucose absorption and glucose transporters expression.

One additional mechanism possibly contributing to energy metabolism regulation by polyphenols intake could be the delay and (or) reduction of the absorption of dietary lipids (TGs, cholesterol). Apple procyanidins (Vidal et al., 2005), a polyphenol-rich cinnamon extract (Qin et al., 2012), and resveratrol (Dash et al, 2013) have all been shown to reduce the synthesis and secretion of ApoB48 (a specific marker essential for the assembly of TGs-rich lipoproteins) that can alter the production and secretion of chylomicrons by intestinal cells. Also, the perfusion of rat intestine with polyphenols caused a significant reduction in the absorption of cholesterol (Frejnagel and Wroblewska, 2010). Very recently, it has been demonstrated that a number of flavonoids including hesperetin, apigenin, luteolin, quercetin, and ECG reduced cholesterol absorption in Caco-2 cells by decreasing the levels of the Niemann-Pick C1-like 1 cholesterol transporter (NPC1L1) expressed in the intestine (Nekohashi et al., 2014). Other products such as black tea polyphenols (Ikeda et al., 2010) and the major polyphenols present in grape seed (catechin, epicatechin, and gallic acid) can reduce micellar cholesterol (Ngamukote et al., 2011). These results are all suggestive of the potential for various polyphenols to moderate the absorption of dietary fats. However, these effects on sugar and fat transporters and fat absorption occur in the small intestine, where apart from the flavan-3-ols, glycosides are more abundant than the aglycones tested.

Potential prebiotic effects

An increasing number of articles reported that the intake of some polyphenols and (or) polyphenol-containing products can modify bacterial counts and microbial populations in the intestine and that these changes may be associated with some metabolic and anti-inflammatory benefits. As listed in Table 2, the consumption of pomegranate products (Bialonska et al., 2010; Larrosa et al., 2010; Neyrinck et al., 2013), grape extracts (Tabasco et al., 2011; Cueva et al., 2013; Wang et al., 2013), resveratrol (Larrosa et al., 2009; Qiao et al., 2014), tea and some tea phenolics (Lee et al., 2006; Molan et al., 2010), a wild blueberry drink (Vendrame et al., 2011; Guglielmetti et al., 2013), and various other plant derived products containing polyphenols (Mandalari et al., 2010b; Boto-Ordóñez et al., 2014; Cowan et al., 2014; Espley et al., 2014; Noratto et al., 2014) have all been shown to alter certain bacterial groups in the gut. Some of these variations have been related to the reduction of lipids, inflammatory markers, body weight, or adiposity and with changes in the production of short chain fatty acids (SCFA) which participate in the regulation of energy metabolism and inflammatory status of the host (Soldavini and Kaunitz, 2013). Despite the variability and differences between studies (i.e., experimental model, analytical methodology, bacterial groups/species investigated, etc.), it is becoming apparent that polyphenol-containing products display growth promoting effects for specific groups of bacteria. One of the most consistently described changes is a general induction of Bifidobacteria and Lactobacilli groups (see Table 2). Other bacteria show variable results, e.g., various members of *Clostridium* can be induced (Larrosa et al., 2010; Mandalari et al., 2010b), decreased (Molan et al., 2010; Viveros et al., 2011; Cueva et al., 2013; Cowan et al., 2014) or not affected (Bialonska et al., 2010; Vendrame et al., 2011) following the intake of various polyphenol-rich products. Bacteroides or Enterobacteria also show variable outcomes. Polyphenols also exhibit antimicrobial effects against some pathogens (Mandalari et al., 2010a). These results need to be taken with caution due to critical limitations of the studies. As shown in Table 2, many of these studies have been carried out with complex products which may have other nonspecified constituents such as fiber, minerals, or nutrients (e.g., carbohydrates) which may be responsible for the observed effects. Also, the groups of bacteria investigated so far constitute only a small percentage of the total bacteria living in the gut and it has not yet been fully established which of them are truly beneficial. These issues still need to be investigated.

Furthermore, gut bacteria are known to metabolize polyphenols through a sequence of reactions (hydrolysis, reductions, oxidations, dehydroxylation, demethylation, decarboxylation, lactonization) and to produce a variable and wide range of metabolites (metabotype), mostly composed by more simple phenolics (Bolca et al., 2013) and which may be implicated themselves in the alteration of specific bacterial groups. Some of these microbial derived compounds (urolithins, gallic acid, cinnamic acids, phenylpropionic acid, phenylacetic acid, benzoic acid, or their hydroxylated derivatives) have been tested

Table 2. Changes in microbiota population and association with metabolic and anti-inflammatory benefits of polyphenol-rich extracts and or polyphenols.

Compound/Product	Dose/Model	Effect on bacteria	Associated health benefit	Reference
Pomegranate peel extract	6 mg/d 4-w, HF-fed mice	↑ *Bifidobacterium* spp ↑ *Bacteroides-Prevotella* spp	↓ Total and LDL-cholesterol	Neyrinck et al. (2013)
Pomegranate extract, Urolithin-A	250 mg/kg d, 20-d15 mg/kg d 20-d, DSS-colitis rat model	↑ Bifidobacteria, Lactobacilli and *Clostridium* spp ↓ *E. coli*, Enterobacteria	↓ Inflammatory markers	Larrosa et al. (2010)
Pomegranate by-product POMx but not punicalagins	Batch culture fermentation system	↑ Total bacteria, *Bifidobacterium* spp, *Lactobacillus* spp≈ *Clostridium coccoides–Eubacterium rectale, Clostridium Histolyticum*	↑ SCFA production	Bialonska et al. (2010)
Grape seed extract	GSE 1%, 16-w, IL10-KO mice	↑ *Bacteroides, Lactobacilli* ↓ *Faecalibacterium prausnitzii*	Ameliorated inflammatory bowel disease indices	Wang et al. (2013)
Grape seed extracts	*In vitro* culture	General inhibitory effect on *Streptococcus, Lactobacillus* and *Bifodobacterium* species	Not reported	Tabasco et al. (2011)
Grape seed extracts	600 mg/L, 48-h, Fecal batch culture fermentation	↑ *Lactobacillus/Enterococcus* ↓ *Clostridium histolyticum*	Not reported	Cueva et al. (2013)
Resveratrol	1 mg/Kg d, 25-d, DSS-colitis rat model	↑ Bifidobacteria, Lactobacilli ↓ *E. coli*, Enterobacteria	Protected the colonic mucosa and reduced inflammation markers	Larrosa et al. (2009)
Tea phenolics and metabolites: epicatechin, catechin, gallic acid, 3-*O*-methyl gallic acid, caffeic acid, phenylpropionic acid, phenylacetic acid	Fecal batch culture fermentation	Variable effects depending on compound or bacteria analyzed	Not reported	Lee et al. (2006)
Benzoic, phenylacetic, phenylpropionic acid and hydroxylated derivatives	*In vitro* culture	General inhibitory effect on *Escherichia coli, Lactobacillus* spp., *Staphylococcus aureus, Candida albicans*	Not reported	Cueva et al. (2010)
Gallic acid, ferulic acid, caffeic acid	*In vitro* culture	Various inhibitory effects on *Staphylococcus aureus, Enterobacter sakazakii, Listeria monocytogenes, Enterococcus faecalis, Escherichia coli*	Not reported	López-Nicolás et al. (2014)
Green tea	Rats, 6-d, 10 mL 1% tea gavaged	↑ *Lactobacillus, Bifidobacterium* ↓ *Bacteroides, Clostridium*	Not reported	Molan et al. (2010)
Polyphenol rich grape seed GSE and pomace GPE extracts	Broiler chicks, 21-d	↑ *E. coli, Lactobacillus, Enterococcus* caecum ↑ *Enterococcus* ↓ *Clostridium* ileum	↓ Body weight (GSE)	Viveros et al. (2011)
Polyphenol-rich almond skin extracts	Fecal batch culture fermentation	↑ Bifidobacteria, *Clostridium coccoides/ Eubacterium rectale*	No effect on the production of SCFA	Mandalari et al. (2010a)
Almond skin extracts, naringenin, catechin, epicatechin, protocatechuic acid	*In vitro* cultures	↓ *Staphylococcus aureus, Salmonella enterica, Listeria monocytogenes*	Not reported	Mandalari et al. (2010b)
Wild blueberry powder drink	Human volunteers, 6-w	↑ *Bifidobacterium* spp, ≈ *Lactobacillus acidophilus, Bacteroides* spp., *Prevotella* spp., *Enterococcus* spp., *Clostridium coccoides*	Not reported	Vendrame et al. (2011)
Wild blueberry powder drink	Human volunteers, 6-w	↑ *Bifidobacterium longum* subsp. *infantis*	Not reported	Guglielmetti et al. (2013)
Fermented rutin, quercetin, chlorogenic and caffeic acid, hydroxylated phenylacetic and phenylpropionic metabolites	Fecal batch fermentation	↑ *Bifidobacterium* spp. ↓ Firmicutes-to-Bacteroides ratio ↑ *Bifidobacterium longum*	Stimulates SCFA production	Parkar et al. (2013)
Red wine and dealcoholized red wine	Human volunteers, 20-d	↑ *Bifidobacterium, Enterococcus, Eggertella lenta*	Not reported	Boto-Ordóñez et al. (2014)
Flavonoid enriched apple product	Mice, 7-d	↑ Total bacteria, *Bifidobacterium* spp.	Decrease the expression of inflammation genes in the ileum and of plasma inflammatory marker PGE2	Espley et al. (2014)
Coffee solution	Caffeinated coffee solution 10-w, HF fed rats	↓ Firmicutes-to-Bacteroidetes and *Clostridium* Cluster XI associated with HF feeding ↑Enterobacteria	↓ Body weight, adiposity, liver TGs and energy intake	Cowan et al. (2014)
Plum carbohydrates-free juice with a high content of polyphenols	Obese Zucker rats, 11-w	↑ Some members of Ruminococcacea family, *Faecalibacterium, Lactobacillus, Turicibacter,* Bacteroidetes, ≈ *Bifidobacterium*	↓ Body weight changes in some SCFA	Noratto et al. (2014)
Resveratrol	High-fat fed mice, 12-w	↑ Firmicutes-to-Bacteroidetes, *Lactobacillus, Bifidobacterium* ↓ *Enterococcus* faecalis	↓ Body and visceral adipose weight ↓ Blood glucose and lipids	Qiao et al. (2014)

↓: decrease; ↑: increase; ≈: no effect; HF: high fat.

against human microorganisms and reported to exert growth inhibition of pathogenic and nonpathogenic human intestinal bacteria (*Lactobacillus, Clostridium, Escherichia, Salmonella, Staphylococcus*) (Lee et al., 2006; Cueva et al., 2010; Larrosa et al., 2010; López-Nicolás et al., 2014). Thus, these metabolites may have an effect on the maintenance of gut normobiosis, i.e., the gut "ecosystem" in which micro-organisms with potential health benefits predominate over potentially harmful ones in

contrast to "dysbiosis," in which one or a few potentially harmful micro-organisms are dominant, thus creating a disease-prone situation (Robertfroid et al., 2010). By altering counts of bacterial groups they may also modify the formation of microbiota metabolites such as SCFA (Parkar et al., 2013) with an important effect in the metabolism and inflammation status in the host.

Whether polyphenols can be currently considered truly prebiotics is a matter to debate (Romo-Vaquero et al., 2014). The general current definition of prebiotics includes only fermentable ingredients (fibers like inulin or oligosaccharides, Slavin 2013). If the ability of polyphenols or their metabolites to modify gut microbiota population with a health benefit for the host organism is further confirmed, the definition of prebiotics may require some modifications to include these compounds.

Regulatory effects on metabolic hormones and inflammatory molecules

Some of the most relevant hormones involved in the regulation of energy metabolism and inflammatory status include gut hormones (ghrelin, incretins, cholecystokinin (CCK)), pancreatic hormones (insulin, glucagon, amylin), sex hormones, cortisol, brain and thyroid-produced hormones and, adipokines produced by the adipose tissue (leptin, adiponectin, resistin) (Konturek et al., 2005). These hormones can affect directly or indirectly food intake, gastrointestinal motility, and energy homeostasis and some of those (e.g., glucagon-like peptide 1 (GLP-1), amylin, ghrelin or combinations of them) are currently investigated for the development of anti-obesity drugs (Hainer and Hainerová, 2012). Many animal studies show significant regulation of the levels of various gut and systemic hormones after consuming polyphenols or polyphenol-rich extracts (Table 3). More specifically, the consumption of polyphenols has been widely reported to be associated with the regulation of the levels of insulin, leptin, and adiponectin. In general, the consumption of these plant-derived compounds appears to upregulate the levels of adiponectin (Mcfarlin et al., 2009; Yao et al., 2011; Park et al., 2013; Tian et al., 2013; Wang et al., 2014) and to downregulate the levels of leptin (Mcfarlin et al., 2009; Huang and Lin, 2012; Park et al., 2013; Babu et al., 2013; Wang et al., 2014) which is consistent with an anti-inflammatory and anti-obesity effect. Changes in insulin are more variable. The levels of this hormone have been upregulated (Babu et al., 2013; Medjakovik and Jungbauer, 2013; Yamashita et al., 2013; Nekooeian et al., 2014), downregulated (Wang et al., 2014; Huang and Lin, 2012; Panickar, 2013), or not affected (Tian et al., 2013) by various polyphenol products. An incipient number of articles is beginning also to report effects of polyphenols or polyphenol-containing products on the production of other metabolic systemic hormones (insulin-like growth factor I (IGF-1), amylin, neuropeptide Y (NPY), resistin) (Yao et al., 2011; Panickar, 2013; Wang et al., 2014) and of gut secreted hormones (GLP-1, ghrelin) (Panickar, 2013; Raasmaja et al., 2013; Yamashita et al., 2013; González-Abuín et al., 2014). Although these effects are modest and variable, they suggest that the regular intake of polyphenols may have a much more important regulatory role affecting hormonal control of food intake, motility, and energy homeostasis than envisaged.

The consumption of polyphenols and polyphenol-containing extracts has also been associated with changes in both, circulating levels and expression tissue levels (intestine, liver, adipose tissue) of key inflammatory and anti-inflammatory molecules (Table 3). According to the reported results, it does appear that, in general, the consumption of polyphenols can be associated with an anti-inflammatory effect. Most studies show consistent evidence of the downregulation of key inflammatory molecules: TNF-α, interleukin 1 alpha (IL-1α), IL-1β, monocyte chemoattractant protein 1 (MCP-1), IL-6, interleukin 8 (IL-8), interferon gamma (IFN-γ) (Terra et al., 2009; Mahmoud et al., 2012; Matos et al., 2012; Lim et al., 2013; Medjakovik and Jungbauer, 2013; Neyrinck et al., 2013; Tomé-Carneiro et al., 2013a, 2013b; Wang et al., 2013; Yoshida et al., 2013; Ahmad et al., 2014a, 2014b) and upregulation of some anti-inflammatory molecules, interleukin 10 (IL-10) (Fu et al., 2011; Ahmad et al., 2014b).

These hormone and anti-inflammatory regulatory effects do not seem to be very specific and the underlying mechanisms are not yet known. It has not been established whether they are a direct consequence of the interaction of a polyphenol or of a derived metabolite with receptors or signaling pathways in the specific endocrine cell or tissue, or if these hormones and cytokine changes are a consequence of the alteration of the digestion and absorption of energetic nutrients (glucose, fats), or if they are mediated through signaling molecules produced by the microbiota. Based on all the above reported effects of polyphenols, it is conceivable that these changes may be a consequence of a combination of some of these mechanisms.

Cell mechanisms underlying the metabolic and anti-inflammatory effects of polyphenols: *In vitro* studies

To date, the mechanisms of action of polyphenols in cells and tissues are not yet fully understood, but several possibilities have been proposed and constitute an area of intense research. Polyphenols may interact directly with proteins (enzymes, receptors, signaling molecules, transcription factors) and affect signaling pathways (Fraga et al., 2010) and (or) interact with nucleic acids (epigenetic mechanisms) affecting DNA methylation, histones modifications or modulating the levels of noncoding regulatory molecules such as microRNAs (Pan et al., 2013). Both types of interaction may trigger gene and protein expression regulation of metabolic and inflammatory related molecules in the different implicated tissues. What evidences do we have about these mechanisms occurring in cells? A plethora of *in vitro* studies have shown that polyphenols such as flavonols, procyanidins, catechins, resveratrol, or ellagitannins can interfere with cell metabolic or inflammatory pathways through the modulation of key transcription factors and metabolic regulatory proteins: nuclear factor NF-kappa-B (NFκB), CCAAT-enhancer binding protein alpha/beta (CEBPα/β), peroxisome proliferator-activated receptors (PPARs) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PPARGC1A), 5′-AMP-activated protein kinase (AMPK), sirtuins, etc (Larrosa et al., 2010; Martínez-Micaelo et al., 2012; Wang et al., 2014). However, a significant amount of these studies were carried out using inadequate experimental designs, i.e., the original plant compounds or full extracts containing mixed compounds were

Table 3. Reported changes in metabolic hormones and inflammation-related molecules associated with the consumption of polyphenols or polyphenol-containing products.

Compound/Product	Model	Effect on levels/expression	Reference
Effects on metabolic hormones			
Green tea catechins	Various rodent models of obesity (genetic or HF-induced)	↓ Insulin, ↑↓ Adiponectin, ↓ Leptin, ↓ IGF-1, ↓ Ghrelin	Wang et al. (2014), and Panickar, (2013)
Green, black, oolong and pu-erh tea	Rats fed a HF-diet	↓ Insulin, ↓ Leptin	Huang and Lin (2012)
Green tea polyphenols	Rats fed a high-fat diet	≈ Insulin, ↑Adiponectin	Tian et al. (2013)
Resveratrol	Various rodent models of obesity genetic or HF-induced	↓ IGF-1, ↓ Leptin, ↑ Adiponectin, ↓ Insulin,↑ GLP-1, ↓ Amylin, ↓ NPY	Wang et al. (2014), and Panickar (2013)
Polyphenol-rich grape skin extract	Mice fed a HF-diet	↓ Leptin, ↑ Adiponectin	Park et al. (2013)
Flavanones: naringin, Berry: anthocyanins Flavonols kaempferol, quercetin, genistein	Rodent models of induced diabetes	↑ Insulin, ↑ Leptin, ↑↓ Insulin, ↓ Leptin,↑ Insulin	Babu et al. (2013)
Pomegranate peel extract	Induced diabetic rats	↑ Insulin	Medjakovik and Jungbauer, 2013
Pomegranate seed oil	High-fat CD-1 mice, Diabetic induced rats	↓ Leptin, ↑ Adiponectin,↑ Insulin	Mcfarlin et al. (2009) Nekooeian et al. (2014)
Naringin	Rats with gastrointestinal motility dysfunction	Activation of ghrelin receptors	Jang et al. (2013a), (2013b)
Citrus extract rich in naringin	Obese Zucker rats fed a HF diet	↓ GLP-1, ↑ Ghrelin	Raasmaja et al. (2013)
Grape seed procyanidins	Rats fed a cafeteria diet	Prevents GLP-1 reduction caused by the cafeteria diet	González-Abuín et al. (2014)
Cinnamtannin A2 tetrameric procyanidin	Mice/oral dose in water 10 μg/kg b.w.	↑ Plasma levels of Insulin and GLP-1	Yamashita et al. (2013)
Silybin	HF-fed rats	↑ Adiponectin, ↓ Resistin	Yao et al. (2011)
Effects on inflammatory molecules			
EGCG	Mice	↑ IL-10	Fu et al. (2011)
Green tea catechins	Various rodent models of obesity (genetic or HF-induced)	↓ mRNA TNF-α, MCP-1;↓ levels of IL-6, MCP-1; ↓ TNF-α; ↓ IL-1β;↓ IL-1α, IL-2, IL-4, IL-10, IFN-γ	Wang et al. (2014)
Resveratrol	Rabbits fed a high cholesterol diet	↓ MCP-1, ↓ IL-6	Matos et al. (2012)
Resveratrol	Various rodent models of obesity (genetic or HF-induced)	↓ TNF-α, MCP-1, IFN-α,β, IL-6, ↓ TNF-α, IL-6, IL-8, MCP-1, IFN-γ, IL-1α	Wang et al. (2014), and Tomé-Carneiro et al. (2013a), (2013b)
Pomegranate compounds: ellagic acid, punicalagins and pomegranate extracts	Various animal models of inflammation	↓ TNF-α, IL-6, IL-1β, MCP-1	Medjakovik and Jungbauer (2013)
Pomegranate extract	HF fed mice	↓ mRNA levels of IL-1β, IL-6 in colon, liver and adipose tissue	Neyrinck et al. (2013)
Grape seed procyanidin extract	Carrageenan-induced lung inflammation in mice	↓ mRNA levels of ICAM-1, IFN-γ, IL-6, IL-1β, TNF-α, IL-17A, MCP-1; ↑ TGFβ, IL-10 in lung tissue	Ahmad et al. (2014a)
Naringin	Arthritis induced mice	↓ mRNA levels of IL-1β, IL-17F, MCP-1;↑ IL-4	Ahmad et al. (2014b)
Naringenin	HF-fed mice	↓ mRNA levels of TNF-α, MCP-1 in adipose tissue	Yoshida et al. (2013)
Hesperidin and Naringin	HF-fed and STZ-treated diabetic rats	↓ Serum levels of TNF-α and IL-6	Mahmoud et al. (2012)
Grape seed procyanidins	Zucker rats	↓ mRNA levels of TNF-α, IL-6 and CRP in adipose tissue	Terra et al. (2009)
Mulberry leaf and fruit extract	HF-fed mice	↓ MCP-1, CRP, TNF-α, IL-1β in liver and adipose tissue	Lim et al. (2013)

↓: decrease; ↑: increase; ≈: no effect; HF: high fat; b.w.: body weight.

added directly to pancreatic, hepatic, muscle, adipose or immune cells, usually at rather high concentrations, disregarding the bioavailability and metabolic transformation of these compounds. These designs do not represent the *in vivo* situation and therefore, the results are of dubious transference to the *in vivo* system.

To better understand the molecular mechanisms triggered in cells by dietary polyphenols, *in vitro* studies need to be redesigned toward a better simulation of the *in vivo* plausible conditions: i.e., cells should be exposed to nM to low μM levels of the polyphenol metabolites identified in plasma and tissues. A step in this direction is shown by a limited but increasing number of studies (Table 4). Some glucuronide, sulfate, and methylated conjugates of quercetin (Tribolo et al., 2008; Winterbone et al., 2009; Boesch-Saadatmandi et al., 2011; Derlindati et al., 2012; Chuang et al., 2012; Guo et al., 2013), resveratrol (Lasa et al., 2012; Eseberri et al., 2013; Lu et al., 2013; Calleri et al., 2014; Walker et al., 2014), epicatechin (Claude et al., 2014), or flavonoids (Fang et al., 2003; Chanet et al., 2013) appear to counteract in cells some of the effects of stimulated-inflammation as shown by the reduction of the levels and expression of some key inflammatory cytokines (TNF-α, IL-1β, MCP-1, IL-6, IL-8) and by the regulation of the production of various adipokines. At the low μM levels, these metabolites exhibit, in general, very modest effects and it is conceivable that at nM concentrations, more representatives of the quantities detected in tissues, the results may be less significant.

Absorbed and circulating conjugates may account for as much as 5%–10% of the total polyphenol ingested and thus, the remaining 90%–95% proceeds to the large intestine where they undergo major metabolic transformation by the microbiota. The metabolites produced by the activity of bacteria yields a number of simple phenolics that can also be absorbed and conjugated before they can be eliminated with the urine or bile

Table 4. Metabolic and anti-inflammatory effects of polyphenol derived compounds: phase I/phase II conjugates and microbial metabolites, in cell models.

Metabolite	Cell model/dose	Effect on inflammatory molecules	Reference
Polyphenol derived conjugates			
Quercetin-3-gluc	Human primary adipocytes treated with TNF-α, 0.5 nM up to 30 μM	No effect on the expression of TNF-α-induced MCP-1 or IL-1β	Chuang et al. (2012)
Quercetin-3′-sulf, quercetin-3-gluc, 3′-methylquercetin 3-gluc, isorhamnetin 3-gluc	LPS + TNF-α treated human endothelial cells, 2.0–10 μM	Small counteracting effects on the levels and expression of adhesion molecules and MCP-1	Tribolo et al. (2008)
Quercetin-3′-sulf, quercetin-3-gluc, 3′-methylquercetin 3-gluc, isorhamnetin 3-gluc	TNF-α treated human artery smooth muscle cells, 2.0–10 μM	No effect on adhesion molecules and MCP-1	Winterbone et al. (2009)
3′-Methylquercetin isorhamnetin	LPS stimulated macrophages, 10 ng/mL	↓ TNF-α mRNA and protein, IL-1β, IL-6, MIP1α mRNA; ↓ pro-inflammatory mir-155	Boesch-Saadatmandi et al. (2011)
Quercetin-3-gluc	Isolated and induced human M1 and M2 macrophages, 500 nM	General downregulation of genes involved in inflammation pro-inflammatory cytokines	Derlindati et al. (2012)
Quercetin-3-gluc	Palmitate-stimulated human umbilical endothelial cells, 1 and 10 μM	↓ secretion of TNF-α and IL-6	Guo et al. (2013)
Resveratrol-3-sulf, resveratrol-disulf	U-937 macrophages treated with LPS, 1 and 10 μM	↓ Release of TNF-α and IL-6	Walker et al. (2014)
Resveratrol-3-*O*-gluc, resveratrol-4′-*O*-gluc, resveratrol-3-*O*-sulf	Pre-adipocytes, mature adipocytes	Various changes in adiponectin, leptin, apelin and vistafin	Eseberri et al. (2013)
Resveratrol-3-*O*-gluc, resveratrol-4′-*O*-gluc, resveratrol-3-*O*-sulf	Pre-adipocytes, mature adipocytes, 10–25 μM	↓ TGs, effects on mRNA levels of CEBPα/β, PPARγ, SIRT1, and various other genes related to lipid metabolism	Lasa et al. (2012)
Resveratrol-3-*O*-gluc, resveratrol-4-*O*-gluc	Binding affinity to ligand-binding domains of PPARs	Bind to PPARγ but not to PPARα ligand domain	Calleri et al. (2014)
Dehydro-resveratrol, resveratrol-3-*O*-gluc, resveratrol-4′-*O*-gluc,	*In vitro* anti-inflammatory effects	Inhibit COX-2 activity and NO production	Lu et al. (2013)
Morin sulfates/glucuronides	LPS-activated macrophages, 2.0–2.5 μM	↓ TNF-α and IL-12	Fang et al. (2003)
4′-*O*-methyl-epicatechin, 4′-*O*-methyl-epicatechin-7-β-D-gluc, and -epicatechin-4′-sulf	TNF-α treated human endothelial cells, 0.2–1 μM	Regulation of gene expression involved in monocyte migration and adhesion	Claude et al. (2014)
Naringenin gluc, hesperetin gluc and sulf	TNF-α treated human endothelial cells, 2.0–10 μM	Counteract gene expression effects caused by the inflammatory cytokine TNF-α	Chanet et al. (2013)
Microbiota-produced simple phenolics			
4-*O*-methyl gallic acid	LPS treated murine macrophages, 2.5–20 μg/mL	↓ Expression of TNF-α, IL-1β	Na et al. (2006)
Protocatechuic acid metabolite of cyanidin-3-*O*-β-glucoside	Human and murine adipocytes treated with oxLDL, 100 μM	↑ Adiponectin mRNA and secretion, ↑ PPARγ mRNA and activity	Scazzocchio et al. (2011)
Protocatechuic acid metabolite of cyanidin-3-*O*-β-glucoside	LPS+INFγ inflammaed macrophages, > 50 μM	↓ TNF-α	Hidalgo et al. (2012)
4-hydroxyhippuric acid, 3,4-dihydroxyphenyl propionic acid, 3,4-dihydroxyphenylacetic acid	LPS-stimulated peripheral blood mononuclear cells, 1 μM	↓ TNF-α, IL-1β, IL-6	Monagas et al. (2009)
3,4-dihydroxytoluene metabolite of the flavonol rutin	HepG2 liver cells	↓ Synthesis of cholesterol by inhibiting the uptake of acetate into liver cells	Glässer et al. (2002)
3,4-dihydroxytoluene	LPS-stimulated murine macrophage cell line, 5–10 μM	↓ TNF-α, IL-1β, IL-6↓ COX-2, iNOS	Su et al. (2014)
3,4-dihydroxyphenylacetic acid, 2,3-dihydroxybenzoic acid, 3-hydroxyphenylpropionic acid	Pancreatic beta cells	Induce the production of glucose-stimulated insulin	Fernández-Millán et al. (2014)
Urolithin-A, urolithin-B, ellagic acid	TNF-α/IL-1β treated human colon fibroblasts 40 μM Uro-A, 5 μM Uro-B, 1 μM ellagic acid	↓ PGE2, PAI-1, and IL-8, as well as other key regulators of cell migration and adhesion	Giménez-Bastida et al. (2012b)
Urolithin A, B and C	PMA-differentiated THP1 monocytes primed with IFNγ and LPS treated, 0.078–20 μM	↓ TNF-α	Piwowarski et al. (2014)
Urolithin-A-gluc metabolite of ellagitannins	Human aortic endothelial cells, 5–15 μM	↓ TNF-α-induced levels of IL-8, MCP-1	Giménez-Bastida et al. (2012a)

Gluc: glucuronide; sulf: sulfate; ↓: decrease; ↑: increase.

(Duynhoven et al., 2011). Currently, the biological activities of these microbiota derived metabolites are largely unknown and only a few cell studies have been conducted to investigate the potential anti-inflammatory and metabolic effects of some of these compounds (Table 4). It does appear that some of these simple phenolics also exhibit some capacity to decrease the levels of pro-inflammatory cytokines in various cell models (Na et al., 2006; Monagas et al., 2009; Hidalgo et al., 2012;

Giménez-Bastida et al., 2012a, 2012b; Piwowarski et al., 2014; Su et al., 2014) as well as to regulate lipid metabolism (Glässer et al., 2002) and hormone production (Scazzocchio et al., 2011; Fernández-Millán et al., 2014). These phenolic compounds may also contribute to the metabolic and inflammatory effects of polyphenols.

Metabolic and anti-inflammatory effects of polyphenols: Evidence in humans

For the past decade researchers looking at the health benefits of polyphenols have agreed on the necessity to perform more clinical intervention trials to unequivocally demonstrate the benefits of these compounds against chronic disorders in humans. As the number of human studies increase, meta-analyses provide a first overview of the metabolic and anti-inflammatory effects of some polyphenols and polyphenol-containing products and indicate that, for example, grape seed extracts appear to lower systolic blood pressure but have no effect on lipids or C-reactive protein (CRP) levels (Feringa et al., 2011); berries, berry extracts, and anthocyanins can modify the levels of key inflammatory biomarkers (Joseph et al., 2014); green tea and tea extracts can reduce circulating levels of glucose, insulin, and lipids (Johnson et al., 2012; Liu et al., 2013; Zheng et al., 2013) and cocoa products rich in flavan-3-ols and procyanidins appear to improve blood pressure, insulin resistance, platelet function and circulating lipids (Latham et al., 2014). Single compounds such as resveratrol, EGCG or quercetin have also been thoroughly reviewed for their metabolic and anti-inflammatory properties (Peluso et al., 2013; Sahebkar, 2013; Timmers et al., 2013). All these analyses coincide, however, in that the results reported in humans are still inconsistent and lack of sufficient evidence to support the metabolic benefits of polyphenols. To illustrate the current situation and further discuss the main factors involved in it, Table 5 presents some examples of recent clinical trials investigating metabolic and anti-inflammatory effects of various polyphenols and polyphenol-containing extracts. A first glance at this table shows that results are heterogeneous with various articles reporting no effects or inconsistent effects. For example, the daily intake of pomegranate polyphenols (1.5 g) had no effect on body weight, blood pressure, glucose, lipids, CRP and oxidized low density lipoprotein (oxLDL) in both obese patients with type 2 diabetes (T2D) and in healthy volunteers (Basu et al., 2013) or ellagitannin-rich berries did not modify lipid levels, blood pressure and leptin in participants with MetS (Puuppone-Pimiä et al., 2013). Pomegranate juice did not alter plasma levels of IL-6 and CRP in hypertensive patients (Asgary et al., 2014) although it significantly reduced these two parameters in patients with T2D (Sohrab et al., 2014). Results reported for grape products and for resveratrol are also of little impact. A red grape extract appeared to decrease the levels of total and LDL-cholesterol in mildly hyperlipidemic volunteers but did not modify HDL-cholesterol, TGs, blood pressure or body weight (Razavi et al., 2013) and a grape extract containing resveratrol slightly increased adiponectin but had no effect on circulating cytokines, CRP, body mass, blood pressure and lipids (Tomé-Carneiro et al., 2013a, 2013b). Two recent studies using very high doses of resveratrol showed no effect on glucose, insulin, lipid levels and various adipokines and cytokines (Poulsen et al., 2013; Chachay et al., 2014). Table 5 includes also some studies using EGCG, tea catechins or tea extracts which show inconsistent or no effects on body weight, lipid levels or adiposity (Bogdanski et al., 2012; Suliburska et al., 2012; Miyazaki et al., 2013; Mielgo-Ayuso et al., 2014). Two recent examples further support the lack of significant metabolic benefits of polyphenols in humans by showing that the intake of mixed polyphenols at high doses do not seem to exert any substantial metabolic or anti-inflammatory effects in healthy individuals (Soare et al., 2014) or in healthy overweight volunteers (Most et al., 2014).

There are many critical differences between these trials, i.e., large variability in the composition of the products tested (juices, extracts, single compounds) that need to be fully characterized and standardized, different doses and intervention duration (from days to several months) and large variability of the individuals investigated: from overweight healthy volunteers to patients with a well-developed disorder (obesity or T2D) and with different phenotypes, age, gender, etc. A particular and critical limitation of all these interventional studies is the very small number of participants and low statistical power of the results. All these factors may contribute to explain the lack of consistent evidence of the beneficial metabolic and anti-inflammatory effects of polyphenols or polyphenol-containing products in humans.

The relevance of the genotype-dependent response to dietary constituents is recognized as an additional key variability factor. An increasing number of genetic variants, mostly single nucleotides polymorphisms (SNPs), have been identified and related to obesity and diet-interaction and, the studied population has been segregated into groups of responders and non-responders in association with the specific genetic variations (Corella and Ordovás, 2013). A few articles have now reported the potential interaction between the consumption of polyphenols or polyphenol-containing products with specific genes and genetic variants and attempted to establish the differences in response between individuals (Table 5). For example, the reduction of the percentage of total body fat reported in obese men following the intake of a polyphenol-rich apple juice was significantly associated with those individuals carrying a CC homozygous variant in the IL-6–174 G/C polymorphism associated with obesity. No other significant effects on plasma lipids, adipokine and cytokine levels, including IL-6, were found (Barth et al., 2012). Quercetin also exhibited different modulatory effects in blood pressure and HDL-cholesterol in overweight volunteers carrying different apolipoprotein E (ApoE) genotypes (Egert et al., 2010) and, the consumption of a fruit and vegetable-based drink containing polyphenols was associated with a significant reduction of *ex vivo* LDL oxidation lag phase in GG carriers of the glutamic298aspartic (Glu298Asp) polymorphism in the endogenous nitric oxide synthase (eNOS) gene (George et al., 2012). A deeper look at these studies shows that the small magnitude of the reported changes together with the reduced and unbalanced number of participants per genetic variant subgroup decreases considerably the significance of the results. Because some of these modest changes may be of biological or clinical relevance, future intervention trials need to be redesigned and the number of participants largely increased to enhance the statistical power. In addition, the mechanisms

Table 5. Recently reported metabolic and anti-inflammatory effects of various polyphenols and or polyphenol-rich extracts in human volunteers.

Compound/Product	Human trial design	Effect on metabolism/inflammatory molecules	Reference
Pomegranate extract 1000 mg, ~600 mg gallic acid in combination + simvastatin	Double blind, placebo-controlled randomized trial; 2-m; 23 male adults with hypercholesterolemia	No effects on lipid levels or on serum oxidative stress. ↓ TGs in isolated blood monocytes/macrophages	Hamoud et al. (2014)
Pomegranate extract capsules POMx = 753 mg polyphenols × 2/day	4-w; 8 obese patients with T2D and 9 healthy non-diabetic volunteers	No effect on body weight, blood pressure, glucose, lipids. No effects on CRP and oxLDL	Basu et al. (2013)
Pomegranate juice, 250 mL/day	Double blind, placebo-controlled randomized; 12-w, 50 patients with T2D	Significant reduction of plasma IL-6 and CRP	Sohrab et al. (2014)
Pomegranate juice, 150 mL/day	Single blind, placebo-controlled randomized; 2-w, 21 hypertensive patients	Significant ↓ in SBP/DBP and of VCAM1; ↑ E-selectin. No effects on CRP, IL-6, lipids, apolipoproteins, ICAM1	Asgary et al. (2014)
Ellagitannin-rich berries, 300 g/day	Randomized-controlled trial; 8-w trial, 32 participants with metabolic syndrome	No significant effects on lipid levels, blood pressure, leptin and resistin levels	Puupponen-Pimiä et al. (2013)
Grape seed extract, 300 mg	Double blind, placebo-controlled, randomized, parallel-group; 8-w; 70 healthy subjects with systolic BP between120 and 159 mmHg	No effects on blood pressure	Ras et al. (2013)
Red grape seed extract, 200 mg	Double blind, placebo-controlled, randomized, crossover; 8-w; 52 mildly hyperlipidemic volunteers	↓ Total cholesterol, LDL-cholesterol and oxLDL. No significant effect on body weight, blood pressure, TGs, HDL-cholesterol	Razavi et al. (2013)
Grape extract+ resveratrol (350 mg + 8 mg or 700 mg + 16 mg)	Triple-blind, randomized, placebo-controlled, 3-arm pilot clinical trial; 6-m and 1-y; 75 stable-CAD patients	↑ adiponectin, ↓ gene expression of inflammatory cytokines in PBMCs; No effects on TNF-α, IL-6, IL-10, CRP, body mass, BP, lipids	Tomé-Carneiro et al. (2013a), (2013b)
Resveratrol, 1500 mg	Randomized, placebo-controlled, double-blind, parallel group; 4-w; 24 obese healthy men	No effect on glucose, insulin, lipids, leptin, IL-6, TNF-α, MCP-1	Poulsen et al. (2013)
Resveratrol, 3000 mg	Randomized parallel-group study; 8-w; 20 overweight or obese men with NAFLD	No effect on insulin resistance, abdominal fat and lipid levels.	Chachay et al. (2014)
EGCG, 300 mg/d	Double blind, placebo-controlled randomized; 12-w; 83 premenopausal obese women	No effects on body weight, adiposity, blood lipid levels, insulin resistance	Mielgo-Ayuso et al. (2014)
Green tea catechins, 630 mg/day	Randomized controlled parallel group trial; 14-w; 52 older adults 69.1 ± 5.9 years	No significant effects on waist/hip circumference, cholesterol total, LDL, LDL/HDL	Miyazaki et al. (2013)
Green tea extract, 379 mg/day	Double blind, placebo-controlled randomized; 3-m; 46 obese patients	Reduction in body mass index, waist circumference, total cholesterol, LDL-cholesterol, TGs, glucose, blood pressure, insulin, TNF-α, CRP.	Suliburska et al. (2012), Bogdanski et al. (2012)
Supplement: 100 mg resveratrol, 800 mg green tea catechins, 250 mg pomegranate, 650 mg quercetin, 500 mg acetyl-carnitine, 600 mg lipoic, 900 mg curcumin, 1 g sesamin, 1.7 g cinnamon extract, Total: 7.5 g	Randomized single-blind controlled trial; 6-m; 54 non-obese healthy men and women 38–55 y	No effects on body fat, blood pressure, plasma lipids, glucose, Insulin, IGF-1, CRP, TNF-α, IL-6	Soare et al. (2014)
Supplement 1: EGCG 282 mg + resveratrol 200 mg, Supplement 2: EGCG 282 mg + resveratrol 200 mg + soy isoflavones 80 mg	Randomized double-blind crossover trial; 3-d; 18 healthy overweight volunteers	↑ Energy expenditure; improved metabolic health and body weight regulation. No other effect reported.	Most et al. (2014)
Polyphenol rich apple juice, 802.5 mg/day	Controlled randomized parallel study; 4-w; 68 non-diabetic obese men	No significant effects on BMI, waist circumference, plasma lipids, adipokine and cytokines IL-6. ↓ Body fat significantly associated to C/C variant in the IL-6–174 G/C polymorphism	Barth et al. (2012)
Quercetin, 150 mg/d	Double blind, placebo-controlled, randomized, crossover; 6-w; 93 overweight obese volunteers 25–65 y	↓ Systolic blood pressure in ApoE3 volunteers. No effect in the ApoE4 group.↓ HDL-cholesterol and ApoA1 in the ApoE4 group. No effect in the ApoE3 group.↓ TNF-α in both genotypes	Egert et al. (2010)
Fruit and vegetable pure based drink containing 192 mg polyphenols/ 100 mL, acute ingestion: 400 mL	Randomized, single-blind, controlled, crossover study; 24 healthy non-obese participants	Significant reduction of *ex-vivo* LDL oxidation lag phase in GG carriers of the Glu298Asp polymorphism in the eNOS gene	George et al. (2012)

↓: decrease; ↑: increase.

underlying the association genetic variant-response need to be elucidated. A further and much more complex matter is to understand the biological relevance of these genetically associated differences in the context of multiple genes and tissues and the applicability to future polyphenols intake recommendations. Nevertheless, these examples show the importance of progressing in the knowledge of the interaction between polyphenols intake and genetic variation in the individuals in order to fully comprehend the metabolic and anti-inflammatory effects of these compounds in humans.

Concluding remarks and future challenges

Over the past decades, a significant number of cell, animal and human studies have been carried out with the aim of demonstrating the beneficial metabolic and anti-inflammatory effects associated with the consumption of polyphenols or polyphenol-containing products. The data gathered in this review show that the evidence of these benefits in humans is still scarce and inconsistent and that the underlying biological and molecular mechanisms of action as well as the bioactive molecules have not been yet elucidated. Many of these polyphenols or polyphenol-containing products appear to exert various and similar effects which suggest that these compounds may work through multiple and common mechanisms of action and that both the original molecules and their derived metabolites can contribute to the final effects. The potential mechanisms and sites of action of polyphenols underlying the metabolic and anti-inflammatory benefits attributed to these compounds are summarized in Fig. 1:

1. In the upper part of the gastrointestinal tract, a proportion of dietary polyphenols may moderate the digestion and absorption of energy-providing nutrients by inhibiting digestive enzymes, modulating gut transit and interacting with hormone receptors and nutrient transporters. Both, plant original compounds and derivatives may contribute to this action. More studies are required to demonstrate these effects *in vivo*.
2. In the lower part of the intestine, the microbiota is modulated following the intake of polyphenols and this may be caused by a direct effect of those polyphenols reaching the large bowel or by alteration of the amount of nutrients (e.g., carbohydrates, lipids) made available to bacteria. The pool of metabolites produced by the microbiota including single phenolics derived from polyphenols and other metabolites such as SCFA or lipopolysaccharide (LPS) may all contribute to the inflammatory and metabolic status of the host individual. The understanding of the complex interaction between the microbiota and dietary polyphenols will be further advanced as the knowledge of the microbiota composition, variability, and benefits of these microorganisms to the host progresses.
3. Within the host organism, all these polyphenol-derived microbial metabolites as well as the human synthesized polyphenol conjugates can reach metabolic tissues and interfere with key signaling and metabolic pathways and

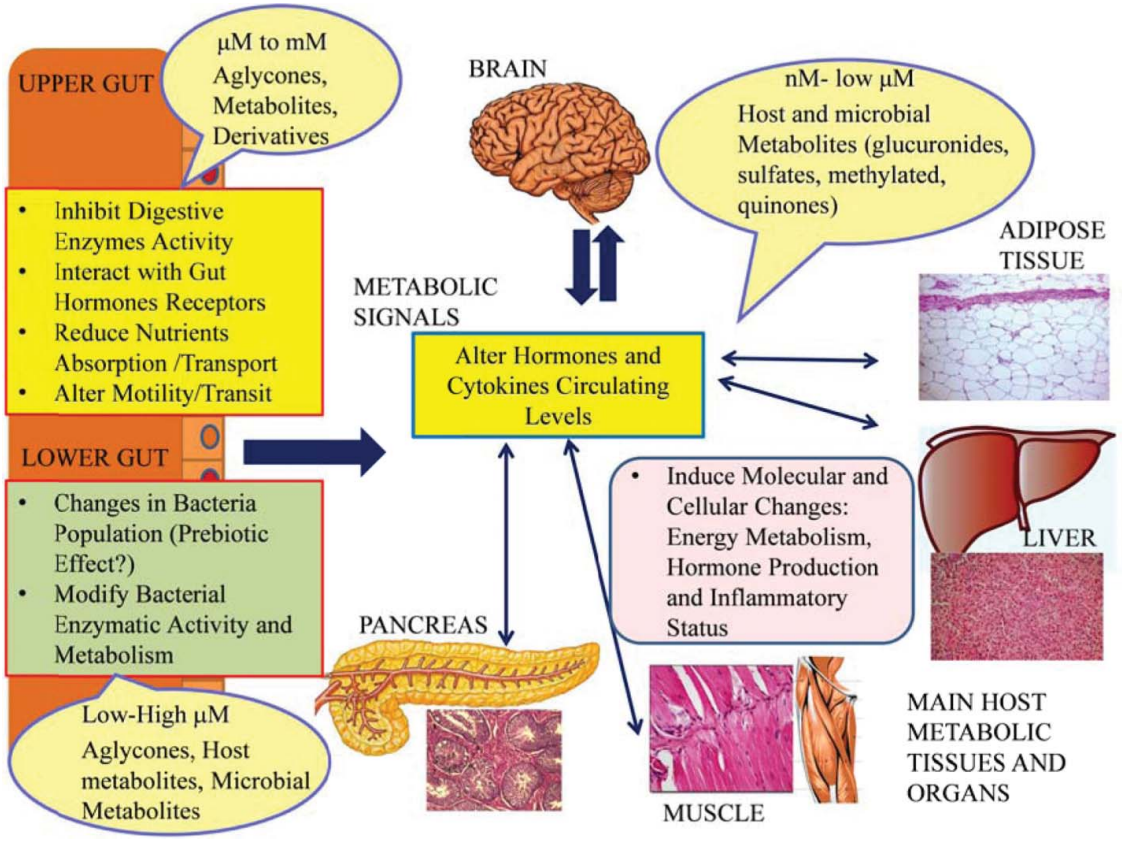

Figure 1. Overview of the potential mechanisms and sites of action of dietary polyphenols and their derived metabolites at the principal organs and tissues involved in the regulation of energy metabolism and inflammation.

alter protein synthesis and activity. Metabolites can therefore contribute to regulate the production and secretion of molecules and signals implicated in energy and metabolism regulation. Yet, more and improved *in vitro* studies using metabolites under suitable conditions are needed in order to fully clarify the contribution of these circulating molecules to the metabolic and inflammatory benefits attributed to polyphenols. Tissue analyses from intervention animal and human studies will further help to confirm the role of these metabolites.

This review has also highlighted that the number and quality of the human intervention studies carried out so far have been insufficient to substantiate a consistent beneficial modulatory effect of polyphenols or polyphenol-containing products on energy metabolism and inflammatory status. The scarcity of significant effects observed in the human trials disagrees with data obtained from rodent models and raises doubts about the justification of polyphenols and polyphenol-containing products as human nutritional supplements against metabolic disorders. However, the general absence of significant effects reported in humans may be associated with the fact that these effects are often very moderate and might have also been diluted within heterogeneous groups of participants. Many more intervention studies are therefore required to demonstrate the beneficial impact of dietary polyphenols against metabolic disorders in humans. These studies need to be performed in larger populations that should account for the identification of genetic variants involved in the response of the individuals and for the stratification of participants into responders and nonresponders. Demonstration of a significant effect in a particular well-defined subpopulation should be then followed by further studies to identify the molecule(s) responsible for the effects, the most efficient dosages and intervention periods and the mechanism of action implicated.

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